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ORIGINAL RESEARCH

Body Composition and Incident Heart Failure in Older Adults: Results From 2 Prospective Cohorts

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BACKGROUND: Aging is associated with central fat redistribution and skeletal muscle decline, yet the relationships of tissue compartments with heart failure (HF) remain incompletely characterized. We assessed the contribution of body composition to incident HF in elders.

METHODS AND RESULTS: Participants from 2 older cohorts who completed dual-energy X-ray absorptiometry (DEXA) and, in one cohort, computed tomography were included. We evaluated associations with incident HF for DEXA principal components (PCs) and total lean, appendicular lean, total fat and trunk fat mass; and for computed tomography measures of abdominal visceral and subcutaneous fat, thigh muscle, intermuscular fat area and thigh muscle density. DEXA analysis included 3621, and computed tomography analysis 2332 participants. During median follow-up of 11.8 years, 927 participants developed HF. DEXA principal components showed no relationship with HF. After adjustment for height, weight, and cardiovascular risk factors, total lean mass was near significantly associated with higher HF (hazard ratio [HR], 1.25 per SD [1.00–1.56]), whereas total fat mass and thigh muscle density were significantly related to lower HF (HR, 0.82 [0.68–0.99] and HR, 0.87 [0.78–0.97], respectively). Patterns were similar for HF subtypes. The relationships with HF for total lean and fat mass were attenuated after adjusting for intercurrent atrial fibrillation or excluding high natriuretic peptide levels.

CONCLUSIONS: Total lean mass was positively associated, while total fat mass and thigh muscle density were inversely associated, with incident HF. These findings highlight the limitations of DEXA for assessment of HF risk in elders and support the preeminence of computed tomography–measured skeletal muscle quality over mass as a determinant of HF incidence.

Key Words: adiposity ■ body composition ■ heart failure ■ skeletal muscle

Heat failure (HF) is a debilitating disease that primarily affects older adults.¹ Its 2 major subtypes, HF with preserved (HFpEF) and reduced ejection fraction (HFrEF), carry a similarly poor prognosis.² Like age, obesity is a major HF risk factor.¹ Overall adiposity, measured by body mass index (BMI), and central adiposity, measured by waist circumference or waist-to-hip ratio, have each been associated with increased risk of HF in middle-aged adults.^{3,4} The same has been true for older cohorts, including the CHS

(Cardiovascular Health Study)⁵ and Health ABC (Health, Aging and Body Composition) study.⁶ Aging, however, is associated with changes in body composition, such as central redistribution of body fat⁷ and decrease in skeletal muscle mass,⁸ that may not be well captured by anthropometric indices. Skeletal muscle decline involves both loss of mass and decrease in quality, resulting in the development of sarcopenia.⁹ The latter is of particular relevance to HF since its clinical hallmark, exercise intolerance, is determined as much by skeletal

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CLINICAL PERSPECTIVE

What Is New?

- Among older adults, using dual-energy x-ray absorptiometry–determined measures, total lean mass was positively associated, while total fat mass was inversely associated, with incident heart failure. Evaluation of thigh muscle density as determined by computed tomography showed an inverse relationship for this measure with heart failure onset.
- The relationships with heart failure for total lean and fat mass were attenuated after adjusting for intercurrent atrial fibrillation or excluding high natriuretic-peptide levels, but that for thigh muscle density was robust to adjustment for interval atrial fibrillation.

What Are the Clinical Implications?

- These findings highlight the limitations of dual-energy x-ray absorptiometry for assessment of heart failure risk in elderly persons and support the preeminence of computed tomography–measured skeletal muscle quality over mass as a determinant of heart failure incidence.

Nonstandard Abbreviations and Acronyms

CHS	Cardiovascular Health Study
Health ABC	Health, Aging and Body Composition study
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
PC	principal component
PCA	principal component analysis

muscle deterioration as by compromised cardiac function.¹⁰ Yet the contributions of alterations in body composition to the development of HF and its subtypes in older adults have not been well characterized.

Compared with anthropometric indices, dual-energy x-ray absorptiometry (DEXA) and computed tomography (CT) offer higher precision and reliability in body composition analysis.¹¹ To better understand the pathophysiologic impact of altered body composition in older adults, we examined the relationships of available DEXA and CT measures in CHS and Health ABC with new-onset HF and its subtypes. We tested the hypotheses that, after accounting for body

size, greater fat mass and lower lean mass by DEXA, and higher abdominal visceral and subcutaneous fat, lower thigh muscle mass, and higher intermuscular and intramuscular fat by CT, are each associated with higher risk of HF.

METHODS

Study Populations

Details of CHS and Health ABC have been reported.^{12–14} CHS enrolled community-dwelling adults aged ≥ 65 years from 4 US centers.^{12,13} An original cohort of 5201 participants was recruited in 1989–1990, followed in 1992–1993 by a supplemental cohort of 687 African-American participants. Health ABC enrolled 3075 functionally independent participants aged 70 to 79 from 2 US sites in 1997 to 1998. In-person examinations in both studies entailed medical history, physical examination, diagnostic testing, and biospecimens collection. Selection of participants for the present analysis is summarized in Figure 1. Institutional review boards approved study methods for each cohort. All participants provided written informed consent. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to CHS at CHSDATA@uw.edu and to Health ABC through <https://healthabc.nia.nih.gov>.

Body Composition Measurements

In CHS and Health ABC, whole-body DEXA was performed using QDR bone densitometers (Hologic, Inc., Bedford/Waltham, MA) with array and pencil beam technology, respectively. Whole-body DEXA data were used to calculate total lean and fat mass with QDR software. Lean mass values do not include bone mineral content. Appendicular lean mass was defined as the sum of right and left arm and leg lean mass. Scans were read blindly at a central reading center.

