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Multisite atherosclerosis in subjects with metabolic syndrome and diabetes and relation to cardiovascular events: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background and aims: The extent and relation of multisite atherosclerosis to cardiovascular disease (CVD) in metabolic syndrome (MetS) and diabetes (DM) are not well documented. We examined the extent of multisite atherosclerosis and its prognostic value for CVD events in MetS and DM.

Methods: In CVD-free subjects from the Multi-Ethnic Study of Atherosclerosis, multisite atherosclerosis was measured as: (1) the number of arterial beds involved (coronary calcium>0, abdominal aortic calcium>0, carotid intima-media thickness ≥1mm and ankle brachial index<1 or ≥1.4); (2) a composite score summing the quartile rank for each atherosclerosis measure. Hazard ratios (HRs) and c-statistics were calculated for incident CVD and coronary heart disease (CHD) over 10.6 years.

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AUTHOR CONTRIBUTIONS:

YZ and MAE conducted statistical analysis and drafted the manuscript. NDW supervised the whole project and drafted the manuscript. Other coauthors participated in drafting and revising the manuscripts, providing suggestion on data analysis.

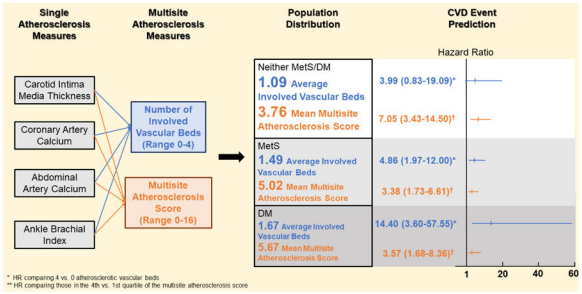
CONFLICT OF INTEREST:

Dr. Matthew J. Budoff receives grant support from General Electric. The other authors have no conflict of interests.

Results: Of 1,675 individuals (mean age 64 years, 51% male), 33.4% had MetS and 15.9% had DM. The number of atherosclerotic sites was higher in those with DM (mean±SD=1.67±1.15) and MetS (1.49±1.12) *versus* neither MetS/DM (1.09±1.09) (p<0.0001). CVD rates per 1000 person-years ranged from 3.5, 8.2, and 10.0 in those with 0 sites positive to 35.1, 79.6 and 103.4 in those with 4 sites positive among neither DM/MetS, MetS and DM groups, respectively. HRs (95% CI) for CVD comparing those with 4 *vs.* 0 atherosclerotic sites were 4.0 (0.8–19.1), 4.9 (2.0–12.0), and 14.4 (3.6–57.6), respectively. C-statistics adding multisite atherosclerosis measures increased over models without the measures and with CIMT or ABI but not CAC.

Conclusions: Multisite atherosclerosis is greater with MetS or DM, and predicts CVD and CHD events. Risk prediction is improved over CIMT and ABI but not CAC.

Graphical Abstract



Keywords

Multisite atherosclerosis; metabolic syndrome; diabetes; cardiovascular disease

Introduction

Individuals with metabolic syndrome (MetS) and/or diabetes mellitus (DM) are at increased risk of cardiovascular disease (CVD) events and mortality[1–3]. In addition, subclinical atherosclerosis is more common based on greater levels of coronary artery calcium (CAC) and carotid intimal-medial thickness (CIMT) [4,5]. We previously showed in the Multiethnic Study of Atherosclerosis (MESA) that CHD risk in those with DM and MetS can be stratified by CAC (and to a lesser extent by CIMT), showing a 10-fold difference in CHD risk between the CAC=0 group and the CAC =400+ group [6]; more recently, the role of CAC in improving long-term risk reclassification, even in those with longer duration DM was demonstrated[7]. It is known that increased levels of CAC, a lower ankle brachial index (ABI), and a higher CIMT predict an increased risk of CHD events and mortality,[8–12] and more recently abdominal aortic calcium (AAC) has been shown to predict higher levels of CHD and CVD events.[13] Moreover, in another MESA investigation, the number of calcified extra-coronary sites was also shown to be associated in a graded fashion with the risk of CHD events and mortality and total mortality.[14]

Not well documented is the distribution of atherosclerosis within different vascular beds in people with MetS or DM and how this adds to CHD and CVD event prediction, and whether there are differences compared to those without MetS or DM. In this study, we aimed at

examining the burden of multisite atherosclerosis and its association as well as prognostic significance for future CVD and CHD events in these individuals using the MESA data.

MATERIALS AND METHODS

Study population

MESA is a prospective community-based study of CVD among 6,814 asymptomatic men and women aged 45–84 recruited from 6 field centers (Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St Paul, MN; and Winston-Salem, NC) between 2000–2002. The study design and methods have previously been presented elsewhere.[15] Subjects were free of known CVD and from one of four race/ethnic groups: Caucasian, African-American, Caucasian, Chinese-American, and Hispanic. Exams 1, 2 and 3 were conducted during 2000–2002, 2003–2004 and 2005–2006, respectively. MESA was approved by the institutional review boards at all participating centers, and all participants provided written informed consent at all study visits.

