Association of Fat Density With Subclinical Atherosclerosis

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Association of Fat Density With Subclinical Atherosclerosis

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Background—Ectopic fat density is associated with cardiovascular disease (CVD) risk factors above and beyond fat volume. Volumetric measures of ectopic fat have been associated with CVD risk factors and subclinical atherosclerosis. The aim of this study was to investigate the association between fat density and subclinical atherosclerosis.

Methods and Results—Participants were drawn from the Multi-Detector Computed Tomography (MDCT) substudy of the Framingham Heart Study (n=3079; mean age, 50.1 years; 49.2% women). Fat density was indirectly estimated by computed tomography attenuation (Hounsfield Units [HU]) on abdominal scan slices. Visceral fat (VAT), subcutaneous fat (SAT), and pericardial fat HU and volumes were quantified using standard protocols; coronary and abdominal aortic calcium (CAC and AAC, respectively) were measured radiographically. Multivariable-adjusted logistic regression models were used to evaluate the association between adipose tissue HU and the presence of CAC and AAC. Overall, 17.1% of the participants had elevated CAC (Agatston score [AS] >100), and 23.3% had elevated AAC (AS >age-sex-specific cutoffs). Per 5-unit decrement in VAT HU, the odds ratio (OR) for elevated CAC was 0.76 (95% confidence interval [CI], 0.65 to 0.89; P=0.0005), even after adjustment for body mass index or VAT volume. Results were similar for SAT HU. With decreasing VAT HU, we also observed an OR of 0.79 (95% CI, 0.67 to 0.92; P=0.004) for elevated AAC after multivariable adjustment. We found no significant associations between SAT HU and AAC. There was no significant association between pericardial fat HU and either CAC or AAC.

Conclusions—Lower VAT and SAT HU, indirect estimates of fat quality, are associated with a lower risk of subclinical atherosclerosis. (J Am Heart Assoc. 2014;3:e000788 doi: 10.1161/JAHA.114.000788)

Key Words: atherosclerosis • epidemiology • fat density • obesity

Obesity affects individuals worldwide, with an estimated 2.8 million related deaths in 2008.1 Adiposity has been associated with a number of cardiovascular disease (CVD) risk factors, including hypertension (HTN) and diabetes mellitus.2–6 Beyond generalized adiposity, different fat depots confer varying degrees of CVD risk. For example, larger visceral adipose tissue (VAT) volume has a stronger adverse CVD risk profile than subcutaneous adipose tissue (SAT).6–9

Although many studies have investigated risk profiles based on absolute fat quantity, fat quality may also play an important role in conferring CVD risk. Molecular and cellular characteristics of adipose tissue, such as adipocyte size,10–13 reduced oxygenation,14,15 and dysfunctional inflammatory response,16–18 are associated with adverse metabolic risk in both animal models and humans. Radiographic imaging may provide a noninvasive alternative for fat quality measurements. Computed tomography (CT) attenuation, measured in Hounsfield Units (HU), is a quantitative measure of radiodensity to differentiate tissue types with the range of −195 to −45 HU that is attributed to adipose tissue.19 We have recently shown that lower CT attenuation was associated with higher CVD risk in both men and women, independent of fat depot volumes.20

Fat volume is adversely associated with vascular calcification, a marker for atherosclerotic burden and a predictor
of future coronary events. However, less is known about the association of fat quality with subclinical atherosclerosis. Thus, the aim of this study was to investigate whether lower fat attenuation is associated with the presence of coronary and abdominal aortic calcium (CAC and AAC, respectively) above and beyond other CVD risk factors and fat depot volumes. Because we have previously shown that lower fat CT attenuation is associated with more-adverse CVD risk factors, we hypothesized that lower fat CT attenuation would be associated with a higher odds of subclinical atherosclerosis.