In Health ABC, CT was performed for measurement of abdominal visceral and subcutaneous fat areas at L4 to L5, and assessment of skeletal muscle and fat through a single axial slice at the femoral midpoint in both legs. The scans were conducted at 120 kVp, 200 to 250 mA seconds, at a slice thickness of 10 mm.⁷ Methods for quantitation of abdominal visceral and subcutaneous fat areas, as well as thigh muscle and intermuscular fat areas, have been described.⁷ Thigh muscle density, a measure of intramuscular fat, was defined as the mean attenuation coefficient of muscle tissue and expressed in Hounsfield units, with higher attenuation indicating denser muscle tissue (lower intramuscular fat).¹⁵

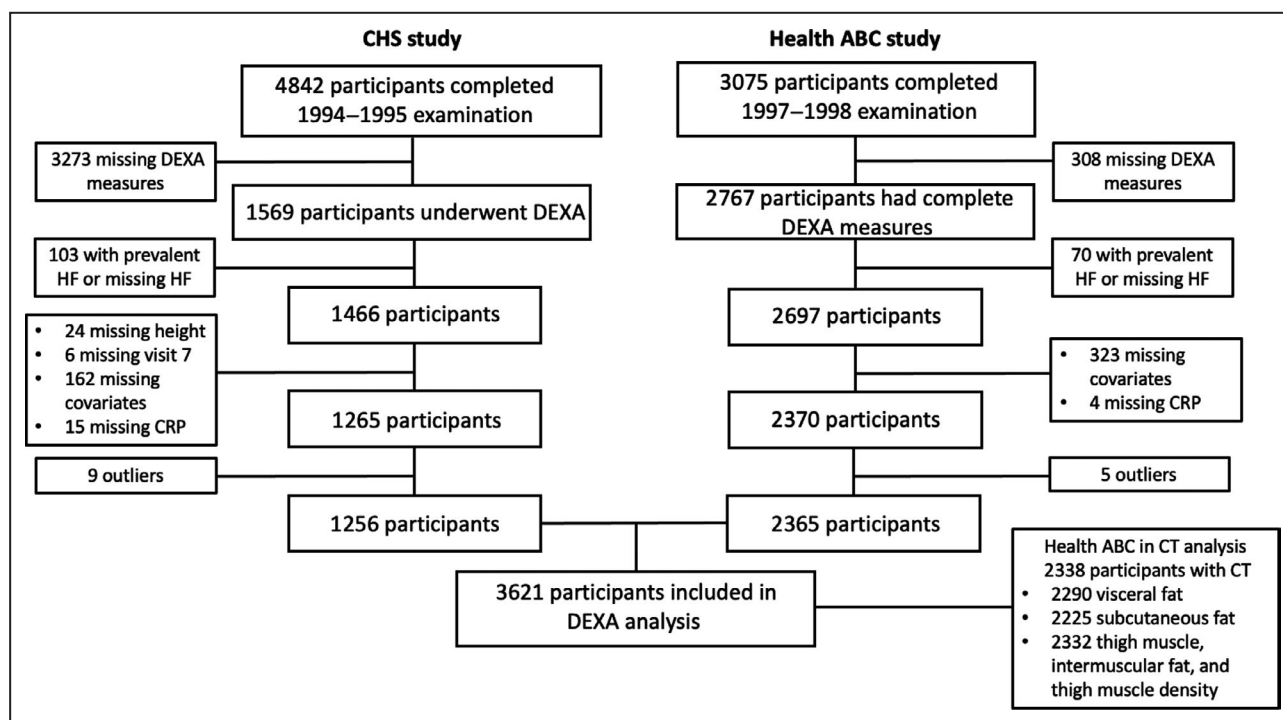


Figure 1. Selection of study participants.

CHS indicates Cardiovascular Health Study; CRP, C-reactive protein; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; Health ABC, Health, Aging and Body Composition study; and HF, heart failure.

Ascertainment of HF

Follow-up in both cohorts occurred semiannually through in-person visits and telephone contacts.^{12–14} The primary end point was incident HF; secondary end points were HFpEF and HFrfEF. CHS and Health ABC used similar centralized adjudication protocols for HF. All potential cases of HF were reviewed and adjudicated by an events committee.^{13,16} Assessment of HF relied on physician diagnosis, confirmatory symptoms and signs, corresponding medical treatment, or findings on diagnostic imaging.^{5,13,16} Determination of HF subtypes in each cohort was based on documented EF (HFrfEF: EF <50%; HFpEF: EF ≥50%). Adjudication of HF extended to June 2014 in CHS, and August 2012 in Health ABC.

Covariates

Baseline covariates were ascertained and defined similarly in CHS and Health ABC. Anthropometry, blood pressure, physical activity level, laboratory tests, and spirometry were obtained using standardized approaches.^{13,15} Diabetes was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or antihyperglycemic therapy. Prevalent coronary heart disease (CHD), stroke, transient ischemic attack, and peripheral arterial disease, were identified using standardized criteria.^{13,17} In both cohorts, atrial fibrillation

(AF) was determined by 12-lead ECG and Centers for Medicare & Medicaid Services administrative claims. Estimated glomerular filtration rate was calculated as estimated glomerular filtration rate = $76.7 \times \text{cystatinC}^{-1.19}$.

