Associations of Body Composition Measures and C2, A Marker for Small Artery Elasticity: The MESA

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Objective: Lower C2, a continuous blood pressure waveform characteristic asserted to represent small artery elasticity, predicts future cardiovascular disease events. It is hypothesized that the paradoxical positive association between body mass index (BMI) and C2 may reflect muscle instead of excess fat.

Methods: In a multi-ethnic, community-living cohort of 1,960 participants, computed tomography scans of the abdomen were used to measure visceral adipose tissue (VAT) and total abdominal muscle tissue (TAMT), and applanation tonometry of the radial arteries was used to assess C2. The period cross-sectional associations between BMI, TAMT, and VAT with C2 were ascertained.

Results: The mean age was 62 ± 9 years and 51% were male. After adjustments for age, gender, ethnicity, pack years smoking cigarettes, diabetes, hypertension, and total and HDL cholesterol, higher BMI (standardized beta = 0.09, P-value < 0.01) and more TAMT (standardized beta = 0.12, P-value < 0.01) were significantly associated with higher C2. In contrast, more VAT (standardized beta = -0.09, P-value < 0.01) was associated with lower C2.

Conclusions: In multivariable analysis, VAT, in contrast to TAMT and BMI, was associated with less compliant small arteries. Visceral fat may be a better marker for detrimental excess body fat than BMI.

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Introduction
Studies investigating correlates and outcomes of excess body fat often use body mass index [BMI, weight (kg)/height (m²)]. The “obesity paradox” is the observation that being overweight with excess body fat may be associated with lower mortality and better cardiovascular disease (CVD) outcomes, despite the fact that obesity is a recognized risk factor for CVD. This observation initially reported over a decade ago in coronary heart disease (CHD) patients undergoing percutaneous coronary intervention has been demonstrated in patients with hypertension, peripheral artery disease, stroke, myocardial infarction, heart failure, and end stage renal disease (1-5). Moreover, a systematic review of 40 cohort studies and 250,152 participants with known CHD found a U-shaped relationship between BMI and CVD mortality, with the lowest and highest weight categories exhibiting the highest risk, while the moderate overweight category was associated with a lower risk compared to the normal-weight group (6).

Several theories for the obesity paradox have been proposed. First, BMI may indicate lean body mass rather than just fat mass. Robero-Corral et al. used body fat percentage (BF%, calculated from bioelectrical impedance analysis) as the gold standard to determine the accuracy of BMI to identify obesity in men (BF% > 25%) and women (BF% > 35%) in a large sample representative of the US population (7). They reported that BMI ≥ 30 had a low sensitivity and high specificity to detect obesity in men (46% and 95%, respectively) and women (49% and 99%, respectively). They also reported that BMI was more strongly correlated with lean mass ($R^2 = 0.44$, P-value ≤ 0.01) than BF% ($R^2 = 0.53$, P-value ≤ 0.01). Second, others have proposed that BMI may not account for excess central fat, which is thought to more adversely affect CVD outcomes than peripheral fat. For example, in a meta-analysis of 15,923 (5,696 deaths) participants with CHD, higher central fat (measured by waist circumference and waist-hip ratio) was associated with mortality even among individuals with normal BMI (8). Finally, because BMI doesn’t discriminate between lean body mass and fat mass, some

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have proposed that low BMI categories may reflect underlying low muscle mass and poor nutritional status commonly found in chronic disease patients (9).

Notably, most observations of the obesity paradox have been made in patients with chronic diseases.

In the Multi-ethnic Study of Atherosclerosis (MESA), a cohort of community dwelling participants free of clinically manifest CVD at enrollment, a positive association was reported between BMI and C2, a continuous blood pressure waveform characteristic asserted to represent small artery elasticity (10). Reduced C2, indicating greater small artery stiffness, was an independent predictor of incident hypertension and future CVD events (10-12). In this same cohort, compared to the 1st C2 quintile, participants in the 5th quintile were at a higher risk of future hypertension (incident relative risk = 2.85, 95% CI: 1.95, 4.16) (12). Also in this cohort, a per-standard deviation increase in C2 was associated with future CVD (HR = 0.71, 95% CI: 0.61, 0.83) (10). Given the paradoxical relationship between BMI and C2, we conducted analysis that aimed to determine the relationship between computed tomographic (CT) measures of abdominal body composition with C2 in an effort to garner additional mechanistic insights into factors contributing to the obesity paradox. We hypothesized that independent of BMI and other CVD risk factors, total abdominal muscle tissue (TAMT, rectus abdominus, oblique, psoas, and paraspinal muscles) area would be positively associated with C2. In contrast, we hypothesized that despite the direct association of BMI with C2 reported previously, visceral adipose tissue (VAT, intra-abdominal fat) area would be inversely associated with C2.

