Visceral Adipose Tissue, a Potential Risk Factor for Carotid Atherosclerosis

Results of the Multicultural Community Health Assessment Trial (M-CHAT)

Scott A. Lear, PhD; Karin H. Humphries, DSc; Simi Kohli, BSc; Jiri J. Frohlich, MD; C. Laird Birmingham, MD; G.B. John Mancini, MD

Background and Purpose—The association between abdominal obesity and atherosclerosis is believed to be due to excess visceral adipose tissue (VAT), which is associated with traditional risk factors. We hypothesized that VAT is an independent risk factor for atherosclerosis.

Methods—Healthy men and women (N=794) matched for ethnicity (aboriginal, Chinese, European, and South Asian) and body mass index range (<25, 25 to 29.9, or ≥30 kg/m²) were assessed for VAT (by computed tomography scan), carotid atherosclerosis (by ultrasound), total body fat, cardiovascular risk factors, lifestyle, and demographics.

Results—VAT was associated with carotid intima-media thickness (IMT), plaque area, and total area (IMT area and plaque area combined) after adjusting for demographics, family history, smoking, and percent body fat in men and women. In men, VAT was associated with IMT and total area after adjusting for insulin, glucose, homocysteine, blood pressure, and lipids. This association remained significant with IMT after further adjustment for either waist circumference or the waist-to-hip ratio. In women, VAT was no longer associated with IMT or total area after adjusting for risk factors.

Conclusions—VAT is the primary region of adiposity associated with atherosclerosis and likely represents an additional risk factor for carotid atherosclerosis in men. Most but not all of this risk can be reflected clinically by either the waist circumference or waist-hip ratio measures. (Stroke. 2007;38:2422-2429.)

Key Words: atherosclerosis ▪ carotid ultrasound ▪ epidemiology ▪ ethnicity ▪ obesity ▪ risk factors ▪ visceral adipose tissue

Obesity (body mass index [BMI] >30 kg/m²) is an independent risk factor for atherosclerosis,1 stroke,2 and cardiovascular disease (CVD).3 However, not all people who are defined as obese by BMI develop atherosclerosis, nor are all people who have atherosclerosis obese. Recent reports conclude that even at desirable BMI levels (18.5 to 24.9 kg/m²), an increased waist circumference (WC) or waist-to-hip ratio (WHR) is associated with an increased risk of CVD.4,5 The deleterious effect of abdominal obesity is believed to be due to visceral adipose tissue (VAT), which is strongly correlated with traditional CVD risk factors: total cholesterol, low HDL cholesterol, triglycerides, apolipoprotein B, blood pressure, insulin resistance, and C-reactive protein.6–8 The predominant theory is that these associations are mediated by the release of free fatty acids by VAT into the hepatic circulation, thus stimulating the release of apolipoprotein B-containing lipoproteins, reducing insulin sensitivity, and increasing plasma glucose values.9,10 Recent research also indicates that a number of cytokines released by adipose tissue may also be involved in the development of atherosclerosis.11 Therefore, individuals with increased VAT, regardless of BMI, may have more CVD risk factors and be at greater risk for developing atherosclerosis.

Indeed, individuals with CVD have a greater amount of VAT compared with control subjects.12,13 An increased amount of VAT is associated with a greater likelihood of future CVD events and mortality,14–16 and direct and indirect measures of VAT have been associated with atherosclerosis as determined by the extent of coronary calcification17,18 and carotid artery intima-media thickness (IMT).19–23 In some studies, this latter relation persisted after adjusting for a number of established risk factors.17,18,21,24 However, those studies have been limited by either the use of indirect measures of atherosclerosis17,18 or imprecise assessment of VAT through abdominal ultrasound,19–23 and none of those studies considered overall body fat. Given the strong association between VAT and total body fat, investigations must consider this relation to rule out the possibility that VAT may...
simply be a surrogate for general obesity. We therefore hypothesized that the association between VAT and atherosclerosis is independent of total body fat, established risk factors, and measures of central adiposity (WC and WHR). We used computed tomography (CT) scans to measure VAT and carotid artery ultrasound to assess carotid artery IMT, plaque area, and the combined value of both IMT area and plaque area (total area) as measures of atherosclerosis. These measures of the carotid artery were chosen because of different mechanisms involved in diffuse intima-media thickening and atherosclerotic plaque formation and the lack of previous studies to distinguish between these and the relation to VAT.

