JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 4, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2011.12.015

# Metabolic Syndrome, Diabetes, and Incidence and Progression of Coronary Calcium

## The Multiethnic Study of Atherosclerosis Study

Nathan D. Wong, PHD, MPH,* Jennifer C. Nelson, PHD,†‡ Tanya Granston, MS,‡ Alain G. Bertoni, MD, MPH,§ Roger S. Blumenthal, MD,‖ J. Jeffrey Carr, MD,§ Alan Guerci, MD,¶ David R. Jacobs, JR, PHD,#§§ Richard Kronmal, PHD,‡ Kiang Liu, PHD,** Mohammed Saad, MD,†† Elizabeth Selvin, PHD, MPH,‖ Russell Tracy, PHD,‡‡ Robert Detrano, MD, PHD*

*Irvine, California; Seattle, Washington; Winston-Salem, North Carolina; Baltimore, Maryland; Roslyn, New York; Minneapolis, Minnesota; Chicago, Illinois; Boston, Massachusetts; Burlington, Vermont; and Oslo, Norway*

OBJECTIVES This study sought to examine and compare the incidence and progression of coronary artery calcium (CAC) among persons with metabolic syndrome (MetS) and diabetes mellitus (DM) versus those with neither condition.

BACKGROUND MetS and DM are associated with subclinical atherosclerosis as evidenced by CAC.

METHODS The MESA (Multiethnic Study of Atherosclerosis) included 6,814 African American, Asian, Caucasian, and Hispanic adults 45 to 84 years of age, who were free of cardiovascular disease at baseline. Of these, 5,662 subjects (51% women, mean age 61.0 ± 10.3 years) received baseline and follow-up (mean 2.4 years) cardiac computed tomography scans. We compared the incidence of CAC in 2,927 subjects without CAC at baseline and progression of CAC in 2,735 subjects with CAC at baseline in those with MetS without DM (25.2%), DM without MetS (3.5%), or both DM and MetS (9.0%) to incidence and progression in subjects with neither MetS nor DM (58%). Progression of CAC was also examined in relation to coronary heart disease events over an additional 4.9 years.

RESULTS Relative to those with neither MetS nor DM, adjusted relative risks (95% confidence intervals [CI]) for incident CAC were 1.7 (95% CI: 1.4 to 2.0), 1.9 (95% CI: 1.4 to 2.4), and 1.8 (95% CI: 1.4 to 2.2) (all $p < 0.01$), and absolute differences in mean progression (volume score) were 7.8 (95% CI: 4.0 to 11.6; $p < 0.01$), 11.6 (95% CI: 2.7 to 20.5; $p < 0.05$), and 22.6 (95% CI: 17.2 to 27.9; $p < 0.01$) for those with MetS without DM, DM without MetS, and both DM and MetS, respectively. Similar findings were seen in analysis using Agatston calcium score. In addition, progression predicted coronary heart disease events in those with MetS without DM (adjusted hazard ratio: 4.1, 95% CI: 2.0 to 8.5, $p < 0.01$) and DM (adjusted hazard ratio: 4.9 [95% CI: 1.3 to 18.4], $p < 0.05$) among those in the highest tertile of CAC increase versus no increase.

CONCLUSIONS Individuals with MetS and DM have a greater incidence and absolute progression of CAC compared with individuals without these conditions, with progression also predicting coronary heart disease events in those with MetS and DM. (J Am Coll Cardiol Img 2012;5:358–66) © 2012 by the American College of Cardiology Foundation

From the *Departments of Medicine and Radiology, University of California, Irvine, California; †Group Health Center for Health Studies, Seattle, Washington; ‡Collaborative Health Studies Coordinating Center, University of Washington, Seattle, Washington; §Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina;

Metabolic syndrome (MetS) and diabetes (DM) predict coronary heart disease (CHD) events and mortality (1–3). Subclinical atherosclerosis as evidenced by coronary artery calcium (CAC) (4–9) and carotid intima-media thickness (10,11) is increased in MetS and DM, but no study has compared the incidence and progression of CAC across these conditions. Progression of CAC may be clinically important because persons experiencing CHD events have greater progression of CAC (12) and, recently, progression of CAC has been shown to predict all-cause mortality (13). The population-based MESA (Multiethnic Study of Atherosclerosis) has demonstrated that most standard CHD risk factors are associated with the incidence and progression of CAC (14).

See page 367

In this report, we compared, in MESA, the incidence and progression of CAC among persons with MetS (but no DM) and DM (with and without MetS) relative to those with neither condition. Our hypothesis was that MetS subjects would be associated with future development and progression of CAC greater than those subjects without MetS would, but less than those with DM would.

## METHODS

**Study population and definitions.** The design of MESA, a prospective epidemiologic study of the prevalence, risk factors, and progression of subclinical cardiovascular disease has been previously published (15). Briefly, 6,814 participants 45 to 84 years of age, who were free of clinical cardiovascular disease and identified as White, African American, Hispanic, or Chinese were recruited from 6 U.S. communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California) from 2000 to 2002. Recruitment included lists of residents, dwellings, telephone exchanges, lists of Medicare beneficiaries, and referrals by participants. Similar numbers of men and women were recruited according to prespecified age and race/ethnicity quotas. All participants gave informed consent, and the study protocol was approved by the Institutional Review Board at each site.