Methods
Study sample
MESA is a multicenter, prospective cohort designed to investigate prevalence, correlates, and progression of subclinical (asymptomatic) atherosclerosis and their associations with incident clinical events. A detailed description of the study design, recruitment methods, examination components, and data collections has been published (13). In brief, participants included 6,814 men and women (age 45-84) of European-, Hispanic-, African-, and Chinese-American descent, free from clinically manifest CVD at baseline. Participants were recruited between July 2000 and August 2002 at six US field centers: New York, NY; Baltimore, MD; Winston-Salem, NC; St. Paul, MN; Chicago, IL; and Los Angeles, CA. Signed informed consent was obtained from all participants, and institutional review board approval was obtained for all participating institutions.

During follow-up visits between August 2002 and September 2005, a randomly selected subsample of 2,202 MESA participants was invited to participate in an ancillary study that aimed to determine the presence and extent of abdominal aortic calcium (AAC) using CT. Of these, 2,172 agreed to participate. Individuals were excluded if they were pre-menopausal, or had a recent (within 6 months) abdominal CT scan. This left 1,970 participants who underwent abdominal CT scans. At follow-up visits between August 2002 and September 2005, abdominal images were obtained using multidetector CT scanners 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). Electron-beam CT scanners were utilized at Northwestern University and University of California, Los Angeles (Imatron C-150, Imatron Inc., South San Francisco, California). Of the 1,970 participants, complete visualization of the visceral cavity was available in 1,960 individuals who represent the analytic sample for this study.

Central body composition measurements
Among individuals who provided abdominal CT scans, an ancillary study focused on abdominal body composition was conducted that interrogated six transverse cross-sectional slices at and just superior to L4/L5, L3/L4, L2/L3 for different measures of adipose tissue and skeletal muscle. Slices centered at L4/L5 junction were selected to quantify TAMT and VAT. Lean tissue was identified as being between 0 and 100 Hounsfield units (HU), and fat tissue was identified as −190 and −30 HU. TAMT was defined by adding the area for the bilateral rectus abdominus, oblique, psoas, and paraspinal lean tissue area, VAT was defined as fat within the visceral cavity. Within each area of interest (TAMT and VAT), 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 and then computed the total area (as cm²). For all analyses, image analyses were performed by technologists blinded to participant clinical information.

C2 measurement
At the baseline visit between 2000 and 2002, arterial waveforms were recorded for the entire cohort using the HDI/PulseWave CR-2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota). Details of this procedure have previously been published (10). In brief, a solid-state pressure transducer array (tonometer) was placed over the radial artery of the dominant arm to record the pulse contour. C2 is estimated by the device from the waveform modeled as a sinusoidal function damped by a decaying exponential. An index estimated directly from the waveform is divided by systemic vascular resistance (SVR) to obtain C2. SVR is estimated as mean arterial blood pressure/cardiac output, and cardiac output is estimated from ejection time taken from the pulse waveform, heart rate, age, height, and weight.

Risk factor assessment
Participants were given standardized questionnaires at baseline, which were used to obtain information on demographics, medical history, and smoking history. A medication inventory was also performed, and medications were grouped based on use to treat high blood pressure, or elevated blood glucose. Blood pressure was measured three times in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer at least 5 min of rest. The average of the last two measurements was used. Standard measurements were taken for height and weight, and blood samples were obtained after a 12 h fast for measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose. BMI was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure \( \geq 140 \text{ mmHg} \), diastolic blood pressure \( \geq 90 \text{ mmHg} \), or current use of anti-hypertensive medication. Diabetes was defined as fasting plasma glucose \( \geq 126 \text{ mg/dL} \), or use of hypoglycemic medications.
TABLE 1 Cohort characteristics

