# Effect of Metabolic Syndrome on Coronary Artery Stenosis and Plaque Characteristics as Assessed with 64–Detector Row Cardiac CT[1]

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**Purpose:** To investigate the prevalence and severity of subclinical coronary atherosclerosis and plaque characteristics in asymptomatic subjects according to the presence or absence of metabolic syndrome (MS) with multidetector computed tomography (CT).

**Materials and Methods:** This study was approved and the requirement for informed patient consent was waived by the local institutional review board. Degree of coronary artery stenosis, multivessel involvement, and plaque characteristics, as well as coronary artery calcium score (CACS), were assessed with 64–detector row CT in 3000 age- and sex-matched asymptomatic individuals (mean age, 50.2 years ± 8.9 [standard deviation]; age range, 30–79 years). Anthropometric and metabolic profiles were also measured. Multivariate logistic regression analyses were performed to identify variables related to coronary atherosclerosis and plaque types.

**Results:** Subjects with MS had significant coronary artery stenosis (>50% stenosis), multivessel involvement, more positive remodeling, more atherosclerotic coronary segments, and higher CACS than subjects without MS ($P < .01$ for all). Mixed and noncalcified plaques were also more prominent in subjects with MS than in those without MS (14.2% ± 4.4 vs 7.6% ± 3.1 and 13.1% ± 4.3 vs 7.3% ± 2.8, respectively; $P < .01$ for both). After adjustment for confounding factors, MS was strongly associated with significant coronary artery stenosis, multivessel involvement, and mixed plaque.

**Conclusion:** Multidetector CT is useful in the early diagnosis and evaluation of subclinical coronary atherosclerosis in asymptomatic patients with MS; however, future prospective studies are needed to address the clinical implications of these findings.



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Metabolic syndrome (MS) is a cluster of cardiovascular disease risk factors, including visceral obesity, dyslipidemia, hypertension, and impaired glucose metabolism, that have been known to be associated with cardiovascular morbidity and mortality (1–3). The prevalence of MS is increasing worldwide, as the pandemic is no longer confined to United States (4–6). Thus, MS presents a major challenge for public health professionals because of its global social and economic burden.

In the past few decades, coronary artery calcium score (CACS) screening has been used to evaluate the risk of cardiovascular diseases. However, CACS is limited in the detection of noncalcified plaque, and as a result it fails to represent the entire spectrum of atherosclerotic plaques. CACS screening is also inadequate in the evaluation of the degree of stenosis by the plaque. Noncalcified plaque is recognized as a rupture-prone plaque that is associated with the occurrence of acute coronary syndrome and should be accurately assessed with appropriate imaging techniques.

In this respect, coronary computed tomographic (CT) angiography performed with a scanner that has more than 64 detector rows yields additional information on CACS with regard to the degree of stenosis and detailed plaque composition, including noncalcified plaque with high diagnostic accuracy (7–9). However, to our knowledge, studies that focus on evaluation of plaque with multidetector CT in a sizable asymptomatic population were previously unavailable. In addition, there are limited data on the clinical implications of plaque characteristics evaluated with multidetector CT in asymptomatic patients with MS (10). Furthermore, although there have been several studies in which researchers examined Asian subjects with electron-beam CT and found a similar prevalence of subclinical atherosclerosis when compared with that in white subjects (11), there is a paucity of comprehensive assessment of coronary arteries in Asian patients with multidetector CT. Thus, we investigated the prevalence and severity of subclinical coronary atherosclerosis and plaque characteristics in asymptomatic subjects according to the presence or absence of MS with 64–detector row CT.

## Advances in Knowledge

- Screening of asymptomatic patients with coronary CT angiography performed with 64–detector row CT enabled identification of the significant association of metabolic syndrome (MS) with higher prevalence of subclinical coronary atherosclerosis, significant coronary stenosis, multivessel involvement, and more positive remodeling.
- After adjusting for confounding factors, including anthropometric and biochemical parameters, MS was strongly associated with significant coronary stenosis and multivessel involvement.
- For each type of plaque, the presence of MS remained a significant independent predictor of mixed plaque after adjustment of various confounding factors.

## Materials and Methods

### Subjects

This study was approved by the institutional review board of Seoul National University Bundang Hospital; the patient informed consent requirement was waived. All patients underwent multidetector CT after they had agreed to participate in the study and had provided informed consent after being informed of the possible risks of CT scanning. Subjects in whom CT angiography was performed with a 64–detector row scanner as part of a routine health check-up were recruited from Seoul National University Bundang Hospital from 2006 to 2007. We included 4281 middle-aged (older than 30 years) asymptomatic individuals who were free of known coronary heart disease, which was determined on the basis of patient history. We excluded subjects who had chest pain or discomfort before enrollment ($n$ = 24), those with a history of myocardial infarction or angina ($n$ = 9) or stent or coronary artery bypass grafting ($n$ = 7), those with cancer ($n$ = 34), and those with insufficient medical records ($n$ = 57). Finally, a total of 4150 self-referred middle-aged asymptomatic subjects were enrolled.

