Relationship of Metabolic Syndrome to Incident Aortic Valve Calcium and Aortic Valve Calcium Progression: the Multi-Ethnic Study of Atherosclerosis

Ronit Katz, DPhil; Matthew J. Budoff, MD; Junichiro Takasu, MD, PhD; David M. Shavelle, MD; Alain Bertoni MD; Roger S. Blumenthal MD; Pamela Ouyang MBBS; Nathan D. Wong, PhD; and Kevin D. O’Brien, MD

University of Washington, Seattle, WA; Harbor-UCLA Medical Center, Torrance, CA; Wake Forest University, Winston-Salem, NC; Johns Hopkins Medical Institutions, Baltimore, MD; University of California, Irvine, CA

Address Correspondence to: Ronit Katz, DPhil
Department of Biostatistics
University of Washington, Box 354922
6200 NE 74th Street
Seattle, WA 98115
Email: rkatz@u.washington.edu

ABSTRACT

Objective: Metabolic syndrome (MetS) has been associated with increased prevalence of aortic valve calcium (AVC) and with increased progression of aortic stenosis. The purpose of this study was to determine whether MetS is associated with increased risks for the development of new (“incident”) AVC or for progression of established AVC, as assessed by computed tomography (CT).

Research Design and Methods: The relationships of MetS or its components, as well as of diabetes mellitus (DM) to risks for incident AVC or AVC progression were studied among participants with CT scans performed at baseline and at either Year 2 or Year 3 examinations in the Multi-Ethnic Study of Atherosclerosis (MESA).

Results: Of 5,723 MESA participants meeting criteria for inclusion, 1,674 had MetS by Adult Treatment Panel (ATP) III criteria, while 761 had DM. Among the 5,123 participants without baseline AVC, risks for incident AVC; adjusted for time between scans, age, gender, race/ethnicity, LDL, lipid lowering meds and smoking; were increased significantly for MetS (OR 1.67, 95% CI: 1.21, 2.31) or DM (OR 2.06, 95% CI: 1.39, 3.06). In addition, there was an increase in incident AVC risk with increasing number of MetS components. Similar results were found using the International Diabetes Federation MetS criteria. Among the 600 participants (10.5%) with baseline AVC, neither MetS nor DM was associated with AVC progression.

Conclusions: In the MESA cohort, MetS was associated with a significant increase in incident (“new”) AVC, raising the possibility that MetS may be a potential therapeutic target to prevent AVC development.
Metabolic syndrome (MetS) is a collection of clinical and laboratory abnormalities comprised of central adiposity, hypertriglyceridemia, low levels of high density lipoprotein (HDL), elevated blood pressure and/or impaired fasting glucose. Overall MetS prevalence has been estimated at approximately 25% in Western populations, but is almost certainly increasing as a consequence of the worldwide epidemic of obesity. MetS is associated both with increased prevalence of coronary atherosclerosis and increased risk for clinical cardiovascular events.

Cross-sectional US data show that the prevalence of MetS increases with age, suggesting that MetS might contribute to risk for diseases with increased prevalence in the elderly. Examples of these diseases include both atherosclerosis and calcific aortic valve disease (CAVD), which has a prevalence of 25% in those over age 65 years. CAVD is comprised of aortic sclerosis, in which the valve is calcified and thickened but does not obstruct left ventricular outflow, and aortic stenosis, in which obstruction to left ventricular outflow is present. Aortic sclerosis is associated with an approximately 50% increase in cardiovascular events, and aortic stenosis is associated with a 5-year risk of 80% risk for valve replacement surgery or clinical cardiovascular events.

Previous studies have shown that the MetS and diabetes mellitus (DM) are associated with the presence of coronary artery calcium (CAC), as assessed by cardiac computed tomography (CT). In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, in which the overall MetS prevalence by ATP III criteria is 21%, not only is MetS associated with increased prevalence of CT-detected aortic valve calcium (AVC), but also increased number of MetS features is associated with increased AVC prevalence. Metabolic syndrome also has been associated with increased progression of aortic stenosis and accelerated degeneration of bioprosthetic aortic valves.

