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Adiposity and Incident Heart Failure and Its Sub-types: The MESA Study

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Abstract

Objectives: To compare various measures of adiposity with risk for incident hospitalized heart failure (HF) with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF).

Background: Obesity is a risk factor for HF, particularly HFpEF. It is unknown which measures of adiposity, including anthropometrics and computed tomography (CT)-measured fat area, are most predictive of HF sub-types.

Methods: We studied 1,806 participants of the Multi-Ethnic Study of Atherosclerosis without baseline cardiovascular disease (CVD) who underwent anthropometrics [Body Mass Index (BMI) and Waist Circumference (WC)] and an abdominal CT. Subcutaneous and visceral adipose tissue (SAT and VAT) were measured from a single CT slice at L2-L3. Cox hazard models were used to examine associations of adiposity with incident hospitalized HFpEF and HFrEF events. Fully-adjusted models included demographics, HF risk factors, and NT-proBNP

Results: Over mean follow-up of 11 years, there were 34 HFpEF and 36 HFrEF events. The fully-adjusted Hazard Ratios (95% CI) per 1-SD higher of each anthropometric and CT-measured adiposity measures for incident HFpEF were as follows: BMI [1.66 (1.12–2.45)]; WC [1.59 (1.05–2.40)]; VAT [2.24 (1.44–3.49)]. None of these adiposity measures were associated with HFrEF.

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Clinical trial registration:
MESA is not a clinical trial. However the cohort is registered at: https://clinicaltrials.gov/ct2/show/NCT00005487

Conflicts of interest: No authors declare a conflict of interest.

Even among overweight/obese adults (BMI≥25 kg/m^2), assessment of VAT (per 1-SD) was strongly associated with HFpEF [2.78 (1.62–4.76)]. SAT was not associated with HFpEF nor HFrEF.

Conclusions: In a multiethnic cohort free of CVD, CT-measured VAT was independently associated with incident hospitalized HFpEF but not HFrEF. Measuring visceral fat at the time of CT imaging for other indications may offer additional prognostication of HF risk.

Condensed abstract:

We examined associations of various adiposity markers [by anthropometrics and CT-assessed fat area] with the risk of incident hospitalized heart failure (HF) and its subtypes among 1,806 adults free of cardiovascular disease at baseline. We found both anthropometrics and CT-measured visceral adipose tissue (VAT) were associated with increased risk for incident HF with preserved ejection fraction (HFpEF) but not HF with reduced ejection fraction (HFrEF). Subcutaneous fat was not associated with HFpEF nor HFrEF. Results from this observational study found differing relationships of these various adiposity measures for HF and its subtypes of HFpEF and HFrEF.

Keywords

Obesity; visceral adiposity; anthropometry; heart failure; HFpEF

Introduction:

Obesity is a stronger risk factor for heart failure (HF) than for other types of cardiovascular diseases (CVD), an association not fully explained by obesity-related cardiometabolic risk factors.(1) Heart failure with preserved ejection fraction (HFpEF) has increased significantly over the past decade and now accounts for ~50% of all heart failure (HF) cases.(2,3) Obesity, and in particular central adiposity, directly correlates with increasing left ventricular stiffness, contributing to the diastolic dysfunction in HFpEF.(4,5) Moreover, in some studies, obesity defined by body mass index (BMI) has been associated with a greater risk for HFpEF, but not for HF with reduced ejection fraction (HFrEF).(3,6) The risk that obesity confers on HFpEF may differ by sex and race/ethnicity (i.e. stronger among African-American women).(7)

Visceral adipose tissue (VAT), which is stored in the abdominal cavity and accounts for approximately 20% of adipose tissue, is pro-inflammatory and increases cardiovascular risk by promoting metabolic diseases such as diabetes, dyslipidemia, and hypertension.(8) VAT appears to have different associations with cardiometabolic risk than adipose tissue residing in other compartments, such as subcutaneous adipose tissue (SAT).(9) Among obese people with coronary artery disease, it appears that the distribution of fat, rather than BMI itself, is more directly associated with mortality.(10)

While obesity is a well-established risk factor for HFpEF,(3,7) it is unclear which of the various anthropometric measures of adiposity (i.e. BMI, weight-to-hip ratio (WHR), or waist circumference (WC)) is most predictive of HFpEF. It is also unknown whether directly measured adipose tissue derived from computed tomography (CT) scans is more predictive of HFpEF risk than anthropometric data, particularly among those considered normal weight

by traditional BMI measures. Additionally, obesity-related biomarkers such as adipokines also have prognostic value in HF risk(11–13), but it is unknown if these biomarkers better predict HF than anthropometrics and CT-measured adiposity.

