Abdominal Visceral and Subcutaneous Adipose Tissue Compartments

Association With Metabolic Risk Factors in the Framingham Heart Study

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Background—Visceral adipose tissue (VAT) compartments may confer increased metabolic risk. The incremental utility of measuring both visceral and subcutaneous abdominal adipose tissue (SAT) in association with metabolic risk factors and underlying heritability has not been well described in a population-based setting.

Methods and Results—Participants (n = 3001) were drawn from the Framingham Heart Study (48% women; mean age, 50 years), were free of clinical cardiovascular disease, and underwent multidetector computed tomography assessment of SAT and VAT volumes between 2002 and 2005. Metabolic risk factors were examined in relation to increments of SAT and VAT after multivariable adjustment. Heritability was calculated using variance-components analysis. Among both women and men, SAT and VAT were significantly associated with blood pressure, fasting plasma glucose, triglycerides, and high-density lipoprotein cholesterol and with increased odds of hypertension, impaired fasting glucose, diabetes mellitus, and metabolic syndrome (P range <0.01). In women, relations between VAT and risk factors were consistently stronger than in men. However, VAT was more strongly correlated with most metabolic risk factors than was SAT. For example, among women and men, both SAT and VAT were associated with increased odds of metabolic syndrome. In women, the odds ratio (OR) of metabolic syndrome per 1–standard deviation increase in VAT (OR, 4.7) was stronger than that for SAT (OR, 3.0; P for difference between SAT and VAT <0.0001); similar differences were noted for men (OR for VAT, 4.2; OR for SAT, 2.5). Furthermore, VAT but not SAT contributed significantly to risk factor variation after adjustment for body mass index and waist circumference (P ≠0.01). Among overweight and obese individuals, the prevalence of hypertension, impaired fasting glucose, and metabolic syndrome increased linearly and significantly across increasing VAT quartiles. Heritability values for SAT and VAT were 57% and 36%, respectively.

Conclusions—Although both SAT and VAT are correlated with metabolic risk factors, VAT remains more strongly associated with an adverse metabolic risk profile even after accounting for standard anthropometric indexes. Our findings are consistent with the hypothesized role of visceral fat as a unique, pathogenic fat depot. Measurement of VAT may provide a more complete understanding of metabolic risk associated with variation in fat distribution. (Circulation. 2007;116:39-48.)

Key Words: abdominal fat ■ diabetes mellitus ■ epidemiology ■ hypertension ■ intra-abdominal fat ■ metabolic syndrome X ■ obesity

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cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States, affecting roughly 70 million people and accounting for nearly 1 million deaths per year.1 Improvements in CVD risk factor profiles have led to significant reductions in death from CVD over the past 50 years,2 but recent data suggest that the increasing prevalence of obesity may have slowed this rate of decline.3 Rates of overweight and obesity continue to increase,4–6

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39
VAT.39 In addition, this initial observation suggested that volu-
mids,25–29 MetS,30 –32 and risk factor clustering. 26 However,
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Available studies report relations of greater SAT and VAT
VAT compartments. Therefore, assessment of VAT requires
developing metabolic traits.10 –16
and other vasoactive substances that can influence the risk of
an endocrine organ, in part because it secretes adipocytokines
Japanese Americans or Southeast Asians, 19,22,26,29,35,37 ethnic
and recent National Health and Nutrition Examination Survey
data demonstrate that two thirds of the US population is either
overweight or obese.8 However, different fat compartments
can be associated with differential metabolic risk.7 In particular,
the visceral adipose tissue (VAT) compartment may be a unique pathogenic fat depot.8–10 VAT has been termed
an endocrine organ, in part because it secretes adipocytokines
and other vasoactive substances that can influence the risk of
developing metabolic traits.10–16

Waist circumference (WC) is an easily obtainable but
imprecise measure of abdominal adiposity17 because it is a
function of both the subcutaneous adipose tissue (SAT) and
VAT compartments. Therefore, assessment of VAT requires imaging with radiographic techniques such as computed
tomography (CT) or magnetic resonance imaging (MRI).
Available studies report relations of greater SAT and VAT
with a higher prevalence of impaired fasting glucose,9,18
diabetes,9,10,19 insulin resistance,9,20,21 hypertension,22–24 lip-
ids,25–29 MetS,30 –32 and risk factor clustering.26 However,
current imaging studies evaluating SAT and VAT are limited to
small, referral-based samples often enriched for adiposity-
related traits.23,25–27,32–34 Furthermore, study samples have
often been limited to either women or men, precluding the study
of sex differences.22,23,25–28,34–36 Some studies have focused on
Japanese Americans or Southeast Asians,19,22,26,29,35,37 ethnic
groups with more visceral fat than expected for a given overall
BMI.38 We recently demonstrated that multidetector CT permits
highly reproducible volumetric measurements of both SAT and
VAT.39 In addition, this initial observation suggested that volu-
metric fat measurements, as opposed to previous studies using
single-slice methodology, can accurately characterize the hetero-
genity of abdominal fat distribution between individuals and
the differences in fat distribution with age and between women
and men.