However, it is not known whether abnormalities in glucose metabolism/insulin resistance, as typified by the clinical syndromes of metabolic syndrome and DM, are associated with increased likelihood of incident (“new”) AVC or AVC progression. Thus, we sought to evaluate potential associations of the MetS and DM, both in the development of incident AVC, as well as in the progression of established AVC, using data from a multi-ethnic cohort of men and women, the Multi Ethnic Study of Atherosclerosis (MESA).

METHODS

A. Study Population. The MESA cohort consists of 6,814 men and women, aged 45–84 years, recruited from six US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) and who were free of clinically evident cardiovascular disease at the time of enrollment (baseline). The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. Participants were excluded if they had a history of any of the following procedures: coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker or defibrillator implantation, or history of any other cardiac surgery. The study was designed to include the following self-identified ethnic groups: whites, African-Americans, Hispanics, and Chinese. Sampling and recruitment procedures have been previously described in detail. Participants were enrolled between August 1, 2000, and July 30, 2002. The institutional
review boards at all participating centers approved the study, and all participants gave informed consent.

Questionnaires were used to obtain information about socio-economic status, medical history, medication, and tobacco use. Smoking was defined as current, former, or never. Waist circumference at the umbilicus was measured to the nearest 0.1 cm using a steel measuring tape (standard 4 oz. tension). Resting blood pressure was measured 3 times with participants in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last two measurements was used in this analysis. Total and HDL cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-hour fast. LDL cholesterol was calculated with the Friedewald equation.(20)

B. Diabetes and Metabolic Syndrome.
Participants were considered to have DM if they met the following criteria: self-reported history of adult onset of DM, fasting glucose $>126$ mg/dL or use of insulin or oral glucose-lowering medications.

Among those without DM, MetS was defined using the Third Adult Treatment Panel of the National Cholesterol Education Program (ATP III)(21) modified criteria. These criteria require: 3 or more of the following 5 criteria for MetS diagnosis: large waist circumference (women $>88$ and men $>102$ cm); elevated triglycerides ($>150$ mg/dL); low HDL-cholesterol (men $<40$ and women $<50$ mg/dL); elevated blood pressure ($>130/85$ mm Hg or self-reported use of medications for hypertension); and impaired fasting glucose (100-125 mg/dL) as defined in the updated AHA/NHLBI guidelines.(1) Results also were analyzed using the International Diabetes Federation (IDF) definition of MetS.

C. Measurement of Aortic Valve Calcium by computed tomography (CT).
AVC was measured using either electron-beam tomography (EBT) (three sites) or multi-detector computed tomography (MDCT) (three sites). A total calcium score was determined by summing individual lesion scores at each anatomic site. Any calcified focus seen extending to the aortic root was deemed AVC, by methodology described previously(22-24) Calcification involving either the aortic or mitral annuli was not included. AVC score was assessed in every patient. The calcium score of each lesion was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield units (Hu) within this area, as described by Agatston.(25) The absence of AVC was deemed a score of 0. Details of the scanning methodology employed for AVC in the MESA study have been reported,(23) and the median interscan variability for Agatston AVC scores within the MESA cohort is 6.4%.(23) All studies were analyzed at the MESA CT reading center at Harbor-UCLA.

To define AVC progression, a second AVC measurement was performed on a random selection of half the cohort at Exam 2 (September, 2002-January, 2004) and on the other half of the cohort at Exam 3 (March, 2004-July, 2005). The mean time between scans was 2.4 (±0.9) years.

D. Data Analyses.
The study population for this analysis includes all MESA participants who had no missing data on any component of MetS with both baseline (Exam 1) and follow-up (Exam 2 or 3) CT scans. After applying these criteria, 5,723 individuals remained for analysis.

Participants were classified by the presence or absence of the MetS and DM, creating three groups (DM, MetS, neither condition). Baseline demographics and laboratory measures were expressed with means and proportions and compared across groups using the Chi square test and analysis of variance (ANOVA). Since the exact date of development of incident AVC is not known, risk time was calculated as the
elapsed time from the baseline to the second or third MESA examination. Unadjusted incident AVC rates were calculated as the number of events divided by person-years at risk, and incident AVC rates were examined according to the three groups of neither condition, MetS or DM.

