

Visceral Adiposity and the Risk of Metabolic Syndrome Across Body Mass Index

The MESA Study

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CME Objective for This Article: After reading this article, the reader should be able to: 1) explain the relationship between visceral and subcutaneous adiposity measures and weight or BMI; 2) discuss the impact of visceral and subcutaneous adiposity on metabolic risk, including metabolic syndrome; 3) explain the importance of changes in weight and fat distribution in addition to overall weight changes in metabolic syndrome risk; and 4) describe imaging methods used to assess adiposity distribution for research and clinical applications.

CME Editor Disclosure: *JACC: Cardiovascular Imaging* CME Editor Ragavendra R. Baliga, MD, has reported that he has no relationships to disclose.

Author Disclosures: Dr. Shah has received consulting fees from Novartis. Dr. Murthy has minor stock in General Electric. Dr. Abbasi has received research support from T32-HL094301. Dr. Goldfine was supported by P30-DK036836 from the National Institutes of Health; has received materials for investigator-initiated research from Amneal Pharmaceuticals, Johnson & Johnson, Novo Nordisk, Nestle Inc., and Merck; and has served as a consultant to Novo Nordisk. Dr. Allison was supported by funding for the MESA Abdominal Body Composition Ancillary study from the National Heart, Lung, and Blood Institute (R01-HL088451). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue Date: December 2014

Expiration Date: November 30, 2015

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ABSTRACT

OBJECTIVES This study sought to evaluate differential effects of visceral fat (VF) and subcutaneous fat and their effects on metabolic syndrome (MetS) risk across body mass index (BMI) categories.

BACKGROUND The regional distribution of adipose tissue is an emerging risk factor for cardiometabolic disease, although serial changes in fat distribution have not been extensively investigated. VF and its alterations over time may be a better marker for risk than BMI in normal weight and overweight or obese individuals.

METHODS We studied 1,511 individuals in the MESA (Multi-Ethnic Study of Atherosclerosis) with adiposity assessment by computed tomography (CT). A total of 253 participants without MetS at initial scan underwent repeat CT (median interval 3.3 years). We used discrete Cox regression with net reclassification to investigate whether baseline and changes in VF area are associated with MetS.

RESULTS Higher VF was associated with cardiometabolic risk and coronary artery calcification, regardless of BMI. After adjustment, VF was more strongly associated with incident MetS than subcutaneous fat regardless of weight, with a 28% greater MetS hazard per 100 cm²/m VF area and significant net reclassification (net reclassification index: 0.44, 95% confidence interval [CI]: 0.29 to 0.60) over clinical risk. In individuals with serial imaging, initial VF (hazard ratio: 1.24 per 100 cm²/m, 95% CI: 1.08 to 1.44 per 100 cm²/m, $p = 0.003$) and change in VF (hazard ratio: 1.05 per 5% change, 95% CI: 1.01 to 1.08 per 5% change, $p = 0.02$) were associated with MetS after adjustment. Changes in subcutaneous fat were not associated with incident MetS after adjustment for clinical risk and VF area.

CONCLUSIONS VF is modestly associated with BMI. However, across BMI, a single measure of and longitudinal change in VF predict MetS, even accounting for weight changes. Visceral adiposity is essential to assessing cardiometabolic risk, regardless of age, race, or BMI, and may serve as a marker and target of therapy in cardiometabolic disease. (J Am Coll Cardiol Img 2014;7:1221-35) © 2014 by the American College of Cardiology Foundation.

Visceral adipose tissue is a relevant, pro-inflammatory endocrine tissue and may account for an increased cardiometabolic risk across body mass index (BMI) (1). A recent report in obese individuals demonstrated that a single measurement of visceral fat (VF) was associated with risk of dysglycemia, independent of weight or metabolic risk (2). Visceral adiposity is associated with an adverse cardiometabolic profile, including inflammation, insulin resistance, and myocardial

dysfunction—hallmarks of an otherwise “obese” phenotype—regardless of adiposity status (1). Nevertheless, several questions critical to using BMI and adiposity in cardiovascular risk remain. Whether standard metrics of adiposity used in the clinic (weight or BMI and waist circumference) adequately reflect pathologic visceral (or subcutaneous) fat and the subsequent risk of metabolic syndrome (MetS) is important. Whether weight gain alone explains most of the hazard of incident MetS—regardless of whether

received materials for investigator-initiated research from Amneal Pharmaceuticals, Johnson & Johnson, Novo Nordisk, Nestle Inc., and Merck; and has served as a consultant to Novo Nordisk. Dr. Allison was supported by funding for the MESA Abdominal Body Composition Ancillary study from the National Heart, Lung, and Blood Institute (R01-HL088451). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Shah and Murthy have contributed equally to this work.

Manuscript received May 22, 2014; revised manuscript received July 21, 2014, accepted July 24, 2014.

it is gained in the visceral or subcutaneous depot—will not only provide valuable translation of the molecular and physiological importance of visceral adiposity, but will also inform clinical assessments of risk with weight reduction.

SEE PAGE 1236

To date, most reports on large, community-based studies have used a single measure of VF to forecast long-term risk (2-4) or are limited to 1 ethnic background (5,6). Here, we address this important gap by studying participants in MESA (Multi-Ethnic Study of Atherosclerosis) with VF measures at 2 time points and detailed metabolic, cardiac, and demographic phenotyping. We define a relationship between visceral and subcutaneous adiposity and BMI, their cross-sectional association with incident MetS across BMI categories and race independent of classic cardiometabolic risk factors, and the longitudinal association of changes in each fat depot versus changes in weight with incident MetS.

METHODS

PARTICIPANT POPULATION. The overall design of the MESA study has been described previously (7). In brief, the MESA study consists of 6,814 men and women of different ethnicities (white, African American, Chinese American, and Hispanic) enrolled from 6 different national sites, all of whom were free of clinical cardiovascular disease (history of myocardial infarction, angina pectoris, prior revascularization, heart failure, atrial fibrillation, stroke, or peripheral arterial disease) at the time of enrollment.

Baseline demographics, medical history (including cardiac risk factors), medications (for hypertension, dyslipidemia, and diabetes), and physical examination were assessed at 5 clinic visits in MESA (examinations 1 to 5, between 2000 and 2011), as has been described (8). MetS was determined at each MESA clinic visit as defined by updated National Cholesterol Education Panel Adult Treatment Panel III guidelines (including abdominal obesity by waist circumference, serum triglyceride level, high-density lipoprotein [HDL] cholesterol, systolic and diastolic blood pressure, and fasting glucose) (9).

At examinations 2 and 3, a random subset of 1,970 MESA participants underwent abdominal computed tomography (CT) scans for aortic calcium that were subsequently used for quantifying visceral/subcutaneous fat mass: examination 2: $n = 756/n = 577$; examination 3: $n = 1,172/n = 1,114$, respectively. For the purposes of the current study, we defined the

“baseline” examination as the first examination at which the CT scan was performed (either examination 2 or 3). Of this initial cohort with both baseline subcutaneous and VF data ($n = 1,687$), we excluded participants with: 1) missing data for BMI at baseline examination ($n = 1$); or 2) any history of cirrhosis, cancer, or self-reported renal disease at index examination (to limit confounding by chronic illness and inflammation; $n = 175$). The final population was composed of 1,511 individuals with baseline measures for visceral adiposity. Of this subcohort, 253 participants without MetS or dysglycemia (impaired fasting glucose ≥ 100 mg/dl or diabetes) at baseline were reimaged at examination 4 (median interval 3.2 years, interquartile range [IQR]: 3.0 to 3.3 years) and had complete data for subcutaneous and visceral adiposity.

Fasting blood samples collected at examination 3 were used to quantify selected adipokines reflecting insulin resistance and systemic inflammation (interleukin-6, high-sensitivity C-reactive protein [CRP], leptin, adiponectin, insulin, and tumor necrosis factor- α) as previously described (10,11). Protocols were approved by the Institutional Review Board at each participating institution. All participants provided written informed consent.

MEASUREMENT OF VISCERAL AND SUBCUTANEOUS ADIPOSITY. Electron-beam CT scanners were utilized at Northwestern University and University of California, Los Angeles (Imatron C-150, Imatron Inc., South San Francisco, California), with the following

ABBREVIATIONS AND ACRONYMS

- BMI** = body mass index
- CT** = computed tomography
- HR** = hazard ratio
- MetS** = metabolic syndrome
- SQ** = subcutaneous fat
- VF** = visceral fat

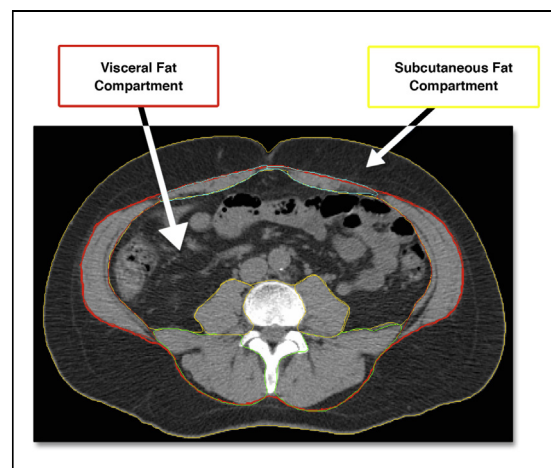


FIGURE 1 Diagram of Visceral and Subcutaneous Fat Compartments Analyzed by CT Imaging in MESA

A description of the delineation of these compartments is provided in the text. CT = computed tomography; MESA = Multi-Ethnic Study of Atherosclerosis.