Thus, our aims in a community-based sample of women
and men free of CVD across the spectrum of BMI were to
assess whether the volume of SAT and VAT are associated
with metabolic risk factors cross-sectionally, to assess
whether VAT is more strongly associated with metabolic risk
factors than is SAT, and to determine whether sophisticated
volumetric imaging methods of SAT and VAT provide
information about metabolic risk other than that offered by
simpler measures such as BMI and WC.

Methods

Study Sample

Participants for this study were drawn from the Framingham Heart
Study Multidetector Computed Tomography Study, a population-
based substudy of the community-based Framingham Heart Study
Offspring and Third-Generation Study cohorts. Beginning in 1948,
5209 men and women 28 to 62 years of age were enrolled in the
original cohort of the Framingham Heart Study. The offspring
and spouses of the offspring of the original cohort were enrolled in the
Offspring Study starting in 1971. Selection criteria and study design
have been described elsewhere.40–41 Beginning in 2002, 4095 Third
Generation Study participants, who had at least 1 parent in the
offspring cohort, were enrolled in the Framingham Heart Study and
underwent standard clinic examinations. The standard clinic exami-
nation included a physician interview, a physical examination, and
laboratory tests. For the present study, the study sample consisted of
Offspring and Third Generation Study participants who were part of
the multidetector CT substudy.

Between June 2002 and April 2005, 3529 participants (2111 third
generation, 1418 offspring participants) underwent multidetector CT
assessment of coronary and aortic calcium. Inclusion in this study
was weighted toward participants from larger Framingham Heart
Study families and those who resided in the greater New England
area. Overall, 755 families were included in our analysis. Men had to
be ≥35 years of age; women had to be ≥40 years of age and not
pregnant; and all participants had to weigh <350 pounds. Of the
participants, 433 (222 offspring and 211 third generation) were
imaged as participants in an ancillary study using an identical
imaging protocol, the National Heart, Lung, and Blood’s Family
Heart Study.42 Of the total 3529 subjects imaged, 3394 had inter-
pretable CT measures; of those, 3329 had both SAT and VAT
measured; of those, 3124 of them were free of CVD; of those, 3102
attended a contemporaneous examination; and of those, 3001 had a
complete covariate profile. Thus, the overall sample size for analysis
is 3001.

The study was approved by the institutional review boards of the
Boston University Medical Center and Massachusetts General Hos-
pital. All subjects provided written informed consent.

Volumetric Adipose Tissue Imaging

Subjects underwent 8-slice multidetector CT imaging of the abdo-
men in a supine position as previously described (LightSpeed Ultra,
General Electric, Milwaukee, Wis). Briefly, 25 contiguous 5-mm-
thick slices (120 kVp; 400 mA; gantry rotation time, 500 ms; table
feed, 3:1) were acquired covering 125 mm above the level of S1.

Abdominal Adipose Tissue Measurements

SAT and VAT volumes were assessed (Aquisus 3D Workstation,
TeraRecon Inc, San Mateo, Calif). To identify pixels containing fat,
an image display window width of −195 to −45 Hounsfield units
(HU) and a window center of −120 HU were used. The abdominal
muscular wall separating the visceral from the subcutaneous com-
partement was traced manually. Interreader reproducibility was as-
sessed by 2 independent readers measuring VAT and SAT on a
subset of 100 randomly selected participants.99 Interclass correla-
tions for interreader comparisons were 0.992 for VAT and 0.997 for
SAT. Similarly high correlations were noted for intrarreader
comparisons.

Risk Factor and Covariate Assessment

Risk factors and covariates were measured at the contemporaneous
examination. BMI, defined as weight (in kilograms) divided by the
square of height (in meters), was measured at each index examina-
tion. WC was measured at the level of the umbilicus. Fasting plasma
glucose, total and high-density lipoprotein (HDL) cholesterol, and
triglycerides were measured on fasting morning samples. Diabetes
was defined as a fasting plasma glucose level ≥126 mg/dL at a
Framingham examination or treatment with either insulin or a
hypoglycemic agent. Participants were considered current smokers if
they had smoked at least 1 cigarette per day for the previous year.
Assessed through a series of physician-administered questions,
alcohol use was dichotomized on the basis of consumption of >14
drinks per week (in men) or 7 drinks per week (in women). Physical
activity, assessed with a questionnaire, is a score based on the
average daily number of hours of sleep and sedentary, slight,
moderate, and heavy activity of the participant. Women were
considered menopausal if their periods had stopped for ≥1 year.
Impaired fasting glucose was defined as a fasting plasma glucose
level of 100 to 125 mg/dL among those not treated for diabetes.
Hypertension was defined as systolic blood pressure ≥140 mm Hg,
diastolic blood pressure $\geq 90$ mm Hg, or on treatment. MetS was defined from modified Adult Treatment Panel criteria.43