AAC and CAC were measured in 1,793 participants in either exam 2 or exam 3. ABI was measured in exam 1 and exam 3. CIMT was measured in exam 1. The baseline exam in this study was either exam 2 or exam 3 according to the time of AAC and CAC scanning. For participants followed up from exam 2, ABI and CIMT at exam 1 were used; for participants followed up from exam 3, ABI from exam 3 (no ABI was done at Exam 2) and CIMT from exam 1 (a complete CIMT was only done in exam 1; Exam 2 only had right sided CIMT and no CIMT was done in Exam 3) were used. We finally included 1,675 MESA participants who had valid Exam 2 or 3 data on AAC, CAC, ABI and CIMT measures, as well as follow-up for CVD events. Participants were excluded if they had incident cardiovascular events or revascularization procedures prior to their Exam 2 or 3 CT examination.

Study measurements

Information about participant demographics (including socioeconomic status measured by educational and income level), medical history, current medication use, and family history was collected using standardized questionnaires. Resting blood pressure was measured three times with the average of the last two blood pressures used. Glucose, total cholesterol and high-density lipoprotein cholesterol (HDL-C) measurements were obtained after a 12-hour fast. The Friedewald equation was used to estimate LDL-C.[15]

DM was defined as physician diagnosed DM, or fasting glucose ≥ 126 mg/dL, or taking insulin or taking oral hypoglycemic medications as previously used in MESA.[7] Severity of DM was examined separately according to the following: (1) DM duration < 5 years *vs.* ≥ 5 years; (2) HbA1c < 7% *vs.* ≥ 7%; (3) 10-year ASCVD risk score (PCE) < 7.5% *vs.* ≥ 7.5%; (4) DM + MetS *vs.* DM only. MetS without DM was defined based on the AHA/NHLBI 2005 definition of ≥ 3 risk factors based on: waist circumference (> 88cm in men or > 102 cm in women), HDL-cholesterol (< 40 mg/dl in men or < 50 mg/dl in women), blood pressure (≥ 130/85 mmHg or on antihypertensive medication), fasting triglycerides (≥ 150 mg/dl), and fasting glucose ≥ 100 mg/dl. Participants were stratified by these disease states based on data taken from MESA Exam 2 or 3 concomitant to their CT examination date.

Subclinical atherosclerosis measurements

CAC and AAC were detected with either an electron-beam CT scanner (Chicago, Los Angeles, and New York) or a multi-detector CT system (Baltimore, St Paul, and Winston-Salem), with calcium scores calculated using the Agatston method.[16] CIMT was assessed using B-mode ultrasound (Logiq 700 ultrasound device; General Electric Medical Systems, Waukesha, WI) and calculated as the mean of common carotid IMT and inner carotid IMT (from Exam 1). [17] Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a handheld Doppler instrument with a 5-mHz probe. The higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. A borderline or abnormal ABI, which has been shown to be associated with increased mortality, was defined as < 1.0 or ≥ 1.4.[18]

We defined multisite atherosclerosis in two different ways: (1) *number of involved vascular beds (ranged 0–4):* the primary multisite atherosclerosis index consisted of the number of vascular beds positive for disease defined as follows: 1) CAC >0, 2) AAC >0, 3) CIMT ≥1mm, 4) ABI < 1.0 or ≥ 1.4; (2) *multisite atherosclerosis score:* we assigned a score of 0 to 4 to each measure as: 1) CAC (scored as 0 if absent, or 1–4 according to gender-specific quartiles of positive score); 2) AAC (scored as 0 if absent, or 1–4 according to gender-specific quartiles of positive score); 3) CIMT (0 if in the first gender-specific quintile, 1–4 according to subsequent 2^{nd}-5^{th} quintiles); 4) ABI (scored as 0 if 1.0 ≤ ABI <1.4, 1–4 for the highest to the lowest gender-specific quartiles of ABI <1.0, and 1 if ABI ≥ 1.4). The multisite atherosclerosis score is the sum of the above four scores, with a range of 0 −16. We further divided the multisite atherosclerosis score into quartiles. In the sensitivity analysis, we excluded 16 subjects with ABI ≥1.4 and defined a positive ABI as <1.0.

Ascertainment of CVD and CHD events

After the baseline exam (either exam 2 or 3), we utilized follow-up data for CVD and CHD events through December 2015. The mean follow-up time was 10.6 years. At intervals of 9–12 months, a telephone interview was conducted to inquire about interim hospital admissions, cardiovascular diagnoses, and deaths. An adjudication committee received copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses and conducted next-of-kin interviews for out-of-hospital cardiovascular deaths for verification. Two physicians independently classified and assigned incidence dates. For disagreements, a full mortality and morbidity review committee made the final classification. Follow-up of each subject continued to first event, death, loss to follow-up, or the last follow-up call during 2015, whichever occurred first. Incident CHD included myocardial infarction, resuscitated cardiac arrest, angina, or coronary heart disease death, revascularization, percutaneous coronary intervention and coronary artery bypass grafting; incident CVD included CHD (from above) plus stroke, heart failure, transient ischemic attack, and peripheral vascular disease.