TABLE 1 Baseline Characteristics for All MESA Participants Meeting Inclusion Criteria, Stratified by Obesity Status and by VF Area (by Median Value 500 cm²/m)

	Normal Weight (BMI <25 kg/m ²)			Overweight (BMI 25-30 kg/m ²)			Obese (BMI >30 kg/m ²)		
	Low VF (n = 396)	High VF (n = 99)	p Value	Low VF (n = 293)	High VF (n = 364)	p Value	Low VF (n = 66)	High VF (n = 293)	p Value
Age, yrs	65.0 (56.0-72.0)	66.0 (58.0-75.0)	0.05	61.0 (54.0-69.5)	66.0 (58.0-73.0)	<0.0001	60.0 (54.0-69.0)	64.0 (57.0-70.0)	0.02
Male	164 (40.2)	71 (81.6)	<0.0001	101 (36.1)	253 (67.1)	<0.0001	11 (16.4)	145 (49.7)	<0.0001
Race			0.008			<0.0001			<0.0001
Caucasian	160 (39.2)	39 (44.8)		91 (32.5)	168 (44.6)		13 (19.4)	109 (37.3)	
Chinese American	123 (30.1)	26 (29.9)		28 (10.0)	49 (13.0)		0 (0.0)	9 (3.1)	
African American	69 (16.9)	4 (4.6)		103 (36.8)	37 (9.8)		43 (64.2)	68 (23.3)	
Hispanic	56 (13.7)	18 (20.7)		58 (20.7)	123 (32.6)		11 (16.4)	106 (36.3)	
Smoking status			0.15			0.09			0.003
Never smoker	216 (52.9)	39 (44.8)		150 (53.6)	183 (48.5)		36 (53.7)	118 (40.4)	
Former smoker	151 (37.0)	42 (48.3)		94 (33.6)	157 (41.6)		19 (28.4)	146 (50.0)	
Current smoker	41 (10.0)	6 (6.9)		36 (12.9)	37 (9.8)		12 (17.9)	28 (9.6)	
Metabolic syndrome	38 (9.3)	24 (27.6)	<0.0001	60 (21.4)	156 (41.4)	<0.0001	26 (38.8)	187 (64.0)	0.0002
BP, mm Hg			0.14			0.07			0.24
Optimal BP	238 (58.3)	38 (43.7)		147 (52.5)	168 (44.6)		29 (43.3)	98 (33.6)	
Normal BP	56 (13.7)	17 (19.5)		49 (17.5)	82 (21.8)		9 (13.4)	49 (16.8)	
High-normal BP	48 (11.8)	16 (18.4)		36 (12.9)	56 (14.9)		7 (10.4)	67 (22.9)	
Stage 1 HTN	51 (12.5)	12 (13.8)		31 (11.1)	50 (13.3)		16 (23.9)	56 (19.2)	
Stage 2 HTN	7 (1.7)	3 (3.4)		15 (5.4)	11 (2.9)		4 (6.0)	14 (4.8)	
Stage 3 HTN	8 (2.0)	1 (1.1)		2 (0.7)	10 (2.7)		2 (3.0)	8 (2.7)	
Glycemic control			0.0002			<0.0001			0.01
Normoglycemia	349 (85.5)	57 (65.5)		235 (83.9)	249 (66.0)		52 (77.6)	164 (56.2)	
IFG	28 (6.9)	15 (17.2)		28 (10.0)	73 (19.4)		8 (11.9)	61 (20.9)	
Untreated diabetes	5 (1.2)	3 (3.4)		3 (1.1)	10 (2.7)		1 (1.5)	16 (5.5)	
Treated diabetes	26 (6.4)	12 (13.8)		14 (5.0)	45 (11.9)		6 (9.0)	51 (17.5)	
Cholesterol, mg/dl	192.0 (171.0-214.0)	193.0 (167.0-213.0)	0.79	190.0 (171.0-212.5)	187.0 (165.0-209.0)	0.13	180.0 (160.0-207.0)	186.5 (160.5-213.0)	0.43
HDL, mg/dl	58.0 (48.0-71.0)	45.0 (39.0-54.0)	<0.0001	54.0 (46.0-64.5)	45.0 (38.0-53.0)	<0.0001	51.0 (46.0-61.0)	44.0 (38.0-53.0)	<0.0001
Triglycerides, mg/dl	90.0 (65.0-127.5)	139.0 (89.0-195.0)	<0.0001	88.0 (64.0-123.0)	134.0 (98.0-187.0)	<0.0001	84.0 (63.0-123.0)	133.0 (96.0-187.5)	<0.0001
LDL, mg/dl	111.0 (91.0-130.0)	116.0 (93.0-133.0)	0.23	114.0 (93.0-131.0)	111.0 (90.0-130.0)	0.2	111.0 (92.0-131.0)	109.5 (90.0-136.0)	0.84
BMI, kg/m ²	22.7 (21.1-23.9)	23.9 (23.1-24.5)	<0.0001	26.8 (25.8-27.8)	27.7 (26.4-28.7)	<0.0001	32.0 (30.9-35.6)	32.9 (31.1-35.6)	0.14
Systolic BP, mm Hg	115.0 (103.3-132.5)	121.0 (111.5-135.5)	0.006	117.5 (107.5-134.5)	121.5 (111.0-135.0)	0.03	125.5 (113.0-150.5)	129.0 (113.8-140.0)	0.79
Waist circumference, cm	83.5 (78.9-88.6)	90.3 (87.2-94.5)	<0.0001	92.3 (87.3-97.2)	98.5 (94.5-102.5)	<0.0001	106.5 (97.2-114.0)	110.4 (104.7-117.4)	0.001
Waist to hip ratio	0.9 (0.8-0.9)	0.9 (0.9-1.0)	<0.0001	0.9 (0.9-0.9)	1.0 (0.9-1.0)	<0.0001	0.9 (0.9-1.0)	1.0 (0.9-1.0)	<0.0001
Weight, lbs	133.0 (121.3-147.0)	149.0 (135.0-161.0)	<0.0001	161.0 (146.6-177.0)	172.0 (154.3-186.0)	<0.0001	192.0 (184.0-215.0)	204.8 (181.5-229.5)	0.04
Glucose, mg/dl	87.0 (82.0-93.5)	92.0 (87.0-104.0)	<0.0001	89.0 (83.5-95.0)	94.0 (88.0-103.0)	<0.0001	89.0 (84.0-96.0)	95.0 (88.0-108.0)	<0.0001
Hemoglobin A1c	5.4 (5.2-5.6)	5.4 (5.2-5.8)	0.17	5.5 (5.2-5.7)	5.5 (5.3-5.9)	0.01	5.6 (5.3-5.8)	5.6 (5.3-6.1)	0.15
Coronary artery calcium score	0.0 (0.0-63.8)	54.3 (0.0-244.7)	<0.0001	0.0 (0.0-37.8)	31.8 (0.0-227.0)	<0.0001	0.0 (0.0-57.0)	19.5 (0.0-145.0)	0.01
Visceral fat, cm ²	478.7 (335.6-636.5)	1,004.1 (929.0-1,205.8)	<0.0001	636.9 (486.8-729.4)	1,168.8 (975.8-1,382.5)	<0.0001	632.1 (563.8-771.2)	1,327.4 (1,074.2-1,696.6)	<0.0001
Subcutaneous fat, cm ²	743.2 (571.2-967.6)	754.6 (628.5-903.0)	0.42	1,256.0 (969.3-1,444.6)	1,093.3 (843.9-1,267.0)	<0.0001	1,994.4 (1,608.2-2,449.9)	1,702.1 (1,295.4-2,252.7)	0.008
Height-indexed visceral fat, cm ² /m	292.5 (200.9-384.3)	598.5 (540.3-703.9)	<0.0001	386.6 (298.7-443.6)	706.5 (589.4-821.1)	<0.0001	404.4 (349.0-471.6)	839.1 (662.5-1,021.3)	<0.0001