Subjects and Methods

Participants recruited for the Multicultural Community Health Assessment Trial (M-CHAT) were used in the present investigation. The M-CHAT study consists of a multiethnic cohort of apparently healthy men and women (between 30 and 65 years of age) matched for ethnicity (aboriginal, Chinese, European, and South Asian) and BMI. Those who had recent weight change (>2.2 kg in 3 months), had a previous diagnosis of CVD or significant comorbidity (such as HIV, immunocompromised condition, type 1 diabetes mellitus), or had significant prosthetics or amputations were excluded. Those who were currently taking medications for CVD risk factors (ie, lipid-lowering, antihypertensive, or hypoglycemic medications) were also excluded to adequately adjust for the physiologic relation between risk factors, VAT, and atherosclerosis. Only those participants who had both VAT and carotid IMT assessed were included in this investigation (794 of the 829 in the M-CHAT cohort). All participants provided informed consent. This study was approved by the Simon Fraser University Research Ethics Board.

Participant Assessment

Participants were assessed for sociodemographics, medical history, and family history of CVD and type 2 diabetes mellitus (occurrence in parents or siblings at any age) according to a standardized interview. BMI was calculated as weight in kilograms divided by height in meters squared. WC was the average of 2 measurements taken against the skin at the point of maximal narrowing of the waist. Hip circumference was the average of 2 measurements taken at the point of maximal gluteal protuberance over undergarments. The WHR was calculated by dividing waist circumference by hip circumference.

Fasting blood samples were collected and immediately processed for total cholesterol, HDL cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), C-reactive protein, glucose, insulin, fibrinogen, and homocysteine. All measurements were carried out in the same clinical laboratory with standard enzymatic procedures. LDL cholesterol was calculated with the Friedewald equation. Blood pressure was recorded as the average of 5 successive measurements after 10 minutes of seated rest with an automated oscillometric office blood pressure monitor (VSM MedTech Ltd, Coquitlam, Canada). Smoking status and alcohol intake were assessed by self-report. A 3-day food record was analyzed for macronutrients by a registered diettian using ESHA Food Processor SQL software (Salem, Ore). Leisure time physical activity was assessed as the average minutes per week of activity during the previous year.

Body Composition Assessment

VAT was measured by CT with a CTi Advantage scanner (General Electric, Milwaukee, Wis). A cross-sectional 10-mm slice at the L4/L5 intervertebral disc was obtained, and the attenuation range of $-190$ to $-30$ Hounsfield units was used to identify adipose tissue. Computation of surface areas from the CT scans was conducted with the use of SliceOmatic 4.2 medical imaging software (SliceOmatic v.4.2, Tomovision, Montreal, Canada). Total abdominal fat area was calculated as all pixels within the attenuation range, and VAT was defined as the area of adipose tissue within the inside edge of the abdominal wall. Subcutaneous abdominal adipose tissue (SAT) was the difference between total abdominal adipose tissue and VAT. Total body fat was assessed by dual-energy x-ray absorptiometry with a Norland XR-36 scanner (Norland Medical Systems, White Plains, NY) and reported as total fat mass and as a percentage of total body mass.