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD) for continuous variables and frequencies for categorical variables. ANOVA tested for continuous variables and Chi-squared tests for categorical variables across disease states. CVD and CHD event rates per 1000 person-years were calculated according to the two different measures of multisite atherosclerosis. Cox regression examined the relationship between both the number of vascular beds positive and the quartiles of the multisite atherosclerosis score in relation to incident CVD and CHD events in the total sample and within each disease group. All models were adjusted for the 2013 AHA/ACC ASCVD Pooled Cohort Equation (PCE) risk score, race/ethnicity and family history of premature CVD.[19] In sensitivity analysis, we adjusted risk factors in the PCE instead of risk scores. We included interaction terms for MetS and DM with each multisite atherosclerosis measure to examine the possible heterogeneous association in each disease group. Single atherosclerosis measures (CAC, AAC, CIMT and ABI) were examined in relation to CVD and CHD events adjusted for each other and other risk factors. In addition, we compared the number of atherosclerotic sites and multisite atherosclerosis score with the measures of atherosclerosis at single site, namely CAC score, AAC score, CIMT and ABI abnormality (Yes/No) regarding their additional predictive value beyond the traditional risk factors using C-statistics for survival data. SAS 9.4 (North Carolina, US) were used for statistical analysis. A p value <0.05 (and p<0.1 for interaction test) was considered as statistically significant.

RESULTS

Out of 1,675 eligible MESA subjects (mean age 64.5 years, 51.2% male, 38.8% Caucasian, 25.6% Hispanic, 21.1% African American, 14.6% Chinese), 560 (33.4%) had MetS and 266 (15.9%) had DM. Participant characteristics in demographics and cardiovascular risk factors significantly differed among the disease groups, except for smoking status (Table 1). Compared to those with neither disease, those with MetS and DM had poorer risk profiles. Those with MetS were less likely male (42.7%), while those with DM were more likely male (57.1%); Caucasians had a lower proportion with DM compared to other races, while Asians had a lower proportion of MetS. A family history of CVD was also less prevalent in those with DM. Compared to those with neither condition, those with MetS and DM were successively more likely to have positive subclinical atherosclerosis measures.

The mean number of sites positive for atherosclerosis was significantly higher in those with DM (mean ± SD =1.67±1.15) and MetS (1.49±1.12) compared to neither condition (1.09±1.09) (Table 2). Those with 0 or 1 vascular beds positive for atherosclerosis were the most common in the non-disease group while those with 3 or 4 beds involved were most common in those with DM. The multisite atherosclerosis score showed a similar distribution pattern. 44.5% of those with neither MetS nor DM were in the lowest quartile of multisite atherosclerosis score while those with DM had the highest percentage of subjects (29.3%) in the highest quartiles. Among those with 476 subjects with only one involved vascular bed, 65.8% had CAC, followed by CIMT, AAC and ABI (Supplemental Fig. 1). Among 723 of those with CAC=0, an average of 70% had no other atherosclerotic vascular sites, with a lower percentage seen in those with DM (56%) and higher in the neither disease group

(78%) (Supplemental Fig. 2). In contrast, among those with coronary calcification only 32% had no other positive atherosclerosis vascular beds. Of the four measures of DM severity, PCE ≥ 7.5% and DM duration ≥ 5 years were significantly associated with the extent of multisite atherosclerosis while HbA1c ≥7% and MetS status were not (Supplemental Table 1).

During the mean follow-up time of 10.6 years, 263 CVD and 175 CHD events occurred, among which 59 were myocardial infarction, 5 were resuscitated cardiac arrest, 61 were angina, 41 were percutaneous coronary intervention, 9 were coronary artery bypass grafting, 13 were other revascularization, 16 were CHD death, 58 were stroke, 41 were heart failure, 17 were transient ischemic attack, 12 were peripheral vascular disease and 3 were other CVD deaths.

We examined CVD and CHD event rates in the total sample, as well as in the three disease groups during a mean follow-up of 10.6 years (Fig. 1). Overall, those with 4 positive atherosclerotic vascular sites had a CVD rate as high as 66.9 per 1,000 person-years, nearly 13 times that of those with 0 atherosclerotic vascular sites (5.2 per 1,000 person-years). Corresponding CHD event rates were 54.5 *vs.* 2.7 per 1,000 person-years. CVD event rates were 5.8, 9.2, 20.7 and 42.3 per 1000 person-years for those in the first, second, third and fourth quartile of multisite atherosclerosis score, respectively. In each disease group, those with more atherosclerotic vascular sites or with higher multisite atherosclerosis scores had higher CVD/CHD event rates. The DM group had the highest CVD/CHD event rates within the same level of extent of multisite atherosclerosis while the group with neither DM/MetS had the lowest event rates. In those whose DM duration ≥ 5 years, CVD/CHD event rates were similar by multisite atherosclerosis measures (Supplemental Fig. 3).