Statistical Analysis
SAT and VAT were normally distributed. Sex-specific age-adjusted Pearson correlation coefficients were used to assess simple correlations between SAT and VAT and metabolic risk factors. Multivariable linear and logistic regression was used to assess the significance of covariate-adjusted cross-sectional relations between continuous and dichotomous metabolic risk factors and SAT and VAT. For continuous risk factors, the covariate-adjusted average change in risk factor per 1-standard deviation (SD) increase in adipose tissue was estimated; for dichotomous risk factors, the change in odds of the risk factor prevalence per 1-SD increase in adipose tissue was estimated. All models were sex specific to account for the strong sex interactions observed. Covariates in all models included age, smoking (3-level variable: current/former/never smoker), physical activity, alcohol use (dichotomized at $>14$ drinks per week in men or $>7$ drinks per week in women), menopausal status, and hormone replacement therapy. In addition, lipid treatment, hypertension treatment, and diabetes treatment were included as covariates in models for HDL cholesterol, log triglycerides, systolic and diastolic blood pressures, and fasting plasma glucose, respectively. $R^2$ values were computed for continuous models and c statistics were computed for dichotomous models to assess the relative contribution of SAT and VAT to explain the outcomes (risk factors). For each risk factor, tests for the significance of the difference between the SAT and VAT regression coefficients were carried out within a multivariate standardized regression (in which variables were first standardized to a mean of 0 and an SD of 1) to assess the relative importance of each adipose tissue measurement in predicting the risk factor. To assess the incremental utility of adding VAT to models that contain BMI or WC, the above multivariate analyses were repeated for VAT with SAT alone did not yield higher $R^2$ or c statistics than models that included BMI and WC alone. As a secondary analysis, the above multivariate regressions were rerun using the general estimating equation linear and logistic regression to account for correlations among related individuals (siblings) in the study sample. SAS version 8.0 was used to perform all computations; a 2-tailed value of $P<0.05$ was considered significant.44

Heritability Analysis
Heritability quantifies the proportion of trait variability resulting from the additive effect of genes; the contributions of both genes and early common environment cannot be differentiated. Heritability calculations rely on the assumption that trait variation can be partitioned into genetic, known covariates and environmental (unknown) components. It is further assumed that the genetic component is polygenic; there is no variation attributable to dominance components. To determine the heritability of SAT and VAT, we created sex-specific and cohort-specific residuals from multivariable regression after adjusting for age, age squared, smoking, and menopausal status using the overall sample with interpretable CT scans. Residuals were then pooled, and SOLAR was used to calculate heritabilities using variance-components analysis. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Overall, 1452 women and 1549 men were available for analysis. The mean age was 50 years (Table 1); approximately one quarter of the sample was hypertensive, 5% had diabetes, and approximately one third had MetS. Approximately half of the women were postmenopausal.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of Study Participants Free of Clinical CVD Who Underwent Radiographic Assessment of SAT and VAT Volumes</th>
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<tbody>
<tr>
<td><strong>Women (n=1452)</strong></td>
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<tr>
<td><strong>Men (n=1549)</strong></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
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<tr>
<td><strong>WC, cm</strong></td>
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<tr>
<td><em><em>Triglycerides,</em> mg/dL</em>*</td>
</tr>
<tr>
<td><strong>HDL cholesterol, mg/dL</strong></td>
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<tr>
<td><strong>Total cholesterol, mg/dL</strong></td>
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<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
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<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
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<tr>
<td><strong>Hypertension, %</strong></td>
</tr>
<tr>
<td><strong>Impaired fasting glucose,</strong> † %</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, %</strong></td>
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<tr>
<td><strong>MetS, %</strong></td>
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<tr>
<td><strong>Smoking, %</strong></td>
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<tr>
<td><strong>Current</strong></td>
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<tr>
<td><strong>Former</strong></td>
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<tr>
<td><strong>Never</strong></td>
</tr>
<tr>
<td><strong>Postmenopausal, %</strong></td>
</tr>
<tr>
<td><strong>Hormone replacement therapy, %</strong></td>
</tr>
<tr>
<td><strong>Alcohol use,</strong> † %</td>
</tr>
<tr>
<td><strong>SAT, cm³</strong></td>
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<tr>
<td><strong>VAT, cm³</strong></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD when appropriate. *Median (25th, 75th percentiles), †Fasting plasma glucose of 100 to 125 mg/dL; percentage is based on those without diabetes. **Defined as $>14$ drinks per week (men) or $>7$ drinks per week (women).