Two endpoints were created and modeled separately. The primary outcome of interest was incident progression of AVC defined as detectable AVC (AVC score > 0) at follow-up (either exam 2 or 3) among those with no AVC (AVC=0) at the baseline exam. This was treated as a dichotomous end-point and yearly incidence rates were calculated among the three groups. Logistic regression was used to evaluate the association between incident AVC and the MetS and DM groups. First, unadjusted analyses were performed, followed by multivariable modeling that included age, ethnicity and time between scans. A second adjusted model added LDL, lipid lowering medication use, smoking status and scanner type (to account for scanner changes that were made at some of the sites).

A secondary outcome looked at AVC progression defined as an absolute change in AVC score among those with detectable AVC at exam 1. The absolute change was calculated as the difference between AVC score at follow-up and baseline. This was treated as a continuous end-point for which we found that approximately 62 participants (10.3%) had very large residuals, and so therefore used robust linear regression to down weight their influence.(26;27) The same modeling strategy, used for incident AVC as described above, was employed for AVC progression, with additional adjustment for baseline AVC score.

Finally, we also looked at the number of MetS risk factors, treating DM as a separate category in order to explore relative associations of both individual MetS components and of the number of components with incidence and progression of AVC, using those with 0 MetS risk factors as the reference group. As the numbers of participants who had 4 or 5 risk factors were relatively small, they were grouped together.

Interactions were evaluated between the three groups and gender as well as between each of these and race. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed with S-Plus (release 6.1, Insightful Inc, Seattle, WA) and SPSS 15.0.1 software for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

A. Participant characteristics. The study population for these analyses included 5,723 MESA subjects with mean age 62 years (SD=10), 52% were female, 27% were African-American, 12% were Chinese and 22% were Hispanic. Of these, 1674 (29%) met the ATP III definition for MetS and an additional 761 (13%) met the definition for DM. Table 1 shows the distribution of demographics and components of the MetS, by MetS and DM groups Participants with neither MetS nor DM were more likely to be younger, have lower values for BMI, triglycerides and systolic blood pressure, and higher values for HDL. Large waist circumference was the most common component for the MetS (83%) while high blood pressure was the most common component for DM (77%).

Of the 5123 with an AVC = 0 at baseline, 211 (4%) developed an AVC > 0 over follow-up (new “incident” AVC). The breakdown by condition is 88 (3%) for neither MetS nor DM, 79 (5%) for MetS and 44 (7%) for DM (p<0.0001). At baseline there were 600 (11%) participants with AVC>0 and were, therefore, classified as at risk for AVC progression. Of these, 266 (8%) had neither MetS nor DM, 204 (12%) had the MetS only and 130 (17%) had DM (p<0.001). The median baseline AVC score for these 600 participants was 68 Agatston units (IQR=25,
The median (IQR) baseline AVC scores were, by condition, 54 (IQR=22, 144) for neither MetS nor DM, 80 (IQR=25, 178) for MetS and 63 (IQR=27, 113) for DM (p = 0.335).

B. Incident AVC.

1. Rates for Incident AVC by MetS, DM or Neither Condition. Incident (“new”) AVC was higher among those with either MetS or DM as compared to those with neither condition. The yearly rate of incident AVC per 100 person-years (among participants without AVC at baseline) in subjects with the MetS was lower than in those with DM (Figure 1, left). Rates of incident AVC were 2.2%/year in those with ATP III-defined MetS, and 3.0%/yr in those with diabetes, as compared to 1.2%/yr in those with neither (p=0.0001 for ATP III MetS vs. neither condition and p<0.0001 for DM vs. neither condition). Similar results were obtained using the International Diabetes Federation criteria for MetS (Figure 1, right). There was no gender or race interaction for the relationship of either MetS or DM with incident AVC (p-interaction=0.633 and 0.581 respectively).