This report includes 5,662 subjects with both baseline (Exam 1) and follow-up (at Exams 2 or 3) computed tomography (CT) scans, available data to define DM or MetS, and with no incident CHD event occurring between baseline and follow-up CT. This resulted in excluding 1,056 subjects who did not have follow-up scans (or were out of protocol), 26 with incomplete data to define DM or MetS, and 70 who had an intervening CHD event. Diabetes was defined as having a fasting glucose ≥7.0 mmol/l (126 mg/dl) or being on insulin or oral hypoglycemic medications. Among nondiabetics, MetS was defined to be present if ≥3 of the following were present: 1) abdominal obesity based on waist circumference >88 cm (35 inches) for women and >102 cm (40 inches) for men; 2) high-density lipoprotein cholesterol <1.0 mmol/l (40 mg/dl) for men or <1.3 mmol/l (50 mg/dl) for women; 3) fasting triglycerides ≥1.7 mmol/l (150 mg/dl); 4) blood pressure of ≥130 mm Hg systolic or ≥85 mm Hg diastolic, or on treatment; or 5) impaired fasting glucose defined as a fasting glucose of 5.55 to 6.99 mmol/l (100 to 125 mg/dl), based on the American Heart Association/National Heart, Lung, and Blood Institute definition (16).

**ABBREVIATIONS AND ACRONYMS**

**CAC** = coronary artery calcium
**CHD** = coronary heart disease
**CI** = confidence interval
**CT** = computed tomography
**DM** = diabetes mellitus
**MetS** = metabolic syndrome
**MI** = myocardial infarction
**RR** = relative risk

**Measurement of CAC.** CAC was measured by electron-beam (3 sites) or multidetector (3 sites) CT. Participants were scanned twice consecutively and scans were read by a trained physician-reader at a centralized reading center (Los Angeles Biomedical Research Institute, Torrance, California). The methodology for acquisition and interpretation of the scans has been published (17). Calcium volume scores (17) and Agatston scores (18) were based on averaging results from each scan and adjusted using a standard calcium phantom (scanned with the participant) to calibrate X-ray attenuation between measurements conducted on different machines (19). Detectable calcium was defined as a CAC score >0. A second scan was performed on one-half

‖Johns Hopkins University, Baltimore, Maryland; ¶The Heart Center, St. Francis Hospital, Roslyn, New York; #Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; **Department of Preventive Medicine, Northwestern University, Chicago, Illinois; ††Carnitas Carney Hospital, Boston, Massachusetts; ‡‡Department of Pathology, University of Vermont, Burlington, Vermont; and the §§University of Oslo, Oslo, Norway. This research was supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute. Dr. Wong reports research funding from Bristol-Myers Squibb through the University of California, Irvine. Dr. Nelson has been a statistical consultant for GlaxoSmithKline. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 24, 2011; revised manuscript received December 8, 2011, accepted December 22, 2011.

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 4, 2012
APRIL 2012:358–66

of the cohort (randomly selected) at a second exam (September 2002 to January 2004) and on the other one-half at a third exam (March 2004 to July 2005), averaging 1.6 and 3.2 years after the first scan, respectively (average 2.4 years between). The distribution of CAC in MESA at baseline by age, sex, and race has been published previously (20).

**Examination data and covariates.** Information on demographics, smoking, medical conditions, and family history was obtained by questionnaire. Height, weight, total and high-density lipoprotein cholesterol, triglycerides, and fasting glucose levels were determined. Resting blood pressure was measured 3 times, with the average of the last 2 measurements used in analysis. Use of cholesterol, blood pressure, and diabetes medications was determined by questionnaire and from medication containers (15).

**Follow-up for CHD events.** The cohort was followed for incident CHD events for a mean of 4.9 ± 1.3 years following the second scan. At intervals of 9 to 12 months, a telephone interviewer inquired 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. Two physicians independently classified and assigned incidence dates. For disagreements, a full mortality and morbidity review committee made the final classification. We followed participants for occurrence of all CHD endpoints, which included myocardial infarction, angina, resuscitated cardiac arrest, or CHD death. CHD death was based on review of hospital records and interviews with families. The reviewers were blinded to CT scan and cardiac magnetic resonance results and used pre-specified criteria.