Statistical Analysis

Individual-level data were combined across CHS and Health ABC. Given the multitude of lean and fat mass measures ($n=12$) afforded by DEXA, we undertook a sex-specific principal component analysis (PCA) of DEXA measures in an effort to reduce these measures to factors capturing overall lean mass and adiposity. We calculated sex-specific unrotated principal components (PCs) as the linear combination of PC weightings of individual DEXA measures. Male and female PCs were pooled and used as continuous variables in the survival analysis. We also examined as exposures standard summary DEXA measures: total lean, appendicular lean, total fat, and trunk fat mass; and CT-determined body components: visceral and subcutaneous abdominal fat, thigh muscle area and intermuscular fat, and thigh muscle density. Cox regression was used to evaluate associations in sequential models that accounted for potential confounding or possible mediation. All DEXA and CT components were standardized and modeled linearly after assessment of generalized additive model

plots. Model 1 adjusted for age, sex, height, weight, and cohort. Model 2 (main model) additionally adjusted for education, systolic blood pressure, antihypertensive medication, diabetes, smoking, physical activity, prevalent CHD, stroke/transient ischemic attack, peripheral arterial disease, AF, forced expiratory volume in 1 second, and estimated glomerular filtration rate. Model 3 additionally adjusted for C-reactive protein.

We performed various exploratory analyses. For DEXA summary measures, we replaced weight with total fat mass in the models for total lean and appendicular lean mass, and with total lean mass in the models for total and trunk fat mass. To assess the potential impact of volume expansion from subclinical or clinically unrecognized baseline HF on DEXA-measured total lean and total fat mass, we leveraged availability of NT-proBNP (N-terminal pro-B-type natriuretic peptide) in a subset of CHS participants¹⁸ and excluded those with levels ≥ 300 pg/mL.¹⁹ For CT measures, we adjusted for thigh muscle area in the assessment of intermuscular fat's association with HF and vice versa. For both DEXA and CT measures, we examined time-varying AF as a potential mediator and delayed the start of follow-up by 1 year to assess for reverse causality. Finally, we tested for effect modification by sex, race, cohort, and BMI. All analyses were performed with STATA, version 12. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics are presented in Table 1. CHS participants were older; had higher physical activity, prevalent CHD, and C-reactive protein; but were less often Black individuals than Health ABC participants. Men in 1 or both cohorts had higher weight, height, physical activity, forced expiratory volume in 1 second, total and appendicular lean mass, abdominal visceral fat, thigh muscle area; and prevalent diabetes, CHD, and peripheral arterial disease, compared with women. Female participants had greater total and trunk fat mass, abdominal subcutaneous fat, and thigh intermuscular fat than their male counterparts.

Correlations

Pairwise correlations for body size/composition measures in women and men combined are presented in Figure 2. In the DEXA sample (Figure 2A), total lean and appendicular lean mass each showed strong correlations with height, weight, and each other, as well as moderate correlations with total fat and trunk fat mass (all positive). Total fat and trunk fat mass were highly correlated with weight, BMI, and each other. In the CT

sample (Figure 2B), visceral fat showed moderate to high positive correlations with weight, BMI, total fat, and trunk fat, as well as mild to moderate correlations (positive or negative) with other measures. Subcutaneous fat exhibited strong positive correlations with BMI, total and trunk mass, and moderate correlations (positive or negative) with other measures. Intermuscular fat and thigh muscle area showed moderate to high correlations with thigh muscle density (negative) and weight, BMI, total fat, and trunk fat (positive). Thigh muscle area had a high positive correlation with subcutaneous fat, but a mild to moderate positive correlation with visceral fat. For thigh muscle density, mild to moderate negative correlations were observed with weight, BMI, and all DEXA measures except appendicular lean mass.

DEXA Measures and HF

During a median follow-up of 11.8 years, 927 participants developed HF (314 HF_{rEF}, 298 HF_{pEF}). The results of sex-specific PCA are presented in Table 2. PC1 was strongly positively correlated with all individual fat and lean mass measures ($r = 0.74$ – 0.91) in women and men, whereas PC2 showed moderate positive correlations with individual lean mass measures ($r = 0.33$ – 0.57), and moderate negative correlations with individual fat mass measures ($r = -0.34$ to -0.49). Contrary to expectation, PCA did not generate components that captured the variance of lean and fat mass measures separately. Neither PC exhibited a significant association with incident HF or its subtypes (Figure S1).

In the analysis of summary DEXA measures (Figure 3), none was significantly associated with HF in the minimally adjusted model (model 1). After main-model adjustment (model 2), total lean and total fat mass, but not appendicular lean or trunk fat mass, exhibited near-significant or significant associations with incident HF. Specifically, each SD increment in total lean mass was associated with an almost significant 27% (95% CI, 0%–56%) increase in risk of HF, whereas each SD increment in total fat mass was associated with a significant 18% (1%–32%) decrease in HF risk. The only significant associations with HF subtypes were for total and trunk fat mass, for which each SD increment was associated with 29% (1%–49%) and 30% (10%–46%) lower risk of HF_{rEF} (Figure S2). Additional adjustment for C-reactive protein did not materially affect the results. In a sensitivity analysis where total and appendicular lean mass were each adjusted for total fat mass instead of weight, and total and trunk fat mass were each adjusted for total lean mass rather than weight, associations for all DEXA measures with HF were similar, except that total fat mass ceased to show an inverse relationship (Table S1).