Carotid Artery Measurements

Carotid artery ultrasound scans were recorded for each participant with a 10-MHz linear-array transducer as previously described. The IMT was assessed by measuring over a uniform length of 10 mm in the far wall of the right and left common carotid arteries within 2 cm proximal to the carotid bulb. The region with the thickest IMT, excluding areas with focal lesions, was measured. The average IMT was calculated from the right and left IMT measurements. All focal plaques within the carotid tree (common, internal, and external carotid arteries and bulb) identified as wall thickness that was increased compared with the surrounding IMT were measured. The area of each plaque was calculated as the average lesion thickness (in mm) multiplied by the lesion length (in mm). In those participants with multiple plaques, plaque area was the sum of the areas of all plaques observed in the carotid tree. Total area, a superior correlate of risk factors and a better prognostic indicator than IMT alone, was calculated as the sum of IMT area and plaque area. IMT area (in mm$^2$) was calculated as the length (10 mm) multiplied by the average IMT for the measured length. The values of IMT area of both right and left IMTs were summed. The intraclass and interobserver correlation values for this method were $0.922$ to $0.948$ and $0.850$ to $0.901$, respectively. For repeated measures in the same subject, the accuracy and precision were $0.001$ mm and $0.04$ mm, respectively, for IMT and $0.21$ mm$^2$ and $3.61$ mm$^2$, respectively, for total area.

Statistical Analyses

Normally distributed continuous variables are reported as mean±SD, and categorical and binary factors are reported as percentages and counts. The following variables were not normally distributed and were (natural log) transformed before analyses: average IMT, plaque area, total area, VAT, SAT, triglycerides, apolipoprotein B, lipoprotein(a), C-reactive protein, glucose, insulin, and weekly physical activity and are presented as geometric means and 95% CIs. Differences between men and women in categorical variables were analyzed with the Pearson $\chi^2$ test and the independent-samples $t$ test for continuous factors. The Pearson correlation coefficient was used for bivariate associations. Differences in IMT, plaque area, and total area among VAT tertiles were analyzed by 1-way ANOVA. Post hoc comparisons were analyzed with Tukey’s test to adjust for multiple comparisons.

Regression models were created to determine the relation between VAT and each of the 3 dependent variables of interest: plaque area (in only those participants with plaques; n=397), average IMT, and total area. Models were investigated to determine whether the relations differed by sex by using a sex×VAT interaction term. Initial models were created with adjustment for age, sex, ethnicity, women’s menopausal status, education, household income, family history of CVD, smoking, and percent body fat. Variables that were significantly correlated with either IMT or total area were entered in a stepwise fashion. These included glucose, insulin and homocysteine together; systolic and diastolic blood pressure, and lipids (total to HDL cholesterol ratio, LDL cholesterol, triglycerides, and apolipoprotein B). We found no correlations between lipoprotein(a), C-reactive protein, and fibrinogen with any of the carotid artery measures, so these were not included in the models. To determine the independent association of VAT with anthropometric measures of central adiposity, the models were further adjusted for WC and WHR. Because further adjustment by diet and physical activity did not change the interpretation of the regression models (data not shown), these variables were also excluded from the final models. For those variables that were not normally distributed, the logarithm-
TABLE 1. M-CHAT Demographics

<table>
<thead>
<tr>
<th></th>
<th>Women n=408</th>
<th>Men n=386</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47.3±8.7</td>
<td>46.5±8.7</td>
<td>0.208</td>
</tr>
<tr>
<td>Maximum education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ High school</td>
<td>21% (84)</td>
<td>21% (82)</td>
<td>0.540</td>
</tr>
<tr>
<td>Postsecondary</td>
<td>54% (221)</td>
<td>51% (198)</td>
<td>0.002</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20 000</td>
<td>14% (56)</td>
<td>13% (52)</td>
<td></td>
</tr>
<tr>
<td>&gt; $60 000</td>
<td>29% (119)</td>
<td>42% (163)</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>36% (147)</td>
<td>37% (141)</td>
<td>0.884</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9% (37)</td>
<td>13% (49)</td>
<td>0.074</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Never/≤1 drink/wk</td>
<td>76% (312)</td>
<td>67% (258)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5/wk</td>
<td>5% (21)</td>
<td>14% (65)</td>
<td></td>
</tr>
<tr>
<td>Physical activity (min wk)*</td>
<td>190 (28, 829)</td>
<td>214 (26, 1231)</td>
<td>0.141</td>
</tr>
<tr>
<td>Average daily intake (kcal)</td>
<td>1747±496</td>
<td>2095±645</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary fat (% daily kcal)</td>
<td>32.4±7.8</td>
<td>31.3±7.8</td>
<td>0.065</td>
</tr>
<tr>
<td>Saturated fat (% daily kcal)</td>
<td>9.8±3.2</td>
<td>9.4±3.2</td>
<td>0.054</td>
</tr>
</tbody>
</table>

*Geometric means and 95% CIs presented.