**Statistical analysis.** Subjects were classified as having: 1) neither MetS nor DM; 2) MetS without DM; 3) DM without MetS; and 4) DM with MetS. The first 2 groups were also classified by number of MetS risk factors (0, 1, 2, 3, and 4 to 5). To assess bivariate associations between these groups, risk factors, and CAC score/volume measures, the chi-square test (for categorical covariates) or an $F$ test from analysis of variance (for continuous covariates) was used. Incident CAC was defined among those without baseline CAC (n = 2,927) as those who developed detectable CAC at the follow-up scan. Absolute progression of CAC was defined among those with CAC at baseline (n = 2,735) as the difference between the CAC volume score on follow-up ($CAC_{FU}$) and that at baseline ($CAC_{BL}$) (14). We used relative risk (RR) regression (21) to obtain asymptotically unbiased estimates of the RR of incident CAC among those free of CAC at baseline. This involved modeling the probability of incident CAC score as an exponential function of risk factors (including each MetS/DM classification relative to the reference group) and performing nonlinear least-squares estimation. To account for misspecification of the variance, we computed model-robust (Huber-White) standard errors. To estimate the absolute progression of CAC among those with detectable CAC at baseline, we used robust linear regression, down-weighting the influence of participants with very large progression to increase model robustness. We also present our findings as relative progression, defined as the median annualized percentage of change in CAC from baseline to follow-up scan. Our analyses also adjusted for time between scans, age, sex, ethnicity, baseline total cholesterol, lipid-lowering medication use, smoking status, and family history of myocardial infarction. Adjusting for the time between scans in a progression model of the absolute change in CAC implicitly standardizes CAC change with respect to time and is equivalent to directly modeling the annualized absolute CAC change. Absolute progression analyses (but not relative progression) were additionally adjusted for the scanner pair used at baseline and follow-up to account for scanner changes over time. As a sensitivity analysis, we also performed progression analyses additionally adjusted for baseline calcium volume score. We also investigated the independent contribution of each MetS component to predicting the incidence or progression of CAC, and we evaluated incidence and progression models that included each of the 5 separate MetS components in the model together. To examine if the composite of MetS/DM still predicted incidence and progression of CAC after accounting for the individual MetS components, we added this in a final model. Finally, Cox proportional hazards regression was used to examine the relation of progression of CAC to the incidence of total CHD events within each disease group separately. All statistical analyses were performed using SAS (version 9.1, SAS Institute, Cary, North Carolina) (22).

## RESULTS

Overall, 5,662 subjects were included (51% women, mean age 61.0 ± 10.3 years): 3,528 (62.3%) had neither MetS nor DM; 1,426 (25.2%) had MetS

without DM; 198 (3.5%) had DM without MetS; and 510 (9.0%) had both MetS and DM. Subjects excluded (n = 70) because of intervening CHD events between baseline and follow-up scans were more likely to have both MetS and DM (23%) and less likely to have neither condition (40%); also, 31% had MetS (without DM) and 6% had DM without MetS. Scanners used for the initial and follow-up scan were electron-beam CT (n = 2,852, 50.4%), multidetector (n = 2,630, 46.4%), and the remainder were electron-beam multidetector (n = 180, 3.2%). Table 1 shows the distribution of demographic and clinical risk factors and calcium scores by the 4-category MetS/DM classification. Systolic and diastolic blood pressure, triglycerides, and waist circumference were highest and high-density lipoprotein cholesterol was lowest in those with MetS, and fasting glucose levels were highest in those with DM (all $p < 0.01$). The prevalence of CAC ranged from 44% to 62% by MetS/DM classification ($p < 0.01$). Among those with CAC, baseline volume score was highest in those with DM.

The unadjusted incidence of CAC increased progressively according to MetS/DM status (Fig. 1). Among men with DM and women with DM plus MetS, incidence of CAC was highest. Incidence was unexpectedly low, however, in women with DM but without MetS (although uncertain because of a low sample size).

Table 2 shows the adjusted RRs for incident CAC for the 4- and 7-category MetS/DM classifications. Compared with those with neither MetS nor DM, those with MetS (without DM) and those with DM (regardless of the presence of MetS) had a greater incidence of CAC. In gender-stratified analyses, results were generally similar to the overall group, except for those with DM (without MetS) where findings were not significant for women. In analyses stratified by ethnicity (results not shown), the RR for incident CAC was significantly greater for those with both DM and MetS among Chinese

**Table 1. Baseline Risk Factor Distributions and Baseline and Follow-Up Coronary Calcium Volume and Scores by MetS and DM Grouping**