2. Rates of Incident AVC by Number of MetS Components. Furthermore, there was a graded, linear association between the rate of incident AVC and the number of MetS components. Those with DM had the highest rates of incident AVC (Figure 2).

3. Multivariable Analyses: Odds Ratios for Incident AVC. In logistic regression analyses adjusted for age, gender, ethnicity and time between scans, the odds ratios (ORs) for incident AVC were significantly higher in participants with either the MetS (OR 1.73, 95% CI 1.25 to 2.38) or DM (OR 2.16, 95% CI 1.46 to 3.19), as compared to those with neither condition. These associations persisted after additional adjustment for LDL cholesterol, lipid-lowering medication use, and smoking (MetS: OR 1.67, 95% CI 1.21 to 2.31 and DM: OR 2.06, 95% CI 1.39 to 3.06) (Table 2).

4. Risks for Incident AVC by Number of MetS Components. When examining the ORs for incident AVC by number of MetS components (Figure 3) a similar pattern emerged. As compared to those with no MetS components, participants with three MetS risk factors, 4-5 MetS risk factors and DM had a significantly increased risk of incident AVC in a model adjusted for age, gender, ethnicity, time between scans, LDL, use of lipid lowering medication and smoking (OR 1.88, 95% CI 1.01 to 3.51, OR 2.24, 95% CI 1.16 to 4.30; OR 2.50, 95% CI 1.32 to 4.73, respectively).

5. Incident AVC and Individual MetS Components. Finally, we evaluated the association of individual components of the MetS with incident AVC (Table 3) in those participants without DM. Each of the five MetS components was added in the model simultaneously, and the model then further adjusted for age, gender, ethnicity, time between scans, LDL, lipid lowering medication and smoking. Incident AVC was only related to low HDL (adjusted OR=1.54, 95% CI 1.08 to 2.19). In both unadjusted and demographic adjusted analyses there were associations between IFG and incident AVC, but these associations were attenuated, and of marginal statistical significance, after multivariable adjustment (adjusted OR = 1.36, 95% CI 0.97 to 1.90).

Given the strong relationship of AVC among those with DM we also looked at the association of continuous glucose (per 10mg/dL). For participants without DM, the unadjusted model showed a strong increased risk between glucose and incident AVC (OR=1.33, 95% CI 1.14 to 1.55). Though this risk was attenuated after full adjustment, it remained significantly elevated (OR=1.18, 95% CI 1.01 to 1.40).

C. AVC progression. Among those with AVC at baseline (n=600), the median (IQR)
MetS and Incident AVC

annualized rate of AVC score change was 5.4 (-2.0, 23.0) Agatston units/year. The rate of AVC score change did not vary significantly by MetS or DM status (p=0.341 by Kruskal-Wallis test) (Figure 4). Similarly, when examining the median AVC change by number of MetS components, no pattern emerged (p=0.634 by Kruskal-Wallis test, results not shown). Adjusted robust regression also showed that there was no significant AVC progression in Agatston units per year for either the MetS or DM compared to those with neither condition (results not shown).

DISCUSSION

Only one prospective study has demonstrated an association of MetS with increased risk for prevalent AVC,(16) while retrospective studies have demonstrated that MetS is associated with increased rates of aortic stenosis progression(17) and bioprosthetic valve deterioration.(18) AVC incidence is more important than prevalent AVC because it provides stronger evidence in establishing causality. By separating predictor and outcome variable over time, the longitudinal analysis reduces systematic bias and enhances causal inference. The present study is the first to prospectively examine the relationship of MetS to risks for incident (“new”) AVC and AVC progression. In fully adjusted analyses, both MetS and the number of MetS components were associated strongly with increased risk for incident AVC. We did not, however, identify an association of either MetS or DM with the rate of AVC progression.