The mean SAT volume was 3071±1444 cm³ in women and 2603±1187 cm³ in men. The mean VAT volume in women was 1306±807 cm³ and in men was 2159±967 cm³.

Correlations With SAT and VAT
Correlations of SAT and VAT with metabolic risk factors are shown in Table 2. SAT was positively correlated with age in women ($r=0.13$, $P<0.001$) but not men, and VAT was positively correlated with age in both sexes ($r=0.36$ in women and men, $P<0.001$). SAT and VAT were highly correlated, with an age-adjusted correlation coefficient between SAT and VAT of 0.71 ($P<0.0001$) in women and 0.58 ($P<0.0001$) in men. Both BMI and WC were strongly correlated with SAT and VAT after adjustment for age (Table 2). All risk factors were highly correlated with both SAT and VAT, except for serum total cholesterol with SAT in men and physical activity index with VAT in men.

Multivariable-Adjusted Regressions With SAT, VAT, and Metabolic Risk Factor Variables
Results of multivariable-adjusted general linear regression analyses for SAT and VAT for both continuous and dichotomous metabolic risk factors are shown in Table 3. In
TABLE 2. Age-Adjusted Pearson Correlation Coefficients Between Metabolic Risk Factors and SAT and VAT Volumes

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAT</td>
<td>VAT</td>
<td>SAT</td>
<td>VAT</td>
</tr>
<tr>
<td>Age</td>
<td>0.13†</td>
<td>0.36†</td>
<td>0.03</td>
<td>0.36†</td>
</tr>
<tr>
<td>BMI</td>
<td>0.88†</td>
<td>0.75†</td>
<td>0.83†</td>
<td>0.71†</td>
</tr>
<tr>
<td>WC</td>
<td>0.87†</td>
<td>0.78†</td>
<td>0.88†</td>
<td>0.73†</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>0.31†</td>
<td>0.46†</td>
<td>0.18†</td>
<td>0.37†</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.25†</td>
<td>−0.35†</td>
<td>−0.17†</td>
<td>−0.33†</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.11†</td>
<td>0.15†</td>
<td>0.02</td>
<td>0.08*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.26†</td>
<td>0.30†</td>
<td>0.18†</td>
<td>0.24†</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.26†</td>
<td>0.28†</td>
<td>0.21†</td>
<td>0.27†</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>0.23†</td>
<td>0.34†</td>
<td>0.12†</td>
<td>0.19†</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>−0.14†</td>
<td>−0.09*</td>
<td>−0.08*</td>
<td>−0.03</td>
</tr>
</tbody>
</table>

*P<0.01; †P<0.001.

women, per 1-SD increase in SAT, systolic blood pressure increased on average 3.9±0.4 mm Hg (±1 SE), whereas VAT was 4.8±0.4 mm Hg higher. For systolic blood pressure in women, the difference between the magnitude of effect of the SAT versus VAT was not significant (P=0.10; Table 3). In men, the magnitude of the association of the average systolic blood pressure increase per 1-SD increase in VAT was larger than for SAT (3.3 versus 2.3 mm Hg, respectively; P=0.01 for difference in the regression coefficients between SAT and VAT). Similar results were obtained for diastolic blood pressure.

In women and men, the association of both SAT and VAT with continuous measures of metabolic risk factors was highly significant. For fasting plasma glucose, the effect of VAT was stronger than that of SAT (P<0.0001 for difference in women, P=0.001 in men). Strong and significant results for log triglycerides and HDL cholesterol followed similar patterns (Table 3).

Highly significant associations with SAT and VAT also were noted for dichotomous risk factor variables. Among women and men, both SAT and VAT were associated with an increased odds of hypertension (Table 3). In women, the odds ratio of hypertension per 1-SD increase in SAT (odds ratio, 2.1) was stronger than that for SAT (odds ratio, 1.7; P=0.001 for difference between SAT and VAT); similar differences were noted for men. Similar highly significant differences also were noted for impaired fasting glucose, diabetes, and MetS and are presented in Table 3.

The magnitude of association between VAT and all risk factors examined was consistently greater for women than for men (Table 3). Weaker sex differences were observed for SAT.