Additional adjustment for AF as a time-varying covariate led to substantial attenuation of the associations for total lean and total fat mass (hazard ratio [HR],

Table 1. Baseline Characteristics by Sex and Cohort

Characteristics	Women		Men	
	Health ABC (n=1207)	CHS (n=732)	Health ABC (n=1158)	CHS (n=524)
Demographic and clinical				
Age, y	73.4±2.8	75.7±4.4	73.6±2.8	76.6±4.9
Black, n (%)	524 (43.4)	146 (19.9)	419 (36.2)	93 (17.7)
High school education or more	940 (77.9)	621 (84.8)	859 (74.2)	438 (83.6)
Height, cm	160±6	159±6	173±6	173±7
Weight, kg	69.7±14.2	67.8±13.0	80.9±13.0	79.4±11.7
Body mass index, kg/m ²	27.4±5.3	26.9±4.8	26.9±3.9	26.6±3.6
SBP, mm Hg	136±20	134±21	136±20	131±20
Antihypertensive medication	653 (54.1)	366 (50.0)	550 (47.5)	269 (51.3)
Diabetes	148 (12.3)	90 (12.3)	219 (18.9)	93 (17.7)
Physical activity, kcal/wk	751±1370	899±1222	1473±2431	1697±1935
Prevalent CHD	117 (9.7)	112 (15.3)	223 (19.3)	140 (26.7)
Prevalent stroke/TIA	84 (7.0)	32 (4.4)	72 (6.2)	47 (9.0)
Prevalent PAD	44 (3.6)	10 (1.4)	68 (5.9)	30 (5.7)
Prevalent atrial fibrillation, n (%)	36 (3.0)	48 (6.6)	46 (4.0)	50 (9.5)
Smoking status				
Never smoker	691 (57.2)	385 (52.6)	344 (29.7)	150 (28.6)
Former smoker	393 (32.6)	281 (38.4)	686 (59.2)	329 (62.8)
Current smoker	123 (10.2)	66 (9.0)	128 (11.1)	45 (8.6)
eGFR _{cys}	73.6±18.3	69.7±17.5	72.6±18.2	69.1±16.9
CRP, mg/L	3.2±4.6	5.3±8.9	2.6±4.8	4.0±6.0
NT-proBNP, pg/mL	NA	191.5±284.9	NA	210.4±395.5
FEV ₁ , L	1.8±0.4	1.7±0.4	2.5±0.6	2.4±0.7
DEXA measurements				
Total fat mass, kg	28.7±9.1	29.3±9.7	23.9±7.1	22.9±7.9
Trunk fat mass, kg	13.7±5.1	13.6±5.2	12.9±4.5	11.9±5.2
Total lean mass, kg	39.2±5.9	37.2±4.9	54.2±7.0	54.5±6.3
Appendicular lean mass, kg	16.5±3.1	14.6±2.6	23.9±3.6	23.1±3.3
CT measurements				
Abdominal visceral fat area, cm ²	130.7±60.4	NA	153.3±72.6	NA
Abdomen subcutaneous fat area, cm ²	333.0±121.6	NA	226.2±87.9	NA
Thigh muscle area, cm ²	431.6±117.1	NA	402.3±76.9	NA
Thigh intermuscular fat area, cm ²	20.7±12.1	NA	19.6±13.4	NA
Thigh muscle density (attenuation), Hounsfield units	34.1±6.8	NA	37.7±6.2	NA

Values are mean±SD or n (%). CHD indicates coronary heart disease; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; eGFR_{cys}, estimated glomerular filtration rate by cystatin; FEV₁, forced expiratory volume in 1 second; Health ABC, Health, Aging and Body Composition; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease; SBP, systolic blood pressure; and TIA, transient ischemic attack.

1.10 per SD [0.87–1.39] and HR, 0.93 [0.76–1.13], respectively). Delaying the study start had no meaningful impact.

There were 157 participants (of 1059 with available measures) in CHS with NT-proBNP ≥300 pg/mL at baseline, of whom only 15 met diagnostic criteria for (clinically undetected) HF (n=11 aged 50–75 with NT-proBNP ≥900 pg/mL and n=4 aged >75 with NT-proBNP ≥1800 pg/mL).¹⁹ Excluding these individuals

with NT-proBNP ≥300 pg/mL attenuated the associations with incident HF for both total lean mass (from HR, 1.25 per SD [0.89–1.76] to HR, 1.05 [0.71–1.55]) and total fat mass (from HR, 0.85 per SD [0.64–1.13] to HR, 1.00 [0.72–1.37]).

CT Measures and HF

The relationships of CT measures with incident HF in Health ABC are also shown in Figure 3. There were

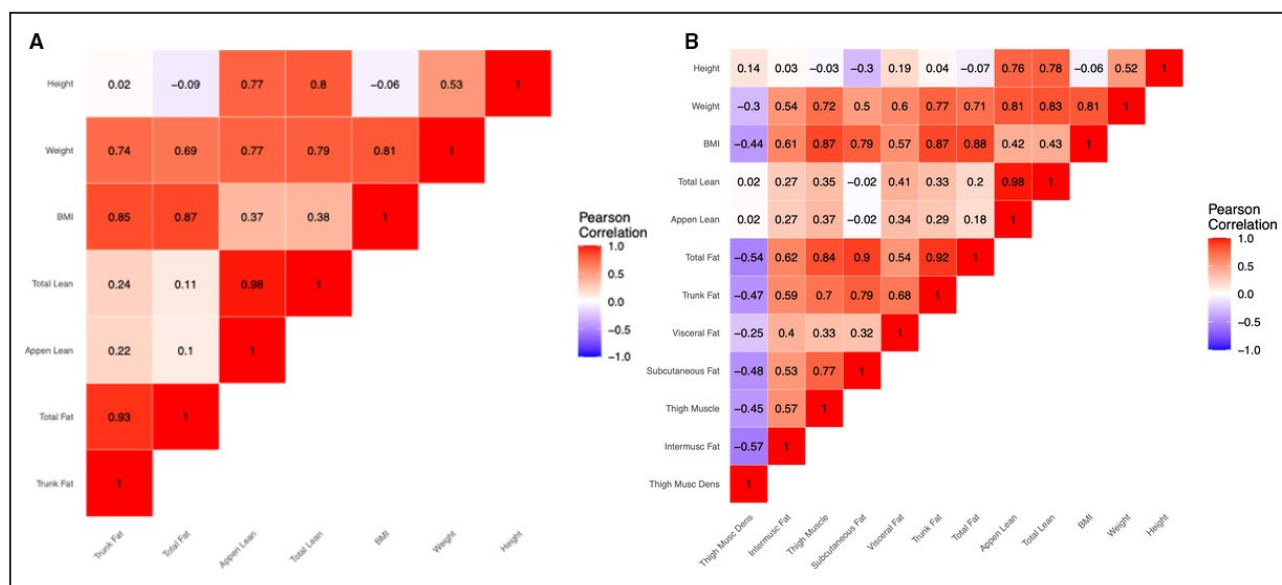


Figure 2. Pearson correlations for DEXA measures in CHS and Health ABC (A) and DEXA and CT measures in Health ABC (B).