From this group, we consecutively allocated each individual into either the MS group (500 men, 500 women) or the non-MS group (1000 men, 1000 women) by matching age (within 3 years), sex (male-to-female ratio, 1:1), and MS criteria (MS-to-non-MS ratio, 1:2). In accordance with National Cholesterol Education Program–Adult Treatment Panel III criteria (12), an individual may receive a diagnosis of MS if he or she meets three or more of the following five criteria: *(a)* Waist circumference

## Implication for Patient Care

- Multidetector CT coronary angiography may be of importance in the early diagnosis and evaluation of subclinical atherosclerosis in asymptomatic individuals with MS, particularly in assessment of plaque characteristics and severity.

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**Abbreviations:**
BMI = body mass index
CACS = coronary artery calcium score
CAD = coronary artery disease
hsCRP = high-sensitivity C-reactive protein
LDL = low-density lipoprotein
MS = metabolic syndrome
SBP = systolic blood pressure

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Potential conflicts of interest are listed at the end of this article.

is more than 90 cm in men and more than 80 cm in women with the International Obesity Task Force criteria for the Asian-Pacific population to determine waist circumference criteria (13). *(b)* Triglyceride level is 150 mg/dL (1.7 mmol/L) or higher. *(c)* High-density lipoprotein cholesterol level is less than 40 mg/dL (1.0 mmol/L) in men and less than 50 mg/dL (1.3 mmol/L) in women. *(d)* Blood pressure is 130/85 mm Hg or higher or the patient uses antihypertensive medication. *(e)* Fasting glucose level is 110 mg/dL (6.1 mmol/L) or higher or the patient takes medication (insulin or oral agents).

### Measurement of Anthropometric and Biochemical Parameters

Height (measured in centimeters) and body weight (measured in kilograms) were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as weight divided by height (in meters) squared. Waist circumference was measured to the nearest 0.1 cm at the narrowest point between the lower limit of the ribcage and the iliac crest. Blood pressure was recorded three times between 7 AM and 9 AM and after the subjects had been in a relaxed state for at least 10 minutes. A 5-minute resting period was allowed between each measurement. After a 14-hour overnight fast, venous blood samples were drawn from the antecubital vein. Plasma was separated immediately with centrifugation (2000 rpm for 20 minutes at 4°C), and biochemical measurements were obtained immediately. The fasting plasma concentrations of glucose, blood urea nitrogen, creatinine, total cholesterol, triglycerides, and high-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol were measured enzymatically with a Hitachi 747 chemical analyzer (Hitachi, Tokyo, Japan). Hemoglobin A1c level was measured with an immunoturbidimetric assay performed with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland). Serum high-sensitivity C-reactive protein (hsCRP) levels were measured with a high-sensitivity automated immunoturbidimetric method (CRP II Latex ×2; Denka Seiken, Tokyo, Japan).

Clinical information, including current medications, and family history of premature coronary artery disease (CAD) (first-degree relative younger than 55 years for men and younger than 65 years for women) were systematically acquired via personal interviews. Smoking status was defined as follows: Patients were classified as current smokers if they currently smoked for at least 1 year. Patients were classified as nonsmokers if they had never smoked. Patients were classified as ex-smokers if they had smoked but quit. Patients were classified as nondrinkers or current drinkers by determining their average daily alcohol consumption. This was calculated by multiplying the number of drinks typically consumed by the fraction of days that alcohol was consumed. Nondrinkers were those who had not consumed alcohol within the past 30 days (14). Diabetes mellitus was defined as a fasting plasma glucose level of 126 mg/dL (6.99 mmol/L) or higher or current antidiabetic treatment (15). Hypertension was defined as two consecutive systolic/diastolic blood pressure measures greater than 140/90 mm Hg or current treatment with antihypertensive medication. Dyslipidemia was defined as an LDL-cholesterol level of 160 mg/dL or higher or current use of a lipid-lowering agent. Global CAD risk was estimated with the Framingham risk score, which was calculated on the basis of National Cholesterol Education Program–Adult Treatment Panel III guidelines (16).