Methods

Study Sample

Participants were drawn from the Multi-Detector Computed Tomography (MDCT) substudy from the offspring and third-generation cohorts of the Framingham Heart Study, which has been described previously. Briefly, between June 2002 and April 2005, this substudy enrolled a total of 3394 participants, of which 3079 (1516 women) were eligible for the study after exclusion for missing outcome and risk factor/covariate data and current CVD. For the pericardial fat analysis, a subset of 1120 individuals (621 women), who had complete data on pericardial fat volume and CT attenuation, were drawn from this overall sample.

Institutional review board approval was obtained from both the Boston University Medical Center (Boston, MA) and Massachusetts General Hospital (Boston, MA). All participants provided written informed consent.

Measurement of Fat Volumes and Density

Each participant received supine 8-slice MDCT scans of the abdomen and chest for VAT, SAT, and pericardial fat and calcification measurements, as previously described (Light-Speed Ultra; General Electric, Milwaukee, WI). In the abdomen, 25 contiguous 5-mm slices were imaged. A dedicated offline workstation (Aquarius; Terarecon, San Mateo, CA) was used for all radiographic measurements. Fat was defined by CT attenuation as any pixel between −195 and −45 HU. VAT and SAT volumes and CT attenuation values were measured by manually tracing the abdominal wall separating the VAT and SAT depots. In the chest, scans averaging 48 contiguous 2.5-mm slices of the heart were taken. Pericardial fat was defined as any adipose tissue located within the pericardial sac, and fat volume and CT attenuation were measured by manual tracing. This technique has produced high inter- and intrareader correlation in previous work.

Measurement of Calcium

Chest MDCT images were captured with a CT scanning protocol that was prospectively triggered by ECG readings, which allowed images to be taken at 70% of the cardiac cycle. This procedure successfully captured nearly motion-free images of the coronary arteries. CAC lesions were defined as any 3 consecutive pixels located in the coronary arteries with an HU value of greater than 130 units. AAC lesions were defined similarly in the abdominal images. Calcium deposits were then scored according to the Agatston scoring system. The presence of CAC was defined as an Agatston score (AS) greater than 100, and the presence of AAC was defined by age- and gender-specific 90th percentile cutoffs. These thresholds were used in order to be consistent with the existing literature. This protocol has also produced high inter- and intrareader correlation in previous work.

Metabolic Risk Factors and Covariates

Risk factor data were originally obtained at offspring examination cycle 7 or the first examination of the third generation. Body mass index (BMI) was defined as the weight in kilograms divided by the height in meters squared. Waist circumference was measured at the umbilicus using a tape measure. Serum metabolic measures, including total and high-density lipoproteins, triglycerides (TGs), and glucose, were measured from participants’ fasting samples. Current smokers were defined as those who smoked, on average, ≥1 cigarette per day for the past year. Physician-administered questions were used to quantify alcohol use, and drinks/week were dichotomized and stratified by gender using the following criteria: >14 drinks per week in men or >7 drinks per week in women. Diabetes was defined as fasting plasma glucose of ≥126 mg/dL or current treatment with either a hypoglycemic agent or insulin.

Statistical Analysis

TGs were log transformed for normalization. Similarly, CAC and AAC were log transformed after adding 1 unit to CAC and AAC (\(\log(CAC+1)\) and \(\log(AAC+1)\), respectively. Age-adjusted Pearson’s correlation coefficients were computed to assess the association between pericardial fat HU and various continuous CVD risk factors. The Pearson’s correlation coefficients were also calculated between log-transformed CAC and AAC and adiposity measures for each fat depot including HU.