A geometrically transformed variable was used in all regression models. Model adequacy was satisfied as assessed by residual plots. Fully adjusted models were based on the 749 participants (387 women and 362 men) who had complete data. The significance level was set at 0.05 for the regression analyses, and all hypothesis tests were 2-sided. All statistical analyses were performed with SPSS 14.0.

Results

The study cohort consisted equally of men and women of aboriginal, Chinese, European, and South Asian descent. As a matched variable, BMI was similar between men and women, 27.6±4.3 kg/m² and 27.4±5.5 kg/m², respectively. Participant demographics are outlined in Table 1. Men reported higher household income and were more likely to consume alcohol and more dietary calories than women. There were no participants with diabetes, and 136 (33%) of the women were postmenopausal.

Men had significantly lower HDL cholesterol, C-reactive protein, and fibrinogen and significantly higher total to HDL cholesterol ratio, triglycerides, apolipoprotein B, glucose, insulin, homocysteine, and diastolic blood pressure (Table 2). In addition, men had greater WC, WHR, and VAT (P<0.001) and lower total fat mass, percent body fat, total abdominal adipose tissue, and SAT (P<0.001) than women. A greater proportion of men had carotid plaques (P=0.023) and a greater IMT (P<0.001), plaque area (P=0.020), and total area than women (P<0.001; Table 3).

VAT was the only body fat measure positively correlated with IMT, plaque area, and total area, and these correlations were modestly greater than those of WC and WHR (Table 4). Neither WC nor WHR was correlated with plaque area. Both WC and WHR were highly correlated with VAT, r=0.729 and r=0.554, respectively (P<0.001). When stratified by VAT tertiles, mean IMT and total area were significantly

<table>
<thead>
<tr>
<th></th>
<th>Women n=408</th>
<th>Men n=386</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.25±1.02</td>
<td>5.25±0.98</td>
<td>0.963</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.19±0.92</td>
<td>3.30±0.85</td>
<td>0.091</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.43±0.35</td>
<td>1.14±0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L*</td>
<td>1.20 (0.53, 2.99)</td>
<td>1.50 (0.57, 4.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol</td>
<td>3.88±1.23</td>
<td>4.90±1.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L*</td>
<td>0.93 (0.60, 1.43)</td>
<td>1.02 (0.64, 1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/L</td>
<td>177 (43, 856)</td>
<td>157 (39, 844)</td>
<td>0.102</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.6 (0.3, 9.7)</td>
<td>1.2 (0.3, 6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mmol/L*</td>
<td>5.1 (4.3, 6.1)</td>
<td>5.3 (4.6, 6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin, pmol/L*</td>
<td>64 (24, 171)</td>
<td>70 (27, 193)</td>
<td>0.031</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4±0.6</td>
<td>3.1±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine, μ mol/L</td>
<td>7.1±1.9</td>
<td>8.7±2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>116 (98, 145)</td>
<td>118 (101, 145)</td>
<td>0.053</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76±9</td>
<td>79±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC, cm</td>
<td>85.3±12.1</td>
<td>92.5±11.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.83±0.07</td>
<td>0.95±0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>29.2±10.1</td>
<td>22.8±8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>40.0±7.1</td>
<td>26.7±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total abdominal adipose tissue, cm²</td>
<td>430.3±162.5</td>
<td>377.8±154.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAT, cm²</td>
<td>299.7 (125.6, 565.1)</td>
<td>227.5 (94.2, 480.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>93.1 (37.6, 202)</td>
<td>112.5 (47.3, 211.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Geometric means and 95% CIs presented.
higher in those with the highest amounts of VAT in both men and women (Figure 1). There was no difference in plaque area across VAT tertiles.