Compared to those with 0 involved vascular beds, HRs for CVD events were incrementally higher for those with 1, 2, 3 or 4 involved vascular beds (Table 3). The HR for those with all 4 atherosclerotic vascular beds *vs.* 0 involved vascular beds was 6.79 (95% CI: 3.63–12.71) overall and ranged from 3.99 to 14.40 in disease groups. For CHD events, corresponding HR was 10.67 (4.97–22.89) overall. Adjusted HRs and 95% CI for total CVD events per 1 unit increase of multisite atherosclerosis score ranged 1.12 to 1.21 among disease groups. HR for CVD and CHD events comparing those in the 4^{th} *vs.* 1^{st} quartile of the multisite atherosclerosis score was higher in neither disease group than in subjects with MetS and DM. This difference of HRs among groups was statistically significant for CHD events (p=0.03 for interaction test). All other interaction tests were not significant. When the PCE score was replaced with the risk factors in PCE, relationships were only slightly attenuated (Supplemental Table 2). After excluding 16 subjects with ABI ≥ 1.4, HRs remained similar to the main results in Table 3. In the subgroup of 723 subjects with CAC=0, neither the number of vascular beds nor the multisite atherosclerosis score was associated with CVD or CHD risk. Among those with DM, HRs of CVD/CHD events and number of mutisite atherosclerosis measures were significantly heterogenous according to DM duration (< 5 years *vs.* ≥ 5 years) and HbA1c (<7% *vs.* ≥ 7%): HR for CVD per 1 number of vascular bed was 2.63 for those with ≥ 5 years of DM, and was only 1.31 among those with < 5 years DM; corresponding HR was 2.70 among those with HbA1c < 7% and was 1.46 among the HbA1c ≥ 7%. HRs for CHD events were similar (p value <0.05 for interaction test). In a

sensitivity analysis, we also showed our Exam 1 CIMT used to similarly predict CHD and CVD events in those whose index exam (based on CAC) was Exam 2 as compared to Exam 3. In addition, the average of exam 1 ABI and exam 3 ABI (1.12±0.12) was similar to that from Exam 1 ABI (1.11±0.12) and HRs for CVD and CHD events in these subgroups were similar to the total sample.

Single atherosclerosis measures (CAC, AAC, CIMT and ABI) were examined in relation to CVD and CHD events adjusted for each other and other risk factors (Supplemental Table 3). Log-transformed CAC scores showed strong associations with CVD and CHD events adjusted for AAC, CIMT, ABI and other risk factors. However, AAC, CIMT and ABI showed non-significant associations with endpoints after adjustment of CAC and other factors, indicating the predictive value of CAC in the presence of other single atherosclerosis measures but not *vice versa*.

We then compared the C-statistics of risk prediction models containing multisite atherosclerosis measures *vs.* each single site atherosclerosis measure (Table 4). The base model included only traditional risk factors. Models 1–4 each included one more single site atherosclerosis measure (CAC,AAC,CIMT or ABI) in addition to traditional risk factors. Model 5 and 6 included one of the multisite atherosclerosis measures (number of atheroclerotic vascular beds or mulisite atherosclerosis score) in addition to traditional risk factors. In the total population, prediction models for CVD, including number of atheroclerotic vascular beds (Model 5), had significantly higher C-statistics than models with traditional risk factors, or traditional risk factors plus CIMT or ABI, while there was non-siginificant improvement over risk models with AAC or CAC; prediction models for CVD events including multisite atherosclerosis score (Model 6) had significantly higher C-statistics than base models, or traditional risk factors plus AAC, CIMT, or ABI while there was non-siginificant improvement over risk models with CAC. Within each disease group, the improvement of Model 5 compared to all other models was not significant among those with MetS. Other comparisons of C-statistics were similar in each disease group. Improvement of C-statistics were similar for CHD events overall and in those with neither disease but was not significant among those with MetS or DM. Meanwhile the two multisite atherosclerosis measures had similar incremental prediction ability as CAC score for both CVD and CHD event. Further sensitivity analysis examining C-statistics of above models in the CAC=0 subgroup showed that none of the subclinical measures (AAC, CIMT, ABI, number of involved vascular beds, or multisite atherosclerosis scores) had significant improved C-statistics over the base model.

DISCUSSION

Numerous studies have established positive associations between single-site atherosclerosis measures and future CVD or CHD risk.[6,8–13] Among them, CAC has normally been found to be the single strongest predictor beyond traditional risk factors.[20] Several studies have examined atherosclerosis at two or more sites and their association with future mortality or events[13,14,21–24]. These studies have limitations: some used atherosclerosis measures with similar features, i.e. measured by calcification[13,14], or plaques[23,24]. Some have failed to included coronary artery atherosclerosis measures[22], and none specifically examined

multisite atherosclerosis in the DM and MetS populations in comparison to those free of DM/MetS.

Our study created multisites atherosclerosis scores that summarized four specific subclinical atherosclerosis measures: AAC, CAC, CIMT and ABI, representing various features of atherosclerotic disease in four different sites of the body, and examining how the quantity of this multisite or "systemic" atherosclerosis varies according to those with DM, MetS or neither condition and predicts subsequent CHD and CVD events in a long follow-up period. As expected, the extent of multisite atherosclerosis was the highest in those with DM and the lowest in the those with neither condition, consistent with the CVD risk distribution among the three groups. Among those with DM, DM duration and their 10-year ASCVD risk score were also related to the extent of multisite atherosclerosis. CAC was found to be the most prevalent atherosclerotic site among the four examined vascular beds and comprised 65% of those with only one atherosclerotic vascular bed. In addition, the absence of coronary calcification was related to less atherosclerosis in other vascular sites.