Thus, the purpose of this study was to compare the association of anthropometric-measures of adiposity (BMI, WHR, and WC), CT-derived adiposity measures (VAT, SAT), and obesity-related biomarkers with incident hospitalized HFpEF (and compared to HFrEF) in a multi-ethnic cohort.

Methods:

Design and Study Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center cohort investigating risk factors for and clinical implications of subclinical CVD.(14) The study enrolled 6,814 White, Black, Hispanic, and Chinese-American men and women between the ages of 45–84 years, who were free of clinical CVD and HF at enrollment. Participants were enrolled from six different U.S. sites: New York, NY, Baltimore, MD, Chicago, IL, Los Angeles, CA, St. Paul, MN, and Winston-Salem, NC.(14) Visit 1 (enrollment) took place between 2000 to 2002, visit 2 between 2002 to 2004, visit 3 between 2004 to 2005, visit 4 between 2005 to 2007, and visit 5 between 2010 to 2012.

A random subset of MESA participants (n=1,970) underwent abdominal CT scans at either visit 2 or visit 3 (randomly assigned) to measure abdominal aortic calcification as previously described.(15) Among these, 1,947 had visualization of abdominal cavity on the CT that was retrospectively reviewed for body composition.(16) For our analyses, we excluded those with a HF event before the abdominal CT scan date (n=18), missing subcutaneous fat and visceral fat for all slices (n=104), missing ejection fraction at time of HF diagnosis (n=4), or missing other covariates in our main adjusted model (n=15). Thus, we included a total of 1,806 participants in our sample who had both CT-derived adiposity measurements and anthropometrics.

At each MESA visit, demographics, medical history, physical examination, and medication use were obtained for each participant as previously described.(14) Visit 2 or visit 3, the time of the participant's abdominal CT, was considered their baseline for this present analysis. The MESA study and the abdominal CT ancillary study were approved by the Institutional Review Board at each participating site, and informed consent was obtained from each participant.

Measures of Adiposity

Anthropometrics—Anthropometric measures of weight, height, WC, and hip circumference were measured at each visit; each marker was measured twice using a standardized protocol and averaged.(14) Weight was measured to the nearest 0.5 lb. Height was measured using a vertical scale to the nearest 0.5 cm. WC was measured at the level of the minimum abdominal circumference to the nearest 0.1 cm. Hip circumference was measured at the level of the maximum girth at the pubic symphysis to the nearest 0.1cm. WHR was calculated from waist and hip circumference measurements. BMI was calculated

as the ratio of weight to height squared (kg/m^2). For this analysis, we used the anthropometric obtained at the same visit as their CT scan (visit 2 or visit 3).

CT-derived adiposity—Visceral and subcutaneous fat were measured from scans obtained using the Imatron C-150 electron-beam, Siemens S4+ Volume Zoom, or General Electric Hi Speed LX CT scanners. We defined VAT as the total adipose tissue enclosed within the abdominal cavity and SAT as the total adipose tissue outside of the abdominal cavity but not within muscle tissue. For this study, participants had six slices obtained from L2 to L5 vertebral spaces (i.e. two at L2-L3, two at L3-L4, two at L4-L5) interrogated for adipose tissue measurements (in cm^3). Two analysts independently evaluated each CT using the Medical Imaging Processing Analysis and Visualization Software (MIPAV version 4.1.2). Inter- and intra-rater reliability for the different abdominal CT measurements ranged from 0.92 to 0.99. For our primary analysis, VAT and SAT were defined using the average of two slices obtained at L2–L3 and adjusted for height, as has been done previously.(17) In a sensitivity analysis, we also included the sum of all 6 slices for those participants who were not missing any slices.

Obesity-related biomarkers—As previously reported,(16,18) the obesity-related adipokines (adiponectin, leptin, and resistin), were measured from stored (fasting) blood from the CT visit (visit 2 or visit 3) using a Bio-Rad Luminex flow cytometry (Millepore, Billerica, MA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). The coefficients of variation (CV) ranged from 6 to 13%. Insulin was measured by radioimmunoassay using the Linco Human Insulin Specific assay (Linco Research, Inc., St. Charles, MO), with CV of 4.9%. The adipokine and insulin biomarkers had a skewed distribution and were log-transformed for all analyses.