| N = 1,960 | Mean ± SD [Range], N (%) |
|-----------|-------------------------|
| Age, years | 62 ± 9 [44-84]          |
| Male sex   | 991 (51%)               |
| European ethnicity | 787 (40%) |
| African ethnicity | 410 (21%) |
| Hispanic ethnicity | 508 (26%) |
| Chinese ethnicity | 255 (13%) |
| Body mass index, BMI (kg/m²) | 28 ± 5 [15-53] |
| Total abdominal muscle tissue, TAMT (cm²) | 123 ± 27 [62-246] |
| Visceral adipose tissue, VAT (cm²) | 148 ± 69 [16-469] |
| Pack years smoking | 12 ± 21 [0-187] |
| Type 2 diabetes mellitus | 77 (8%) |
| Hypertension | 787 (40%) |
| Total cholesterol (mg/dl) | 196 ± 34 [65-462] |
| HDL cholesterol (mg/dl) | 51 ± 15 [21-121] |
| C2, small artery elasticity (ml/mmHg ×100) | 4.6 ± 2.9 [1.0-20.7] |

C2 = continuous blood pressure waveform characteristic asserted to represent small artery elasticity.

Statistical analysis

This is a period cross-sectional analysis of the 1,960 participants with available CT scans of the visceral cavity obtained between 2002 and 2005 and C2 measured at the baseline examination in MESA approximately 18 and 36 months previously, respectively. Descriptive statistics for the study cohort were summarized by means (SD) and ranges for continuous variables, and frequencies for categorical variables. Spearman rank correlations of BMI, TAMT, and VAT with C2 were calculated. Mean C2 for quartiles of TAMT crossed with VAT were determined using ethnic- and sex-specific cut points. Multivariable stepwise backward deletion (P criterion < 0.1) linear regression was used to determine the independent association of BMI, TAMT, and VAT with C2. Model 1 adjusted for BMI, TAMT, and VAT; model 2 included model 1 plus demographics (age, gender, and ethnicity), and traditional CVD risk factors (pack years smoking, diabetes, hypertension, total and HDL cholesterol, higher BMI and more TAMT were significantly associated with lower C2, indicating more compliant small arteries. In contrast, more VAT was associated with lower C2. Interaction terms: BMI × gender (Standardized Beta = 0.01, P-value = 1.0); TAMT × gender (Standardized Beta = −0.01, P-value = 0.8); and VAT × gender (Standardized Beta = 0.18, P-value = 0.3) were not significant (not shown).

Table 2 presents independent associations with C2. In multivariable analysis adjusted for age, gender, ethnicity, pack years smoking cigarettes, diabetes, hypertension, total and HDL cholesterol, higher BMI and more TAMT were significantly associated with lower C2, indicating more compliant small arteries. In contrast, more VAT was associated with lower C2. Interaction terms: BMI × gender (Standardized Beta = 0.01, P-value = 1.0); TAMT × gender (Standardized Beta = −0.01, P-value = 0.8); and VAT × gender (Standardized Beta = 0.18, P-value = 0.3) were not significant (not shown). Variance inflation factors among body composition measures in fully adjusted models were 1.8 for BMI, 2.5 for TAMT, and 1.8 for VAT (also not shown).

Discussion

In this study of a multi-ethnic cohort of men and women free of clinically apparent CVD, we observed a “BMI-C2 paradox” in a healthy, community-living, older population. Specifically, and after adjustment for CVD risk factors, as well as VAT and TAMT, higher BMI was associated with increased C2, even though lower C2 is a subclinical marker for CVD events. More TAMT was positively associated with higher C2. In contrast to TAMT and BMI, more VAT was independently associated with lower C2.

Reduced C2 is a subclinical marker for future CVD (10). However, BMI, a common clinical measure of excess body fat, was positively associated with C2. We hypothesized that VAT, a more precise measure of excess fat, especially around the central organs, would be inversely associated with C2, while TAMT would be positively associated with C2. We postulated that these associations may support the primary theories explaining the “obesity paradox” which are
that BMI does not discriminate well between lean tissue and excess fat, or between peripheral and more harmful central fat.

In support of our hypothesis, more VAT was independently associated with lower C2. Our results corroborated a prior study by Sutton-Tyrrell et al. which reported larger VAT area was associated with higher aortic pulse wave velocity (aPWV), another subclinical marker for CVD and a marker of greater arterial stiffness (14,15). Notably, in that study, investigators did not account for the potential effects of lean muscle tissue on vascular health. Thus, we confirm this important finding, and extend the data by demonstrating that associations are also evident for small artery elasticity, and independent of the quantity of lean muscle in the abdomen.