BMI indicates body mass index; CHS, Cardiovascular Health Study; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; and Health ABC, Health, Aging and Body Composition study.

significant, but directionally opposite, associations for abdominal visceral fat (18% [5%–33%] higher risk per SD increment) and abdominal subcutaneous fat (20% [1%–35%] lower risk) with incident HF after minimal adjustment. The association for abdominal visceral fat disappeared after additional adjustment for model 2 covariates, while that for subcutaneous fat weakened slightly and became nonsignificant. Thigh muscle area was inversely associated with HF in the

minimally adjusted model (25% [7%–39%] lower risk per SD increment), but not in the fully adjusted model. Intermuscular fat did not show an association with incident HF at either level of adjustment. When thigh muscle area and intermuscular fat were adjusted for each other, risk estimates for each were unchanged (not shown). Thigh muscle density did show a significant inverse association with incident HF. Compared with the minimally adjusted model, the association

Table 2. Principal Component Analysis Using DEXA Measurements: Nonrotated Factor Loadings and Correlation Coefficients in Women and Men Across CHS and Health ABC

Variable	PC factor loadings				Correlation coefficients			
	Women (n=1939)		Men (n=1682)		Women (n=1939)		Men (n=1682)	
	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2
Left arm fat mass	0.28	-0.29	0.29	-0.29	0.81	-0.43	0.80	-0.47
Right arm fat mass	0.28	-0.30	0.29	-0.29	0.81	-0.44	0.80	-0.46
Trunk fat mass	0.29	-0.23	0.27	-0.31	0.82	-0.34	0.76	-0.49
Left leg fat mass	0.28	-0.30	0.30	-0.26	0.79	-0.45	0.82	-0.41
Right leg fat mass	0.28	-0.29	0.30	-0.25	0.80	-0.43	0.83	-0.39
Total fat mass	0.31	-0.29	0.30	-0.31	0.89	-0.43	0.85	-0.49
Left arm lean mass	0.26	0.38	0.26	0.34	0.74	0.56	0.72	0.54
Right arm lean mass	0.26	0.38	0.26	0.36	0.75	0.56	0.73	0.57
Trunk lean mass	0.29	0.22	0.29	0.21	0.84	0.33	0.81	0.33
Left leg lean mass	0.31	0.22	0.30	0.27	0.89	0.34	0.83	0.44
Right leg lean mass	0.31	0.24	0.29	0.29	0.88	0.36	0.82	0.46
Total lean mass	0.32	0.25	0.31	0.27	0.91	0.38	0.88	0.44

CHS indicates Cardiovascular Health Study; DEXA, dual-energy X-ray absorptiometry; Health ABC, Health, Aging and Body Composition; and PC, principal component.

for thigh muscle density in the main model showed moderate attenuation, characterized by a 13% (3%–22%) lower risk of HF for every SD increment. Similar findings were observed for HF subtypes (Figure S2). Further adjustment for C-reactive protein or time-varying AF had no substantive effect, nor did delay of study start.

There was no evidence that sex, race, cohort, or BMI modified the associations between DEXA or CT measures and HF ($P \geq 0.128$).

DISCUSSION

In this study, PCs of individual DEXA measures showed no significant associations with HF. Analysis of standard aggregate DEXA measures revealed that, after adjustment for height, weight, and other covariates, total lean mass was near significantly associated with higher risk of HF, while total fat mass was significantly associated with lower risk of HF. CT-assessed thigh muscle density was significantly associated with lower risk of HF. Associations for total lean and fat mass dissipated, however, after adjustment for interval AF or exclusion in

CHS of subjects with high NT-proBNP. Findings were broadly consistent across HF subtypes.

Multiple longitudinal studies have evaluated anthropometric measures of adiposity, documenting their positive associations with HF,^{3,4,20} and particularly HFpEF.²¹ Among older adults, previous analyses in CHS and Health ABC found that waist circumference is associated with incident HF independently of BMI.^{5,6} The impact on HF risk of regional fat depots quantified by CT has also been studied. Among middle-aged to older adults, both abdominal visceral and subcutaneous fat were associated with higher HF incidence after limited adjustment for risk factors,²² as was visceral fat with higher risk of HFpEF.²³ But additional adjustment for body size or BMI either eliminated these associations or was not performed. Prior work in Health ABC also linked visceral and subcutaneous fat, as well as DEXA-derived fat mass, to incident HF after partial adjustment, but no measures of body size were included.⁶

To our knowledge, these analyses are the first to evaluate associations of DEXA and CT measures of body composition with incident HF in elders after accounting for body size. We applied PCA to separate fat