Residual Effect of VAT in Multivariable Models That Contain BMI and WC

To address whether radiographic imaging of abdominal adipose tissue explains variation in metabolic risk factors over and above the contribution of BMI and WC, we examined the residual effect size of each metabolic risk factor from multivariable models that additionally contained BMI and WC. Because models with BMI and WC routinely yielded higher R² or c statistic than models with SAT (Table I in the online-only Data Supplement), the addition of all 3 variables into one model was not pursued. For example, in women, SAT plus covariates were associated with 21% of the variation in log triglycerides (R²=0.21), VAT plus covariates were associated with 30% of the variation in log triglycerides, and both BMI and WC plus the covariates were associated with 26% of the variation in triglycerides. Models with VAT, BMI, and WC demonstrated significant additional contribution of VAT for all variables except diabetes in men. Statistically significant residual effect sizes for VAT were observed for all metabolic risk factors except diabetes in men (Table 3).

Risk Factor Distribution Based on Quartiles of VAT

Because VAT adds to risk factor variation above and beyond BMI and WC, we assessed the impact of stratifying individuals by VAT quartile within clinically defined categories of BMI (normal weight, BMI <25 kg/m²; overweight, BMI of 25 to 29.9 kg/m²; and obese, BMI ≥30 kg/m²). Thirty-three percent of the sample was normal weight, 41% was overweight, and 26% was obese. Among normal-weight, overweight, and obese individuals, there was a highly statistically significant stepwise linear increase in the prevalence of the MetS across quartiles of VAT in both women and men (see the Figure) after adjustment for age and BMI; similar relations were noted for additional risk factors, including hypertension and impaired fasting glucose.

Secondary Analysis

When education status was included as an additional covariate, relations between SAT and VAT and the continuous and dichotomous metabolic risk factors were not materially different (data not shown). When analyses were rerun using the general estimating equation procedure, the resulting probability values were not substantively changed from those discussed above (data not shown).

Heritability Analysis

Heritability for SAT was 57%, whereas heritability for VAT was 36%.

Discussion

In our community-based sample, volumetric CT measures of both SAT and VAT were correlated with multiple metabolic risk factors, although risk factor correlations with VAT were consistently significantly stronger than those for SAT. VAT, not SAT, provided information above and beyond simple clinical anthropometrics, including BMI and WC, and consistently provided differences in risk factor stratification among individuals who were overweight and obese. VAT was more strongly associated with metabolic risk factors in women than in men. Finally, both SAT and VAT are heritable traits.

VAT has traditionally been considered the more pathogenic adipose tissue compartment compared with SAT, but data confirming these relations using high-resolution volumetric imaging assessments in large, community-based sam-
TABLE 3. Sex-Specific Multivariable-Adjusted* Regressions for SAT and VAT With Continuous Metabolic Risk Factors (Top) and Dichotomous Risk Factors (Bottom)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
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<th>Men</th>
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<tbody>
<tr>
<td></td>
<td>MV-Adjusted</td>
<td>P for Either SAT or VAT†</td>
<td>P for SAT vs VAT‡</td>
<td>Residual Effect Size</td>
<td>MV-Adjusted</td>
<td>P for Either SAT or VAT†</td>
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<tr>
<td></td>
<td>Residual Effect Size</td>
<td></td>
<td></td>
<td>Size After MV/BMI/WC Adjustment</td>
<td>Residual Effect Size</td>
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<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td>3.9±0.4</td>
<td>&lt;0.0001</td>
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<td></td>
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<td></td>
<td></td>
<td>VAT</td>
<td>4.8±0.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td>2.2±0.2</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VAT</td>
<td>2.6±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td>3.4±0.3</td>
<td>&lt;0.0001</td>
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<td></td>
<td>VAT</td>
<td>4.8±0.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>Log TG</td>
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<td></td>
<td>SAT</td>
<td>0.14±0.01</td>
<td>&lt;0.0001</td>
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<td></td>
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<td></td>
<td>VAT</td>
<td>0.23±0.01</td>
<td>&lt;0.0001</td>
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<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td>−3.9±0.4</td>
<td>&lt;0.0001</td>
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<td></td>
<td></td>
<td>VAT</td>
<td>−5.9±0.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>HTN</td>
<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td>1.7 (1.5–2.0)</td>
<td>&lt;0.0001</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>VAT</td>
<td>2.1 (1.8–2.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IFG</td>
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<td></td>
<td></td>
<td>SAT</td>
<td>2.0 (1.7–2.3)</td>
<td>&lt;0.0001</td>
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<td></td>
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<td></td>
<td></td>
<td>VAT</td>
<td>2.5 (2.1–2.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
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<td></td>
<td></td>
<td>SAT</td>
<td>1.6 (1.2–2.0)</td>
<td>0.007</td>
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<td>VAT</td>
<td>2.1 (1.6–2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetS</td>
<td></td>
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<td></td>
<td>SAT</td>
<td>3.0 (2.6–3.5)</td>
<td>&lt;0.0001</td>
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<td>VAT</td>
<td>4.7 (3.9–5.7)</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

MV indicates multivariable; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; HTN, hypertension; IFG, impaired fasting glucose; and DM, diabetis mellitus. Data presented include effect size (the average change in risk factor±SE) per 1 SD in adipose tissue for continuous data, and the change in odds of the condition per 1 SD of adipose tissue with 95% CIs for dichotomous data.