The relationship of advanced dysglycemia, i.e., clinical diabetes mellitus, to aortic valve disease pathology has been demonstrated in previous small, retrospective studies reporting associations of diabetes with increased prevalence of aortic valve calcium(28) as well as with increased prevalence(29) and progression(30) of aortic stenosis. More recently, we and others have extended the relationship of less severe dysglycemia, i.e., MetS, to aortic valve disease pathology by demonstrating that MetS is associated not only with increased prevalence of AVC,(16) but also with faster aortic stenosis progression(17) and more rapid deterioration of bioprosthetic aortic valves.(18) The results of the present study further extend the relationship of MetS to early stage aortic valve disease pathology by demonstrating that MetS and MetS components are associated with an increased rate of new (“incident”) AVC. Furthermore, in our study participants with diabetes and the MetS had the highest prevalence of new (“incident”) AVC.

The association of the dysglycemias, including diabetes and MetS with increased risks for prevalent vascular(6;7) and valvular(16) calcification have been established, and interesting studies have begun to elucidate potential mechanisms that may underlie these associations. For example, the key osteogenic regulatory factor, bone morphogenic protein (BMP) 2, is up-regulated by hyperglycemia in vitro.(31;32) BMP2 has been demonstrated to play a role in vascular calcification(33;34) and has been detected in areas of valvular calcification.(35) BMP2 upregulates both “osteogenic” differentiation regulated by the transcription factor, Msx2 and “chondro-ostegenic” differentiation regulated by the transcription factor, Runx2/Cbfa1.(36)

In addition, diabetes is characterized by a pro-oxidant state.(37;38) Not only are oxidized lipoproteins present in human aortic valve lesions,(39) but oxidized lipids also have been shown to up-regulate the rate of calcium nodule formation in valvular cells in vitro.(40) Thus, several potential mechanisms may contribute to the increased risk of incident aortic valve calcium seen with metabolic syndrome and diabetes.
These observational findings also are interesting in light of the recent demonstration that an elevated Total/HDL cholesterol ratio is associated with a consistent increase in relative risk for AVC across all ages in the MESA cohort. Clinical abnormalities of glucose metabolism (which include impaired fasting glucose, impaired glucose tolerance and Type 2 diabetes), are associated with both a progressive increase triglyceride-rich VLDL and a progressive decrease in HDL. Together, these changes increase the Total/HDL cholesterol ratio. Retrospective studies had suggested a potential benefit of statin therapy (which primarily lowers LDL levels) in aortic valve disease. However, the results of subsequent, properly-controlled clinical trials of atorvastatin or of simvastatin plus ezetimibe have been convincingly negative, despite average therapy-related LDL reductions of over 50% in both trials. Because the characteristic MetS lipid abnormalities of high triglycerides and low HDL, result in an increase in the Total/HDL cholesterol ratio, it is not known whether more specifically targeting this MetS-associated dyslipidemia might represent an effective strategy for decreasing the MetS-associated risks for incident AVC.

In addition, recent studies have implicated the renin-angiotensin system, which is up-regulated in MetS, in aortic valve disease pathogenesis. Retrospective studies of angiotensin converting enzyme inhibitor therapy have been mixed in the general population of individuals with aortic sclerosis or aortic stenosis. However, the results of the present study raise the possibility that renin-angiotensin system inhibitor therapy targeted to those with MetS might prove effective at slowing the rate of development of CAVD.

Finally, the association of progressive increase in plasma glucose with progressive increase in risk for incident AVC risk raises the possibility that dysglycemia may represent an additional therapeutic target in this disease, as has been demonstrated for atherosclerosis.

This study has limitations, which include: 1) the possibility of survival bias, since those with clinical CVD were excluded from MESA, 2) statistical power, since the exclusion of those with known CVD from MESA may have also resulted in the exclusion of individuals with MetS(1;2) and AVC, thereby limiting our power to show a relationship between MetS and AVC progression, 3) dichotomization of continuous measures, such as MetS components, which may decrease available information and result in misclassification of exposure, 4) survival bias attributed to participants who did not attend the follow-up exams and 5) given the relatively short follow-up time it is possible that AVC may not have developed between visits or AVC may not have been captured by CT scans. Nonetheless, MetS is defined using cutpoints in clinical practice. Further, it is reassuring that similar results were found using both ATPIII and IDF MetS criteria. In addition, strengths of this study include use of a large, well-characterized, population-based cohort, and of a highly reproducible technique for quantifying aortic valve calcium.