Multivariable-adjusted logistic regression models were constructed to assess the association between VAT and SAT HU with the presence of CAC (AS>100) and AAC (AS>age- and sex-specific cutoffs). For each outcome,
5 models were constructed and the corresponding odds ratio (OR) for a 5-unit decrease in VAT or SAT HU was calculated. We opted to standardize our data to a 5-unit decrease in HU because this is nearly 1 SD across all measurements. This is analogous to using a continuous scale in that the $P$ value is identical. By standardizing the data, we are able to present it in a way that is more clinically meaningful. Furthermore, the HU data were modeled per decrement to be consistent with our a priori hypothesis that lower HU levels would be associated with increased calcium risk. Model 1 adjusted for age and sex, and model 2 adjusted for age, sex, lipid treatment, HTN treatment, smoking status, systolic blood pressure (SBP), diabetes, total/high-density lipoprotein (HDL) cholesterol, and (log-transformed) TG. Models 3, 4, and 5 included all covariates of model 2 with the following additional adjustments: Model 3 included BMI, model 4 included the corresponding fat volume (ie, the models for SAT HU were adjusted for SAT volume), and model 5 included the other fat

### Table 1. Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=3079)</th>
<th>Women (n=1516)</th>
<th>Men (n=1563)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>50.1 (9.9)</td>
<td>51.6 (9.5)</td>
<td>48.7 (10.1)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49.1 (1512)</td>
<td>45.2 (685)</td>
<td>52.9 (827)</td>
</tr>
<tr>
<td>Former</td>
<td>38.1 (1174)</td>
<td>42.3 (641)</td>
<td>34.1 (533)</td>
</tr>
<tr>
<td>Current</td>
<td>12.8 (393)</td>
<td>12.5 (190)</td>
<td>13.0 (203)</td>
</tr>
<tr>
<td>Moderate alcohol use*, %</td>
<td>15.4 (473)</td>
<td>14.9 (226)</td>
<td>15.8 (247)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>197 (35)</td>
<td>198 (36)</td>
<td>196 (34)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54 (17)</td>
<td>61 (17)</td>
<td>46 (12)</td>
</tr>
<tr>
<td>Total: HDL cholesterol, mg/dL</td>
<td>4.0 (1.4)</td>
<td>3.4 (1.1)</td>
<td>4.5 (1.4)</td>
</tr>
<tr>
<td>TGs, mg/dL†</td>
<td>102 (71 to 153)</td>
<td>112 (75 to 171)</td>
<td>93 (66 to 137)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>98 (19)</td>
<td>95 (17)</td>
<td>101 (20)</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>N/A</td>
<td>48.9 (741)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hormone replacement, %</td>
<td>N/A</td>
<td>19.4 (290)</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.4 (165)</td>
<td>4.7 (71)</td>
<td>6.0 (94)</td>
</tr>
<tr>
<td>Hypertensive treatment, %</td>
<td>16.6 (512)</td>
<td>17.0 (258)</td>
<td>16.3 (254)</td>
</tr>
<tr>
<td>Lipid treatment, %</td>
<td>11.4 (351)</td>
<td>9.2 (140)</td>
<td>13.5 (211)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 (16)</td>
<td>120 (18)</td>
<td>123 (14)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76 (9)</td>
<td>74 (9)</td>
<td>78 (9)</td>
</tr>
<tr>
<td>CAC AS$&gt;100$, %</td>
<td>17.1 (527)</td>
<td>10.8 (164)</td>
<td>23.2 (363)</td>
</tr>
<tr>
<td>AAC AS$&gt;$age-/sex-specific cutoffs†, %</td>
<td>23.3 (716)</td>
<td>24.5 (371)</td>
<td>22.1 (345)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 (5.2)</td>
<td>27.0 (5.8)</td>
<td>28.3 (4.4)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>97 (14)</td>
<td>93 (15)</td>
<td>100 (12)</td>
</tr>
<tr>
<td>VAT, cm$^3$</td>
<td>1759 (994)</td>
<td>1340 (828)</td>
<td>2166 (971)</td>
</tr>
<tr>
<td>VAT HU</td>
<td>−93.9 (4.6)</td>
<td>−92.4 (4.4)</td>
<td>−95.2 (4.5)</td>
</tr>
<tr>
<td>SAT, cm$^3$</td>
<td>2878 (1397)</td>
<td>3154 (1523)</td>
<td>2611 (1204)</td>
</tr>
<tr>
<td>SAT HU</td>
<td>−101.0 (5.0)</td>
<td>−102.3 (5.1)</td>
<td>−99.6 (4.4)</td>
</tr>
<tr>
<td>Pericardial fat, cm$^{38}$</td>
<td>121.1 (48.0)</td>
<td>109.3 (40.7)</td>
<td>135.7 (52.2)</td>
</tr>
<tr>
<td>Pericardial fat HU$^3$</td>
<td>−94.4 (3.0)</td>
<td>−95.0 (3.1)</td>
<td>−93.7 (2.6)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) for continuous characteristics or percentage (count) for categorical characteristics. AAC indicates abdominal aortic calcium; AS, Agatston score; BMI, body mass index; CAC, coronary artery calcium; HDL, high-density lipoprotein; HU, Hounsfield Units; N/A, not available; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue.