‡For SAT vs VAT difference.

†For SAT or VAT in the model.

*Adjusted for age, smoking, alcohol use, physical activity, and menopausal status (women only), hormone replacement therapy (women only); for blood pressure, FPG, HDL cholesterol, and log triglycerides, an additional covariate of treatment for HTN, diabetes, or lipid disorders, respectively, was included.

The mechanism of increased metabolic risk is hypothesized to be related to the metabolically active adipose tissue found in the visceral region, in addition to the drainage of these substances directly into the portal circulation. Multiple small studies have demonstrated that the visceral fat compartment is metabolically active, secreting such vasoactive substances as inflammatory markers, adipocytokines, markers of hemostasis and fibrinolysis (including plasminogen activator inhibitor-1), and growth factors (including vascular endothelial growth factor), which may contribute to its role in cardiometabolic risk factor manifestation.

Our results are consistent with these prior findings in small studies and extend these findings to a well-characterized, community-based sample of men and women in that we show that all cardiometabolic risk factors examined were more strongly associated with VAT than SAT. We also extend the current literature to note statistically significant, albeit weaker, correlations with SAT. Although SAT and VAT are highly correlated with each other, we used the β-coefficients for SAT compared with VAT in relation to the outcome variables, and in nearly every situation, the β-coefficient from the regression model was stronger for VAT than for SAT. Of note, SAT volume is greater than VAT volume in both women and men. Therefore, although the...
Effect sizes between VAT and risk factors may be higher, it is possible that SAT volume actually contributes to more absolute risk.

Of interest are recent findings from the Dallas Heart Study, which examined metabolic risk factors relations in 1934 black and white women and men with SAT and VAT as assessed by MRI. An important difference between our study and the Dallas Heart Study is the inclusion of percent body fat in regression models. Given that we do not have a measure of percent body fat, our findings are not directly comparable. Nonetheless, the results of Vega et al. also show considerably higher $R^2$ for models that include VAT than for SAT, particularly among white participants, and increased $R^2$ for models that include VAT above and beyond percent body fat and WC.

Our results show that both SAT and VAT are associated positively with prevalence of hypertension, but only VAT provides significant information above and beyond BMI and WC. Other studies have demonstrated relations between VAT and hypertension. Among Japanese Americans and whites, VAT but not SAT was associated with hypertension, even after adjustment for BMI and WC, whereas among blacks, both SAT and VAT were associated with hypertension in men and women, underscoring the relative importance of fat depots among different ethnic groups.

We also found that both SAT and VAT were associated with triglycerides and HDL cholesterol in women and men. Our results build on those of others, which confirm the known association between VAT and lipids. However, we extend these findings to include strong and significant relations of SAT with HDL cholesterol and triglycerides. The primary difference with prior studies may be our large sample size in a community-based cohort compared with the few other studies that were adequately powered to compare the difference between SAT and VAT.

Similarly, for impaired fasting glucose and diabetes, multiple prior studies have demonstrated relations between VAT and prediabetic hyperglycemia and diabetes, but few have yielded significant relations for SAT. However, SAT has been shown in multiple studies to be more strongly associated with insulin resistance than is VAT; this has been reviewed previously. Some studies of insulin resistance have demonstrated stronger correlations with SAT than with VAT, especially in women. In the Insulin Resistance Atherosclerosis Study (IRAS), both SAT and VAT were important correlates of insulin resistance. One small study of 47 women and men demonstrated equivalent correlations of deep SAT and VAT with respect to cardiometabolic risk factors.

Although our results show that VAT is more highly correlated with MetS than is SAT, SAT was an important

![Graph](http://circ.ahajournals.org/)

Prevalence of hypertension (HTN), impaired fasting glucose (IFG), diabetes (DM), and MetS among normal-weight (A), overweight (B), and obese (C) individuals. Probability values represent those for linear trend across VAT quartiles and are adjusted for age and BMI.
correlate of the MetS. These findings are in contrast to prior studies, which have reported that SAT is only weakly associated with MetS. For example, in the Health, Aging, and Body Composition (Health ABC) Study, SAT was associated only with MetS in normal-weight and overweight men; however, unlike our study, the Health ABC Study focused primarily on older individuals. Therefore, SAT may be an important adipose tissue compartment that should not be overlooked. Only 1 very small intervention study has been conducted to date to examine the relation of SAT reduction with metabolic variables: In a small study of 15 women who underwent large-volume liposuction, despite the loss of nearly 10 kg subcutaneous fat, improvements in cardiometabolic risk factors were not observed. However, the small sample size, associated low power, and inclusion of morbidly obese study participants make it difficult to rule out a beneficial effect.