Covariates

Using data from their respective CT visit (visit 2 or visit 3), we considered demographics and socioeconomic factors (age, sex, race/ethnicity, and study site), behavioral factors (smoking status and physical activity), systolic blood pressure (BP), use of anti-hypertensive medications, diabetes, total cholesterol (mg/dL), HDL cholesterol (mg/dL), use of lipid lowering medications, estimated glomerular filtration rate (eGFR), and N-terminal pro b-type natriuretic peptide (NT-proBNP; pg/mL) for covariate adjustment. Physical activity was determined using a 28-item Typical Week Physical Activity Survey and measured in MET-minutes per week.(16) Resting BP was measured three times in the seated position, with the average of the last two measurements used. Diabetes was defined as a fasting blood glucose ≥126 mg/dL and/or the self-reported history of a physician-diagnosis of diabetes, or the use of diabetes medications. Renal function was measured during visit 1 and 3; visit 1 eGFR was used for those who had a CT at visit 2. NT-proBNP was measured at visit 1 and in a subset at visit 3; visit 1 values were used for those who had a CT at visit 2 and for those with a CT at visit 3 who were missing visit 3 NT-proBNP measurements.

Outcome

The primary outcome of interest was incident hospitalization for HFpEF. As a secondary endpoint, we also reported on HFrEF events for comparison. Study participants were

followed up from baseline (either visit 2 or 3) until death or until December 31, 2015. Every 9–12 months, trained staff contacted participants by telephone to obtain information on hospitalizations. Medical records were reviewed and diagnosis of HF events while hospitalized were adjudicated by a panel of MESA physicians using standardized criteria. We considered probable or definite hospitalized HF events. Probable HF was defined as a physician diagnosis and HF medical treatment. Definite HF required an additional objective criterion such as evidence of pulmonary congestion on chest radiography, reduced left ventricular (LV) function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. HFpEF was defined as a HF event with an ejection fraction ≥45% as identified on echocardiogram or imaging studies at the time of HF hospitalization. HFrEF was a HF event with an ejection fraction of <45%.

Statistical Analysis

Baseline characteristics between participants who developed HFpEF and those who did not were compared using two-sided Student's t test, Wilcoxon's rank-sum test, or Chi-square test, when appropriate. The exposures of interest examined were the anthropometric measures, the CT-derived measures, and the obesity-related biomarkers. Multivariable-adjusted Cox proportional hazard regression models were used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) between the various adiposity measures (per 1 standard deviation (SD) increment for each adiposity marker) with risk of incident HF, HFpEF or HFrEF. To see if VAT provided additional prognostic information over BMI, we assessed the risk of each HF outcome per 1-SD higher VAT, stratified by BMI categories.

We examined 3 progressively adjusted traditional Cox models. In the initial model, we adjusted for the demographic and behavioral factors of age, sex, race/ethnicity, smoking status, and physical activity. A second model, which serves as our primary model (Model 2), further adjusted for CVD/HF risk factors (systolic BP, use of antihypertensive medications, total cholesterol, HDL-C, use of lipid lowering medications, and diabetes) and eGFR. A third model further adjusted for NT-proBNP, which may serve as a marker of subclinical HF. Additionally, since outcome events were few in this subcohort and proportional hazard assumption may not hold, we performed sensitivity analyses in which we used a stratified Cox model approach (instead of the traditional Cox model) to avoid over-fitting the model with too many covariates.(19)

Effect modification by sex were tested by including an interaction term between adiposity markers and sex. All statistical analyses were performed using Stata 14 (StataCorp LP, College Station, Texas).

Results:

Baseline characteristics by incident HF status

The overall baseline characteristics of the 1,806 participants included in this analysis are shown in Table 1. The mean age was 64.5 years, 52% were women, and 40% were White, 14% Chinese-American, 21% Black, and 26% Hispanic-American. Seventy participants

(3.9%) developed HF over a mean follow-up of 10.5 years (SD 2.9 years). Of these HF events, 34 were HFpEF and 36 were HFrEF.