We also showed a graded relationship between the number of arterial atherosclerosis sites and the multisite atherosclerosis composite score with CHD and CVD event risk in those with and without MetS and DM. While the HRs for incident CHD and CVD events comparing the 4^{th} *vs.* 1^{st} quartile of multisite atherosclerosis score were the greatest in those with neither MetS/DM than in those with MetS or DM, absolute event rates were higher in the reference groups among those with MetS and DM compared to neither condition. Prior work from MESA by Tison and colleages has examined the distribution and relation to CHD events and mortality in those with extracoronary calcification (ECC) in the aortic valve, aortic root, mitral valve, and thoracic aorta, noting a graded relationship of risk for CHD events, CHD mortality, and total mortality associated with the number of ECC sites positive.[14]

When added to tranditional risk factors, the two measures of multisite atherosclerosis, namely the number of atherotic vascular beds and the multisite atherosclerosis score, showed better predictive ability for future CVD and CHD events compared to the risk models with CIMT and ABI and sometimes AAC but not CAC. CAC was previously found to be the strongest pedictor for CVD beyond traditonal risk scores or individual risk factors; our study shows that intergreting other subclinical atherosclerosis measures with CAC as multisite atherosclerosis measures did not further improve the risk discrimination beyond CAC. However, others have noted the extent to which CAC is concentrated in one vessel was found to improve prediction over total CAC scores [25]. Wong et al. found AAC positively correlated with CAC, CIMT and ABI.[26] We find CAC to be the most prevalent atherosclerosis measure and the greatest contributor to the positive atherosclerosis sites. These reasons may explain the positive correlation between the number of atherosclerotic vascular beds and CAC score and such collinearity with CAC leads to similar predictive ability between CAC and multisite atheroslerosis measures. Our findings suggest that screening subclinical atherosclerosis at other sites may provide limited utility for risk stratification beyond CAC, including those with MetS and DM.

Current AHA/ACC guidelines for CVD risk assessment indicate CAC and ABI screening as a class IIb level of evidence B recommendation when the treatment decision is uncertain after global risk estimation such as from the PCE.[19] Concerns about population-wide CAC scanning are the potential risk of radation exposure and issues of cost, although radiation is quite low and the cost of CAC scans at most centers now ranges from under $100 to $250 USD. CIMT is not recommended alone due to limited risk reclaassification potential; however, data are stronger to show its risk-reclassification ability in combination with identification of carotid plaques. In the DM population, the role of CAC score in risk stratification has also been shown[17,27–30] and recent American Diabetes Association guidelines have stated that in adults with diabetes ≥40 years of age, measurement of CAC is reasonable for cardiovascular risk assessment.[31] In addition, in a review of algorithms to screen for subclinical atherosclerosis in those with diabetes, CAC was most frequently used in early stages of evaluation to assist risk classification.[32] Our study demostrated that although the multisite atherosclerosis measures are associated future CVD and CHD risks independent of traditional risk factors, they did not have additional prediction value beyond CAC.

The standardized data collection, including measurement of risk factors and subclinical disease measures across sites is an important strength of MESA, as is the systematic adjudication process for CVD and CHD events. Limitations of our study include the modest sample sizes in certain subgroups, precluding the ability to examine gender or ethnic group differences. Also CAC and AAC were measured using Agataston scores but there may be other measures, e.g. calcium volume score and density score that could offer potential additional information.[33]

We show the extent of multisite atheroscerosis is greater in those with MetS and DM than in those without these conditions. Also, those with more extensive subclinical atheroscerosis in multiple sites suffer higher CVD and CHD risk. However, clinical utility of these measures is limited beyond assessment of CAC in those with MetS and DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AAC	abdominal aortic calcium
CAC	coronary artery calcium
CHD	coronary heart disease
CIMT	carotid intimal-medial thickness
CVD	cardiovascular disease
DM	diabetes mellitus
MetS	metabolic syndrome
PCE	pooled cohort equation

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Highlights – ATH-D-18-01306

- Persons with diabetes or metabolic syndrome have more atherosclerotic sites.
- Cardiovascular disease rates are greater the number of atherosclerotic sites.
- Those with 4 vs. 0 atherosclerotic sites have a 4 to 14-fold greater risk of CVD events.
- Multisite atherosclerosis adds to CVD event prediction, except over coronary calcium.