| | Exposure | | | |
|---|---|---|---|---|
| | **No MetS, No DM (n = 3,528, 62.3%)** | **MetS, No DM (n = 1,426, 25.2%)** | **No MetS, DM (n = 198, 3.5%)** | **Both MetS and DM (n = 510, 9.0%)** |
| Age, yrs* | 61.0 (10.3) | 62.6 (9.9) | 64.3 (9.6) | 63.9 (9.4) |
| Women* | 51.3 | 58.8 | 31.8 | 53.1 |
| Ethnicity* | | | | |
| Caucasian | 43.2 | 40.1 | 19.7 | 20.6 |
| Chinese American | 12.9 | 9.6 | 17.2 | 9.6 |
| African American | 25.8 | 24.9 | 38.4 | 37.1 |
| Hispanic | 18.2 | 25.4 | 24.8 | 32.8 |
| Current smoker | 12.1 | 13.0 | 13.6 | 12.6 |
| Family history of MI* | 38.6 | 43.4 | 30.3 | 40.6 |
| Fasting glucose, mg/dl* | 86.9 (8.6)† | 95.2 (11.9)† | 133.2 (53.0)† | 152.0 (52.4)† |
| Triglycerides, mg/dl* | 104.1 (57.5)† | 181.7 (88.5)† | 99.7 (49.2)† | 184.1 (152.8)† |
| Systolic BP, mm Hg* | 121.7 (20.2) | 133.1 (20.2) | 126.4 (18.8) | 133.7 (21.6) |
| Diastolic BP, mm Hg* | 71.1 (10.0) | 73.9 (10.4) | 71.9 (10.2) | 71.6 (10.2) |
| Waist circumference, cm* | 93.6 (13.3) | 105.5 (12.4) | 95.7 (11.8) | 108.0 (13.6) |
| HDL cholesterol, mg/dl* | 55.2 (14.9) | 42.9 (10.0) | 53.5 (13.6) | 43.8 (11.7) |
| Total cholesterol, mg/dl* | 194.3 (33.3) | 196.6 (37.5) | 184.5 (33.1) | 189.9 (40.7) |
| Prevalence of calcium* | 43.9 | 53.4 | 57.1 | 61.6 |
| Baseline volume score (all subjects N = 5,662)* | 84.5 ± 261.4 | 107.3 ± 281.6 | 193.2 ± 477.1 | 171.4 ± 364.2 |
| Follow-up volume score (all subjects N = 5,662)* | 112.0 ± 318.7 | 150.3 ± 358.3 | 282.9 ± 609.2 | 257.6 ± 512.4 |
| Baseline volume score (baseline CAC > 0, n = 2,735)* | 192.6 ± 367.5 | 201.0 ± 360.4 | 338.6 ± 592.3 | 278.4 ± 431.0 |
| Follow-up volume score (baseline CAC > 0, n = 2,735)* | 253.9 ± 442.5 | 279.8 ± 452.4 | 493.7 ± 740.4 | 416.6 ± 600.8 |
| Baseline Agatston score (all subjects N = 5,662)* | 106.7 ± 334.6 | 138.5 ± 365.4 | 244.9 ± 608.3 | 221.0 ± 469.6 |
| Follow-up Agatston score (all subjects N = 5,662)* | 143.9 ± 414.2 | 196.1 ± 468.2 | 362.9 ± 784.7 | 337.7 ± 674.9 |
| Baseline Agatston score (baseline CAC > 0, n = 2,735)* | 243.3 ± 471.3 | 259.5 ± 467.9 | 429.1 ± 755.7 | 359.0 ± 555.8 |
| Follow-up Agatston score (baseline CAC > 0, n = 2,735)* | 326.5 ± 576.1 | 365.2 ± 591.2 | 633.5 ± 954.4 | 546.3 ± 791.9 |

Values are n (%), %, or mean ± SD. *$p < 0.001$ across groups. †Tests for association done on mean of log-transformed data. Among analyses in those with CAC >0, disease group sample sizes are 1,547, 761, 113, and 314 for those with neither MetS nor DM, MetS without DM, DM without MetS, and DM plus MetS, respectively.

BP = blood pressure; CAC = coronary artery calcium; DM = diabetes mellitus; HDL = high-density lipoprotein; MetS = metabolic syndrome; MI = myocardial infarction.

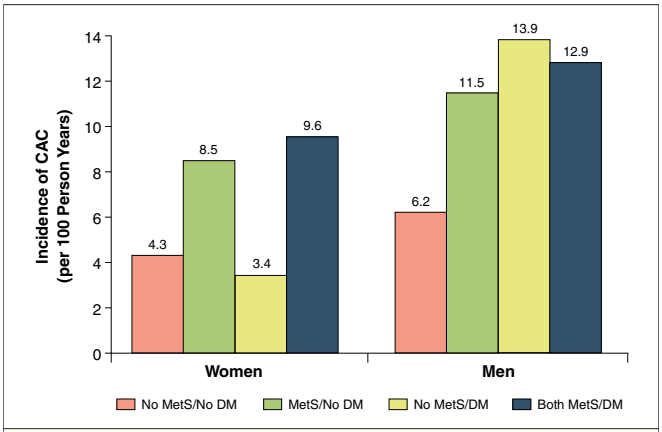


**Figure 1. Incidence of CAC (per 100 Person Years) According to MetS and DM Status, by Sex, Among Persons Without Baseline CAC**

CAC = coronary artery calcium; DM = diabetes mellitus; MetS = metabolic syndrome.

(RR = 3.7, $p < 0.05$), Hispanics (RR = 2.2, $p < 0.01$), and African Americans (RR = 1.8, $p < 0.05$) and was also greater for those with MetS without DM in all ethnic groups (RR = 1.7 to 2.1, $p < 0.05$ to $p < 0.01$). Only in African Americans was incident CAC significantly greater (RR = 2.1, $p < 0.05$) for those with DM (without MetS) versus those without MetS or DM. When examining CAC incidence by number of MetS risk factors, compared with those with no MetS risk factors, those with as few as 2 MetS risk factors had an increased incidence of CAC (RR = 1.5, $p < 0.05$), with increases to RRs of 2.0 or greater in those with 3 or 4 to 5 MetS risk factors, DM without MetS, or both DM and MetS ($p < 0.01$ overall), with stronger associations seen in women.