*Defined as >7 drinks/week (women) or >14 drinks/week (men).
†Presented as median (25th to 75th quartiles).
‡AAC AS age-/sex-specific cutoffs: men: 7 (<45 years old), 231 (45 to 54), 1922 (55 to 64), 4914 (65 to 74), and 8177 (≥75); women: 0 (<45 years old), 73 (45 to 54), 946 (55 to 64), 2263 (65 to 74), and 5742 (≥75).34
§Pericardial fat sample counts: 1120 (overall), 621 (women), and 499 (men).
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Table 2. Age-Adjusted Pearson’s Correlation Coefficients Between Cardiovascular Risk Factors and Pericardial Fat HU

<table>
<thead>
<tr>
<th>Source</th>
<th>Overall (n=1120)</th>
<th>Study Sample Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.10†</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.15†</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.08‡</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−0.03</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.11‡</td>
<td></td>
</tr>
<tr>
<td>Total: HDL cholesterol</td>
<td>0.07*</td>
<td></td>
</tr>
<tr>
<td>Log TGs</td>
<td>—0.03</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.20‡</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.22‡</td>
<td></td>
</tr>
<tr>
<td>VAT (volume)</td>
<td>0.10‡</td>
<td></td>
</tr>
<tr>
<td>SAT (volume)</td>
<td>0.11‡</td>
<td></td>
</tr>
<tr>
<td>Pericardial fat (volume)</td>
<td>−0.15‡</td>
<td></td>
</tr>
<tr>
<td>CAC</td>
<td>—0.02</td>
<td></td>
</tr>
<tr>
<td>AAC</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>SAT</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

CAC and AAC presented as log(CAC+1) and log(AAC+1), respectively. AAC indicates abdominal aortic calcium; BMI, body mass index; CAC, coronary artery calcium; HDL, high-density lipoprotein; HU, Hounsfield Units; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue.

Table 3. Age-Adjusted Pearson’s Correlation Coefficients Between Adiposity Measures and Coronary and Abdominal Aortic Calcium Presence

<table>
<thead>
<tr>
<th>Source</th>
<th>Overall</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.13‡</td>
<td>0.04</td>
<td>0.14‡</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.17‡</td>
<td>0.05</td>
<td>0.13‡</td>
</tr>
<tr>
<td>VAT (volume)</td>
<td>0.25‡</td>
<td>0.07‡</td>
<td>0.17‡</td>
</tr>
<tr>
<td>VAT HU</td>
<td>−0.10</td>
<td>0.02</td>
<td>−0.09‡</td>
</tr>
<tr>
<td>SAT (volume)</td>
<td>−0.02</td>
<td>0.05‡</td>
<td>0.09‡</td>
</tr>
<tr>
<td>SAT HU</td>
<td>0.14‡</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Pericardial fat (volume)</td>
<td>0.24‡</td>
<td>0.13‡</td>
<td>0.12‡</td>
</tr>
<tr>
<td>Pericardial fat HU</td>
<td>0.07*</td>
<td>−0.02</td>
<td>−0.02</td>
</tr>
</tbody>
</table>

CAC and AAC presented as log(CAC+1) and log(AAC+1), respectively. AAC indicates abdominal aortic calcium; BMI, body mass index; CAC, coronary artery calcium; HDL, high-density lipoprotein; HU, Hounsfield Units; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue.