The strong correlation between SAT and cardiometabolic risk factors may be driven by the results from some studies but not all studies that have shown that insulin sensitivity is related to SAT and VAT. In addition to insulin resistance, relations between specific fat depots and adipokines may be responsible for mediating the relations with risk factors. In particular, leptin has been shown to be equally, if not more, correlated to SAT compared with VAT. Leptin also has been implicated in vascular dysfunction, which suggests another potential mechanism whereby SAT may be associated with cardiometabolic risk factors.

Despite the statistically significant results observed with both SAT and VAT, only VAT provided information above and beyond BMI and WC, suggesting that VAT may be a unique pathogenic fat depot. Similar findings have been noted among Japanese Americans, for whom VAT but not SAT was associated with hypertension, even after adjustment for BMI and WC. Unfortunately, we were unable to analyze SAT in the same models as BMI and WC because of the high collinearity between the variables. In fact, the $R^2$ of SAT versus BMI/WC is much higher for SAT than for VAT (0.76 versus 0.54 for men, 0.81 versus 0.64 for women).

Sex Differences
In our study, we found evidence for sex interactions in that increasing volumes of SAT and of VAT were consistently and more strongly associated with more adverse risk factors levels in women than in men. To the best of our knowledge, our findings are the most comprehensive examination of sex differences reported to date. In the Health ABC Study, a significant sex interaction was observed between VAT and diabetes. Among women and men from the Quebec Family Study and the Health, Risk factors, Exercise Training, and Genetics (HERITAGE) Family Study, only in women were higher amounts of VAT associated with adverse CVD risk factor profiles. The cause of these sex differences is uncertain but may be related to the higher amount of hepatic free fatty acid delivery derived from lipolysis from VAT that has been observed in women than in men.

Heritability
We demonstrate moderate to high heritability for VAT and SAT, respectively, indicating that a significant portion of the variability in these traits is familial. Two prior studies that investigated the heritability of intra-abdominal fat depots have found estimates for VAT ranging from 42% to 56% and estimates for SAT of 42%. Differences between our findings and prior published work may be due to the inclusion of younger participants with lower mean BMI, exclusion of certain metabolic conditions, and inclusion in a fitness study, which may have biased estimates. Overall, these findings suggest that a significant proportion of variability in VAT and SAT may be due to genetic causes. Further research is warranted to explore this further, including uncovering genomic regions of linkage and novel candidate genes.

Implications
The relation of MetS and its components with increasing VAT quartiles, particularly in overweight and obese individuals, suggests that VAT in particular may confer increasing risk within clinically defined categories of body weight. Two thirds of our study sample were either overweight or obese, statistics that mirror national data. Our data suggest that further observational and possibly interventional studies are warranted to test the impact of weight reduction and, in particular, the reduction of VAT on metabolic risk factors and overall CVD risk. Additionally, our work demonstrates strong and significant results for SAT and VAT in relation to cardiometabolic risk factors, suggesting that SAT should not be overlooked in regional adipose tissue research. Nonetheless, we note that the proportion of overall variation of VAT and of SAT with metabolic risk factors is moderate at best. This finding, which has been observed previously, suggests that other factors not accounted for in this study may be responsible for the variation in metabolic risk factors. In fact, many of these traits have a substantial heritable component, with reported heritabilities for glucose being 34% to 51%; for systolic blood pressure, 53%; and for total cholesterol, 40%. Therefore, the potential role of gene–adiposity interactions should be considered in future research.

Strengths and Limitations
Strengths of our study include the use of a community-based sample with participants not enriched for adiposity-related traits. Routine screening of metabolic risk factors was performed, and adjustment was made for several potential confounders. We used a highly reproducible volumetric method of SAT and VAT assessment, which accounts for heterogeneity of fat distribution throughout the abdomen. We were able to assess the role of SAT and VAT above and beyond clinical anthropometry. Our study participants were primarily middle-aged, allowing assessment of relations between fat compartments and risk factors in the absence of significant comorbidity. Lastly, we have a large sample with adequate power to detect potentially smaller but significant relations with SAT. Limitations include the cross-sectional design; because the associations are not prospective, causality cannot be inferred. Because the Framingham Offspring Study is primarily a white sample, generalizability to other ethnic groups is uncertain. For example, Japanese Americans and Southeast Asians have groups with more visceral fat than expected for a given overall BMI, whereas blacks have less...
visceral fat than do whites for a given BMI. Although we accounted for sibling–sibling correlations, current analytical methods did not allow us to account for all familial relations. Because we did not subdivide subcutaneous fat into superficial and deep compartments, we cannot comment on the relative importance of these compartments. Furthermore, we measured only abdominal, not truncal, SAT. Truncal SAT has been shown to be more correlated to insulin resistance than is abdominal SAT in men. Finally, we had only radiographic CT measures of intra-abdominal fat, not other techniques such as MRI or ultrasound. MRI may provide a better resolution of fat depots, and ultrasound may be a reasonable alternative to CT and is less invasive. Neither MRI nor ultrasound places patients at risk of radiation exposure, but MRI is limited by its expense and amount of time needed to perform the actual scan.