Continued on the next page

TABLE 1 Continued

	Normal Weight (BMI <25 kg/m ²)		Overweight (BMI 25-30 kg/m ²)		Obese (BMI >30 kg/m ²)		p Value
	Low VF (n = 396)	High VF (n = 99)	Low VF (n = 293)	High VF (n = 364)	Low VF (n = 66)	High VF (n = 293)	
Height-indexed subcutaneous fat, cm ² /m	447.4 (337.1-598.9)	447.7 (376.5-526.7)	760.5 (559.7-882.1)	641.4 (503.0-778.5)	1,221.8 (997.0-1,511.3)	1,030.0 (787.4-1,351.2)	0.007
Adiponectin, µg/ml	23,162.9 (15,232.1-33,462.2)	15,200.3 (10,923.8-20,538.4)	19,699.2 (13,017.4-29,096.1)	15,655.8 (10,769.8-22,592.2)	17,912.8 (12,754.2-25,611.7)	14,690.5 (10,232.3-20,510.9)	0.003
High-sensitivity C-reactive protein, mg/l	0.8 (0.4-1.9)	1.1 (0.7-1.9)	1.4 (0.7-2.5)	1.4 (0.8-3.1)	1.7 (1.0-4.2)	2.3 (1.2-5.5)	0.21
Interleukin-6, pg/ml	1.3 (0.9-2.1)	1.7 (1.0-2.6)	1.5 (1.0-2.2)	1.9 (1.3-3.0)	2.2 (1.4-2.8)	2.4 (1.7-3.6)	0.05
Insulin, pg/ml	155.5 (113.9-214.4)	196.2 (139.5-261.4)	186.3 (138.8-255.1)	242.8 (182.4-325.1)	277.1 (177.2-383.6)	345.9 (239.8-509.6)	<0.0001
Leptin, ng/ml	5,327.1 (2,471.6-12,672.3)	6,442.9 (3,594.7-9,963.2)	16,102.5 (6,697.8-27,960.2)	10,759.4 (5,610.8-19,974.4)	37,274.5 (25,508.7-55,790.5)	29,725.5 (16,010.6-47,079.2)	0.005
Tumor necrosis factor-α, pg/ml	4.0 (3.0-5.5)	4.3 (3.3-6.4)	4.4 (3.3-5.8)	4.8 (3.8-6.4)	4.8 (3.6-6.7)	4.9 (3.6-6.3)	0.82

Values are median (interquartile range) or n (%). Nonparametric tests (continuous variables) or chi-square testing (categorical variables) were used to determine p values. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HTN = hypertension; IFG = impaired fasting glucose; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis; VF = visceral fat.

settings: collimation 3 mm, slice thickness 6 mm, reconstruction using 25 6-mm slices with 35-cm field of view and normal kernel. Multidetector CT scanners were utilized at Columbia University, Wake Forest University, and University of Minnesota field centers (Sensation 64 [Siemens, Malvern, Pennsylvania] and GE Lightspeed [GE Healthcare, Waukesha, Wisconsin], Siemens S4 Volume Zoom, and Siemens Sensation 16, respectively). CT imaging was interpreted blinded to clinical information.

For abdominal visceral and subcutaneous fat areas, slices centered at the L4-L5 disc spaces were selected. Visceral adiposity (Figure 1) was defined as the fat enclosed by the visceral cavity. Subcutaneous adiposity was defined as the fat outside of the visceral cavity but did not include that located within the muscular fascia. Fat tissue was identified as being between -190 and -30 Hounsfield units. Within each area of interest (subcutaneous and visceral), we assigned the density value assigned to each pixel using the MIPAV 4.1.2 software (National Institutes of Health, Bethesda, Maryland) as fat or lean tissue, calculating the total visceral and abdominal fat area (in terms of cm²). Six transverse cross-sectional slices of data were analyzed (2 at L2-3, 2 at L3-4, and 2 at L4-5). Two subjects had only 5 slices scored due to problems with the location where the scan was performed on the body. These 2 subjects were excluded as they also lacked subcutaneous fat data. To calculate visceral and subcutaneous fat area, we calculated the sum of visceral and subcutaneous fat area over all 6 available slices. Fat area was indexed to height (in meters). Inter-rater and intrarater reliabilities for total abdominal, subcutaneous, and visceral cavity areas were 0.99 for all measures.

Due to the size of the field of view used for the CT imaging, the positioning of the subject in the scanner, or the size of the subject, parts of the abdomen for some subjects was outside of the field of view and the affected anatomic data could not be processed. In these cases, different measures of imputation for missing data (described in detail in the Online Appendix) were employed to estimate the missing data for subcutaneous fat (n = 312, 20.7%) using prediction equations (n = 69, 4.6%) or the “half-abdomen” method (n = 292, 19.3%). For 3 subjects, VF was imputed using the “modified” method. Descriptions of these methods are provided in the Online Appendix (additional detail available on request). Of note, different imputation methods could be used for different slices from a single patient, depending on the type of image artifacts present.

STATISTICAL ANALYSIS. All variables were examined for normality, and parametric or nonparametric

tests were selected as appropriate. Visceral and subcutaneous adipose burden were dichotomized at their respective medians. To investigate the clinical impact of VF in different BMI categories, we stratified BMI into 3 levels corresponding to normal weight (<25 kg/m²), overweight (25 to 30 kg/m²), and obese (>30 kg/m²). We compared clinical, laboratory, and imaging findings between those with above versus below median visceral adipose in each category of obesity using Wilcoxon rank-sum tests. We calculated Spearman correlation coefficients to measure the association between visceral and subcutaneous fat area and BMI or weight, as well as the change in fat

depos with changes in BMI or weight. We used discrete-time Cox regression to specify incremental multivariable survival models assessing the additive value of clinical risk factors, MetS components, and visceral and subcutaneous fat burden on hazard of incident MetS. Of note, as a result of participants being imaged at examination 2 or 3 as baseline, regressions for MetS had a limited cohort at examination 3 (e.g., only those imaged on examination 2 would be eligible for developing MetS at examination 3).

To address the association of changes in VF measures with incident MetS, we performed a similar incremental survival analysis among subjects with

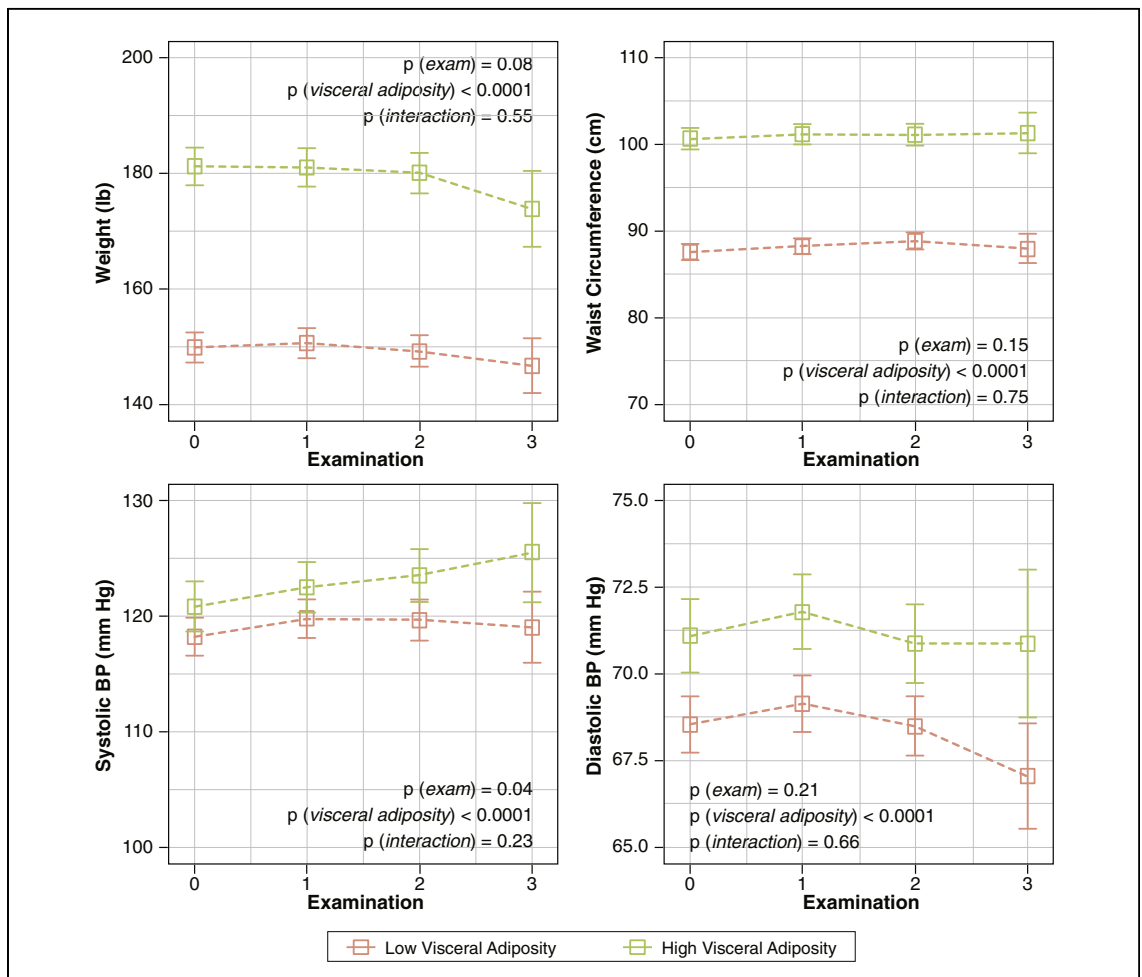


FIGURE 2 Evolution of Metabolic Risk Factors From Index MESA Examination (Time of CT for Visceral Fat Assessments) to More Follow-Up Study Visits