Among those with baseline CAC, progression of CAC (median annualized percent change in CAC) also increased directly according to MetS/DM status (Fig. 2). Robust linear regression (Table 3) showed those with both MetS and DM as well as those with DM but no MetS to have the greatest progression of CAC, and those with MetS but not DM to have an intermediate level of progression. Women with DM and no MetS and men with both DM and MetS had the greatest degree of progression of CAC. Among each individual ethnic group, progression of CAC was greatest in those with both MetS and DM (mean adjusted volume score differences of 15.3 to 27.1, $p < 0.01$, compared with those with neither MetS nor DM), being highest in Caucasians (23.4) and African Americans (27.1). Of other MetS/DM groups, only DM without MetS in African Americans (31.7, $p < 0.01$) and Chinese (17.5, $p < 0.05$) and MetS without DM in Caucasians (11.0, $p < 0.01$) had progression significantly greater than those with neither MetS nor DM did. In analyses by number of MetS risk factors (Table 4), compared with those with 0 MetS risk factors, progression was greater only for those with ≥3 MetS risk factors, DM, or both DM and MetS. The greatest increases were seen for those with DM with MetS. Although in sex-stratified analyses, this was the case for men, but not for women where DM without MetS had the greatest progression. Results presented according to

**Table 2. RR Regression for Incidence of CAC Among Persons Without CAC at Baseline (n = 2,918) by MetS and DM Grouping and by Number of MetS Risk Factors: Incidence and Risk Ratio Estimates by Sex**

| Exposure | n | Overall Adjusted RR (95% CI)* | n | Women Adjusted RR (95% CI)* | n | Men Adjusted RR (95% CI)* |
|---|---|---|---|---|---|---|
| Both DM and MetS | 196 | 2.0 (1.5 – 2.8)† | 130 | 2.0 (1.3 – 3)† | 66 | 2.0 (1.2 – 3.2)† |
| DM and No MetS | 85 | 1.6 (1.0 – 2.6)‡ | 35 | 0.8 (0.2 – 2.5) | 50 | 2.0 (1.2 – 3.4)† |
| MetS and No DM | 661 | 1.8 (1.5 – 2.2)† | 456 | 1.9 (1.4 – 2.4)† | 205 | 1.7 (1.2 – 2.4)† |
| Neither MetS nor DM | 1,976 | 1.0 | 1,209 | 1.0 | 767 | 1.0 |
| Both DM and MetS | 196 | 2.6 (1.7 – 3.9)† | 130 | 3.1 (1.7 – 5.7)† | 66 | 2.2 (1.2 – 3.9)† |
| DM and No MetS | 85 | 2.1 (1.2 – 3.5)† | 35 | 1.2 (0.3 – 4) | 50 | 2.4 (1.3 – 4.3)† |
| No. of MetS risk factors | | | | | | |
| 4–5 | 216 | 2.2 (1.5 – 3.3)† | 155 | 2.8 (1.6 – 5.1)† | 61 | 1.6 (0.8, – 3) |
| 3 | 445 | 2.3 (1.6 – 3.3)† | 301 | 2.8 (1.6 – 4.8)† | 144 | 2 (1.3 – 3.3)† |
| 2 | 688 | 1.5 (1.1 – 2.1)‡ | 454 | 1.8 (1.1 – 3.1)‡ | 234 | 1.2 (0.7 – 1.9) |
| 1 | 741 | 1.2 (0.9 – 1.7) | 451 | 1.4 (0.8 – 2.4) | 290 | 1.1 (0.7 – 1.8) |
| 0 | 547 | 1.0 | 304 | 1.0 | 243 | 1.0 |

*Estimates adjusted for age, sex (except in sex-stratified analyses), ethnicity, time between scans, smoking status, total cholesterol, lipid-lowering medications use, family history of MI, and scanner pair. †$p < 0.01$ compared reference group of neither MetS nor DM, or No MetS risk factors; 9 observations were missing covariates and are not reflected in these analyses. ‡$p < 0.05$.
CI = confidence interval; RR = relative risk; other abbreviations as in Table 1.

Agatston score showed similar findings with the expected greater magnitude of differences due to absolute Agatston scores being higher than volume scores.

When additionally adjusting for baseline volume score, our findings regarding progression of CAC were not substantially affected and remained statistically significant. Mean differences (compared with those subjects with neither MetS nor DM) in volume score change were 6.2 (95% confidence interval [CI]: 3.0 to 9.4) for those with MetS without DM, 13.4 (95% CI: 6.5 to 20.4) for those with DM without MetS, and 14.6 (95% CI: 10.1 to 19.1) for those with DM and MetS (all $p < 0.01$).

We also evaluated the relation of individual MetS components to the incidence and progression of CAC. With all components in the model simultaneously, only increased waist circumference (adjusted RR = 1.4, $p < 0.001$) and increased glucose (adjusted RR = 1.25, $p < 0.01$) predicted CAC incidence. Progression of CAC was driven most strongly by elevated glucose (volume score change of 10.7, $p < 0.001$) and blood pressure (volume score change of 5.8, $p < 0.05$).

When examining the relation of CAC progression to total CHD events in each disease group, total CHD events per 1,000 person years increased progressively according to extent of change in volume score in those with neither MetS nor DM, those with MetS and no DM, and those with both MetS and DM (Fig. 3). Corresponding hazard ratios, adjusted for age, sex, ethnicity, and risk factors, compared with those subjects with no or negative change, were increased in those subjects in the second and third tertiles of positive CAC change: 4.5 (95% CI: 2.2 to 9.4), $p < 0.01$ and 7.6 (95% CI: 3.7 to 15.5), $p < 0.01$, respectively in those subjects with neither MetS nor DM, 2.3 (95% CI: 1.0 to 4.9), $p < 0.05$ and 4.1 (95% CI: 2.0 to 8.5), $p < 0.01$, respectively, in those subjects with MetS and no DM and 4.0 (95% CI: 1.1 to 14.9), $p < 0.05$ and 4.9 (95% CI: 1.3 to 18.4), $p < 0.05$, respectively, in those subjects with both MetS and DM. After additional adjustment for baseline CAC, these estimates were similar: 4.5 (95% CI: 2.2 to 9.4), $p < 0.01$ and 7.0 (3.4 to 14.7), $p < 0.01$, respectively, in those subjects with neither MetS nor DM, 2.3 (95% CI: 1.1 to 5.0), $p < 0.05$ and 3.5 (95% CI: 1.6 to 7.3), $p < 0.01$, respectively, in those subjects with MetS and no DM and 3.9