**Conclusions**

Both SAT and VAT are associated with an adverse metabolic risk profile. However, only VAT provides information above and beyond easily obtainable clinical anthropometric measurements. Measurement of VAT may provide a more complete understanding of metabolic risk, and further studies are warranted to prospectively assess the impact of the lowering of VAT and SAT on the incidence of MetS and CVD.

**Sources of Funding**

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**Disclosures**

Dr Meigs has been the recipient of research grants from GlaxoSmithKline, Pfizer, and Wyeth and has served on Advisory Boards for GlaxoSmithKline, Merck, Pfizer, and Lilly. The other authors report no conflicts.

**References**


Visceral adipose tissue (VAT) compartments may confer increased metabolic risk. The incremental utility of measuring both VAT and subcutaneous abdominal adipose tissue (SAT) in association with metabolic risk factors and underlying heritability has not been well described in a population-based setting. Participants from the Framingham Heart Study underwent multidetector computed tomography assessment of SAT and VAT volumes. SAT and VAT were significantly associated with increased odds of hypertension, impaired fasting glucose, diabetes, and metabolic syndrome. In women, relations between VAT and risk factors were consistently stronger than in men. VAT was more strongly correlated with most metabolic risk factors than was SAT. Furthermore, VAT but not SAT contributed significantly to risk factor variation after adjustment for body mass index and waist circumference. Among overweight and obese individuals, the prevalence of hypertension, impaired fasting glucose, and metabolic syndrome increased linearly and significantly across increasing VAT quartiles. Heritability values for SAT and VAT were 57% and 36%, respectively. Although both SAT and VAT are correlated with metabolic risk factors, VAT remains more strongly associated with an adverse metabolic risk profile even after accounting for standard anthropometric indices. Our findings are consistent with the hypothesized role of visceral fat as a unique, pathogenic fat depot. Measurement of VAT may provide a more complete understanding of metabolic risk associated with variation in fat distribution.
Abdominal Visceral and Subcutaneous Adipose Tissue Compartments: Association With Metabolic Risk Factors in the Framingham Heart Study
Caroline S. Fox, Joseph M. Massaro, Udo Hoffmann, Karla M. Pou, Pal Maurovich-Horvat, Chun-Yu Liu, Ramachandran S. Vasan, Joanne M. Murabito, James B. Meigs, L. Adrienne Cupples, Ralph B. D'Agostino, Sr and Christopher J. O'Donnell

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### Online Supplement Table – $R^2$ (for continuous data) and c-statistics (for dichotomous data) for multivariate models of Individual Metabolic Risk Factors before and after adding VAT to the Models.

<table>
<thead>
<tr>
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<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
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<td></td>
<td>$R^2$</td>
<td>p-value for VAT in models with BMI/WC</td>
<td>$R^2$</td>
<td>p-value for VAT in models with BMI/WC</td>
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**Adjusted for age, smoking, alcohol use, physical activity, and menopausal status (women only), hormone replacement therapy (women only); for blood pressure, FPG, and HDL cholesterol, and log triglycerides, an additional covariate of treatment for HTN, diabetes, or lipid disorders, was included.

**Adjusted for age, smoking, alcohol use, physical activity, and menopausal status (women only), hormone replacement therapy (women only)

***For metabolic syndrome, models were only adjusted for BMI because of the inclusion of WC criteria in the metabolic syndrome definition

Abbreviations: MV=multivariable; SAT=subcutaneous adipose tissue, VAT=visceral adipose tissue, SD=standard deviation, SBP=systolic blood pressure, DBP=diastolic blood pressure, FPG=fasting plasma glucose, TG=triglycerides, HDL=high density lipoprotein, HTN=hypertension, IFG=impaired fasting glucose, DM=diabetes, metS=metabolic syndrome, BMI=body mass index. WC=waist circumference

*Adjusted for age, smoking, alcohol use, physical activity, and menopausal status