Higher visceral adiposity was associated with worse risk factor profile ($p < 0.0001$ for visceral adiposity). Over time, systolic blood pressure (BP) and glucose control worsened ($p = 0.04$ and $p < 0.0001$, respectively). In contrast, triglycerides and high-density lipoprotein (HDL) improved over time ($p = 0.0001$ and $p < 0.0001$). There was no evidence of different risk factor trajectories for those with high or low visceral fat, except for triglycerides (interaction $p = 0.004$). All analyses were performed with longitudinal mixed effect models with per subject random intercepts. Abbreviations as in Figure 1.

repeated VF measures, adjusted for clinical, demographic, and cardiometabolic risk. Multicollinearity was addressed by examination of hazard ratios (HRs) in incremental survival analysis to ensure stability. We purposefully included the individual components of MetS in the regression for MetS to afford the greatest statistical barrier for adiposity measures to achieve significant association with MetS. Effect modification for age (dichotomized around median in MESA), sex, and race was measured in all models. Direct adjusted survival curves from the final Cox models were used to visualize survival free of MetS across follow-up examinations (12). C-index, integrated discrimination improvement, and net reclassification improvement were assessed (13). Because there are no widely accepted risk categories for incident MetS, the continuous net reclassification index was used. SAS (version 9.4, SAS Institute, Cary, North Carolina) and R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

VISCERAL ADIPOSITY IDENTIFIES AN ADVERSE CARDIOMETABOLIC PROFILE IN BOTH NORMAL WEIGHT AND OVERWEIGHT/OBSE INDIVIDUALS. Demographic, clinical, and biochemical characteristics of our study population stratified by World Health Organization BMI categories (normal <25 kg/m²; overweight 25 to 30 kg/m²; obese >30 kg/m²) and by median height-indexed visceral adipose tissue mass (500.2 cm²/m) are shown in Table 1. In each BMI category, individuals with above-median visceral adiposity were older, were more frequently male, and had greater cardiometabolic risk. In addition, individuals with a normal BMI but higher visceral adiposity had higher glucose (p < 0.0001), lower adiponectin (p < 0.0001), higher high-sensitivity CRP (p = 0.02), and higher insulin (p < 0.0001), a biochemical phenotype similar to overweight/obese individuals (1). Similar associations were observed in overweight/obese individuals. In addition, there was a trend toward

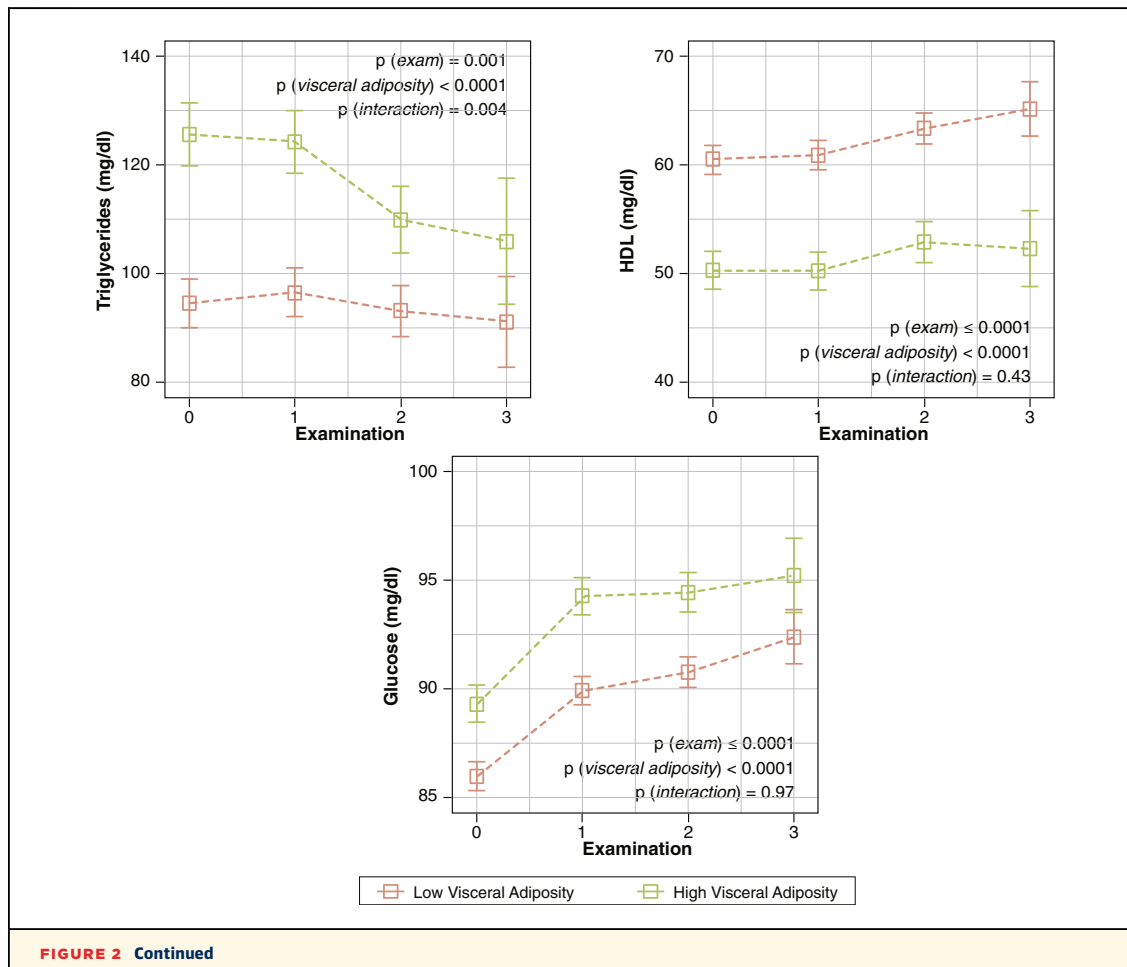


FIGURE 2 Continued

progressively lower adiponectin, higher high-sensitivity CRP and interleukin-6, and higher insulin with higher weight categories. Finally, MESA participants with above-median visceral adiposity ultimately had a greater burden of subclinical atherosclerosis, as indicated by coronary artery calcium score ($p < 0.05$ for all BMI categories). Baseline characteristics stratified by median subcutaneous fat area (median 653.3 cm^2/m) are shown in [Online Table 1](#). Notably, a greater degree of subcutaneous adiposity was associated with a higher CRP and leptin concentration (potentially markers of generalized adiposity) and a lower coronary artery calcium score (potentially suggesting a protective role for subcutaneous fat).

We further investigated the evolution of metabolic risk factors over time from the baseline CT examination to the most contemporary MESA study visit, stratified by above- or below-median VF area at baseline CT examination ([Figure 2](#)). MESA participants with above-median VF area at baseline examination had higher weight, waist circumference, blood pressure, and triglyceride and glucose concentration and a lower HDL concentration at baseline and every subsequent MESA visit ($p < 0.05$ for all). (This analysis was not adjusted for medication use or interval weight changes.)

SINGLE AND LONGITUDINAL MEASURES OF ADIPOSITY ARE ONLY MODESTLY ASSOCIATED WITH BMI. BMI was closely associated with both