The 397 participants who had carotid plaques had significantly greater WC (89.8±12.0 versus 87.9±12.2 cm, \( P=0.024 \)), WHR (0.90±0.09 versus 0.88±0.09, \( P=0.002 \)), and VAT (107.3 [45.2, 209.7] versus 97.1 [37.1, 208.8] cm², \( P=0.005 \)) than did those without plaques. There were no differences in BMI, total fat mass, percent body fat, total abdominal adipose tissue, and VAT in those with versus without carotid plaques. In those with plaques, VAT was a significant, independent predictor of plaque area after adjusting for age, sex, ethnicity, education, household income, family history of CVD, smoking, and percent body fat (\( P=0.029 \)). However, VAT was no longer a significant predictor after additional adjustment for any of the following factors: insulin, glucose, homocysteine, lipids, and blood pressure. There were no significant sex×VAT interactions.

The relations between VAT and IMT and between VAT and total area were significantly modified by sex after adjusting for age, ethnicity, education, household income, family history of CVD, smoking, and percent body fat (\( P=0.012 \) and \( P=0.048 \), respectively, for interaction), indicating that the slopes of these relations were different for men and women. Therefore, further analyses were conducted for men and women separately, as per Nicklas et al.\textsuperscript{16}

In men, VAT was an independent predictor of both IMT (\( P<0.001 \)) and total area (\( P=0.002 \)) after adjusting for age, ethnicity, education, household income, family history of CVD, smoking, and percent body fat (\( P=0.012 \) and \( P=0.048 \), respectively, for interaction), indicating that the slopes of these relations were different for men and women. Therefore, further analyses were conducted for men and women separately, as per Nicklas et al.\textsuperscript{16}

In women, VAT was significantly greater in postmenopausal women (88.2 [31.8, 198.3] versus 104.6 [45.2, 212.7] cm²) and was an independent predictor of IMT (\( P=0.003 \)) and total area (\( P=0.021 \)) after initial adjustment for age, ethnicity, menopausal status, education, household income, family history of CVD, smoking, and percent body fat (Figure 3). However, VAT was not a significant predictor of either IMT or total area in the final model, which included all risk factors and either WC or WHR. In addition, when percent body fat was replaced by total body fat mass in the initial model, VAT was not an independent predictor for either IMT (\( P=0.069 \)) or total area (\( P=0.104 \)) (data not shown).

### Discussion

Our data indicate that VAT is the primary region of adiposity associated with atherosclerosis, independent of total adiposity. This relation remained significant in men even after adjusting for common risk factors, indicating that increased amounts of VAT may have an additional effect on the development of carotid atherosclerosis. We further adjusted for WC and WHR separately to determine whether the risk associated with VAT was independent of these simple measures of central adiposity and found that although the independent association between VAT and IMT remained, this was no longer apparent for the association between VAT and total area. Given the associated inconvenience of measuring VAT (costs, radiation exposure), WC and WHR, which were both strongly associated with VAT, are still the preferred clinical measures for identifying those at increased risk.

Our results also indicate that SAT and total fat mass were not associated with atherosclerosis; this is in contrast to previous reports that SAT is positively associated with CVD risk.\textsuperscript{33} Furthermore, these variables were similar in those with and without plaques, whereas those with plaques had significantly greater VAT, WC, and WHR values. Although the cross-sectional area of SAT is \( \approx \) 2- to 3-fold greater than VAT, our results indicate that the association between WC and atherosclerosis is likely mediated by its representation of VAT area only and that those with low VAT but high WC may not be at increased risk for atherosclerosis. This may explain previous conflicting reports on the association be-

---

**TABLE 3. Results of Carotid Artery Ultrasound**

<table>
<thead>
<tr>
<th></th>
<th>Women (n=408)</th>
<th>Men (n=386)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average IMT, mm*</td>
<td>0.64 (0.52, 0.84)</td>
<td>0.69 (0.53, 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of plaques</td>
<td>46% (188)</td>
<td>54% (209)</td>
<td>0.023</td>
</tr>
<tr>
<td>Total plaque area, mm*</td>
<td>7.91 (2.17, 30.63)</td>
<td>9.78 (2.45, 49.13)</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>Total area, mm*</td>
<td>16.31 (10.54, 38.09)</td>
<td>19.19 (10.80, 55.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Geometric means and 95% CIs presented.