In summary, this study formally tests the hypothesis that MetS is associated with increased risk for the development of AVC. These findings further underscore the clinical importance of identifying MetS in populations without clinical cardiovascular disease and, further, raise the possibility that screening for the presence of aortic valve disease in those with MetS. Finally, these findings suggest future studies targeting the MetS-associated “atherogenic dyslipidemia” of high triglycerides and low HDL, as well as renin-angiotensin system components and/or insulin resistance may identify useful strategies to decrease the development of aortic valve disease.
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Table 1. Characteristics of participants with DM, ATP-III defined MetS, or neither condition.

<table>
<thead>
<tr>
<th></th>
<th>Neither condition (n=3288)</th>
<th>Metabolic syndrome (n=1674)</th>
<th>Diabetes (n=761)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61 (10)</td>
<td>63 (10)</td>
<td>65 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>1601 (49%)</td>
<td>716 (43%)</td>
<td>406 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>1440 (44%)</td>
<td>677 (40%)</td>
<td>151 (20%)</td>
<td></td>
</tr>
<tr>
<td>Chinese-American</td>
<td>428 (13%)</td>
<td>151 (9%)</td>
<td>95 (13%)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>823 (25%)</td>
<td>435 (26%)</td>
<td>285 (38%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>597 (18%)</td>
<td>411 (25%)</td>
<td>230 (30%)</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>93 (9)</td>
<td>101 (10)</td>
<td>155 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 (4.7)</td>
<td>30.9 (5.2)</td>
<td>30.6 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>194 (33)</td>
<td>196 (36)</td>
<td>189 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>56 (15)</td>
<td>44 (11)</td>
<td>46 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>118 (30)</td>
<td>117 (31)</td>
<td>112 (33)</td>
<td>0.111</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>93 [68, 124]</td>
<td>162 [112, 210]</td>
<td>134 [87, 199]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering meds</td>
<td>393 (12%)</td>
<td>326 (20%)</td>
<td>206 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>71 (10)</td>
<td>74 (10)</td>
<td>72 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>121 (20)</td>
<td>133 (21)</td>
<td>132 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-hypertensive meds</td>
<td>714 (22%)</td>
<td>821 (49%)</td>
<td>465 (61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>405 (12%)</td>
<td>229 (14%)</td>
<td>91 (12%)</td>
<td>0.556</td>
</tr>
<tr>
<td>Metabolic Syndrome components*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Obesity (large waist)</td>
<td>1140 (35%)</td>
<td>1393 (83%)</td>
<td>518 (68%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>1263 (38%)</td>
<td>1301 (78%)</td>
<td>584 (77%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low High-density Lipoprotein</td>
<td>547 (17%)</td>
<td>1119 (67%)</td>
<td>385 (51%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High Triglycerides</td>
<td>359 (11%)</td>
<td>994 (59%)</td>
<td>334 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impaired Fasting Glucose (100-125 mg/dl)†</td>
<td>568 (17%)</td>
<td>1013 (61%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*At least 3 of the 5 following conditions define presence of metabolic syndrome: high BP, low HDL, high TG, impaired fasting glucose, or large waist, †ADA definition of IFG.
Table 2. Logistic regression models for the risk of incident AVC (among those free of AVC at baseline) and Diabetes, Metabolic Syndrome (ATP III), or neither condition.

<table>
<thead>
<tr>
<th></th>
<th>Neither condition ( (n=3022) )</th>
<th>Metabolic Syndrome ( (n=1470) )</th>
<th>Diabetes ( (n=631) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR( 95% CI)</td>
<td>OR( 95% CI)</td>
<td>OR( 95% CI)</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>1.0 (ref)</td>
<td>1.84 (1.35, 2.53)</td>
<td>2.54 (1.75, 2.53)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>1.0 (ref)</td>
<td>1.73 (1.25, 2.38)</td>
<td>2.16 (1.46, 3.19)</td>
</tr>
<tr>
<td><strong>Adjusted</strong>†</td>
<td>1.0 (ref)</td>
<td>1.67 (1.21, 2.31)</td>
<td>2.06 (1.39, 3.06)</td>
</tr>
</tbody>
</table>

*adjusted for time between scans, age gender and race/ethnicity  
†adjusted for time between scans, age, gender, race/ethnicity, scanner type, LDL, lipid lowering meds and smoking
Table 3: Logistic regression models for the risk of incident AVC (among those free of AVC at baseline) for each Component of the Metabolic Syndrome in participants free of diabetes.