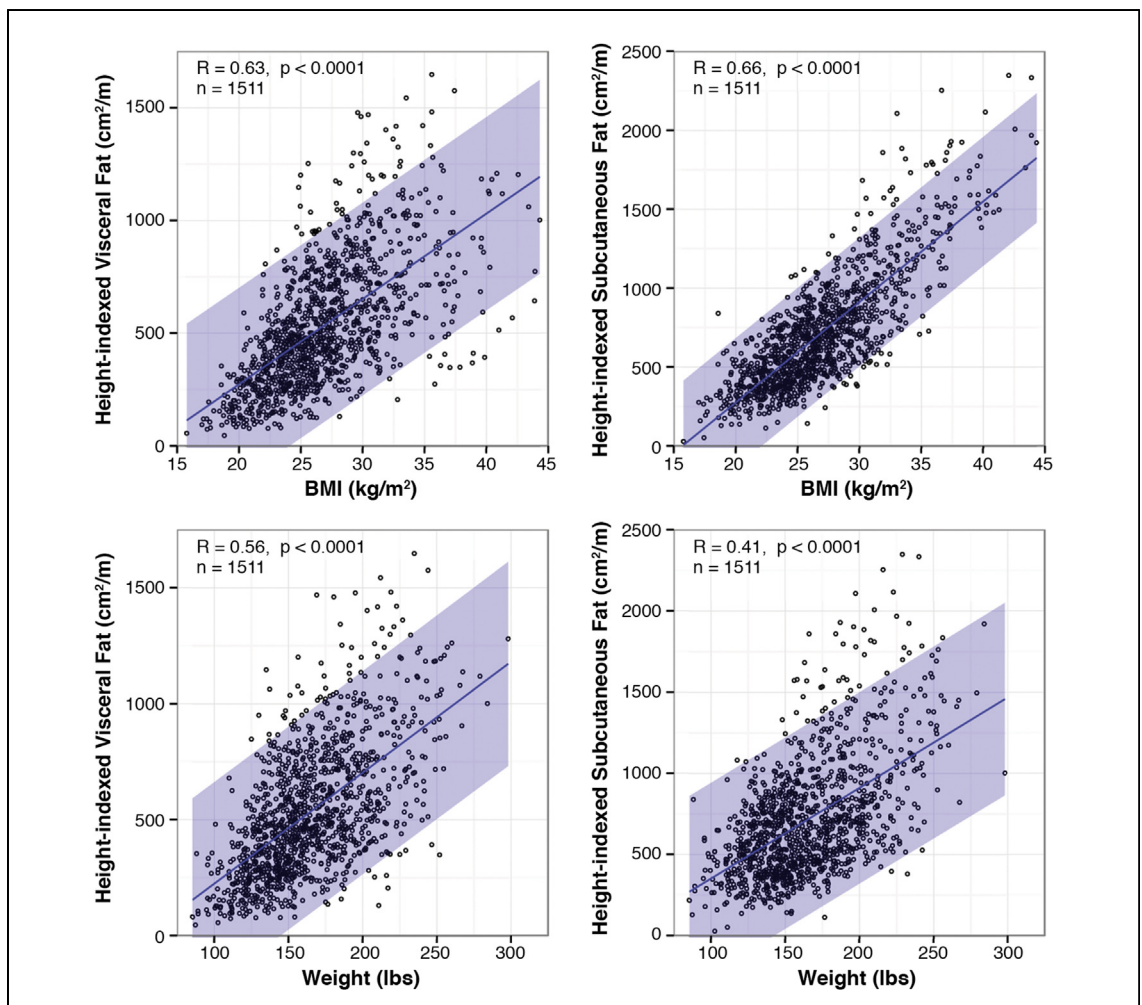


FIGURE 3 Scatterplots and Spearman Correlation Between Height-Indexed Visceral Fat Area and Height-Indexed Subcutaneous Fat Area With BMI and Weight

Visceral fat associations are shown on the **left** and subcutaneous fat associations are on the **right**. Visceral fat area is expressed as cm^2/m . BMI = body mass index.

subcutaneous adiposity and visceral adiposity (Spearman $R = 0.63$ for visceral, $R = 0.66$ for subcutaneous, both $p < 0.0001$) (Figure 3), whereas total body weight was more closely associated with visceral than subcutaneous adiposity ($R = 0.56$ for visceral vs. $R = 0.41$ for subcutaneous, both $p < 0.0001$) (Figure 3). There was a weak association between subcutaneous and VF burden at baseline (Spearman $R = 0.26$, $p < 0.0001$) (Figure 4).

In 253 patients with serial CT assessments for both visceral and subcutaneous fat measures, weight changes between CT examinations were modest (median 0.3%, IQR: -3% to +3%) compared with changes in visceral (median 7%, IQR: -8% to +23%) and subcutaneous adipose tissue burden (median 6%, IQR: -6% to +19%) (Figure 5). Furthermore, the variability of changes in visceral or subcutaneous adiposity was considerably greater than the variability of changes in weight (Figure 5), demonstrating that even modest changes in weight may result in large changes in fat distribution. The longitudinal association between percent change in subcutaneous fat and percent change in VF was modest (Spearman $R = 0.44$, $p < 0.0001$), suggesting that changes in one fat depot do not completely mirror changes in the other. Importantly, the correlation between change in VF and change in weight was stronger than for the baseline measures (Spearman $R = 0.70$, $p < 0.0001$).

A SINGLE MEASUREMENT OF VISCERAL ADIPOSITY PREDICTS RISK OF INCIDENT METS INDEPENDENT OF BMI, RACE, OR CARDIOMETABOLIC RISK.

Over a median follow-up of 6.2 years (IQR: 3.1 to 7.0 years), 203 (24%) of 862 participants without MetS at baseline were newly diagnosed with MetS. In a discrete unadjusted Cox regression (Online Table 2), subcutaneous fat area was associated with incident MetS (HR: 1.16 per 100 cm^2/m increase, 95% confidence interval [CI]: 1.12 to 1.20 per 100 cm^2/m increase, $p < 0.0001$), although a similar increment in VF area was associated with a higher hazard of MetS (HR: 1.31 per 100 cm^2/m increase, 95% CI: 1.24 to 1.39 per 100 cm^2/m increase, $p < 0.0001$). In addition, higher adiponectin was associated with a lower risk of MetS, whereas biomarkers of inflammation and insulin resistance (fasting insulin, tumor necrosis factor- α) were associated with an increased hazard of MetS.

To investigate whether visceral and subcutaneous fat burden are incrementally prognostic for MetS beyond known cardiometabolic risk factors, we performed incremental multivariable survival analysis for incident MetS (Table 2). After adjustment for age, sex, race, weight, smoking status, and MetS risk factors, height-indexed VF burden was associated with incident MetS (HR: 1.28 per 100 cm^2/m , 95% CI: 1.17 to 1.40 per 100 cm^2/m , $p < 0.0001$) (Table 2, Model 3; Figure 6) and effectively reclassified risk of incident MetS (continuous net reclassification index: 0.44, 95% CI: 0.29 to 0.66 vs. a fully adjusted clinical risk model) (Table 2, Model 2). Subcutaneous adiposity was significant when added to a model containing VF (HR: 1.08 per 100 cm^2/m , 95% CI: 1.01 to 1.15 per 100 cm^2/m , $p = 0.03$) (Table 2, Model 4), although risk reclassification and model fit were not appreciably affected. Importantly, estimates of effect size for visceral adiposity was similar in the fully adjusted model compared with its univariable association with MetS, suggesting that the association between MetS and visceral adiposity is largely independent of other cardiometabolic risk factors. Finally, there was no evidence of modification of the association between visceral or subcutaneous adiposity and incident MetS by race or sex.

Given the amount of imputation required for the adiposity measures used, we also evaluated the associations between VF and subcutaneous fat and incident MetS excluding imputed data (Table 3). Results were similar when imputed data were excluded, specifically with significant associations between incident MetS and VF (HR: 1.38, 95% CI: 1.23 to 1.55, $p < 0.0001$) (Table 3, Model 4). In addition to VF, glucose ($p = 0.0001$), systolic blood pressure