### Cardiac Multidetector CT Data Acquisition

Subjects with a heart rate higher than 70 beats per minute received 10–30 mg of intravenous esmolol (Brevibloc; Jeil Pharmaceutical, Seoul, Korea) before multidetector CT. With the exception of patients with contraindications to nitroglycerin, 0.6 mg of nitroglycerine was immediately administered sublingually before contrast material injection (17).

In all patients, CT angiography was performed with a 64–detector row CT scanner (Brilliance 64; Philips Medical Systems, Best, the Netherlands) with 64 × 0.625-mm section collimation and 420-msec rotation time. Scanning for CACS was performed with 120-kV tube voltage, 220-mA tube current, and 2.5-mm scection thickness. CT angiography was performed with 120-kV tube voltage and 800-mA tube current with electrocardiographically gated dose modulation. An 80-mL bolus of iomeprol (Iomeron 400; Bracco, Milan, Italy) was intravenously injected at a rate of 4 mL/sec and followed by a 50-mL saline chaser. Images were initially reconstructed in the middiastolic phase (75% of the RR interval) of the cardiac cycle. Additional reconstructions were performed at other cardiac phases during retrospectively gated helical acquisitions if motion artifacts were observed. The CACS was calculated with the Agaston score by using a threshold of 130 HU on precontrast images (18).

### Multidetector CT Image Analysis

All images were analyzed independently in a blind fashion by two experienced radiologists (S.I.C., E.J.C.; 7 and 5 years of experience with cardiac multidetector CT) using a three-dimensional workstation (Brilliance; Philips Medical Systems). After independent evaluations were performed, a consensus interpretation regarding the final multidetector CT diagnosis was reached. Each lesion was identified by using a multiplanar reconstruction technique and maximum intensity projection of the short-axis and two- and four-chamber views. We analyzed the plaque characteristics on a per-segment basis according to the modified American Heart Association classification (19). All coronary segments larger than 1.5 mm in diameter were assessed. Image quality was evaluated on a per-segment basis by using a four-point grading scale (1, absence of any artifacts; 2, slight artifacts but fully evaluable; 3, artifacts but evaluable; 4, noninterpretable). A segment with noninterpretable image quality was not included in the analysis. Thereafter, the interpretable segments were evaluated for plaque severity and characteristics. Plaques were identified as structures larger than 1 $mm^2$ within or adjacent to the vessel lumen, which should be

clearly distinguished from the lumen and surrounding epicardial fat.

For multidetector CT image analysis, we evaluated the number of atherosclerotic coronary segments, degree of stenosis, multivessel involvement, plaque type, and presence of additional positive remodeling. For the number of atherosclerotic coronary segments, coronary segments with any plaque were included. The coronary artery stenosis was estimated when the contrast material–enhanced portion of the coronary lumen was semiautomatically traced at the maximal stenotic site and compared with the mean value for the proximal and distal reference sites (20). Stenosis of more than 50% was defined as significant. Multivessel disease was defined as the presence of stenosis of more than 50% in at least two vessels. Plaque type was classified as follows: *(a)* Plaques that contained calcified tissue that comprised more than 50% of the plaque area (attenuation >130 HU on native images) were classified as calcified. *(b)* Plaques with less than 50% calcium in the plaque area were classified as mixed. *(c)* Plaques without any calcium were classified as noncalcified lesions (20). Positive remodeling was defined as the compensatory increase (>1.05) in local vessel size in response to plaque determined by cross-sectional vessel area at plaque divided by the reference site (21).

### Statistical Analysis

All data are expressed as the mean ± standard deviation. Baseline characteristics and multidetector CT findings were compared by using the Student *t* test or a $\chi^2$ test (Tables 1, 2). Multivariate logistic regression analyses were performed to identify variables related to coronary artery lesions and each type of plaque (Tables 3, 4). Statistical significance was defined as $P < .05$. All analyses were performed with the SPSS, version 12.0, software package (SPSS, Chicago, Ill).

## Results

Clinical characteristics and biochemical parameters were compared according to the presence of MS (Table 1). The mean age of study participants was 50.2 years ± 8.9 (range, 30–79 years), without a significant difference in age between men (mean, 49.8 years ± 9.3; range, 30–78 years) and women (mean, 50.4 years ± 10.2; range, 30–79 years) ($P > .05$). When grouped according to presence of MS, the mean age of patients in the MS group was significantly higher than that of patients in the non-MS group for both men and women.

Body weight and BMI were greater in the MS group than in the non-MS group. Hemoglobin A1c, total cholesterol, LDL cholesterol, and hsCRP levels and Framingham risk score were significantly higher in the MS group than in the non-MS group. The prevalence of hypertension, diabetes mellitus, and dyslipidemia was higher in the MS group than in the non-MS group. Consequently, more medications for regulation of blood pressure, glucose, and lipid levels were taken by subjects with MS than by those without MS (hypertension, 63.6% vs 14.7%; diabetes mellitus, 34.6% vs 5.3%; dyslipidemia, 14.3% vs 4.6%; $P < .001$ for all).