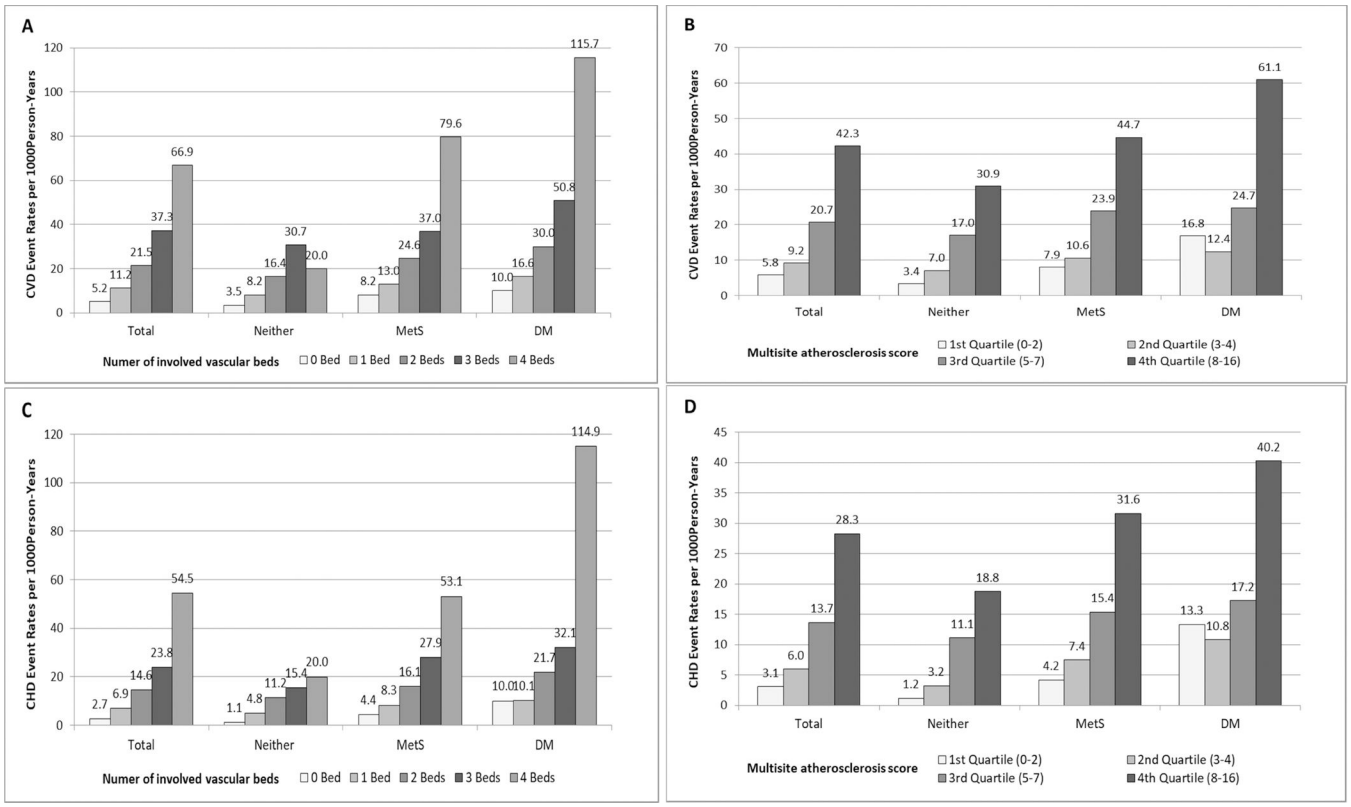

Figure 1.

CVD (A and B) and CHD (C and D) event rates per 1,000 person-years, stratified by disease group and multisite atherosclerosis measures. Persons with more atherosclerotic vascular beds and higher multisite atherosclerosis score showed higher CVD and CHD event rates.

Table 1.

Baseline characteristics across disease groups

	All n=1,675	Neither disease n=849 (50.7%)	Metabolic syndrome n=560 (33.4%)	Diabetes n=266 (15.9%)	*p* value *b*
Baseline age (year)	64.5 ± 9.7	63.4 ± 9.8	65.5 ± 9.4	65.8 ± 9.3	<0.01
Male	857 (51.2%)	466 (54.9%)	239 (42.7%)	152 (57.1%)	<0.01
Ethnicity					<0.01
Caucasian	650 (38.8%)	358 (42.2%)	229 (40.9%)	63 (23.7%)	
Chinese American	244 (14.6%)	147 (17.3%)	62 (11.1%)	35 (13.2%)	
African American	353 (21.1%)	175 (20.6%)	105 (18.8%)	73 (27.4%)	
Hispanic	428 (25.6%)	169 (19.9%)	164 (29.3%)	95 (35.7%)	
Current smoker	182 (10.9%)	97 (11.4%)	54 (9.6%)	31 (11.7%)	0.52
SBP (mm Hg)	123.8 ± 20.6	118.6 ± 19.2	128.8 ± 20.1	129.8 ± 21.5	<0.01
DBP (mm Hg)	70.2 ± 9.90	69.5 ± 9.5	71.4 ± 10.4	70.0 ± 9.9	<0.01
On HTN medication	703 (42.0%)	220 (25.9%)	310 (55.4%)	173 (65.0%)	<0.01
LDL-C (mg/dL)†	112.4 ± 31.1	114.3 ± 29.2	113.6 ± 33.1	103.6 ± 32. 0	<0.01
HDL-C (mg/dL)†	51.7 ± 15.3	57.6 ± 15.9	45.3 ± 11.1	46.1 ± 13.2	<0.01
On lipid medication	403 (24.1%)	153 (18.0%)	152 (27.1%)	98 (36.8%)	<0.01
Triglycerides (mg/dL)†	134.8 ± 98.2	102.1 ± 53.6	167.8 ± 86.0	169.4 ± 171.1	<0.01
Fasting glucose (mg/dL)†	98.1 ± 27.5	88.2 ± 8.0	95.2 ± 10.6	135.6 ± 51.1	<0.01
Waist circumference (cm)	97.7 ± 13.9	91.9 ± 12.1	103.8 ± 12.0	103.6 ± 15.2	<0.01
BMI (kg/m^2)	27.9 ± 5.11	25.9 ± 4.3	30.0 ± 4.6	30.2 ± 6.0	<0.s0 1
Family history of CVD	899 (53.7%)	439 (51.7%)	334 (59.6%)	126 (47.4%)	<0.01
Prevalence of single-site atherosclerosis					
CAC	952 (56.8%)	422 (49.7%)	349 (62.3%)	181 (68.1%)	<0.01
AAC	560 (33.4%)	236 (27.8%)	208 (37.1%)	116 (43.6%)	<0.01
CIMT	523 (31.2%)	203 (23.9%)	209 (37.3%)	111 (41.7%)	<0.01
Abnormal ABI	164 (9.8%)	63 (7.4%)	66 (11.8%)	35 (13.2%)	<0.01
Incident events					
CVD	175 (10.5%)	91 (6.1%)	108 (13.4%)	64 (18.1%)	<0.01
CHD	263 (15.7%)	52 (10.7%)	75 (19.3%)	48 (24.1%)	<0.01