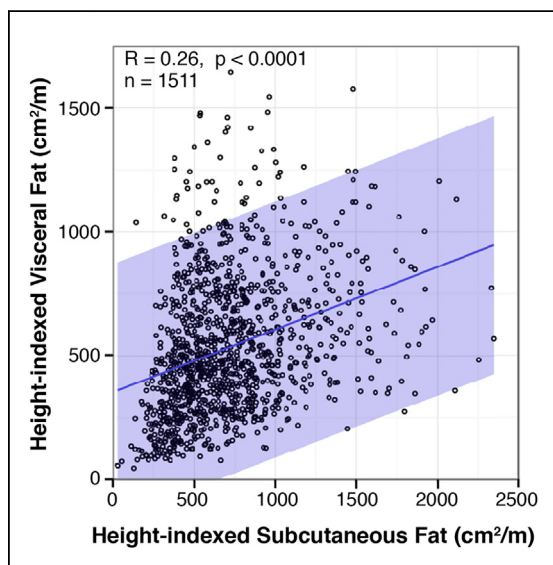
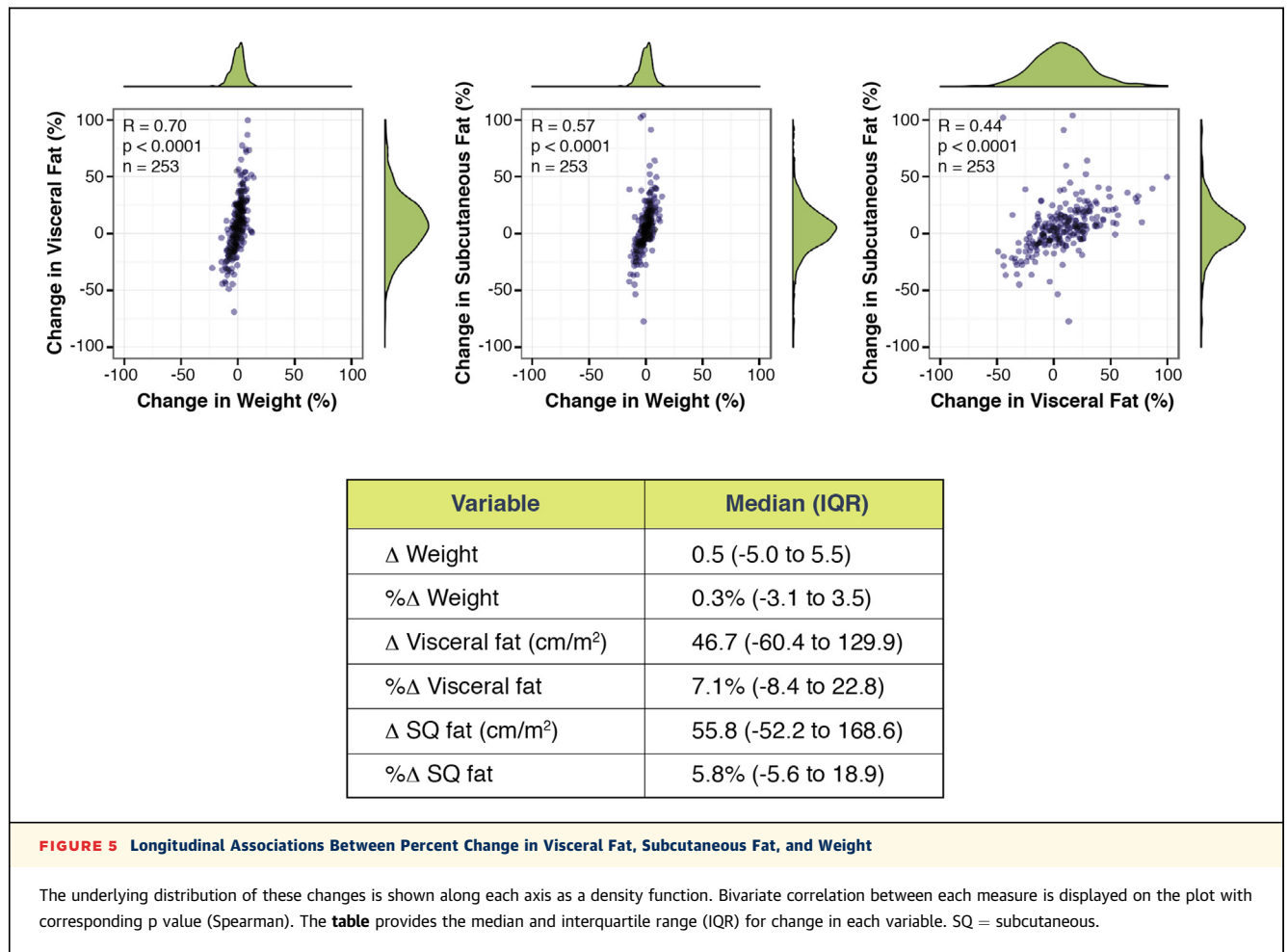


FIGURE 4 Scatterplot and Correlation Between Height-Indexed Visceral Fat Area and Height-Indexed Subcutaneous Fat Area

The blue band represents 95% prediction limits for the estimated regression line.



($p = 0.009$), HDL concentration ($p < 0.0001$), and weight ($p = 0.03$) were also associated with MetS.

A GAIN IN VISCERAL ADIPOSITY IS ASSOCIATED WITH INCIDENT METS INDEPENDENT OF CHANGE IN WEIGHT OR CARDIOMETABOLIC RISK. Of the 862 MESA participants with a baseline CT scan and without MetS, 253 participants had a repeat scan at examination 4. Of these, 72 (28%) developed MetS. In this longitudinal cohort, we determined whether change in visceral and subcutaneous fat area is associated with incident MetS, independent of baseline weight or change in weight over time using multivariable survival analysis (Table 4). Univariable Cox regression models for incident MetS in this subgroup are presented in Online Table 3. To address the separate fat compartments separately (without the influence of weight change), we added VF area and weight change separately to our models for incident MetS (Models 2 to 4). Change in weight was associated with incident MetS (HR: 1.33 per 5% increase; 95% CI: 1.02 to 1.72 per 5% increase, $p = 0.03$),

whereas a 5% change in VF area was associated with a corresponding 5% increase in risk of MetS (95% CI: 1.01 to 1.08, $p = 0.02$). Changes in subcutaneous fat area were not associated with risk of MetS ($p = 0.77$).

To understand the evolution of metabolic risk factors over time in this cohort (e.g., components of MetS), we examined the prevalence of metabolic risk factors that qualify under the definition of MetS (Table 5). Abdominal obesity (near 40%) and hypertension (40% or higher) were prevalent at each examination in the population studied, whereas dyslipidemia patterns were not as prevalent. However the prevalence of low HDL appeared to increase over time.

DISCUSSION

In a multiracial, multiethnic, community-based population, we demonstrated that visceral adiposity is associated with greater cardiometabolic risk regardless of BMI or race. We show that variability in both

TABLE 2 Multivariable Discrete Cox Survival Analysis for Incident Metabolic Syndrome in MESA Participants in the Study

	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Degrees of freedom	9		15		16		17	
AIC	1,173.2	Ref	1,090.9	<0.0001	1,065.2	<0.0001	1,062.4	0.09
LR chi-square	70.7	Ref	164.9	<0.0001	192.6	<0.0001	197.4	0.03
C-index	0.70 (0.66 to 0.74)	N/A	0.78 (0.75 to 0.82)	<0.0001	0.80 (0.77 to 0.83)	0.06	0.80 (0.77 to 0.83)	0.78
NRI	N/A	Ref	0.65 (0.50 to 0.80)	<0.05	0.44 (0.29 to 0.60)	<0.05	0.11 (-0.05 to 0.27)	>0.05
Relative IDI	N/A	Ref	0.92 (0.67 to 1.24)	<0.05	0.19 (0.10 to 0.30)	<0.05	0.02 (-0.02 to 0.06)	>0.05
Age, yrs	1.02 (1.00 to 1.04)	0.02	1.01 (0.98 to 1.03)	0.63	0.99 (0.97 to 1.02)	0.54	1.00 (0.97 to 1.02)	0.70
Female	2.23 (1.58 to 3.14)	<0.0001	3.27 (2.10 to 5.08)	<0.0001	4.72 (2.94 to 7.59)	<0.0001	3.71 (2.20 to 6.25)	<0.0001
Race								
Caucasian American	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Chinese American	1.42 (0.84 to 2.41)	0.19	0.91 (0.52 to 1.57)	0.72	1.01 (0.57 to 1.77)	0.98	0.98 (0.56 to 1.73)	0.95
African American	0.75 (0.50 to 1.14)	0.18	0.78 (0.50 to 1.21)	0.27	1.01 (0.64 to 1.60)	0.96	0.98 (0.62 to 1.56)	0.92
Hispanic	1.46 (0.99 to 2.16)	0.06	1.05 (0.69 to 1.59)	0.82	1.04 (0.68 to 1.59)	0.86	1.01 (0.66 to 1.54)	0.97
Weight, lbs	1.02 (1.02 to 1.03)	<0.0001	1.01 (1.00 to 1.02)	0.19	1.01 (1.00 to 1.02)	0.31	1.00 (0.99 to 1.02)	0.45
Former smoker	0.90 (0.64 to 1.27)	0.56	1.08 (0.75 to 1.54)	0.69	1.10 (0.76 to 1.58)	0.61	1.14 (0.79 to 1.64)	0.49
Current smoker	1.19 (0.72 to 1.95)	0.50	1.17 (0.70 to 1.96)	0.56	1.24 (0.74 to 2.11)	0.42	1.23 (0.73 to 2.09)	0.44
Exercise per 1,000 MET × min/week	0.98 (0.90 to 1.06)	0.57	1.00 (0.92 to 1.08)	0.98	1.00 (0.93 to 1.08)	0.96	1.00 (0.93 to 1.09)	0.93
Waist circumference, cm			1.03 (1.00 to 1.05)	0.02	1.01 (0.98 to 1.03)	0.56	0.99 (0.97 to 1.02)	0.68
Triglycerides, mg/dl			1.00 (1.00 to 1.01)	0.01	1.00 (1.00 to 1.01)	0.14	1.00 (1.00 to 1.01)	0.14
HDL, mg/dl			0.96 (0.95 to 0.98)	<0.0001	0.97 (0.95 to 0.98)	<0.0001	0.97 (0.95 to 0.98)	<0.0001
SBP, mm Hg			1.02 (1.01 to 1.03)	0.006	1.02 (1.00 to 1.03)	0.01	1.02 (1.00 to 1.03)	0.02
DBP, mm Hg			1.01 (0.98 to 1.03)	0.54	1.01 (0.98 to 1.03)	0.66	1.01 (0.98 to 1.03)	0.55
Glucose, mg/dl			1.07 (1.04 to 1.10)	<0.0001	1.06 (1.04 to 1.09)	<0.0001	1.06 (1.03 to 1.09)	<0.0001
Visceral fat per 100 cm ² /m					1.28 (1.17 to 1.40)	<0.0001	1.29 (1.18 to 1.41)	<0.0001
Subcutaneous fat per 100 cm ² /m							1.08 (1.01 to 1.15)	0.03

Values are hazard ratio (95% confidence interval). "Ref" indicates referent category for comparisons. NRI and IDI statistics are calculated for each model relative to the model immediately preceding (e.g., model 4 NRI represents model 4 vs. model 3). NRI, IDI, and C-index are calculated at second examination after computed tomography. Similar results were obtained when age, weight, smoking, exercise, waist circumference, triglycerides, HDL, SBP, DBP, and glucose were modeled as time varying covariates as assessed at each MESA examination (except exercise, which was not assessed at examination 4 and was assumed to be unchanged from examination 3).