Results

Study Sample Characteristics

Table 1 presents characteristics of the study cohort (n=3079). Mean age was 50 years, and approximately half of the participants (49.2%; n=1516) were women. Approximately 17% of the participants had CAC present (AS=100) and 23% had AAC present (AS=age-/sex-specific cut-offs). Overall mean and SD of SAT HU was −101.0 and 5.0, VAT HU was −93.9 and 4.6, and pericardial fat HU was −94.4 and 3.0.

Pearson’s Correlation Coefficients

Pericardial fat HU was directly correlated with most CVD risk factors in the overall cohort (Table 2). For example, pericardial fat HU was directly correlated with both SBP (r=0.10; P<0.001) and BMI (r=0.20; P<0.001). We also observed direct correlations overall between pericardial fat HU and SAT volume (r=0.11; P<0.001) and VAT volume (r=0.10; P<0.01). However, there was an inverse correlation between pericardial fat HU and pericardial fat volume (r=−0.15; P<0.001).

Table 3 presents correlation coefficients between measures of adiposity and calcium. For example, BMI was directly correlated with CAC (r=0.13; P<0.001). CAC was directly and the presence of CAC and AAC. The first 3 models adjusted for the same covariates as models 1, 2, and 3 above. The fourth model adjusted for VAT volume, and the fifth model adjusted for pericardial fat volume.

SAS statistical software (version 9.2; SAS Institute, Cary, NC) was used for all analyses. P<0.05 was considered statistically significant.
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OR of 0.76 for CAC (hypothesis, per 5-unit decrement in VAT HU, we observed an (OR, 0.71; P=0.001), SAT volume (OR, 0.60; P=0.0001), and SAT HU (OR, 0.83; P=0.04). For SAT HU, we observed an OR of 0.79 for CAC per 5-unit decrement in SAT HU (P=0.0004) in the multivariable model. Similarly, this association persisted after adjustment for BMI (OR, 0.76; P=0.0001), SAT volume (OR, 0.71; P=0.0001), and VAT HU (OR, 0.85; P=0.04).

For VAT HU and AAC, there was an 18% higher risk of calcification in the age-sex adjusted model (P<0.001). This association was nonsignificant after multivariable adjustment (OR, 0.9; P=0.09) and slightly stronger after additional adjustment for VAT volume (OR, 0.79 for AAC; P=0.004).

We observed no significant association between SAT HU and AAC in the multivariable or serial fat-depot adjusted models. Furthermore, we did not find significant associations between pericardial fat HU and either CAC or AAC in any of the models performed. Associations did not differ by sex (all P≥0.17).

Discussion

Our principal findings are 3-fold. Contrary to our a priori hypothesis, we observed that lower VAT and SAT HU were associated with a lower OR for CAC. These associations remained after further adjustment for CVD risk factors as well as VAT or SAT volumes. Similarly, lower VAT HU was associated with lower OR for AAC. Finally, we observed no association with pericardial fat HU and the presence of either CAC or AAC. Taken together, these findings suggest that indices of abdominal fat density are associated with subclinical atherosclerosis.

Table 4. Multivariable-Adjusted Logistic Regression for CAC and AAC With Cardiovascular Risk Factors by VAT HU, SAT HU, and Pericardial Fat HU Per 5 Unit Decrement in VAT, SAT, or Pericardial Fat HU