[a] AAC – presence of abdominal aortic calcium on CT scan; ABI – ankle brachial index < 1.0 or ≥ 1.4; BMI -body mass index; CAC – presence of coronary artery calcium on CT scan; CIMT – carotid intimal medial thickness ≥ 1.0 mm (maximal IMT of internal and common carotids); CVD – cardiovascular disease; DBP – diastolic blood pressure; HDL-C – high density lipoprotein-cholesterol; HTN – hypertension; LDL-C – low density lipoprotein-cholesterol; SBP – systolic blood pressure.

Conversion factors into SI units: LDL-C and HDL-C divide by 38.5, triglycerides divide by 88.5, and glucose divide by 18.

[b] Values shown are n (%) or mean ± SD.

[c] Indicates *p* value across disease groups.

[d] Some participants had missing values for some variables: LDL-C n=30; HDL-C n=6; triglycerides n=5; fasting glucose n= 5.

Table 2.

Distribution of multisite atherosclerosis measures overall and each disease group

	All n=1,675	Neither disease n=849 (50.7%)	Metabolic syndrome n=560 (33.4%)	Diabetes n=266 (15.9%)	*P* value [a]
Number of vascular beds positive for atherosclerosis					
Mean number of involved vascular beds	1.31 ± 1.13	1.09 ± 1.09	1.49 ± 1.12	1.67 ± 1.15	<0. 01
0 bed	509 (30.4%)	334 (39.3%)	127 (22.7%)	48 (18.1%)	<0.01
1 bed	476 (28.4%)	227 (26.7%)	169 (30.2%)	80 (30.1%)	
2 beds	391 (23.3%)	179 (21.1%)	149 (26.6%)	63 (23.7%)	
3 beds	255 (15.2%)	97 (11.4%)	95 (17.0%)	63 (23.7%)	
4 beds	44 (2.6%)	12 (1.4%)	20 (3.6%)	12 (4.5%)	
Multisite atherosclerosis score					
Mean score	4.49 ± 3.54	3.76 ± 3.28	5.02 ± 3.54	5.67 ± 3.79	<0.01
Median [inter quartile range]	4 [2–7]	3 [1–6]	4 [2–7]	5 [3–8]	
1st quartile (score 0–2)	593 (35.4%)	378 (44.5%)	155 (27.7%)	60 (22.6%)	<0.01
2nd quartile (score 3–4)	360 (21.5%)	170 (20.0%)	127 (22.7%)	63 (23.7%)	
3rd quartile (score 5–7)	384 (22.9%)	177 (20.9%)	142 (52.4%)	65 (24.4%)	
4th quartile (score 8–16)	338 (20.2%)	124 (14.6%)	136 (24.3%)	78 (29.3%)	

[a] Indicates *p* value across disease groups

Table 3.

Adjusted hazard ratio and 95% confidence interval of number of vascular beds and multisite atherosclerosis score for CVD and CHD events