AIC = Akaike information criterion; DBP = diastolic blood pressure; IDI = integrated discrimination improvement; LR = likelihood ratio; MET = metabolic equivalent; NRI = net reclassification index; SBP = systolic blood pressure; other abbreviations as in Table 1.

subcutaneous and VF stores is much greater than variability in weight over time. Importantly, this study within MESA is novel in that it specifies that *changes* in VF are strongly associated with incident MetS and that the association between VF and incident MetS is greater for a similar increase in VF as compared with subcutaneous fat. Effect modification by age, race, or sex was not present, suggesting that the VF depot is critical in all groups to define cardiometabolic risk. To our knowledge, these findings represent the first demonstration in a longitudinal, community-based, multiethnic study of this link between changes in visceral adiposity and cardiometabolic risk, suggesting that visceral adiposity is a BMI-independent, dynamic, mechanistic hallmark of cardiometabolic disease.

The notion that BMI may not fully define risk has led to increased attention on aspects of obesity-related cardiometabolic disease distinct from BMI (14). Visceral adiposity has been suggested as a

complementary risk factor, given its pathogenic consequences in animal models and the significant epidemiologic data suggesting its role in metabolic dysfunction (1). In animal models of obesity, dysfunctional visceral adipocytes represent a locus of inflammation and insulin resistance (15,16). Indeed, in humans, an improvement in insulin sensitivity is associated with changes in VF (17), and inflammation within visceral adipose tissue is associated with systemic insulin resistance, inflammation, and endothelial dysfunction (18). VF has been associated with cardiovascular events (4), left ventricular remodeling (19), and dysglycemia (2,3,20,21) in multiple large, community-based cohorts (e.g., the Dallas, Jackson, and Framingham Heart Studies). Most large, community-based studies have demonstrated an association between visceral adiposity, metabolic disease, and cardiovascular outcomes in obese (2) and other select populations (e.g., African Americans [3,21] or the Framingham area [4,20]). However,

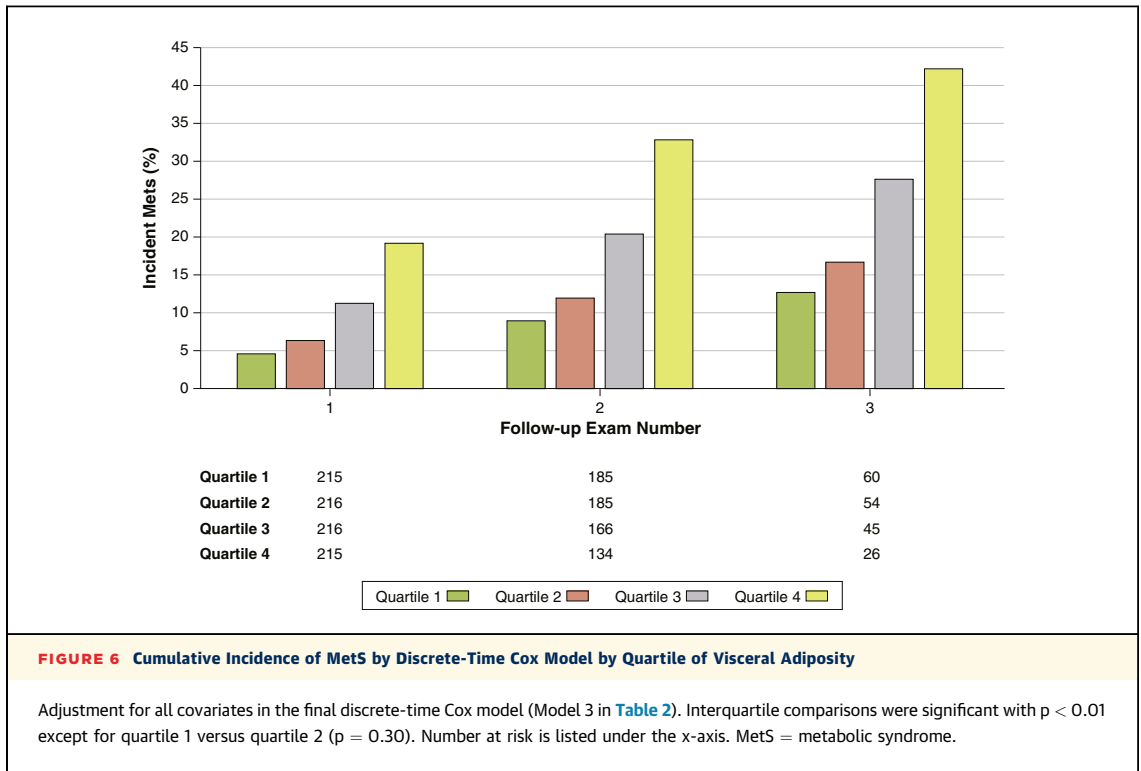


TABLE 3 Discrete Cox Proportional Hazards Model for Incident MetS, Excluding Individuals With Imputed Data

	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Degrees of freedom	9		15		16		17	
AIC	865.8	Ref	797.8	<0.0001	769.1	<0.0001	771.1	1.00
LR chi-square	88.4	Ref	168.4	<0.0001	199.1	<0.0001	199.1	1.00
C-index	0.74 (0.69 to 0.78)	N/A	0.81 (0.78 to 0.85)	<0.0001	0.83 (0.80 to 0.86)	0.05	0.83 (0.8 to 0.86)	0.72
NRI	N/A		0.72 (0.55 to 0.89)		0.52 (0.33 to 0.69)		0.11 (-0.07 to 0.30)	
Relative IDI	N/A		0.59 (0.38 to 0.87)		0.13 (0.03 to 0.25)		0 (0 to 0)	
Age, yrs	1.03 (1.01 to 1.05)	0.005	1.01 (0.99 to 1.04)	0.39	1.00 (0.97 to 1.03)	0.94	1.00 (0.97 to 1.03)	0.94
Female	3.20 (2.11 to 4.84)	<0.0001	4.75 (2.81 to 8.02)	<0.0001	7.88 (4.42 to 14.06)	<0.0001	7.9 (3.92 to 15.93)	<0.0001
Race								
Caucasian American	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Chinese American	2.47 (1.36 to 4.5)	0.003	1.60 (0.85 to 3.01)	0.14	1.89 (0.98 to 3.63)	0.06	1.89 (0.98 to 3.64)	0.06
African American	0.92 (0.57 to 1.47)	0.71	0.94 (0.57 to 1.56)	0.81	1.38 (0.80 to 2.36)	0.24	1.38 (0.8 to 2.38)	0.25
Hispanic	1.81 (1.12 to 2.92)	0.02	1.30 (0.78 to 2.17)	0.31	1.44 (0.86 to 2.43)	0.17	1.44 (0.85 to 2.45)	0.17
Weight, lbs	1.03 (1.02 to 1.04)	<0.0001	1.02 (1.00 to 1.03)	0.01	1.02 (1.00 to 1.03)	0.02	1.02 (1.00 to 1.03)	0.03
Former smoker	1.11 (0.75 to 1.66)	0.60	1.42 (0.93 to 2.18)	0.10	1.57 (1.01 to 2.44)	0.05	1.57 (1.01 to 2.44)	0.05
Current smoker	1.25 (0.70 to 2.23)	0.45	1.35 (0.73 to 2.47)	0.34	1.50 (0.81 to 2.79)	0.20	1.50 (0.81 to 2.79)	0.20
Exercise per 1,000 MET × min/week	0.97 (0.89 to 1.05)	0.46	1.00 (0.92 to 1.09)	0.93	1.00 (0.92 to 1.10)	0.94	1.00 (0.92 to 1.10)	0.94
Waist circumference, cm			1.02 (0.99 to 1.05)	0.13	0.99 (0.96 to 1.02)	0.60	0.99 (0.95 to 1.03)	0.69
Triglycerides, mg/dl			1.00 (1.00 to 1.01)	0.02	1.00 (1.00 to 1.01)	0.31	1.00 (1.00 to 1.01)	0.31
HDL, mg/dl			0.96 (0.94 to 0.98)	<0.0001	0.96 (0.94 to 0.98)	<0.0001	0.96 (0.94 to 0.98)	<0.0001
SBP, mm Hg			1.02 (1.01 to 1.03)	0.004	1.02 (1.01 to 1.03)	0.009	1.02 (1.01 to 1.03)	0.009
DBP, mm Hg			1.00 (0.97 to 1.03)	0.99	1.00 (0.97 to 1.03)	0.96	1.00 (0.97 to 1.03)	0.96
Glucose, mg/dl			1.07 (1.04 to 1.11)	<0.0001	1.07 (1.03 to 1.10)	0.0001	1.07 (1.03 to 1.10)	0.0001
Visceral fat per 100 cm ² /m					1.38 (1.23 to 1.54)	<0.0001	1.38 (1.23 to 1.55)	<0.0001
Subcutaneous fat per 100 cm ² /m							1.00 (0.9 to 1.12)	0.99

Values are hazard ratio (95% confidence interval). "Ref" indicates referent category for comparisons. NRI and IDI statistics are calculated for each model relative to the model immediately preceding (e.g., model 4 NRI represents model 4 vs. model 3).
Abbreviations as in Tables 1 and 2.