Multidetector CT findings (Table 2) show that subjects with MS had more significant subclinical coronary atherosclerosis than did subjects without MS; this was true for both men and women. Analysis of plaque types revealed all kinds of plaque types were greater in the MS group than in the non-MS group, with the exception of calcified plaques in women. Among plaque types, there was more than twice the difference in mixed plaques according to the presence of MS. Subjects with MS also had more positive remodeling and a higher calcium score in coronary arteries. A sex comparison indicates that twice as many men had significant subclinical coronary atherosclerosis than did women in both the MS group and the non-MS group (Table 2).

Analysis of atherosclerosis per segment revealed that patients with MS had a greater number of atherosclerotic coronary segments than did those without MS for both men and women (Fig 1). In addition, the Framingham risk score was different among plaque types in the MS group; it was highest in patients with the mixed plaque type and lowest in those with the calcified plaque type. However, there was no significant association between Framingham risk score and plaque type in the non-MS group (Fig 2).

We used the multivariate logistic regression models to investigate independent risk factors for significant coronary stenosis, multivessel involvement, and high CACS (>100). After we adjusted for confounding factors, including anthropometric and biochemical parameters, MS was strongly associated with significant coronary stenosis and multivessel involvement (Table 3). MS was also associated with high CACS after adjusting for age and sex; however, after adjusting for age, sex, BMI, SBP, smoking status, alcohol consumption, and family history of CAD and further adjusting for total cholesterol, LDL cholesterol, serum creatinine, and hsCRP levels, MS was not associated with high CACS. Old age, male sex, and high SBP were associated with high CACS after adjusting for age, sex, BMI, SBP, smoking status, alcohol consumption, and family history of CAD (Table 3).

For each type of plaque, similar logistic regression analysis was performed. The presence of MS was not associated with calcified plaque after we adjusted for BMI, SBP, smoking status, alcohol consumption, and family history of CAD or after we further adjusted for total cholesterol, LDL cholesterol, serum creatinine, and hsCRP levels (Table 4). Old age and male sex were found to increase the risk of calcified plaque.

Subjects with MS were at higher risk for noncalcified plaque after we adjusted for age and sex (odds ratio, 1.632; $P < .05$) and further adjusted for BMI, SBP, smoking status, alcohol consumption, and family history of CAD (odds ratio, 1.534; $P < .05$) (Table 4). However, further adjustment with total cholesterol, LDL cholesterol, creatinine, and hsCRP levels resulted in slightly attenuated association between MS and noncalcified plaque. Old age and male sex were also associated with noncalcified plaque.