Table 1 also shows the baseline characteristics of those who developed incident hospitalized HFpEF during follow-up vs. the characteristics of those who did not. Participants who developed HFpEF were more likely to be older, had higher systolic BP and use of antihypertensive medications, a greater prevalence of diabetes, lower eGFR, and a higher NT-proBNP. With respect to anthropometric measures, those with incident hospitalized HFpEF had higher baseline BMI, WHR and WC ($p<0.05$ for all). Average total VAT was also higher among those with incident hospitalized HFpEF vs. not (231 vs. 163 cm^3, $p<0.001$), but total SAT did not differ between the two groups.

The baseline characteristics stratified by incident HFrEF status are shown in Supplemental Table 1. There was no difference in adiposity measures at baseline between those with and without incident HFrEF.

Measures of Adiposity and Heart Failure Events

The HRs (95% CI) associated with risk of incident hospitalized HFpEF (n=34 events) by adiposity measures are shown in Table 2. After adjusting for demographic and behavioral factors (Model 1), the adiposity measures of BMI, WHR, WC, VAT, leptin, and insulin were all significantly associated with incident HFpEF. However, in our primary model adjusted for CVD risk factors (Model 2), only BMI, WC, and VAT remained statistically significantly associated with HFpEF with HRs (95% CI) per 1-SD higher adiposity measures as follows: BMI [1.57 (1.08, 2.27)], WC [1.61 (1.09, 2.38)], and VAT (single CT-slice) [1.94 (1.29, 2.91)]. These adiposity measures remained statistically significantly associated with HFpEF after further adjusting for NT-proBNP (Model 3). The obesity-related biomarkers were not associated with increased HFpEF risk in our primary model. Notably, SAT was not associated with HFpEF risk in any model.

The HRs (95% CI) associated with risk of incident HFrEF (n=36 events) by adiposity measures are shown in Table 3. There were no statistically significant associations of the anthropometric and CT adiposity measures or the obesity-related biomarkers with HFrEF events in any model.

Supplemental Table 2 shows the associations of these adiposity measures (per 1-SD) with all HF events combined (n=70). In our primary model adjusted for CVD risk factors (Model 2), only VAT was associated with combined HF risk with HR (95% CI) of VAT (single slice) [1.35 (1.02, 1.79)] However after further adjustment for NT-proBNP (Model 3), BMI, WC, and VAT were all associated with HF, similar to their associations with HFpEF.

Table 4 shows the HRs (95% CI) of VAT (per 1 SD increment) stratified by BMI categories. Among participants who were obese or overweight (BMI ≥25 kg/m^2), greater VAT was predictive of any HF [1.66 (1.18, 2.33)] and HFpEF [2.37 (1.44, 3.89)], but not HFrEF [1.17 (0.72, 1.91)] in our primary adjusted model. There was a similar trend for greater HFpEF risk with increasing VAT among those with normal BMI (<25 kg/m^2) but this was not statistically significant with wide confidence intervals [1.21 (0.28, 5.16)] given few HFpEF

events (n=12) among those with normal BMI. Findings were similar after further adjustment for NT-proBNP in Model 3.

Findings for the aforementioned analyses were similar in sensitivity analysis when VAT and SAT were defined using the total of all 6 abdominal slices, rather than a single slice at L2-L3 (also shown in Tables 2–4). Findings were also generally similar using a stratified Cox model (with limited covariates included to avoid over-fitting, as shown in Supplemental Table 3) instead of a traditional Cox proportional model. In this stratified model, BMI, WC, and VAT remained statistically significantly associated with incident hospitalized HFpEF, but WHR, leptin, insulin, and resistin were also statistically significantly associated with HFpEF as well.

There was no meaningful interaction by sex for all analyses examined, although the power to detect interactions was limited by few events.

Discussion:

In this longitudinal, multiethnic cohort study, we compared anthropometric-measured adiposity, CT-measured adiposity, adiposity-related adipokines, and insulin with their risk for incident hospitalized HF. The adiposity measures of BMI, WC, and VAT were all associated with incident hospitalized HFpEF risk, but not HFrEF, in our models adjusted for demographic, lifestyle, and CVD risk factors. These associations remained statistically significant after further adjusting for NT-proBNP, which may serve as a subclinical (intermediate) marker for HF. The association of VAT with incident hospitalized HFpEF was qualitatively stronger than the associations attributed to the anthropometric measures; however, confidence intervals for these adiposity measures overlapped. In contrast to anthropometrics and VAT, the adiposity-related measures of SAT was not associated with either HFpEF or HFrEF risk.