	All n=1,675	Neither disease n=849 (50.7%)	Metabolic syndrome n=560 (33.4%)	Diabetes n=266 (15.9%)	*p* value for interaction test
			CVD		
Number of involved vascular beds					
0 bed	Reference	Reference	Reference	Reference	0.71
1 bed	1.87 (1.19–2.93) †	2.70 (1.02–4.20) *	1.32 (0.64–2.72)	1.54 (0.55–4.38)	
2 beds	3.04 (1.1.95–4.74) §	3.60 (1.76–7.37) ‡	2.03 (1.01–4.11) *	3.32 (1.18–9.37) *	
3 beds	4.67 (2.95–7.40) §	6.06 (2.90–12.68) §	2.54 (1.20–5.36) *	6.27 (223–17.68) ‡	
4 beds	6.79 (3.63–12.71) §	3.99 (0.83–19.09)	4.86 (1.97–12.00) ‡	14.40 (3.60–57.55) ‡	
Multisite atherosclerosis score					
1st quartile	Reference	Reference	Reference	Reference	0.15
2nd quartile	1.35 (0.85–2.15)	1.89 (0.88–4.06)	1.12 (0.52–2.40)	0.69 (0.27–1.78)	
3rd quartile	2.83 (1.88–4.25) §	4.38 (2.23–8.60) §	2.10 (1.07–4.10) *	1.71 (0.73–3.99)	
4th quartile	4.72 (3.11–7.16) §	7.05 (3.43–14.50) §	3.38 (1.73–6.61) ‡	3.57 (1.68–8.36) †	
			CHD		
Number of involved vascular beds					
0 bed	Reference	Reference	Reference	Reference	0.23
1 bed	2.25 (1.22–4.13) †	4.21 (1.35–13.18) *	1.58 (0.61–4.09)	0.31–2.94)	
2 beds	3.99 (2.21–7.22) §	9.74 (3.16–30.00) §	2.01 (0.91–5.84)	0.88–7.68)	
3 beds	5.66 (3.07–10.45) §	12.44 (3.81–40.65) §	3.18 (1.22–8.26) *	1.26–10.83) *	
4 beds	10.67 (4.97–22.89) §	18.16 (2.98–110.63) †	5.72 (1.85–17.73) †	13.89 (3.25–59.29) ‡	
Multisite atherosclerosis score					
1st quartile	Reference	Reference	Reference	Reference	0.03
2nd quartile	1.69 (0.92–3.09)	2.70 (0.82–8.89)	1.47 (0.56–3.90)	0.80 (0.29–2.25)	
3rd quartile	3.41 (2.00–5.82) §	9.52 (3.44–26.33) §	2.33 (0.96–5.64)	1.39 (0.53–3.67)	
4th quartile	5.71 (3.32–9.83) §	16.14 (5.49–47.44) §	3.98 (1.66–9.54) †	2.78 (1.12–6.90) *	

[a] Hazard ratios were adjusted for Pooled Cohort Equation, ethnicity, lipid medications and family history of CVD

b

[*] p <0.05

[†] p <0.01

[‡] p <0.001

[§] p <0.0001

Table 4.

C-statistics for prediction of CVD and CHD events comparing models with multisite atherosclerosis measures and single site measures

	All n=1,675			Neither disease n=849 (50.7%)			Metabolic syndrome n=560 (33.4%)			Diabetes n=266 (15.9%)		
CVD												
Model	C--statistic	*p* value *	*p* value †	C-statistic	*p* vSalue *	*p* vSalue †	C-statistics	*p* value *	*p* value †	C-statistics	*p* value *	*p* value †
Model 0: RFs	0.72	0.002	<0.001	0.75	0.020	0.007	SS	0.128	0.064	0.66	0.035	0.020
Model 1: RF + CAC	0.76	0.244	0.608	0.78	0.668	0.809	0.73	0.298	0.563	0.72	0.738	0.567
Model 2: RF + AAC	0.74	0.110	0.011	0.76	0.087	0.069	0.71	0.105	0.035	0.72	0.402	0.152
Model 3: RF + CIMT	0.73	0.005	<0.001	0.75	0.025	0.005	0.71	0.136	0.037	0.68	0.050	0.028
Model 4: RF + ABI	0.72	0.005	0.001	0.75	0.031	0.009	0.71	0.314	0.166	0.67	0.036	0.022
Model 5: RF + number of atherosclerotic vascular beds	0.75	/	/	0.78	/	/	0.72	/	/	0.73	/	/
Model 6: RF + multisite	0.75	/	/	0.78	/	/	0.73	/	/	0.74	/	/
CHD												
Model	C-statistic	*p* value *	*p* value †	C-statistic	*p* value *	*p* value †	C-statistics	*p* value *	*p* value †	C-statistics	*p* value *	*p* value †
Model 0: RFs	0.73	0.001	<0.001	0.76	0.047	0.001	0.SS74	0.169	0.108	0.69	0.046	0.042
Model 1: RF + CAC	0.77	0.386	0.995	0.81	0.445	0.941	0.76	0.417	0.592	0.73	0.303	0.550
Model 2: RF + AAC	0.75	0.050	0.002	0.78	0.273	0.023	0.74	0.163	0.108	0.74	0.601	0.835
Model 3: RF + CIMT	0.74	0.002	<0.001	0.77	0.080	<0.001	0.74	0.306	0.133	0.71	0.120	0.167
Model 4: RF + ABI	0.73	0.003	<0.001	0.75	0.033	<0.001	0.74	0.344	0.250	0.71	0.143	0.149
Model 5: RF + number of atherosclerotic vascular beds	0.77	/	/	0.80	/	/	0.75	/	/	0.75	/	/
Model 6: RF + multisite atherosclerosis score	0.77	/	/	0.82	/	/	0.76	/	/	0.74	/	/

[a] AAC – abdominal aortic calcium; ABI – ankle brachial index; CAC – coronary artery calcium; CIMT –carotid intimal medial thickness; RF-risk factor. RFs include age, gender, ethnicity, smoking, SBP, HTN medication, HDL-C, lipid medications and family history of CVD.

b

* *p* value comparing Model 5 *vs.* Model 1–4

† *p* value comparing Model 6 *vs.* Model 1–4.