## Table 1

### Comparison of Clinical and Biochemical Characteristics According to MS

| | Men ($n = 1500$) | | | Women ($n = 1500$) | | |
|---|---|---|---|---|---|---|
| Characteristic | Non-MS Group ($n = 1000$) | MS Group ($n = 500$) | *P* Value | Non-MS Group ($n = 1000$) | MS Group ($n = 500$) | *P* Value |
| Age (y) | 49.6 ± 9.0 | 50.2 ± 8.9 | NS | 49.7 ± 9.6 | 50.7 ± 6.5 | NS |
| BMI (kg/m$^2$) | 24.4 ± 2.3 | 26.7 ± 2.4 | <.01 | 22.7 ± 2.6 | 25.1 ± 2.5 | <.05 |
| Waist circumference (cm) | 86.0 ± 6.5 | 93.2 ± 5.9 | <.01 | 79.5 ± 7.8 | 87.0 ± 6.5 | <.01 |
| SBP (mm Hg) | 115.3 ± 12.6 | 127.8 ± 14.5 | <.01 | 110.8 ± 13.8 | 126.5 ± 13.8 | <.01 |
| Diastolic blood pressure (mm Hg) | 75.9 ± 9.8 | 84.7 ± 9.7 | <.01 | 67.3 ± 11.2 | 76.6 ± 11.4 | <.01 |
| Fasting glucose level (mg/dL)* | 95.5 ± 20.1 | 122.4 ± 42.1 | <.01 | 89.7 ± 13.4 | 111.2 ± 30.0 | <.01 |
| Hemoglobin A1c level (%)† | 5.7 ± 0.6 | 6.4 ± 1.2 | <.01 | 5.6 ± 0.5 | 6.4 ± 1.1 | <.01 |
| Total cholesterol level (mg/dL)‡ | 204.9 ± 32.1 | 216.8 ± 38.4 | <.05 | 200.4 ± 35.7 | 221.6 ± 36.9 | <.01 |
| Triglyceride level (mg/dL)§ | 137.6 ± 79.9 | 231.6 ± 132.6 | <.01 | 85.4 ± 36.9 | 186.5 ± 77.5 | <.01 |
| High-density lipoprotein cholesterol level (mg/dL)‡ | 47.8 ± 12.6 | 41.7 ± 11.5 | <.01 | 57.3 ± 14.2 | 49.4 ± 11.4 | <.01 |
| LDL cholesterol level (mg/dL)‡ | 120.6 ± 30.0 | 124.5 ± 33.2 | NS | 116.1 ± 32.7 | 126.9 ± 35.5 | <.01 |
| Creatinine level (mg/dL)‖ | 1.2 ± 0.1 | 1.2 ± 0.1 | NS | 0.9 ± 0.1 | 1.0 ± 0.1 | NS |
| hsCRP level (mg/dL)# | 0.14 ± 0.36 | 0.23 ± 0.47 | <.01 | 0.09 ± 0.21 | 0.18 ± 0.22 | <.01 |
| Framingham risk score | 2.8 ± 2.6 | 8.5 ± 2.7 | <.01 | 0.7 ± 5.7 | 6.7 ± 3.4 | <.01 |
| Current smoker (%) | 37.7 | 46.6 | <.01 | 5.1 | 7.2 | NS |
| Current drinker (%) | 42.3 | 51.2 | <.01 | 17.7 | 21.8 | NS |
| Hypertension (%) | 18.0 | 71.6 | <.01 | 12.4 | 69.8 | <.01 |
| Diabetes mellitus (%) | 6.5 | 41.2 | <.01 | 5.7 | 37.2 | <.01 |
| Dyslipidemia (%) | 13.4 | 34.4 | <.01 | 9.0 | 21.6 | <.01 |
| Family history of premature CAD (%) | 12.7 | 17.2 | <.01 | 11.3 | 18.6 | <.01 |

Note.—Unless otherwise indicated, data are mean ± standard deviation. NS = not significant, SBP = systolic blood pressure.

* To convert to SI units (millimoles per liter), multiply by 0.05551.

† To convert to SI units (proportion of total hemoglobin), multiply by 0.01.

‡ To convert to SI units (millimoles per liter), multiply by 0.02586.

§ To convert to SI units (millimoles per liter), multiply by 0.01129.

‖ To convert to SI units (micromoles per liter), multiply by 88.4.

# To convert to SI units (nanomoles per liter), multiply by 9.524.

## Table 2

### Comparison of Cardiac CT Findings According to MS

| | Men ($n = 1500$) | | | Women ($n = 1500$) | | |
|---|---|---|---|---|---|---|
| Finding | Non-MS Group ($n = 1000$) | MS Group ($n = 500$) | *P* Value | Non-MS Group ($n = 1000$) | MS Group ($n = 500$) | *P* Value |
| Atherosclerotic coronary segments (any plaque) | 24.7 | 38.9 | <.01 | 8.7 | 20.8 | <.01 |
| Plaque type | | | | | | |
| Calcified | 9.9 | 18.7 | .007 | 4.5 | 6.3 | NS |
| Noncalcified | 11.8 | 17.6 | .021 | 1.3 | 2.2 | <.05 |
| Mixed | 9.7 | 18.2 | <.01 | 5.4 | 10.1 | <.01 |
| Significant coronary artery stenosis | 7.7 | 14.2 | <.01 | 2.9 | 6.4 | <.01 |
| Multivessel disease | 1.5 | 4.4 | <.01 | 1.3 | 2.6 | <.01 |
| Positive remodeling | 5.5 | 7.4 | <.01 | 2.3 | 4.6 | <.01 |
| CACS* | 20.1 ± 4.7 | 42.8 ± 16.3 | <.01 | 5.7 ± 2.5 | 18.3 ± 7.8 | <.01 |

Note.—Unless otherwise indicated, data are percentages. NS = not significant.

* Data are mean ± standard deviation.