<table>
<thead>
<tr>
<th>VAT HU</th>
<th>CAC&gt;100</th>
<th>P Value*</th>
<th>AAC&gt;Age-/Sex-Specific Cutoffs‡</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender adjusted</td>
<td>1.02 (0.89 to 1.16)</td>
<td>0.81</td>
<td>1.18 (1.07 to 1.30)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Multivariable adjusted‡</td>
<td>0.76 (0.65 to 0.89)</td>
<td>0.0005</td>
<td>0.90 (0.80 to 1.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multivariable+BMI adjusted</td>
<td>0.71 (0.61 to 0.84)</td>
<td>&lt;0.0001</td>
<td>0.90 (0.79 to 1.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multivariable+SAT HU adjusted</td>
<td>0.60 (0.49 to 0.74)</td>
<td>&lt;0.0001</td>
<td>0.79 (0.67 to 0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>Multivariable+VAT HU adjusted</td>
<td>0.83 (0.70 to 0.99)</td>
<td>0.04</td>
<td>0.92 (0.81 to 1.05)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAT HU</th>
<th>CAC&gt;100</th>
<th>P Value*</th>
<th>AAC&gt;Age-/Sex-Specific Cutoffs‡</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender adjusted</td>
<td>0.87 (0.77 to 0.99)</td>
<td>0.03</td>
<td>1.03 (0.94 to 1.13)</td>
<td>0.53</td>
</tr>
<tr>
<td>Multivariable adjusted‡</td>
<td>0.79 (0.69 to 0.90)</td>
<td>0.0004</td>
<td>0.93 (0.84 to 1.03)</td>
<td>0.15</td>
</tr>
<tr>
<td>Multivariable+BMI adjusted</td>
<td>0.76 (0.67 to 0.88)</td>
<td>0.0001</td>
<td>0.93 (0.83 to 1.03)</td>
<td>0.16</td>
</tr>
<tr>
<td>Multivariable+SAT adjusted</td>
<td>0.71 (0.61 to 0.83)</td>
<td>&lt;0.0001</td>
<td>0.94 (0.84 to 1.05)</td>
<td>0.29</td>
</tr>
<tr>
<td>Multivariable+VAT HU adjusted</td>
<td>0.85 (0.73 to 0.99)</td>
<td>0.04</td>
<td>0.96 (0.85 to 1.08)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pericardial fat HU</th>
<th>CAC&gt;100</th>
<th>P Value*</th>
<th>AAC&gt;Age-/Sex-Specific Cutoffs‡</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender adjusted</td>
<td>1.02 (0.79 to 1.31)</td>
<td>0.89</td>
<td>1.14 (0.92 to 1.41)</td>
<td>0.24</td>
</tr>
<tr>
<td>Multivariable adjusted‡</td>
<td>0.97 (0.74 to 1.27)</td>
<td>0.82</td>
<td>1.10 (0.87 to 1.38)</td>
<td>0.44</td>
</tr>
<tr>
<td>Multivariable+BMI adjusted</td>
<td>0.98 (0.75 to 1.29)</td>
<td>0.89</td>
<td>1.07 (0.84 to 1.36)</td>
<td>0.58</td>
</tr>
<tr>
<td>Multivariable+VAT adjusted</td>
<td>0.97 (0.74 to 1.27)</td>
<td>0.85</td>
<td>1.10 (0.87 to 1.38)</td>
<td>0.44</td>
</tr>
<tr>
<td>Multivariable+pericardial fat adjusted</td>
<td>0.93 (0.70 to 1.23)</td>
<td>0.60</td>
<td>1.11 (0.88 to 1.42)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Estimates for HU are given as odds ratio (95% confidence intervals). AAC indicates abdominal aortic calcium, BMI, body mass index; CAC, coronary artery calcium; HU, Hounsfield Units; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 4. Multivariable-Adjusted Logistic Regression for CAC and AAC With Cardiovascular Risk Factors by VAT HU, SAT HU, and Pericardial Fat HU Per 5 Unit Decrement in VAT, SAT, or Pericardial Fat HU

*P values for sex interaction for CAC: VAT HU (P=0.90); SAT HU (P=0.63); and pericardial fat HU (P=0.81). P values for sex interaction for AAC: VAT HU (P=0.82); SAT HU (P=0.83); and pericardial fat HU (P=0.17). P values for age interaction for CAC: VAT HU (P=0.73); SAT HU (P=0.17); and pericardial fat HU (P=0.94). P values for age interaction for AAC: VAT HU (P=0.38); SAT HU (P=0.47); and pericardial fat HU (P=0.47).