Consistent with previously described cohorts,(2,3) nearly half of our study population who developed HF had HFpEF. Among people who are overweight or obese (BMI ≥25), higher VAT levels provided additional value in predicting HFpEF events. Furthermore, VAT was strongly associated with HFpEF risk, whereas SAT had no association. Thus, our work confirms that the distribution of adiposity is relevant to HFpEF risk. This relationship may provide clues into the pathophysiology of obesity and HFpEF, and expand on prior literature describing the association of visceral fat and cardiovascular risk factors, including diabetes, hypertension, and dyslipidemia(8,20) and the HF-related biomarker of NT-proBNP.(21)

While it is unlikely that abdominal CT will ever replace anthropometrics (i.e. BMI, WC, WHR) for routine screening due to cost and radiation exposure, many individuals undergo CT scanning for other indications. Quantitative assessment of VAT at the time of CT scanning for other purposes may further identify people who are at increased risk of HFpEF, who might benefit from more aggressive preventive lifestyle interventions.

Prior studies have demonstrated BMI is a risk factor for HF,(1) yet few investigated differences in HF subtypes.(3,6) Similar to our findings, several other studies have found that obesity, measured by BMI, was associated with HFpEF but not HFrEF.(3,7) In contrast,

a Dutch cohort demonstrated equal hazards of both incident HFpEF and HFrEF by BMI.(22) Our study compared several measures of adiposity, both by anthropometrics and CT-measured, with the goal of determining if one adiposity measure was more strongly predictive of HFpEF than the others. However, we found that the various anthropometric measures and VAT generally had similar magnitudes of associations for HFpEF, but none were predictive of HFrEF. Despite the risk that BMI has on some types of incident HF, other studies have noted a paradoxical relationship between higher BMI and all-cause mortality among people with established HF and particularly within HFrEF(23,24) – the so called "obesity-paradox". Contrary to this trend, following diagnosis of HFpEF, mortality appears to be higher among those who are obese.(25,26) Investigating whether changes in visceral adiposity after HF diagnosis affects long-term outcomes may clarify the protective role obesity confers in those with HFrEF diagnosis and provide insight into disease progression in those with HFpEF.

The distribution of adipose tissue affects mortality risk,(10) and unlike VAT, prior work has found the relationship of SAT and diabetes to be inversely related among women and no association among men.(27) The present study found that SAT is not predictive of any HF events, which is consistent with SAT associations with other subclinical and clinical CVD.(9)

Among measured hormones, our primary analysis (fully-adjusted for CVD risk factors including diabetes) did not demonstrate an association between serum adipokines or insulin and incident HFpEF. However, in our stratified Cox models with more conservative (limited) covariate adjustment (Supplemental Table 3), leptin, resistin, and insulin were all strongly associated with HFpEF. Rising insulin levels may serve as an intermediate marker of the insulin resistance in diabetes, a known risk factor for HFpEF, which is why associations perhaps no longer remained significant after adjusting for diabetes status. Leptin levels are known to be positively, and adiponectin levels are inversely, associated with BMI.(28) In this limited stratified analysis, higher leptin levels were predictive of HFpEF, consistent with previous work demonstrating leptin levels to correlate with diastolic dysfunction.(29) Adiponectin, however, was not associated with incident HFpEF. Also in the limited stratified model, resistin, which is derived from adipocytes and associated with inflammation, was associated with incident HFpEF. This is consistent with a prior MESA study which found that resistin was predictive of incident CVD, coronary heart disease (CHD), and all HF.(30) In sum, biomarkers associated with HFpEF appear to differ from those associated with HFrEF.(31)

Study Strengths and Limitations

Our study has many strengths including the comparison of several measures of anthropometric-derived adiposity, CT-derived adiposity, and adiposity-related biomarkers among men and women free of CVD and HF at baseline from a multi-ethnic cohort, who were followed for long-term HF events (adjudicated by an expert panel and further sub-classified as either both HFpEF and HFrEF). Our study provides further insight into the relative contributions of various adiposity markers to HF risk and its subtype, which may guide further work in this area.