**Table 3**

**Multivariate Logistic Regression Models for Variables Associated with Coronary Artery Lesions**

| | Significant Stenosis | | Multivessel Involvement | | High CACS | |
|---|---|---|---|---|---|---|
| Variable | Odds Ratio | *P* Value | Odds Ratio | *P* Value | Odds Ratio | *P* Value |
| | Adjusted for Age and Sex | | | | | |
| Age | 1.132 (1.128, 1.165) | .002 | 1.132 (1.028, 1.265) | .012 | 1.121 (1.098, 1.145) | .001 |
| Sex | 4.765 (2.603, 8.242) | .001 | 4.265 (2.603, 8.242) | .006 | 5.765 (3.603, 9.222) | .001 |
| MS | 1.987 (1.367, 4.244) | .008 | 1.527 (1.267, 3.843) | .012 | 1.791 (1.167, 2.749) | .008 |
| | Adjusted for Age, Sex, BMI, SBP, Smoking, Alcohol, and Family History of CAD | | | | | |
| Age | 1.138 (1.079, 1.137) | .002 | 1.201 (1.123, 1.543) | .022 | 1.128 (1.103, 1.153) | .001 |
| Sex | 4.328 (2.589, 9.919) | .001 | 3.628 (2.282, 5.712) | .010 | 4.728 (2.828, 7.905) | .001 |
| BMI | 1.034 (1.003, 1.132) | .032 | 1.014 (0.973, 1.123) | .043 | ND | ND |
| Smoking | 1.543 (1.106, 2.632) | .026 | 1.443 (1.126, 2.532) | .034 | 1.630 (1.065, 2.494) | .024 |
| MS | 1.739 (1.467, 3.249) | .012 | 1.413 (1.242, 3.492) | .043 | ND | ND |
| | Adjusted for Age, Sex, BMI, SBP, Smoking, Alcohol, Family History of CAD, Total Cholesterol Level, LDL Cholesterol Level, Creatinine Level, and hsCRP | | | | | |
| Age | 1.164 (1.127, 1.256) | .002 | 1.134 (1.027, 1.356) | .032 | 1.134 (1.107, 1.161) | .001 |
| Sex | 4.365 (2.344, 8.799) | .003 | 3.462 (1.978, 7.340) | .002 | 4.420 (2.323, 8.409) | .001 |
| Smoking | 1.522 (1.256, 4.391) | .043 | 1.222 (1.102, 3.291) | .049 | 1.512 (0.956, 2.391) | .077 |
| SBP | 1.016 (1.020, 1.053) | .039 | 1.024 (1.005, 1.062) | .024 | 1.015 (1.001, 1.030) | .042 |
| MS | 1.621 (1.267, 3.042) | .017 | 1.462 (1.128, 4.014) | .036 | ND | ND |

Note.—Data in parentheses are 95% confidence intervals. Factors with a *P* value of less than 0.1 remained in the models. ND = no data.

**Table 4**

**Multivariate Logistic Regression Models for Variables Associated with Plaque Types**

| | Calcified Plaque | | Noncalcified Plaque | | Mixed Plaque | |
|---|---|---|---|---|---|---|
| Variable | Odds Ratio | *P* Value | Odds Ratio | *P* Value | Odds Ratio | *P* Value |
| | Adjusted for Age and Sex | | | | | |
| Age | 1.104 (1.077, 1.131) | .001 | 1.059 (1.033, 1.084) | .001 | 1.102 (1.077, 1.128) | .001 |
| Sex | 5.452 (2.935, 10.129) | .001 | 4.427 (2.328, 8.417) | .001 | 5.056 (2.856, 8,950) | .001 |
| MS | 1.246 (0.926, 2.271) | .084 | 1.632 (1.102, 3.987) | .023 | 2.290 (1.421, 3.690) | .001 |
| | Adjusted for Age, Sex, BMI, SBP, Smoking, Alcohol, and Family History of CAD | | | | | |
| Age | 1.108 (1.079, 1.137) | .001 | 1.060 (1.034, 1.088) | .001 | 1.107 (1.080, 1.135) | .001 |
| Sex | 5.068 (2.589, 9.919) | .001 | 3.969 (1.953, 8.068) | .001 | 4.019 (2.160, 7.478) | .001 |
| BMI | 1.561 (0.951, 2.562) | .078 | ND | ND | ND | ND |
| Smoking | ND | ND | ND | ND | 1.675 (1.022, 2.748) | .041 |
| MS | 1.212 (0.875, 2.394) | .104 | 1.534 (1.023, 3.452) | .043 | 1.848 (1.370, 3.190) | .018 |
| | Adjusted for Age, Sex, BMI, SBP, Smoking, Alcohol, Family History of CAD, Total Cholesterol Level, LDL Cholesterol Level, Creatinine Level, and hsCRP | | | | | |
| Age | 1.112 (1.082, 1.144) | .001 | 1.062 (1.034, 1.090) | .001 | 1.115 (1.086, 1.146) | .001 |
| Sex | 7.849 (3.361, 18.332) | .001 | 2.959 (1.275, 6.868) | .012 | 2.832 (1.328, 6.041) | .007 |
| Smoking | ND | ND | ND | ND | 1.673 (0.973, 2.878) | .063 |
| SBP | ND | ND | 1.646 (0.956, 3.153) | .078 | 2.741 (1.523, 4.934) | .001 |
| MS | 1.323 (0.752, 2.987) | .164 | 1.364 (0.986, 2.871) | .065 | 1.734 (1.247, 3.172) | .034 |

Note.—Data in parentheses are 95% confidence intervals. Factors with a *P* value of less than 0.1 remained in the models. ND = no data.