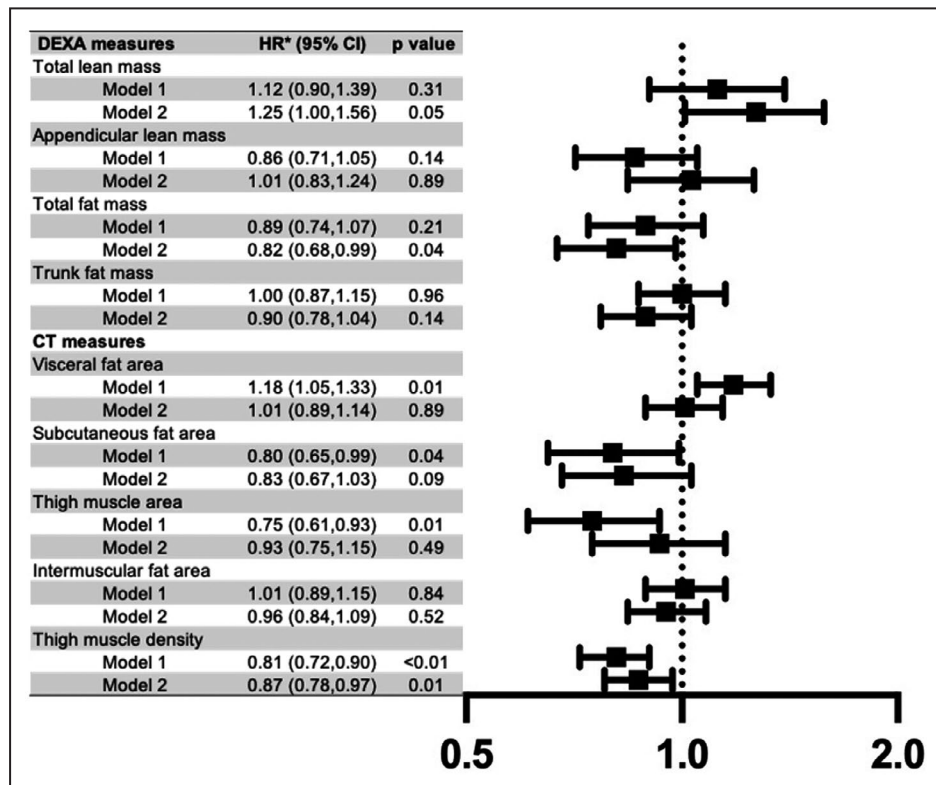


Figure 3. Associations of DEXA and CT measures with incident HF.

*Per SD increment. Model 1: adjusted for age, sex, race, height, weight, cohort. Model 2: additionally adjusted for education, systolic blood pressure, antihypertensive medication, diabetes, smoking status, physical activity, prevalent CHD, prevalent stroke/transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, forced expiratory volume in 1 second, and estimated glomerular filtration rate. CHD indicates coronary heart disease; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; and HF, heart failure.

and fat-free DEXA components, as done previously for mortality in CHS.²⁴ We abandoned indexation of individual measures by height² in favor of broader adjustment by height and weight,^{9,25} but this PCA approach did not achieve useful discrimination.

We therefore evaluated summary DEXA measures as our key exposures, but the results obtained were contrary to our hypotheses. That higher lean mass for any given body size was nearly associated with greater risk of HF conflicts with reports linking lower muscle mass by arm circumference or magnetic resonance imaging with reduced survival.^{26,27} The finding is also at odds with the notion that sarcopenia¹⁰ would be more apt to elicit HF symptoms in the setting of cardiac dysfunction.

Because the positive association for lean mass became more apparent after adjustment for CHD and its risk factors, one possibility is that this unexpected relationship is a consequence of overadjustment. In the sensitivity analysis adjusting for fat mass instead of weight, however, similar associations were seen in the minimal and main model, arguing against this premise.

The more likely explanation involves the inherent limitations of DEXA. While DEXA provides accurate assessment of soft-tissue lean mass, this measure does not reflect only skeletal muscle mass but also the mass of visceral organs and other nonfat tissue components, including fibrous tissue.²⁸ Such increased fibrosis, organomegaly, or both would heighten susceptibility to future HF.^{29–31} Further, DEXA measurement of lean mass can be affected by fluid status, with large increases in hydration leading to overestimation.³² Along with tissue fibrosis, increased hydration could account for the positive association observed between DEXA lean mass and HF.

Notably, the association of lean mass with HF was sizably reduced by adjustment for interval AF. Lean mass is a foremost risk factor for AF, a relationship that could reflect its imperfect specificity for skeletal muscle mass, but may also be attributable to the latter's influence on left atrial size.³³ Indeed, higher muscle mass imposes a greater circulatory demand on the heart than adipose mass.³⁴ Much like organ-tissue fibrosis and attendant volume expansion, this could foster left atrial enlargement, a key determinant of the arrhythmia.³⁵ Because AF predisposes to HF,³³ the positive association between lean mass and AF appears to be an important driver of the former's relationship with HF. In this regard, that exclusion of high NT-proBNP in CHS attenuated the association of lean mass with HF supports a role for hydration, although only a minority met NT-proBNP thresholds for HF. It is also telling that CT-derived thigh muscle area bore an inverse, not positive, association with HF in the minimal model. While this relationship did not persist after full adjustment, failure of this direct measure of muscle mass to reproduce

the positive association for lean mass suggests that the latter relates to DEXA's limitations.

Unlike DEXA-derived lean mass, CT-determined thigh muscle density, a measure of lower intramuscular fat,¹⁵ did show an inverse relationship with HF at all levels of adjustment, including intercurrent AF. The finding that higher thigh muscle integrity, but not area, was associated with lower HF risk is consistent with evidence of the greater importance of measures of skeletal muscle quality over mass as indicators of sarcopenia and future physical decline.^{36,37}

Regarding the unexpected inverse association between DEXA-determined total fat mass and HF after accounting for height, weight and other covariates, this finding may be partly understood in the context of the associations observed for abdominal CT measures. Visceral adiposity was positively, and subcutaneous adiposity inversely, associated with incident HF after adjustment for demographic and anthropometric variables. These results are compatible with visceral fat's status as an adverse, biochemically active depot, and subcutaneous fat's role as a healthful repository for triglyceride storage.³⁸ There was slight attenuation of the association between subcutaneous fat and HF after main-model adjustment, while that for visceral fat was abolished. The latter points to visceral fat's impact on causal intermediates as the driver of its unfavorable association with HF. Regardless, that DEXA-derived fat mass showed a stronger correlation with subcutaneous than visceral adiposity in Health ABC suggests that its inverse association with HF may owe to its closer reflection of salutary than unhealthy adipose depots.