Nonetheless, our study results should be interpreted in the context of the following limitations. First, reported HF events were adjudicated hospitalized HF cases, so milder HF cases identified and treated as outpatients were missed. Second, only 34 individuals of our subcohort developed incident hospitalized HFpEF and 36 developed HFrEF, so we were underpowered to compare model prediction among the various adiposity measures or to conclusively examine for sex or race/ethnicity interactions. We used a traditional Cox model which has potential risk for over-fitting in the setting of few events. To address this, we performed sensitivity analyses using a stratified Cox model to avoid the potential of violation of proportional hazard assumptions. Results were consistent among adiposity and CT-derived measures, but not serum markers, which showed some significant relationships not seen in the traditional Cox model. Third, our study was observational and, although we adjusted for numerous potential confounding lifestyle variables, residual confounding may be present in these analyses. Finally, we compared multiple measures of adiposity and results may be statistically significant by chance, although results were internally consistent among adiposity measures.

Conclusion

In a large, multiethnic U.S. cohort free of CVD, we demonstrate that the anthropometric measures of BMI and WC, and the CT-measure of VAT were all strong risk factors for incident hospitalized HFpEF but not HFrEF. Subcutaneous fat was not predictive of either HF subtype. Although our study was observational and cannot determine causation, our findings lend support to the potential causal role of visceral fat in the pathogenesis of a phenotype of HFpEF. Future research is warranted to understand the best use of visceral adiposity imaging to identify individuals at high risk of developing HF and best strategies to reduce this risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation list

MESA	Multi-Ethnic Study of Atherosclerosis
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction

HFrEF	Heart Failure with reduced Ejection Fraction
CVD	Cardiovascular Disease
BMI	Body Mass Index
WHR	Waist Hip Ratio
WC	Waist Circumference
CT	Computed Tomography
SAT	Subcutaneous Adipose Tissue
VAT	Visceral Adipose Tissue
BP	Blood pressure
eGFR	Estimated Glomerular Filtration Rate
NT-proBNP	N-terminal pro-B-type natriuretic peptide

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Clinical Perspectives:

Competencies in Medical Knowledge

Among adults free of CVD and HF, both anthropometrics and CT-measured VAT are associated with increased risk for subsequent development of HFpEF, which emphasizes the importance of lifestyle modification and weight management for HFpEF prevention. Among adiposity-related biomarkers, neither leptin, resistin, nor adiponectin were associated with HFpEF in our primary analysis fully adjusted for CVD risk factors. No adiposity measure was associated with HFrEF. Of note, while VAT was associated with HFpEF, SAT was not, suggesting the distribution of body fat matters for HF risk. For those undergoing CT for another indication, the extent of CT-assessed VAT may provide independent prognostic information about HFpEF risk even among those already diagnosed as being overweight/obese by BMI.

Translational Outlook

Results from this observational study provide insight into the relationship of different measures of adiposity (anthropometrics vs. CT-measured vs. obesity-related biomarkers) and found differing relationships of these measures for HF and its subtypes of HFpEF and HFrEF. These results might help identify adults at increased risk for HFpEF, possibly inform future screening protocols, and monitor the impact of lifestyle interventions beyond traditional BMI measures for HFpEF prevention.

Table 1.

Characteristics of participants by development of incident HFpEF status (n = 34): The Multi-Ethnic Study of Atherosclerosis[*,†]