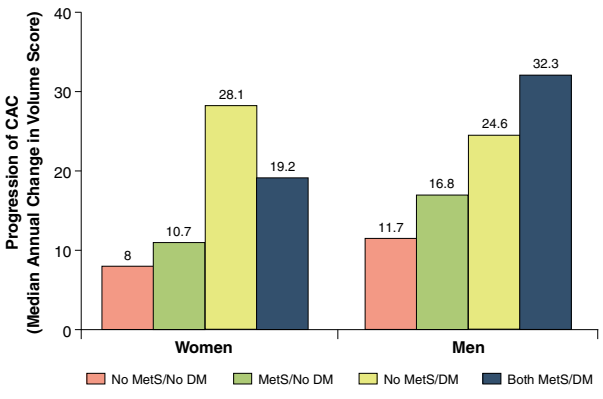


**Figure 2. Progression of CAC (Mean Unadjusted Absolute Change in Volume Score) According to MetS and DM Status, by Sex, Among Persons Without Baseline CAC**

Abbreviations as in Figure 1.

**Table 3. Multivariable Analysis of Absolute Progression of Coronary Calcium by MetS/DM Status Among Persons With CAC at Baseline (n = 2,729)**

| | | All | | Women | | Men | |
|---|---|---|---|---|---|---|---|
| | Exposure | n | Robust Difference in Mean Progression (95% CI) | n | Robust Difference in Mean Progression (95% CI) | n | Robust Difference in Mean Progression (95% CI) |
| Agatston score | Both | 314 | 29.3 (21.8 – 36.7)* | 141 | 20.8 (11.7 – 29.8)* | 173 | 35.4 (24.0 – 46.8)* |
| | DM and No MetS | 113 | 25.0 (13.5 – 36.5)* | 28 | 38.6 (20.4 – 56.8)* | 85 | 21.9 (6.4 – 37.4)* |
| | MetS and Nondiabetic | 758 | 8.2 (3.0 – 13.5)* | 379 | 3.6 ( – 2.6 – 9.8) | 379 | 15.4 (7.2 – 23.7)* |
| | Neither MetS nor DM | 1,544 | 0.0 (0.0 – 0.0) | 596 | 0.0 (0.0 – 0.0) | 948 | 0.0 (0.0 – 0.0) |
| Volume score | Both | 314 | 22.4 (16.9 – 27.9)* | 141 | 16.3 (9.4 – 23.2)* | 173 | 26.6 (18.3 – 34.9)* |
| | DM and No MetS | 113 | 16.7 (8.1 – 25.2)* | 28 | 26.4 (12.5 – 40.4)* | 85 | 14.2 (3.0 – 25.5)† |
| | MetS and Nondiabetic | 758 | 7.4 (3.5 – 11.3)* | 379 | 5.2 (0.5 – 10.0)† | 379 | 10.8 (4.8 – 16.8)* |
| | Neither MetS nor DM | 1,544 | 0.0 (0.0 – 0.0) | 596 | 0.0 (0.0 – 0.0) | 948 | 0.0 (0.0 – 0.0) |

Adjusted for age, sex (except in sex-stratified analyses), ethnicity, time between scans, smoking status, total cholesterol, lipid-lowering medications use, family history of MI, and scanner pair. Relative risk regression adjusted for age, sex (except in sex-stratified analyses), ethnicity, time between scans, smoking status, total cholesterol, lipid-lowering medications use, family history of MI, and scanner pair; reference group comprises those with neither MetS nor DM. *$p < 0.01$ compared with neither MetS nor DM; 6 observations were missing covariates and are not reflected in these analyses. †$p < 0.05$.

Abbreviations as in Tables 1 and 2.

**Table 4. Multivariable Analysis of Absolute Progression of Coronary Calcium by Number of MetS Risk Factors/DM Status Among Persons With CAC at Baseline (n = 2,729)**