**TABLE 4. Pearson Correlation Coefficients Between Body Fat Variables and Carotid Artery Measures**

<table>
<thead>
<tr>
<th></th>
<th>Average IMT</th>
<th>Total Plaque Area (n=394)</th>
<th>Total Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.095*</td>
<td>−0.062</td>
<td>0.022</td>
</tr>
<tr>
<td>WC</td>
<td>0.176\†</td>
<td>0.041</td>
<td>0.123\†</td>
</tr>
<tr>
<td>WHR</td>
<td>0.238\†</td>
<td>0.095</td>
<td>0.189\†</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>−0.109\†</td>
<td>−0.102*</td>
<td>−0.108\†</td>
</tr>
<tr>
<td>Total fat mass</td>
<td>−0.020</td>
<td>−0.058</td>
<td>−0.037</td>
</tr>
<tr>
<td>Total abdominal adipose tissue</td>
<td>0.082*</td>
<td>−0.009</td>
<td>0.045</td>
</tr>
<tr>
<td>SAT</td>
<td>0.031</td>
<td>−0.047</td>
<td>0.010</td>
</tr>
<tr>
<td>VAT</td>
<td>0.266\†</td>
<td>0.139\†</td>
<td>0.189\†</td>
</tr>
</tbody>
</table>

\*\( P<0.05 \), †\( P<0.01 \).
between anthropometric measures of abdominal obesity with atherosclerosis.32–36

Recently, Nicklas et al16 reported that VAT was an independent risk factor for myocardial infarction in women but not in men >70 years of age. In our study, we found VAT to be independently associated with atherosclerosis in men but not in women. These contrasting findings may be due to the difference in age of these study cohorts. The lack of an association between VAT and myocardial infarction in men may be the result of a survivor effect, such that men who had high VAT amounts were unlikely to live to the age of 70 years. In addition, VAT area is usually smaller in women than

Figure 1. Mean IMT, plaque area, and total area by VAT area tertiles for men (gray bars) and women (black bars). *P<0.05, †P<0.001 compared with tertile 1. ‡P<0.005 compared with tertile 2.
men at a given age, and this was true in our cohort. In women,
VAT represent only 10% of adipose tissue but accounts for
20% in men.37,38 It has also been proposed that the relatively
greater amount of subcutaneous fat in younger women may
also be protective.36 With age, however, women’s VAT tends
to increase and approach that of men.39 Indeed, Nicklas et al
reported the VAT area in women to be 30% to 50% greater
than that observed in our cohort of younger women. There-
fore, as women age, VAT may reach critical levels similar to
those seen in men and lead to an increased risk in CVD.

The association of VAT with atherosclerosis in men,
independent of traditional risk factors, suggests that addi-
tional factors may be important in the link between VAT and
atherosclerosis. This may include lipoprotein particle size,
because the presence of small, dense LDL particles is a strong
predictor of CVD risk,40,41 and VAT is inversely associated
with lipoprotein particle size.42 Although we did adjust for
plasma concentrations of apolipoprotein B, this is a marker of
particle number and not particle size. In addition, recent
investigations have reported a number of cytokines released
by adipose tissue that have been implicated as risk factors for
atherosclerosis.31 Production of adiponectin, interleukin-6,
and plasminogen activator inhibitor-1 may be involved in the
link between VAT and atherosclerosis.43–46 Further adjust-
ment for WC or WHR reduced the significance of this
relation between VAT and total area but not for IMT. This
difference may reflect the distinct mechanisms involved in
the thickening of the intima-media wall as opposed to the
development of plaques, of which the total area measure
incorporates.25 Previous reports have indicated that VAT is
correlated with growth factors that may affect artery wall
thickening.47 Indeed, the correlation between VAT and IMT
was greater than that between VAT and total area; therefore,
VAT may play a greater role in intima-media thickening than
in the development of atherosclerotic plaque.