Our principal findings are 3-fold. Contrary to our a priori hypothesis, per 5-unit decrement in VAT HU, we observed an OR of 0.76 for CAC (P=0.0005) in the multivariable-adjusted model. This association persisted after adjustment for BMI (OR, 0.71; P=0.0001), VAT volume (OR, 0.60; P=0.0001), and SAT HU (OR, 0.83; P=0.04). For SAT HU, we observed an OR of 0.79 for CAC per 5-unit decrement in SAT HU (P=0.0004) in the multivariable model. Similarly, this association persisted after adjustment for BMI (OR, 0.76; P=0.0001), SAT volume (OR, 0.71; P=0.0001), and VAT HU (OR, 0.85; P=0.04).

For VAT HU and AAC, there was an 18% higher risk of calcification in the age-sex adjusted model (P<0.001). This association was nonsignificant after multivariable adjustment (OR, 0.9; P=0.09) and slightly stronger after additional adjustment for VAT volume (OR, 0.79 for AAC; P=0.004). We observed no significant association between SAT HU and AAC in the multivariable or serial fat-depot adjusted models. Furthermore, we did not find significant associations between pericardial fat HU and either CAC or AAC in any of the models performed. Associations did not differ by sex (all P≥0.17).

CAC and AAC Risk

Multivariable-adjusted associations between fat density and calcium are presented in Table 4. Contrary to our a priori hypothesis, per 5-unit decrement in VAT HU, we observed an OR of 0.76 for CAC (P=0.0005) in the multivariable-adjusted model. This association persisted after adjustment for BMI (OR, 0.71; P<0.0001), VAT volume (OR, 0.60; P<0.0001), and SAT HU (OR, 0.83; P<0.04). For SAT HU, we observed an OR of 0.79 for CAC per 5-unit decrement in SAT HU (P<0.0004) in the multivariable model. Similarly, this association persisted after adjustment for BMI (OR, 0.76; P<0.0001), SAT volume (OR, 0.71; P<0.0001), and VAT HU (OR, 0.85; P<0.04).

For VAT HU and AAC, there was an 18% higher risk of calcification in the age-sex adjusted model (P<0.001). This association was nonsignificant after multivariable adjustment (OR, 0.9; P=0.09) and slightly stronger after additional adjustment for VAT volume (OR, 0.79 for AAC; P=0.004). We observed no significant association between SAT HU and AAC in the multivariable or serial fat-depot adjusted models. Furthermore, we did not find significant associations between pericardial fat HU and either CAC or AAC in any of the models performed. Associations did not differ by sex (all P≥0.17).

Discussion

Our principal findings are 3-fold. Contrary to our a priori hypothesis, we observed that lower VAT and SAT HU were associated with a lower OR for CAC. These associations remained after further adjustment for CVD risk factors as well as VAT or SAT volumes. Similarly, lower VAT HU was associated with lower OR for AAC. Finally, we observed no association with pericardial fat HU and the presence of either CAC or AAC. Taken together, these findings suggest that indices of abdominal fat density are associated with subclinical atherosclerosis.
We observed very few associations with pericardial fat HU, suggesting that the anatomic location of fat density measurements may be important. We also cannot rule out that differences in our chest, as compared to abdominal, radiographic protocol obscured our ability to identify meaningful associations with pericardial fat HU and risk factors. Finally, pericardial fat HU data were available in our offspring sample only, which is, on average, older than the third-generation sample. It is possible that any potential association is attenuated in older individuals.

Multiple studies have investigated and established associations between obesity, adipose tissue volumes, and vascular calcification. The Muscatine Study, a longitudinal cohort study of 384 individuals, found that higher BMI during late childhood and early adult life was associated with CAC presence in early adult life. Beyond anthropometric measures, the St. Francis Heart Study used CT measures to demonstrate an association between intraabdominal adiposity and the presence of CAC in adults aged 50 to 70. Similarly, our group has previously identified an association between fat volumes and subclinical atherosclerosis using multislice CT scans.