	Overall (n = 1,806)	No HFpEF (n = 1,772)	HFpEF (n = 34)	p-value[§]
Age, years	64.5 (9.6)	64.4 (9.5)	73.1 (8.6)	<0.001
BMI, kg/m^2	27.8 (5.1)	27.8 (5.0)	29.9 (5.3)	0.017
Waist to hip ratio	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	0.002
Waist circumference, cm	97.4 (13.7)	97.2 (13.7)	104.7 (12.9)	0.002
Subcutaneous fat, cm^3	164.4 (87.7)	164.1 (87.5)	181.4 (102.5)	0.34
Visceral fat, cm^3	163.9 (92.3)	162.6 (91.4)	230.7 (117.3)	<0.001
Men	874 (48.4)	857 (48.4)	17 (50.0)	0.85
Race/ethnicity				0.91
White	717 (39.7)	703 (39.7)	14 (41.2)	
Chinese-American	247 (13.7)	243 (13.7)	4 (11.8)	
Black	382 (21.2)	376 (21.2)	6 (17.6)	
Hispanic	460 (25.5)	450 (25.4)	10 (29.4)	
Education				0.41
<High school	322 (17.8)	313 (17.7)	9 (26.5)	
High school, technical school, or associate degree	832 (46.1)	818 (46.2)	14 (41.2)	
College, graduate or professional school	652 (36.1)	641 (36.2)	11 (32.4)	
Smoking				0.78
Never	846 (46.8)	831 (46.9)	15 (44.1)	
Former	753 (41.7)	737 (41.6)	16 (47.1)	
Current	207 (11.5)	204 (11.5)	3 (8.8)	
Total intentional exercise, met-min/week[‡]	3592.5 (1887.5 – 6390.0)	3607.5 (1912.5 – 6442.5)	2876.3 (1050.0 – 4800.0)	0.04
Systolic BP, mm Hg	123.6 (20.8)	123.5 (20.8)	132.4 (21.5)	0.013
Total cholesterol, mg/dl	190.1 (35.6)	190.1 (35.3)	188.3 (49.5)	0.78
HDL cholesterol, mg/dl	52.0 (15.3)	52.1 (15.3)	49.6 (13.9)	0.35
Antihypertension medication	746 (42.5)	718 (41.7)	28 (82.4)	<0.001
lipid lowering medication usage	436 (24.8)	425 (24.7)	11 (32.4)	0.30
Diabetes	241 (13.4)	230 (13.0)	11 (32.4)	0.001
eGFR, mL/min/1.73m^2	76.1 (15.9)	76.3 (15.8)	63.5 (14.5)	<0.001
NT-proBNP, pg/mL[‡]	65.8 (33.7 – 127.3)	65.1 (33.3 – 122.3)	182.6 (86.5 – 239.7)	<0.001

[*] Abbreviations: HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide.

[†] data are mean (SD) or number (percent) unless otherwise noted

[‡] median (IQR)

§ p-value for the comparison between the “no HFpEF” and “HFpEF” categories.

Table 2.

Hazard Ratios (95% Confidence Intervals) for Incident Heart Failure with Preserved Ejection Fraction (n = 34) by Adiposity Measures*

	Model 1†	Model 2‡	Model 3§
Body mass index, kg/m^2	**1.73 (1.23, 2.42)**	**1.57 (1.08, 2.27)**	**1.66 (1.12, 2.45)**
Waist-hip-ratio	**1.54 (1.04, 2.30)**	1.38 (0.91, 2.10)	1.33 (0.84, 2.10)
Waist circumference, cm	**1.74 (1.23, 2.46)**	**1.61 (1.09, 2.38)**	**1.59 (1.05, 2.40)**
Subcutaneous fat, sum of 6 pieces, cm^3	1.23 (0.79, 1.90)	1.04 (0.64, 1.70)	1.12 (0.64, 1.95)
Visceral fat, sum of 6 pieces, cm^3	**1.98 (1.40, 2.79)**	**1.84 (1.25, 2.71)**	**2.02 (1.34, 3.06)**
Subcutaneous fat, single piece at L2–3	1.31 (0.89, 1.93)	1.18 (0.77, 1.83)	1.30 (0.79, 2.12)
Visceral fat, single piece at L2–3	**2.06 (1.44, 2.95)**	**1.94 (1.29, 2.91)**	**2.24 (1.44, 3.49)**
Log transformed leptin, pg/mL	**1.73 (1.09, 2.75)**	1.34 (0.83, 2.15)	1.43 (0.85, 2.38)
Log transformed insulin, pg/mL	**1.44 (1.07, 1.94)**	1.18 (0.85, 1.65)	1.11 (0.78, 1.58)
Log transformed adiponectin, ng/mL	1.03 (0.70, 1.50)	1.12 (0.76, 1.64)	0.90 (0.58, 1.38)
Log transformed resistin, pg/mL	1.40 (0.98, 2.02)	1.13 (0.76, 1.68)	1.09 (0.71, 1.68)

*Associated with 1 standard deviation greater unit of adiposity measure. Bolded results are statistically significant ($p<0.05$). All analyses are conducted with Cox regression.

†Model 1: adjusted for age, sex, race/ethnicity, smoking, and physical activity.

‡Model 2: Model 1 + systolic blood pressure, use of antihypertensive medications, total cholesterol, HDL-cholesterol, use of lipid lowering medications, diabetes, and eGFR.

§Model 3: Model 2 + log-transformed NT-proBNP.

Table 3.