| | | All | | Women | | Men | |
|---|---|---|---|---|---|---|---|
| | Exposure | n | Robust Difference in Mean Progression (95% CI) | n | Robust Difference in Mean Progression (95% CI) | n | Robust Difference in Mean Progression (95% CI) |
| Agatston score | Both | 314 | 32.4 (22.5–42.2)* | 141 | 20.8 (7.9–33.6)* | 173 | 38.8 (24.3–53.3)* |
| | DM and no MetS | 113 | 28.0 (14.8–41.1)* | 28 | 38.5 (18.5–58.6)* | 85 | 25.3 (7.4–43.2)* |
| | 4–5 MetS risks | 294 | 12.9 (3.1–22.8)† | 159 | 5.7 (−6.7–18.0) | 135 | 23.0 (7.7–38.2)* |
| | 3 MetS risks | 464 | 10.5 (1.5–19.4)† | 220 | 4.3 (−7.5–16.0) | 244 | 16.8 (3.7–29.9)† |
| | 2 MetS risks | 650 | 5.9 (−2.5–14.4) | 292 | 4.5 (−6.8–15.7) | 358 | 4.5 (−7.7–16.6) |
| | 1 MetS risk | 613 | 1.6 (−6.9–10.0) | 217 | −2.1 (−13.6–9.5) | 396 | 4.2 (−7.8–16.2) |
| | 0 MetS risks | 281 | 0.0 (0.0–0.0) | 87 | 0.0 (0.0–0.0) | 194 | 0.0 (0.0–0.0) |
| Volume score | Both | 314 | 23.7 (16.3–31.0)* | 141 | 18.5 (8.5–28.5)* | 173 | 26.9 (16.3–37.4)* |
| | DM and no MetS | 113 | 17.9 (8.1–27.7)* | 28 | 28.9 (13.3–44.5)* | 85 | 14.6 (1.5–27.6)† |
| | 4–5 MetS risks | 294 | 10.9 (3.5–18.2)* | 159 | 10.1 (0.5–19.7)† | 135 | 14.6 (3.5–25.7)* |
| | 3 MetS risks | 464 | 7.5 (0.8–14.1)† | 220 | 6.4 (−2.7–15.5) | 244 | 9.5 (−0.0–19.1) |
| | 2 MetS risks | 650 | 3.9 (−2.4–10.1) | 292 | 5.8 (−3.0–14.6) | 358 | 1.2 (−7.7–10.0) |
| | 1 MetS risk | 613 | −1.0 (−7.3–5.3) | 217 | −0.4 (−9.4–8.6) | 396 | −0.3 (−9.0–8.4) |
| | 0 MetS risks | 281 | 0.0 (0.0–0.0) | 87 | 0.0 (0.0–0.0) | 194 | 0.0 (0.0–0.0) |

Relative risk regression adjusted for age, sex (except in sex-stratified analyses), ethnicity, time between scans, smoking status, total cholesterol, lipid-lowering medications use, family history of MI, and scanner. Reference group comprises those with 0 MetS risk factors. *$p < 0.01$ compared to 0 MetS risk factors; 6 observations were missing covariates and are not reflected in these analyses. †$p < 0.05$.
Abbreviations as in Tables 1 and 2.

(95% CI: 1.0 to 14.8), $p < 0.05$ and 4.0 (95% CI: 0.95 to 16.0), p = NS, respectively, in those with both MetS and DM.

## DISCUSSION

In the MESA, persons with MetS or DM have a greater incidence and progression of CAC than those subjects without MetS, and those with MetS (without DM) have an intermediate incidence and progression. Also, insulin resistance (23) and DM (24,25) have been shown in smaller or selected cohorts to relate to progression of CAC, and in those with DM, a glycated hemoglobin ≥7% predicted progression of CAC (26). Progression of CAC has also been shown to predict total mortality over baseline risk factors and CAC (13). In our study, we also found increased progression of CAC in persons with MetS and DM to predict future CHD events.

The baseline calcium score, a strong predictor of CAC progression, is important to understanding the relationship of MetS and DM to progression of CAC (23,27). Because MetS is associated with an intermediate level and DM the highest level of CAC, we might expect a similar pattern for progression. Whereas baseline CAC could be considered a confounder, it can also be considered part of the causal pathway between risk factors such as MetS and DM and the progression of CAC. Such persons likely had more rapid progression of CAC to begin with and continued to show greater future progression; hence, including baseline CAC in the model could condition out the effects that variables of interest (in this case, MetS and DM) may have up to baseline (14). In our study, however, secondary analyses additionally adjusted for baseline calcium volume showed

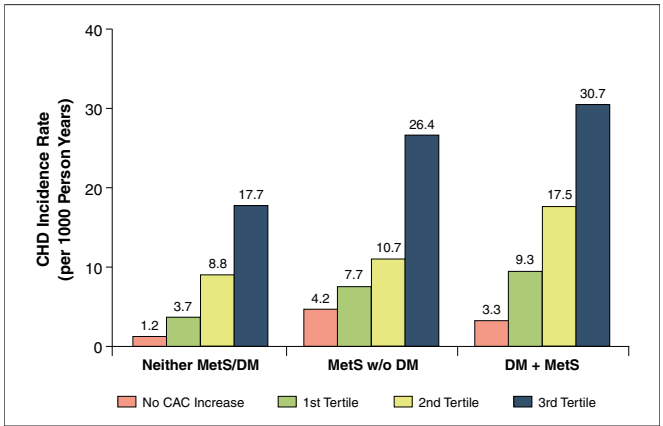


**Figure 3. CHD Event Rates (per 1,000 Person Years) According to Tertile of CAC Progression by Presence of MetS and DM**

Data are not shown for persons with DM without MetS because of an insufficient number of coronary heart disease (CHD) events. Abbreviations as in Figure 1.

only a slight attenuation of our findings, which remained largely significant.

In addition, the choice of the scale for continuous progression (e.g., absolute vs. relative change) and the failure to account for outlying progressors may markedly influence the results obtained (14). Similar to Kronmal et al. (14), we use absolute progression as our primary outcome and account for outlying progressors using robust regression modeling techniques, which limits the influence of outlying observations (e.g., fast progressors).