Our current study advances the literature by using a noninvasive technique to measure fat density. This study builds on previous work from our group regarding the association between abdominal fat density and metabolic risk, where we showed that lower (ie, more-negative HU) was associated with more-adverse metabolic and CVD risk, including fat quantity.

CT attenuation of adipose tissue may indicate a variety of cellular and tissue characteristics. First, more-negative HU values are associated with more-lipid-dense fat tissue. Second, adipose tissue that is poorly vascularized is characterized by a more-negative HU value resulting from the radiographic properties of blood. Third, fibrotic adipose tissue is characterized by a less-negative HU value, compared to nonfibrotic adipose tissue, as a result of higher tissue density from excess collagen deposition. Considering these characteristics in the context of the findings from our study, our results are most consistent with adipose tissue fibrosis explaining the association between fat attenuation and vascular calcification.

Obesity is a chronic inflammatory condition. Diet-induced obesity causes adipocyte hypertrophy and hyperplasia from excess lipid accumulation. Adipocyte hypertrophy and hyperplasia induces tissue hypoxia, because the rapid adipose tissue expansion outpaces vascular growth, ultimately progressing to excess collagen deposition and fibrosis. Both tissue hypoxia and fibrosis result in adipocyte necrosis, leading to a systemic chronic inflammatory state and the development of atherosclerosis. Therefore, more-fibrotic adipose tissue, characterized as less-negative HU values, would be associated with higher odds of vascular calcification, consistent with the results of the present study.

Additionally, adipose-tissue–specific hormones, such as adiponectin and leptin, may also mediate the association between obesity, fibrosis, and subclinical atherosclerosis. Low serum levels of adiponectin and/or high serum levels of leptin have fibrogenic and vascular calcification effects and could mediate an association between adipose fibrosis and subclinical atherosclerosis. In published work, higher adipose tissue density was associated with lower leptin and higher adiponectin values. Taken together, there are several potential mechanisms that may explain our findings of the association between abdominal fat density and subclinical atherosclerosis. One potential reason for our disparate findings is that the cross-sectional nature of our work does not allow us to classify the temporal nature of disease exposure and outcome. CVD risk factors occur before the onset of subclinical atherosclerosis, and it is possible that we are picking up relationships at different points in time. Next, the histological correlates of fat density are uncertain and likely represent multiple different cellular mechanisms. The relative contribution of each component remains uncertain. Ultimately, the disparate findings that we have uncovered, relative to our initial hypothesis, might provide further insights into the relationships between fat quality and subclinical atherosclerosis. Further work, using longitudinal samples, will be necessary to better clarify these associations.

Our current observations indicate the importance of better understanding risks related to abdominal fat density above and beyond fat volume. Though CT imaging provides an indirect, noninvasive marker of fat density, the underlying molecular and structural characterization of varying CT attenuation still requires elucidation. Additionally, further investigation should focus on providing mechanistic insight for the association between abdominal fat density and subclinical atherosclerosis. For example, investigating the association between abdominal fat density and adipose-tissue–derived inflammatory factors would help to clarify this mechanism. Furthermore, associations between abdominal fat density and cardiac procedures, such as coronary artery bypass or stent implantation, could begin to elucidate the effect fat density has on clinical outcomes. However, though fat density estimation by CT imaging could provide CVD risk prediction, such is beyond the scope of this current mechanistic investigation.

Strengths of this current study include the large sample size, community-based design without enrichment for adiposity, and the use of CT imaging and reproducible protocols for fat measurements. Limitations include the cross-sectional
nature of the study, thereby precluding inferences of causality or temporality. Furthermore, the Framingham Heart Study offspring and third-generation cohorts were predominantly white, impeding generalization of our findings to other ethnic groups.

Conclusion
Abdominal fat density is associated with subclinical atherosclerosis. Our findings warrant further investigation into the association between fat density and atherosclerosis.

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Disclosures
Dr Pedley is an employee of Merck and Co, Inc.

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