Our study adds value to previous reports on the association
between VAT and atherosclerosis. First, unlike other inves-

Figure 2. Significance of VAT area as a predictor of IMT (left) and total area (right) in men, expressed as the β coefficient and 95% CIs
with successive adjustment for CVD risk factors. A β coefficient of 0 represents no association between VAT and outcome. *Adjusted
for age, ethnicity, education, household income, family history of CVD, smoking, and percent body fat. Glu/ins/Hcy indicates additional
adjustment for glucose, insulin, and homocysteine; blood pressure, additional adjustment for systolic and diastolic blood pressure; and
lipids, additional adjustment for total to HDL cholesterol ratio, LDL cholesterol, triglycerides, and apolipoprotein B.

Figure 3. Significance of VAT area as a predictor of IMT (left) and total area (right) in women, expressed as the β coefficient and 95%
CIs with successive adjustment for CVD risk factors. A β coefficient of 0 represents no association between VAT and outcome.
*Adjusted for age, ethnicity, menopausal status, education, household income, family history of CVD, smoking, and percent body fat.
Glu/ins/Hcy indicates additional adjustment for glucose, insulin, and homocysteine; blood pressure, additional adjustment for systolic
and diastolic blood pressure; lipids, additional adjustment for total to HDL cholesterol ratio, LDL cholesterol, triglycerides, and apoli-
oprotein B.
tigators,17–23 we used precise, state-of-the-art measures for assessing body fat distribution by dual-energy x-ray absorptiometry and CT scan. Also, the use of carotid ultrasound to assess carotid IMT has the advantage of being a direct measure of atherosclerosis that is highly correlated with coronary atherosclerosis48 and sensitive enough to measure the early stages of atherogenesis. We also analyzed the relation between VAT and measures of atherosclerotic plaque, which have superior prognostic ability than IMT alone.30 Second, whereas other studies reported associations between VAT and atherosclerosis, our investigation considered variables (risk factors, general obesity) not present in earlier studies. Third, our study consisted of healthy men and women across a range of BMI who were free of CVD and not using medications for CVD risk factors. Although our recruitment strategy may have resulted in a healthy volunteer bias, it is unlikely that this bias had an effect on the variables of primary interest, namely, VAT and carotid atherosclerosis. Finally, because ethnicity did not affect our findings, these results have broader implications than do studies in homogeneous populations.

Conclusions
Our results indicate that VAT is independently associated with carotid atherosclerosis and that VAT is the primary region of adiposity associated with carotid atherosclerosis. In men but not women, VAT remained associated with IMT and total area after adjusting for established risk factors. The association between VAT and IMT was also independent of WC and WHR. Our differing findings in men and women may be due to an age-associated delay for women in the accumulation of VAT compared with men. We suggest that there is an absolute or relative VAT threshold that is reached in men at an earlier age than in women. Although this was a cross-sectional study, we can only speculate about cause and effect; nevertheless, the sum of evidence would suggest that VAT accumulation precedes the development of atherosclerosis. This is supported by the finding that VAT was associated with IMT, which is a precursor of atherosclerotic plaque development. In conclusion, VAT is strongly associated with a number of measures of carotid atherosclerosis and likely represents an additional risk factor for atherosclerosis in men. Most but not all of this risk can be reflected clinically by either the WC or WHR measures.

Acknowledgment
We would like to thank May Lee for statistical expertise.

Sources of Funding
This research was funded by the Canadian Institutes of Health Research: Institute of Nutrition, Metabolism and Diabetes and the Heart and Stroke Foundation of British Columbia and Yukon. Drs Lear and Humphries are Michael Smith Foundation Health Research Scholars.

Disclosures
None.

References

Downloaded from http://stroke.ahajournals.org/ by guest on October 31, 2017


Visceral Adipose Tissue, a Potential Risk Factor for Carotid Atherosclerosis: Results of the Multicultural Community Health Assessment Trial (M-CHAT)

*Stroke.* 2007;38:2422-2429; originally published online August 2, 2007;
doi: 10.1161/STROKEAHA.107.484113
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/9/2422

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/