MS was significantly associated with mixed plaque after we adjusted for the same variables (Table 4). Old age, male sex, and a high hsCRP level were also risk factors for mixed plaque.

## Discussion

In this cardiac multidetector CT study, asymptomatic patients with MS had a higher prevalence of atherosclerotic coronary segments, significant coronary stenosis, multivessel involvement, and positive remodeling than did subjects without MS. In addition, MS was strongly associated with significant coronary

**Figure 1**

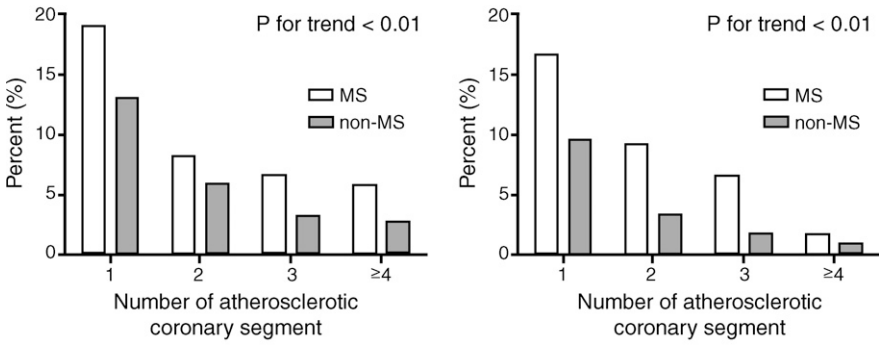


**Figure 1:** Graphs show prevalence comparison of the number of atherosclerotic coronary segments according to group in **(a)** men and **(b)** women.

**Figure 2**

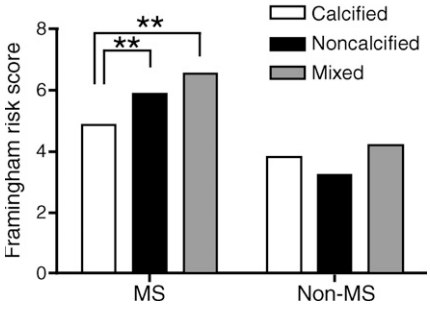


**Figure 2:** Graph shows Framingham risk score by plaque characteristics according to group. ** = $P < .01$.

stenosis and multivessel involvement after we adjusted for confounding factors, including anthropometric and biochemical parameters. For each type of plaque, the presence of MS remained a significant independent predictor of mixed plaque.

Although there are a number of reports on the prognostic value of CACS with CAD (22,23), there have been few studies focused on coronary artery plaque, which is the direct cause of CAD, in which the authors performed multidetector CT in a sizable asymptomatic population. Mitsutake et al (24) reported that MS is associated with coronary stenosis at multidetector CT, but they did not analyze plaque types. Thus, we believe that we are the first to report plaque characteristics, as well as prevalence and severity of subclinical coronary atherosclerosis, in asymptomatic subjects with multidetector CT.

Several trials have been performed to assess coronary plaque composition (8,25). A previous study in which researchers used 16–detector row CT revealed that patients with diabetes had more mixed plaque in their coronary arteries than did subject without diabetes (26). With 64–detector row CT, we reported similar results, namely, that noncalcified and mixed plaques were observed more frequently in subjects with diabetes than in subjects with normal glucose regulation (27). In addition, several studies have suggested that traditional risk factors are closely associated with mixed or noncalcified plaque. Bamberg et al (28) reported that hyperlipidemia and a family history of CAD were significantly associated with the extent of noncalcified plaques. Hausleiter et al (20) found an association between a higher total or LDL cholesterol level and a diagnosis of diabetes with the presence of noncalcified plaque as assessed with 64–detector row CT. Our group also reported that smoking history and LDL cholesterol level were predictors of noncalcified or mixed plaque (29).