TABLE 4 Multivariable Discrete Cox Survival Analysis for Incident Metabolic Syndrome by Change in Visceral Adiposity in All MESA Participants With Serial CT for Visceral Adiposity (n = 253)

	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Degrees of freedom	11		12		12		12	
AIC	399.7		397		396.3		401.6	
LR chi-square	57.2	Ref	61.8	<0.0001	62.5	<0.0001	57.2	0.04
C-index	0.77 (0.71 to 0.83)	N/A	0.78 (0.72 to 0.84)	0.39	0.77 (0.71 to 0.83)	0.68	0.77 (0.71 to 0.83)	0.86
NRI	N/A	Ref	0.28 (-0.03 to 0.55)	>0.05	0.20 (-0.09 to 0.49)	>0.05	-0.21 (-0.49 to 0.11)	>0.05
Relative IDI	N/A	Ref	0.10 (-0.01 to 0.2)	>0.05	0.11 (-0.02 to 0.26)	>0.05	0.01 (-0.01 to 0.02)	>0.05
Age, yrs	0.97 (0.94 to 1.00)	0.03	0.98 (0.95 to 1.01)	0.17	0.98 (0.95 to 1.01)	0.11	0.97 (0.94 to 1.00)	0.03
Female	0.87 (0.40 to 1.89)	0.72	0.89 (0.40 to 1.94)	0.76	0.88 (0.40 to 1.93)	0.74	0.82 (0.34 to 1.98)	0.65
Race								
Caucasian American	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Chinese American	0.51 (0.19 to 1.42)	0.2	0.6 (0.22 to 1.69)	0.34	0.59 (0.21 to 1.66)	0.32	0.51 (0.18 to 1.42)	0.2
African American	1.16 (0.56 to 2.39)	0.69	1.22 (0.59 to 2.53)	0.59	1.16 (0.56 to 2.39)	0.69	1.15 (0.55 to 2.37)	0.72
Hispanic	1.03 (0.49 to 2.16)	0.93	1.14 (0.54 to 2.41)	0.74	1.01 (0.47 to 2.13)	0.99	1.01 (0.48 to 2.15)	0.98
Former smoker	1.14 (0.64 to 2.04)	0.66	1.11 (0.62 to 2.00)	0.73	1.17 (0.65 to 2.10)	0.60	1.14 (0.64 to 2.03)	0.67
Current smoker	1.16 (0.47 to 2.86)	0.75	1.15 (0.47 to 2.85)	0.76	1.23 (0.49 to 3.05)	0.66	1.16 (0.47 to 2.85)	0.75
Weight, lbs	0.99 (0.98 to 1.00)	0.12	0.99 (0.98 to 1.00)	0.18	0.99 (0.98 to 1.00)	0.11	0.99 (0.97 to 1.00)	0.13
Number of MetS components	2.67 (1.76 to 4.06)	<0.0001	2.61 (1.72 to 3.96)	<0.0001	2.47 (1.62 to 3.76)	<0.0001	2.67 (1.75 to 4.05)	<0.0001
Visceral fat per 100 cm ² /m	1.24 (1.08 to 1.44)	0.003	1.23 (1.07 to 1.42)	0.004	1.29 (1.12 to 1.50)	0.0006	1.24 (1.07 to 1.43)	0.005
Subcutaneous fat per 100 cm ² /m	1.08 (0.99 to 1.18)	0.10	1.08 (0.98 to 1.18)	0.11	1.10 (1.00 to 1.20)	0.05	1.09 (0.97 to 1.21)	0.14
ΔWeight, per 5%			1.33 (1.02 to 1.72)	0.033				
ΔVisceral fat, per 5%					1.05 (1.01 to 1.08)	0.02		
ΔSubcutaneous fat, per 5%							1.00 (0.98 to 1.02)	0.77

Values are hazard ratio (95% confidence interval). "Ref" indicates referent category for comparisons. NRI and IDI statistics are calculated for each model relative to the base clinical model (Model 1).
 Abbreviations as in Tables 1 and 2.

studies across racial lines and BMI in large American cohorts as well as longitudinal evaluation of adipose stores on cardiometabolic risk have not been reported.

Small studies utilizing dietary interventions have suggested that changes in visceral adiposity may be linked to improvements in dysglycemia, dyslipidemia, and hypertension (22,23). In 1 of the largest longitudinal studies, Matushita et al. (24) recently reported results from 973 Japanese men with 2 serial CT images over 3 years, demonstrating an increased probability of dyslipidemia with a >50 cm² increase in VF area. In addition, these investigators have demonstrated only a modest association between increases in VF area and change in weight (25), suggesting that generalized adiposity measures may not reflect the VF compartment. Indeed, the observation that modest weight loss produces a disproportionate loss of VF (26) and durable relief of dyslipidemia (27) and insulin resistance (28) may depend on sustaining a reduction in visceral adiposity.

In this context, our study provides definitive support for an emerging hypothesis that BMI may not

fully capture cardiometabolic risk: cross-sectional associations between weight, BMI, and VF were relatively modest. Furthermore, changes in weight over time within our longitudinal cohort in MESA were small relative to concomitant changes in visceral or subcutaneous fat. These findings provide support for the consideration of visceral adiposity as an important, complementary clinical barometer of cardiometabolic risk.

TABLE 5 Prevalence of Components of the Metabolic Syndrome at Each MESA Study Visit in the Population Studied

	Examination 1	Examination 2	Examination 3	Examination 4
Abdominal obesity	34.7	37.5	40.4	40.3
Elevated triglycerides	13.7	16.6	13.5	9.4
Low HDL	16.7	21.6	25.5	33.3
Hypertension	40.1	44.7	44.7	41.0
Hyperglycemia	0.0	2.3	2.8	3.9

Values are %.
 Abbreviations as in Table 1.

STUDY LIMITATIONS. Our results should be viewed in the context of its design. We did restrict our study population to individuals with CT scans available, and our longitudinal cohort was a smaller sampling from the overall MESA cohort. Although some of the CT results in the study were “imputed” (mostly subcutaneous data), we found similar results when only nonimputed data was used, suggesting the robustness of the associations we found. In addition, the 1,511 MESA participants included in this study were a subsample of the overall MESA cohort, and potential for selection bias is present, which we attempted to account for with adjustment in regression. Though not the primary focus of our work, the association of adiposity distribution with coronary artery calcification is intriguing, and requires further exploration with adjustments for comorbid illness to determine its significance. Finally, although we recognize that the effects of dietary and behavioral changes on weight and adiposity status are of great public health importance, MESA is a prospective observational cohort; these important clinical questions require ongoing randomized studies.

CONCLUSIONS

In a large, multiracial, multiethnic population of American adults, we demonstrated that despite modest associations with traditional markers

of adiposity, visceral adiposity stratifies cardiometabolic risk across BMI. Neither BMI nor waist circumference—current clinical tools to estimate obesity-related risk—were closely associated with VF, and changes in weight were small compared with concomitant changes in visceral or subcutaneous fat. Finally, VF (both at a single time point and its change over time) was strongly associated with incident MetS, regardless of changes in weight or initial weight, race, age, or sex. These results provide a much needed extension of the growing recognition of the pathophysiology of visceral adiposity in cardiometabolic disease to a clinical arena and justify a focus on VF as a modifiable risk factor for incident MetS and downstream cardiovascular consequences regardless of BMI.

ACKNOWLEDGMENTS The authors thank the participants in the MESA study and the study coordinators for their tireless efforts in the prevention of cardiovascular disease in our nation.

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KEY WORDS cardiometabolic risk, metabolic syndrome, obesity

APPENDIX For a supplemental section on imputations as well as figures and tables, please see the online version of this article.



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