Strengths of MESA include its large sample size, ethnic diversity, and community-based recruitment. The prospective design allows for assessment of baseline factors including MetS and DM in relation to development and progression of CAC, as well as the evaluation of progression of CAC in relation to subsequent CHD events. In addition, MESA had standardized protocols for scanning and interpretation of scans. Importantly, our estimate of progression of CAC was based only on the change between 2 scans done an average of about 2 years apart, from which progression was then annualized. However, this assumes a linear relation of progression with time, which may or may not be the case, hence results could be different had more measures been available and/or if the time between scans was greater. Also, exclusion of a small number of individuals (n = 70) who had intervening CHD events may have influenced the results. Such persons were more likely to have DM and MetS, progression of CAC, as well as CHD events, so our findings relating progression to events could have been underestimated (thus conservative). However, our intention was to look at the natural progression of CAC not interrupted by CHD events, thus we kept our group homogenous by excluding such individuals. As there is controversy of which definition may be most appropriate, or even whether MetS should be considered a syndrome (28–30), our findings may have differed had other definitions for MetS been used.

Persons with both MetS and DM have the greatest incidence and degree of progression of CAC. Those with MetS without DM have an incidence and degree of progression of CAC intermediate between those with DM and without these conditions. Moreover, in those with MetS or DM, progression predicts future CHD event risk.

**Acknowledgments**

The authors thank the other investigators, staff, and participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The authors also thank Ms. Yanting Luo for her assistance with data analysis and manuscript preparation.

**Reprint requests and correspondence:** Dr. Nathan D. Wong, Heart Disease Prevention Program, Department of Medicine, Sprague Hall 112, University of California, Irvine, California 92697-4101. *E-mail: ndwong@uci.edu.*

## REFERENCES

1. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.
2. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–9.
3. Malik S, Wong ND, Franklin SS, et al. The impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1239–44.
4. Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. J Am Coll Cardiol 2003;41:1547–53.
5. Ellison RC, Zhang Y, Wagenknecht LE, et al. Relation of the metabolic syndrome to calcified atherosclerotic plaque in the coronary arteries and aorta. Am J Cardiol 2005;95:1180–6.
6. Bertoni AG, Wong ND, Shea S, et al. Insulin resistance, metabolic syndrome, and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2007;30:2951–6.
7. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with Type 1 diabetes. Diabetes 2000;49:1571–8.
8. Mileke CH, Shields JP, Broemeling LD. Coronary artery calcium, coronary artery disease, and diabetes. Diabetes Res Clin Practice 2001;53:55–61.
9. Hoff JA, Quinn L, Sevrukov A, et al. The prevalence of coronary calcium among diabetic individuals without known coronary artery disease. J Am Coll Cardiol 2003;41:1008–12.
10. McNeill AM, Rosamond WD, Girman CJ, et al. Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). Am J Cardiol 2004;94:1249–54.
11. Tzou WS, Douglas PS, Srinivasan SR. Increased subclinical atherosclerosis in young adults with metabolic syndrome: the Bogalusa Heart Study. J Am Coll Cardiol 2005;46:457–63.
12. Raggi P, Cooil B, Shaw LJ, et al. Progression of coronary calcium on serial electron beam tomography scanning is greater in patients with future myocardial infarction. Am J Cardiol 2003;92:827–9.
13. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010;3:1229–36.
14. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–30.

15. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
16. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart Lung and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
17. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in Population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005; 234:35–43.
18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
19. Nelson JC, Detrano R, Kronmal RA, et al. Measuring coronary calcium on CT images adjusted for attenuation differences. Radiology 2005;235:403–14.
20. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. The distribution of coronary artery calcium by race, gender and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006;113:30–7.
21. Lumley T, Kronmal RA, Ma S. Relative risk regression in medical research: models, contrasts, estimators and algorithms. UW Biostatistics Working Paper Series 293. Seattle, WA: University of Washington, 2006. Available at: http://www.bepress.com/uwbiostat/paper293. Accessed December 6, 2011.
22. SAS Institute. SAS Procedures Guide, Version 6.12. 3rd edition. Cary, NC: SAS Institute, 1995.
23. Lee KK, Fortman SP, Fair JM, et al. Insulin resistance independently predicts the progression of coronary artery calcium. Am Heart J 2009;157: 939–45.
24. Budoff MJ, Yu D, Nasir K, et al. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005;149:695–700.
25. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M. Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. Hypertension 2005;46:238–43.
26. Anand DV, Lim E, Darko D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes role of glycemic control and inflammatory/vascular calcification markers. J Am Coll Cardiol 2007;50:2218–25.
27. Wong ND, Kawakubo M, LaBree L, Azen SP, Kiang M, Detrano R. Relation of coronary calcium progression and control of lipids according to National Cholesterol Education Program Guidelines. Am J Cardiol 2004;94:431–6.
28. Khan R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28:2289–304.
29. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 2006;47:1093–100.
30. Vaidya D, Szklo M, Liu K, Schreiner PJ, Bertoni AG, Ouyang P. Defining the metabolic syndrome construct: Multi-Ethnic Study of Atherosclerosis (MESA) cross-sectional analysis. Diabetes Care 2007;30:2086–90.

**Key Words:** atherosclerosis ■ calcification ■ diabetes ■ risk factors.