Furthermore, the results of relatively recent studies have supported the potential risk of noncalcified or mixed plaque as assessed with coronary multidetector CT in the evaluation of plaque instability. Pundziute et al (30) showed that thin-cap fibroatheromas, which are markers of plaque vulnerability, were most frequently observed in patients who had plaque with mixed characteristics. In the current study, noncalcified or mixed plaques were significantly associated with higher levels of hsCRP, which is an inflammatory biomarker of plaque instability (31). In addition, Motoyama et al (32) reported that noncalcified plaques and spotty calcifications occurred more frequently in patients with acute coronary syndrome than in those with stable angina. In another study with multidetector CT, noncalcified and mixed plaques were associated with a higher incidence of all-cause mortality than were calcified plaques (33). These data suggest that noncalcified or mixed plaques are more vulnerable in triggering plaque rupture and are associated with poor cardiovascular outcome (34).

Interestingly, when compared with calcified plaque and noncalcified plaque, mixed plaque was more strongly associated with MS and other traditional risk factors for CAD, such as high blood pressure, smoking and LDL cholesterol level, in our study. This finding is supported by the findings of a recent study, which show that the elements of plaque instability have been associated with mixed plaques (35). When one considers the significant correlation of mixed plaque to MS and other traditional risk factors that are well-known predictive risk factors for cardiovascular events, mixed plaque assessed with multidetector CT may be associated with future cardiovascular events.

On a cautionary note, cardiac multidetector CT has, to our knowledge, not been considered as a screening tool in asymptomatic subjects in Western countries because of safety concerns associated with the use of radiation and contrast media, because of its high cost, and because of a lack of evidence in its appropriate use in asymptomatic subjects (36). However, with technical developments in CT resulting in lower radiation dose, the practical use of cardiac multidetector CT can be extended beyond symptomatic patients. In fact, the 2010 American College of Cardiology/American Heart Association expert

consensus document on coronary CT angiography reported that Framingham risk score may not enable adequate risk assessment in patients with comorbid conditions or in young women, and alternative screening tests, such as calcium scoring, can be used to improve risk stratification (36). In addition to calcified plaques, multidetector CT can be used to detect noncalcified plaque and stenosis degree. Furthermore, geographic location, ethnicity, medical care system, risk factors, and prevalence of diseases are different in each country. Thus, guidelines for cardiac multidetector CT use should be modified according to various factors, including ethnicity and locality. Indeed, according to the 2010 appropriateness criteria for cardiac multidetector CT set forth by the Asian Society of Cardiovascular Imaging, which is a society dedicated solely to cardiovascular imaging, patients at moderate risk and those at high risk fall under "appropriate" and "uncertain" criteria, respectively (37). The uncertain designation was assigned to patients with moderate risk because more research is needed; however, the test may be generally acceptable and reasonable per these new criteria. Thus, in Asia, screening of asymptomatic individuals, with the exception of low-risk patients, with cardiac CT angiography is recommended and commonly practiced, contrary to the practice in Western countries (38). Taken together, a prudent decision must be made when introducing a new diagnostic method; one must weigh its benefits, such as early detection, with its risks, such as increased health care costs (39).

In the present study, we observed a substantial percentage of patients (37.5%) with MS who had some plaque despite their asymptomatic status. Early detection of atherosclerosis in a substantial number of patients in our study emphasizes the potential role of multidetector CT as a screening tool for primary prevention. Thus, it is important to consider and develop appropriate criteria for new methods, such as multidetector CT, with which to make diagnoses in potentially high-risk patients who otherwise may not receive a diagnosis with other conventional imaging tools and biomarkers.

This study had several strengths. Coronary multidetector CT with state-of-the-art technology was used to evaluate plaque types and coronary artery stenosis, as well as CACS. A large number of study subjects of the same ethnicity were recruited, and age and sex matching were used to evaluate the effect of MS on CAD with cardiac multidetector CT.

Our study also had some limitations. It was a cross-sectional analysis; therefore, we cannot extrapolate the current data to predict future cardiac events. The enrollment of study subjects from the routine health check-up may have introduced a selection bias and attenuated the relationship between MS and atherosclerosis. However, there was no significant difference in clinical characteristics or laboratory findings between subjects who were included in the study and those who were excluded. Additionally, multidetector CT findings in the current study were not compared with findings obtained with other techniques, such as intravascular ultrasonography, for validation.

In conclusion, asymptomatic subjects with MS were associated with significant coronary artery stenosis, multivessel involvement, and more diseased coronary segments than were subjects without MS. In addition, subjects in the MS group had more noncalcified or mixed plaque, which is presumably more vulnerable, than did subjects in the non-MS group. Evaluation of possible CAD with multidetector CT may be of importance in the early diagnosis of atherosclerosis in asymptomatic patients, particularly in the assessment of plaque characteristics; however, longitudinal studies are required to determine the effect of these findings on future cardiovascular events.

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