<table>
<thead>
<tr>
<th></th>
<th>OR 95% CI</th>
<th>Adjusted*</th>
<th>Adjusted†</th>
<th>Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated BP</td>
<td>1.37 (0.96, 1.95)</td>
<td>1.34 (0.94, 1.91)</td>
<td>1.25 (0.87, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Low HDL</td>
<td>1.64 (1.18, 2.28)</td>
<td>1.63 (1.17, 2.27)</td>
<td>1.54 (1.08, 2.19)</td>
<td></td>
</tr>
<tr>
<td>High Triglycerides</td>
<td>1.25 (0.87, 1.80)</td>
<td>1.22 (0.85, 1.76)</td>
<td>0.96 (0.65, 1.42)</td>
<td></td>
</tr>
<tr>
<td>Impaired Fasting Glucose (≥100 mg/dl)</td>
<td>1.53 (1.10, 2.12)</td>
<td>1.49 (1.07, 2.07)</td>
<td>1.36 (0.97, 1.90)</td>
<td></td>
</tr>
<tr>
<td>Abdominal Obesity</td>
<td>1.41 (1.00, 1.99)</td>
<td>1.39 (0.98, 1.96)</td>
<td>1.20 (0.83, 1.72)</td>
<td></td>
</tr>
</tbody>
</table>

*adjusted for time between scans, age gender and race/ethnicity
†adjusted for time between scans, age, gender, race/ethnicity, scanner type, LDL, lipid lowering meds and smoking
‡adjusted further for components of the MetS
Figure 1: Rates of Incident AVC by Diabetes, Metabolic Syndrome, or Neither Condition. Shown are the rates of incident AVC for Diabetes (Dark Gray Bars), Metabolic Syndrome (MetS) (Light Gray Bars) or neither condition (White Bars), using MetS criteria as defined by ATP III (left) or IDF (right). $^+p=0.05$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. 
**Figure 2: Rates of Incident AVC by Number of Metabolic Syndrome Components.** Shown are the rates of incident AVC by number of metabolic syndrome (MetS) components, as defined by ATP III criteria (Fig. 2A) or IDF criteria (Fig. 2B). *p<0.05, **p<0.01, ***p<0.001.

### A. ATP III Criteria

![Graph A](image)

### B. IDF Criteria

![Graph B](image)
Figure 3: Adjusted Odds Ratios for Incident AVC by Number of Metabolic Syndrome Components or Diabetes. Shown are the adjusted odds ratios (ORs, boxes) and corresponding 95% confidence intervals (CIs, bars) for incident AVC by number of ATP III metabolic syndrome (MetS) criteria or diabetes (DM).

<table>
<thead>
<tr>
<th># ATP III MetS Criteria</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Ref)</td>
<td>1.00 (--)</td>
</tr>
<tr>
<td>1</td>
<td>0.98 (0.51, 1.89)</td>
</tr>
<tr>
<td>2</td>
<td>1.50 (0.81, 2.78)</td>
</tr>
<tr>
<td>3</td>
<td>1.88 (1.01, 3.51)</td>
</tr>
<tr>
<td>4-5</td>
<td>2.24 (1.16, 4.30)</td>
</tr>
<tr>
<td>DM</td>
<td>2.50 (1.32, 4.73)</td>
</tr>
</tbody>
</table>
Figure 4: Median AVC Change by Diabetes, Metabolic syndrome, or Neither Condition.
“Box” plots the median AVC progression score (middle horizontal lines) in Agatston units/yr
and corresponding 25th (lower bound of box) and 75th (upper bound of box) percentile ranges.