Interestingly, the inverse association of total fat mass with incident HF disappeared when lean mass replaced weight as a covariate. It was also attenuated in CHS by exclusion of participants with high NT-proBNP. These findings are consistent with greater fluid content driving a higher lean mass for any given height and weight, linking a reciprocally lower fat mass to higher risk of HF. Keeping total lean mass constant by adjustment, or excluding participants with higher hydration status, would dampen this association. Thus, again, DEXA's lack of specificity for skeletal muscle likely contributed to the association observed for DEXA fat mass.

Our study has several limitations. Because of its observational nature, the current study cannot demonstrate causality, nor exclude residual confounding. DEXA measures were available only in a subset of CHS participants, and CT in none. We were unable to phenotype all HF cases, which reduced statistical power for HF subtypes. Our results in elders may not be generalizable to younger adults. We did not correct for multiple testing to preserve power for available body composition measures. Hence, our findings will require independent replication.

CONCLUSIONS

In older adults, total lean mass was near significantly associated with higher incidence of HF after accounting for height, weight, and other covariates, while total fat mass and thigh muscle density were significantly associated with lower incidence. The relationships of DEXA measures were largely attenuated after adjustment for intercurrent AF and, in CHS, after exclusion of participants with high NT-proBNP. These findings highlight the limitations of DEXA for evaluating the impact of body composition on HF risk in older adults, while documenting that CT determination of skeletal muscle quality represents an informative modality for this purpose. The present results support a focus on skeletal muscle quality as a target for investigation, evaluation, and treatment for HF prevention in the elderly.

ARTICLE INFORMATION

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Disclosures

Dr Kizer reports stock ownership in Abbott, Bristol-Myers Squibb, Johnson & Johnson, Medtronic, Merck, and Pfizer. The remaining authors have no disclosures to report.

Supplementary Material

Table S1

Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Associations of DEXA-determined Body Composition Measures with Incident Heart Failure after Replacing Weight with Total Fat Mass or Total Lean Mass, as Appropriate, as a Covariate in the Analysis.

DEXA Measure	Model 1		Model 2	
	HR* (95% CI)	p Value	HR* (95% CI)	p Value
Total lean mass	1.25 (1.07,1.46)	<0.01	1.24 (1.06,1.45)	0.01
Appendicular lean mass	1.07 (0.92,1.24)	0.41	1.11 (0.95,1.29)	0.19
Total fat mass	1.09 (1.01,1.18)	0.03	0.99 (0.91,1.07)	0.74
Trunk fat mass	1.10 (1.02,1.19)	0.01	0.99 (0.91,1.07)	0.76

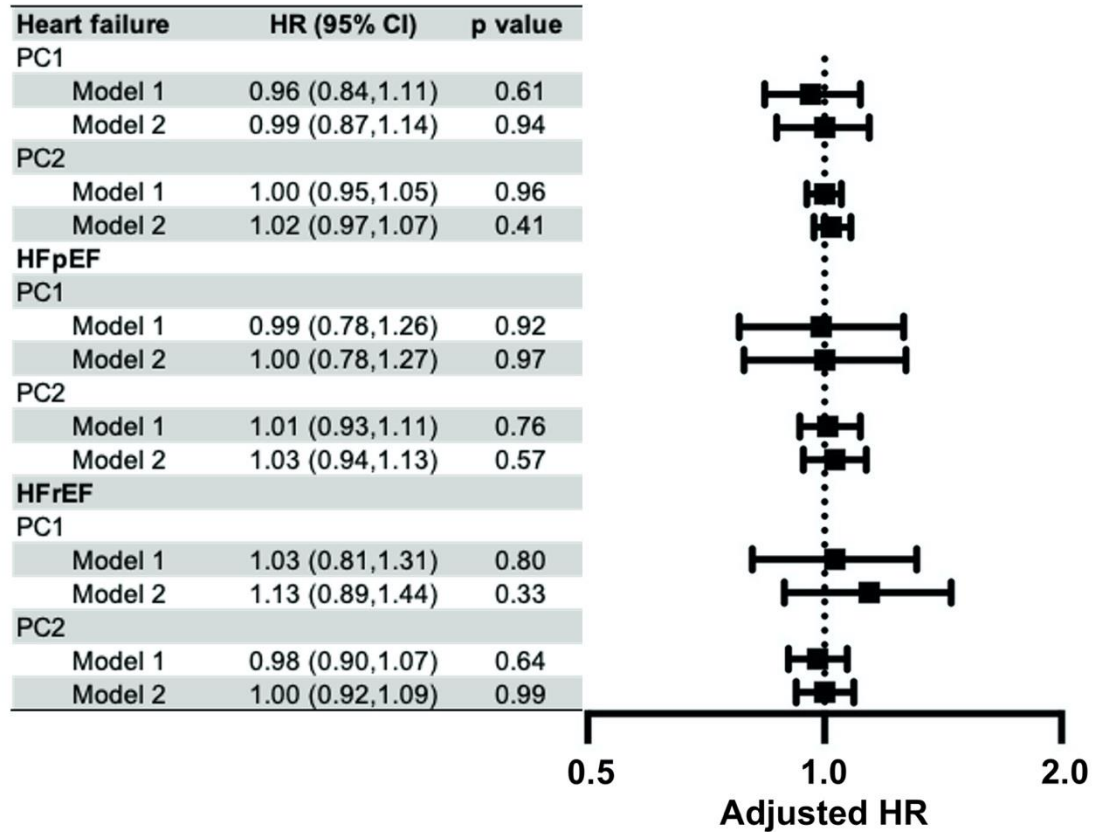
*per standard deviation (SD) increment in body composition measure. Standard deviations follow. Total lean mass: SD=10.1 kg; total appendicular mass: SD=5.1 kg; total fat mass: SD=8.9 kg; trunk fat mass: SD=5.0 kg.