Also supportive of our hypothesis, more TAMT was associated with higher C2. Our findings are supported by a prior study of 648 participants, which found lean leg mass was inversely associated with arterial stiffness (16). Our findings along with others suggest that lean muscle mass may be driving the positive association between BMI and favorable cardiovascular outcomes. If true, BMI may reflect lean muscle tissue generally thought to have favorable effects on vascular health. In a population of participants with known CAD, we have previously published results which showed that greater 24-h urine creatinine excretion (a marker of muscle mass) was strongly protective for CVD (17), and these findings have been corroborated in the general population (18). In further support of our hypothesis, BMI misclassification of body fat status has been previously reported (7,19).

Strengths of our study include precise body composition measures from abdominal CT scans, a community-living sample, representation of multiple ethnicities and both genders, and a relatively large sample size. Also, prevalent CVD at baseline was an exclusion criterion, while prior studies have studied the “obesity paradox” in cohorts with prevalent CVD. However, our study also has important limitations. First, the non-simultaneity of the predictor and outcome measures makes it problematic, even as a period cross-sectional study and we cannot assign temporality. However, it is unlikely that these measures would change systematically over a short period of time. Second, C2 is a quotient of the pressure waveform index and SVR which includes height and weight, components of BMI. However, results of sensitivity analysis with C2×SVR were similar but weaker than those for C2. Finally, use of abdominal CT slices to quantify areas of fat and muscle tissue may not be the best representation of total body fat and muscle composition. Though, abdominal skeletal muscle quantified from a single magnetic resonance imaging at L4/L5 is a strong marker for whole body skeletal muscle (20).

### Conclusion

In community-living individuals without clinically apparent CVD, greater visceral adipose tissue was associated with stiffer small arteries, despite the fact that greater BMI was not. At the same time, greater abdominal muscle was associated with more compliant small arteries, despite the fact that greater BMI was not. At the same time, greater abdominal muscle was associated with more compliant small arteries. The paradoxical association of BMI with compliant small arteries may be because it is not specific to the type of mass (adipose or lean muscle) or the location of fat (visceral vs. peripheral). These findings suggest that lean muscle, instead of excess fat, or between peripheral and more harmful central fat.

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### TABLE 2 Multivariable associations of body composition measures and C2, small artery elasticity

|                         | Model 1         | Model 2         |
|-------------------------|-----------------|-----------------|
|                         | Beta (95% CI)   | P-value         | Beta (95% CI)   | P-value         |
| Constant                | 0.02 (−0.79, 0.84) | 0.96            | 8.50 (7.16, 9.89) | <0.01          |
| Body mass index, BMI (kg/m²) | 0.02 (−0.03, 0.07) | 0.48            | 0.09 (0.04, 0.14) | <0.01          |
| Total abdominal muscle tissue, TAMT (cm²) | 0.39 (0.34, 0.44) | <0.01          | 0.12 (0.06, 0.18) | <0.01          |
| Visceral adipose tissue, VAT (cm²) | −0.14 (−0.19, −0.09) | <0.01          | −0.09 (−0.14, −0.04) | <0.01          |
| Age, years              | −0.36 (−0.31, 0.04) | <0.01          | 0.21 (0.16, 0.27) | <0.01          |
| Male sex (vs. female)   | −0.04 (0.09, 0) | 0.05            |               |               |
| Chinese ethnicity (vs. European) | −0.13 (−0.18, −0.09) | <0.01          |               |               |
| African ethnicity (vs. European) | −0.07 (−0.11, −0.02) | <0.01          |               |               |
| Hispanic ethnicity (vs. European) |               |                 |               |               |

Model summary

- R-squared: 0.13
- Adjusted R-squared: 0.13
- Standard error of estimate: 2.72
- P-value: <0.01

C2 = continuous blood pressure waveform characteristic representing small artery elasticity. Model = backward deletion (P < 0.1 criterion), betas are per SD, two-tailed P < 0.05 considered significant. Model 1 adjusted for BMI, TAMT, and VAT. Model 2 included model 1 plus age, gender, ethnicity, pack years smoking cigarettes, diabetes, hypertension, and total and HDL cholesterol.
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