Hazard ratios (95% Confidence Intervals) for incident Heart Failure with Reduced Ejection Fraction (n = 36) by Adiposity Measures [*]

	Model 1 [†]	Model 2 [‡]	Model 3 [§]
Body mass index, kg/m^2	1.14 (0.77, 1.68)	1.01 (0.67, 1.52)	1.48 (0.95, 2.31)
Waist-hip-ratio	0.95 (0.65, 1.39)	0.86 (0.57, 1.29)	1.11 (0.67, 1.84)
Waist circumference, cm	1.08 (0.74, 1.58)	0.94 (0.62, 1.43)	1.45 (0.91, 2.29)
Subcutaneous fat, sum of 6 pieces, cm^3	0.80 (0.47, 1.35)	0.67 (0.37, 1.19)	0.89 (0.44, 1.78)
Visceral fat, sum of 6 pieces, cm^3	1.07 (0.76, 1.52)	0.95 (0.65, 1.39)	1.14 (0.73, 1.77)
Subcutaneous fat, single piece at L2–3	1.12 (0.73, 1.70)	1.05 (0.68, 1.64)	1.37 (0.80, 2.36)
Visceral fat, single piece at L2–3	1.08 (0.75, 1.55)	0.96 (0.65, 1.43)	1.13 (0.71, 1.79)
Log transformed leptin, pg/mL	0.87 (0.59, 1.29)	0.75 (0.50, 1.12)	1.24 (0.76, 2.02)
Log transformed insulin, pg/mL	1.20 (0.88, 1.64)	1.07 (0.76, 1.50)	1.17 (0.81, 1.70)
Log transformed adiponectin, ng/mL	1.14 (0.78, 1.67)	1.32 (0.87, 2.00)	1.02 (0.58, 1.79)
Log transformed resistin, pg/mL	1.45 (1.00, 2.12)	1.36 (0.91, 2.04)	1.04 (0.62, 1.74)

[*] Associated with 1 standard deviation greater unit of adiposity measure. Bolded results are statistically significant ($p<0.05$). All analyses are conducted with Cox regression.

[†] Model 1: adjusted for age, sex, race/ethnicity, smoking, and physical activity.

[‡] Model 2: Model 1 + systolic blood pressure, use of antihypertensive medications, total cholesterol, HDL-cholesterol, use of lipid lowering medications, diabetes, and eGFR.

[§] Model 3: Model 2 + log-transformed NT-proBNP.

Table 4.

Associations of visceral adiposity (per 1SD increment) with incident HF, HFpEF, and HFrEF stratified by BMI categories [*,‖]

	N events / n total	IR[#]	HR (95% Cl) Model 1[†]	HR (95% Cl) Model 2[‡]	HR (95% Cl) Model 3[§]
HF (any)					
BMI < 25 kg/m^2	18 / 547	3.1	1.23 (0.63, 2.42)	0.85 (0.37, 1.94)	0.61 (0.20, 1.90)
BMI ≥ 25 kg/m^2	52 / 1,259	4.0	**1.71 (1.24, 2.35)**	**1.66 (1.18, 2.33)**	**2.04 (1.39, 3.00)**
HFpEF					
BMI < 25 kg/m^2	12 / 903	1.2	1.59 (0.54, 4.66)	1.21 (0.28, 5.16)	1.46 (0.29, 7.44)
BMI ≥ 25 kg/m^2	22 / 903	2.1	**2.27 (1.46, 3.54)**	**2.37 (1.44, 3.89)**	**2.78 (1.62, 4.76)**
HFrEF					
BMI < 25 kg/m^2	11 / 547	1.9	1.09 (0.46, 2.57)	0.85 (0.30, 2.37)	0.26 (0.01, 6.30)
BMI ≥ 25 kg/m^2	25 / 1,259	1.9	1.23 (0.77, 1.98)	1.17 (0.72, 1.91)	1.45 (0.82, 2.57)

[*] Associated with 1 standard deviation greater visceral fat unit (assessed by single CT-slice at L2-L3). Bolded results are statistically significant ($p<0.05$). Hazard Ratios were calculated using Cox regression models.

[†] Model 1: adjusted for age, sex, race/ethnicity, smoking, and physical activity.

[‡] Model 2: Model 1 + systolic blood pressure, use of antihypertensive medications, total cholesterol, HDL-cholesterol, use of lipid lowering medications, diabetes, and eGFR.

[§] Model 3: Model 2 + log-transformed NT-proBNP.

[‖] Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index ; IR, incidence rates

[#] IR per 1000 person-years