CI = confidence interval; DEXA = dual-energy X-ray absorptiometry; HR = hazard ratio.

Model 1: Adjusted for age, sex, race, height, total fat mass (for total and appendicular lean mass) or total lean mass (for total or trunk fat mass), cohort.

Model 2: Adjusted for age, sex, race, height, total fat or total lean mass (as in Model 1), cohort, education, systolic blood pressure, antihypertensive medication, diabetes, smoking status, physical activity, estimated glomerular filtration rate, prevalent coronary heart disease, prevalent stroke/transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, and forced expiratory volume in 1 second.

Figure S1. Associations of Principal Components with Heart Failure.

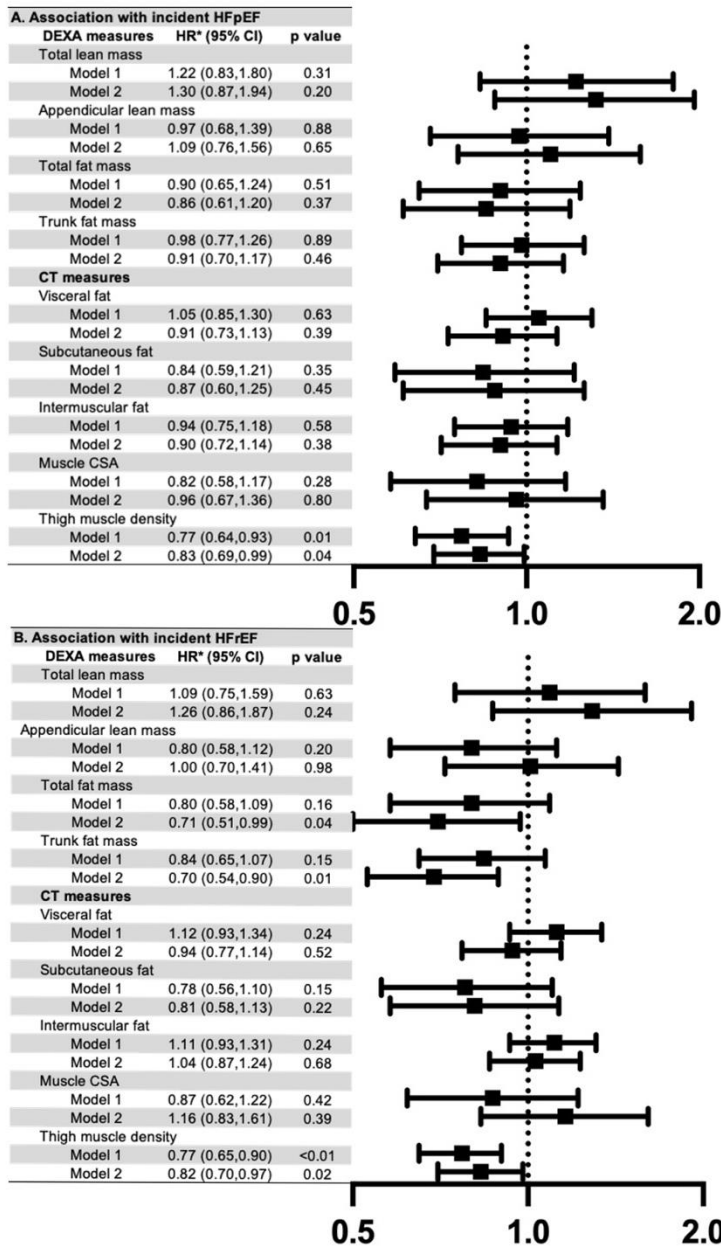


CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; PC = principal component.

Model 1: Adjusted for age, sex, race, height, weight, cohort.

Model 2: Adjusted for age, sex, race, height, weight, cohort, education, systolic blood pressure, antihypertensive medication, diabetes, smoking status, physical activity, estimated glomerular filtration rate, prevalent coronary heart disease, prevalent stroke/transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, and forced expiratory volume in 1 second.

Figure S2. Associations of DEXA and CT measures with incident HFpEF and HFrfEF.



*per standard deviation (SD) increment in body composition measure. Standard deviations follow. Total lean mass: SD=10.1 kg; total appendicular mass: SD= 5.1 kg; total fat mass: SD= 8.9 kg; trunk fat mass: SD= 5.0 kg; visceral fat area: SD= 67.6 cm²; subcutaneous fat area: SD= 119.0 cm²; thigh muscle area: SD= 100.5 cm²; intermuscular fat area: SD=12.7 cm²; thigh muscle density: SD=6.8 HU. Model 1: Adjusted for age, sex, race, height, weight, cohort. Model 2: Adjusted for age, sex, race, height, weight, cohort, education, systolic blood pressure, antihypertensive medication, diabetes, smoking status, physical activity, estimated glomerular

filtration rate, prevalent coronary heart disease, prevalent stroke/transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, and forced expiratory volume in 1 second. CI = confidence interval; CT = computed tomography; DEXA = dual-energy X-ray absorptiometry; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio.