Insulin Resistance, Metabolic Syndrome, and Subclinical Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA)

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OBJECTIVE — To investigate the association of insulin resistance and clinically defined metabolic syndrome (MetS) with subclinical atherosclerosis and examine whether these relationships vary by race/ethnicity or sex.

RESEARCH DESIGN AND METHODS — Subclinical atherosclerosis was assessed by coronary artery calcium (CAC) and carotid intima-medial thickness (IMT) in 5,810 participants without diabetes in the Multi-Ethnic Study of Atherosclerosis, a cohort of adults aged 45–84 years without prior cardiovascular disease (CVD). Fasting insulin and glucose were utilized to estimate insulin resistance by the homeostasis model assessment of insulin resistance (HOMA-IR) index, and the revised National Cholesterol Education Program definition of MetS was utilized. Multivariable linear or relative risk regression was used to analyze the association between HOMA-IR and subclinical atherosclerosis and assess its independence from MetS components.

RESULTS — HOMA-IR was associated with increased IMT after adjustment for demographics (age, site, and education), smoking, education, and LDL cholesterol in each ethnic group, except Hispanic subjects, and in both men and women. After further adjusting for nonglucose MetS components, HOMA-IR was not associated with increased IMT. Subjects in the highest quintile of HOMA-IR had an elevated prevalence of CAC in each ethnic group and both sexes, after adjustment for demographics, smoking, and LDL but not after further adjustment for nonglucose MetS components. Among those with detectable CAC, there was no significant relationship between HOMA-IR and the amount of CAC.

CONCLUSIONS — Although HOMA-IR was associated with increased subclinical atherosclerosis, the association was not independent of the risk factors that comprise MetS. Determination of HOMA-IR is unlikely to contribute to improved determination of risk of subclinical CVD.

Diabetes Care 30:2951–2956, 2007

Metabolic syndrome (MetS) is common among adults in the U.S. (1). There is considerable controversy regarding the validity of the MetS as a clinical construct (2). Data from the Multi-Ethnic Study of Atherosclerosis (MESA) has shown that MetS appears to satisfy common definitions of "syndrome"; however, a supra-additive effect of MetS beyond its component's effects on carotid atherosclerosis was not found (3). Insulin resistance is hypothesized to be the central feature of MetS (4); however, whether it should be a required component of MetS is controversial (5). Recent studies (6–9) have demonstrated an association between various definitions of MetS and subclinical carotid and coronary atherosclerosis. Few studies have considered both insulin resistance and MetS simultaneously as predictors of subclinical atherosclerosis; there have been fewer studies assessing these relationships among nonwhite populations (8,10,11). Recent reports (9,12) have suggested a differential effect of MetS by sex. The focus of this article is *1*) to evaluate the association between insulin resistance (as estimated by the homeostasis model assessment of insulin resistance [HOMA-IR]) and subclinical atherosclerosis, *2*) to determine whether associations of insulin resistance with subclinical atherosclerosis are independent of clinically defined MetS, and *3*) to examine whether differences in these relationships exist by race/ethnicity or by sex.

RESEARCH DESIGN AND METHODS

— MESA is a population-based sample of 6,814 white, black, Hispanic, and Chinese subjects, aged 45–84 years, who showed no evidence of clinical cardiovascular disease (CVD) before recruitment (13). Briefly, participants were recruited from six communities (Baltimore, Maryland; Chicago, Illinois; For-

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Received for publication 1 June 2007 and accepted in revised form 9 August 2007.

Published ahead of print at http://care.diabetesjournals.org on 17 August 2007. DOI: 10.2337/dc07-1042.

N.D.W. has received honoraria from Takeda and Sanofi-Aventis.

Abbreviations: CAC, coronary artery calcium; CC, common carotid; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; IC, internal carotid; IMT, intima-medial thickness; MESA, Multi-Ethnic Study of Atherosclerosis; MetS, metabolic syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

syth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). During the baseline exam (2000–2002), standardized questionnaires and calibrated devices were utilized to obtain demographic data, tobacco usage, medical conditions, currently prescribed medications, weight, waist circumference, and height. Education was classified into one of the following five categories: less than high school, high school, some college/technical school certificate/associate degree, bachelor's degree, and graduate or professional school.

Resting seated blood pressure was measured three times using an automated oscillometric sphygmomanometer (Dinamap PRO 100; Critikon); the last two measurements were averaged for analysis. Hypertension was defined by use of blood pressure medicine or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Waist circumference was measured at the umbilicus to the nearest 0.1 cm using a steel measuring tape with standard 4-oz tension.

Fasting blood glucose and lipids were analyzed at a central laboratory. Serum glucose was measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics). Plasma lipids (cholesterol, HDL cholesterol, and triglycerides) were measured using a standardized kit (Roche Diagnostics). LDL cholesterol was calculated using the formula of Friedewald et al. (14). Insulin was determined by a radioimmunoassay method using the Linco Human Insulin Specific RIA kit (Linco Research). HOMA-IR was calculated as insulin (mU/l) × (glucose [mg/dl] × 0.055)/22.5 (15). Subjects with diabetes were excluded from the analyses.

Subjects were considered to have diabetes if they used hypoglycemic drugs or had a fasting blood glucose ≥126 mg/dl. Subjects were considered to have impaired fasting glucose if they did not have diabetes by the preceding criteria and if their fasting blood glucose was ≥100 mg/dl. MetS was defined according to the revised National Cholesterol Education Program Adult Treatment Panel III criteria (16). The individual components were waist circumference ≥88 cm for women or ≥102 cm for men, glucose ≥100 mg/dl, blood pressure ≥130/85 or on medication for hypertension, HDL <40 mg/dl (men) or <50 mg/dl (women), and triglycerides ≥150 mg/dl. We considered subjects on either a fibrate or niacin therapy to have met the HDL criterion for MetS. We determined for each individual the number of MetS components; those with three or more were classified as having MetS.

Chest computed tomography was performed using previously described methods (13). Briefly, participants were scanned twice over phantoms of known physical calcium concentration. Scans were read centrally. For each scan, a total phantom-adjusted Agatston score, defined as the sum of calcium measures from the left anterior descending, circumflex, and left and right coronary arteries, was calculated. The mean score was used in these analyses. Images of the right and left common carotid (CC) and internal carotid (IC) arteries were captured, including images of the near and far wall, using high-resolution B-mode ultrasound. Images were centrally read using previously described methods (17). Intraclass correlation coefficients for intrareader reproducibility of CC and IC intima-medial thickness (IMT) both exceeded 0.98 and for interreader reproducibility were 0.87 and 0.94, respectively. We report results using the CC IMT, defined as the mean of all available maximum CC IMTs across both left and right sides, across the near and far walls. Analyses with IC IMT gave similar results and are not presented.

Table 1—*Characteristics of 5,810 participants without diabetes in the MESA, 2000–2002*

Age (years)	61.7 ± 10.3
Female subjects	53.6
White subjects	41.7
Chinese subjects	11.7
Black subjects	26.0
Hispanic subjects	20.6
College or higher degree	37.4
BMI (kg/m^2)	28.0 ± 5.3
Waist (cm)	97.0 ± 14.1
Hypertension	40.6
Hypertension medication	31.8
Systolic blood pressure (mmHg)	125.4 ± 21.2
Diastolic blood pressure (mmHg)	71.8 ± 10.3
Current smoker	13.2
Glucose (mg/dl)	95.9 ± 9.8
Insulin (mU/l)	5.1 (3.4–7.9)
HOMA-IR	1.2 (0.7–1.9)
Impaired fasting glucose	32.6
Cholesterol (mg/dl)	195.0 ± 34
HDL cholesterol (mg/dl)	51.8 ± 15
LDL cholesterol (mg/dl)	118.0 ± 31
Triglycerides (mg/dl)	108 (76–156)
MetS	27.4
Carotid IMT (mm)*	0.859 ± 0.19
CAC score more than zero (%)	47.8
Median CAC (if CAC score is more than zero) (Agatson units)	79 (20–272)

Data are percent, means ± SD, or medians (interquartile range) if skewed. *n = 5,738 for IMT data.

Statistical analysis

As HOMA-IR was not normally distributed, we divided the participants into equal quintiles. Unadjusted differences in characteristics across race or sex, and differences in subclinical atherosclerosis across HOMA-IR quintile, or by MetS status, were examined using ANOVA (for continuous variable) or χ^2 analysis. Our primary approach to assess for differential patterns by race/ethnicity or by sex was to perform stratified analyses. We also assessed interaction terms for race and sex by HOMA-IR quintiles; these were placed in models. The significance of the interaction terms was assessed using the Wald χ^2 test statistic. We performed multivariable regressions to examine the association between HOMA-IR quintile and CC IMT or coronary artery calcium (CAC), adjusting for age (years), clinical site, smoking (former or current), education, LDL cholesterol, and either sex or race; these variables constituted model 1. Model 2 added MetS as a categorical variable. Model 3 replaced MetS with the component risk factors utilized to define MetS (HDL cholesterol, triglycerides, waist circumference, systolic and diastolic blood pressure [all continuous], and hypertension medication use). We did not include impaired fasting glucose or glucose in the final model due to potential overadjustment, as glucose is part of HOMA-IR.

About half of MESA's participants have a CAC score of zero. Therefore, odds ratios (as a measure of associations with CAC prevalence) tend to be overestimates of the relative risk. We utilized generalized estimating equations to estimate the relative risks for modeling the prevalence of CAC scores more than zero (generalized linear model, specifying a log link, Gaussian error, and robust SE estimates). Additionally, among those with detectable CAC, we modeled the natural log of the Agatston score utilizing linear regression. We utilized linear regression when analyzing continuous CC IMT. Two-tailed $P < 0.05$ was considered significant. Analyses were performed using STATA 8 (Stata, College Station, TX).

RESULTS

General characteristics of study population

Among 6,814 MESA participants, we excluded 35 due to missing MetS component data and 969 with diabetes. The characteristics of the 5,810 subjects remaining are noted in Table 1. The prevalence of MetS was lowest among Chinese (20.5%), highest among Hispanic (33.4%), and similar in black (25.6%) and white (27.5%) participants. Median HOMA-IR was higher in black (1.3) and Hispanic (1.4) participants compared with white (1.0) or Chinese (1.1) participants. Women had a lower median HOMA-IR than men (1.1 vs. 1.2) but were more likely to have MetS (30.6 vs. 23.7%).

Insulin resistance, MetS, and subclinical atherosclerosis

The unadjusted relationship between HOMA-IR and CC IMT, CAC prevalence, and the amount of CAC among those with CAC is presented in Table 2. CC IMT was progressively higher with increasing HOMA-IR quintile in white subjects; however, the relationship was less consistent in Hispanic and Chinese subjects and did not reach statistical significance in black subjects ($P = 0.07$). There was no evidence for a linear relationship between HOMA-IR and CAC prevalence in Chinese and black subjects; however, for each race/ethnic group, the most insulin resistant had the highest CAC prevalence. When stratifying by sex, both CC IMT and CAC prevalence increased with increasing HOMA-IR quintile. Among those with CAC scores more than zero, there was little variability in the amount by HOMA-IR quintile. The mean CC IMT and the proportion with detectable CAC were significantly higher in those with versus those without MetS in each race/ethnic group and both sexes (Table 2).

Multivariable models

HOMA-IR was linearly associated with carotid IMT after adjustment for age, sex or race, site, education, LDL cholesterol, and smoking (model 1; Table 3) in each race/ethnic group except Hispanic subjects and in both men and women. The association was attenuated when adding MetS to the model, and, in some, strata were no longer significant (model 2; Table 3). In every group, there was no linear association when adding non–glucose-related MetS components (model 3). There was evidence for an interaction be-

Table 2—*CC and coronary atherosclerosis by HOMA-IR quintiles and by MetS, stratified by race/ethnicity and sex in the MESA, 2000–2002*

		CAC score more than zero	
	CC IMT (mm)	%	Median (interquartile range)
White subjects			
Category			
H1	0.813 ± 0.19	48.7	107 (19–300)
H2	0.849 ± 0.18	48.3	103 (22–327)
H3	0.870 ± 0.18	58.7	131 (18–376)
H4	0.891 ± 0.19	61.7	130 (34–449)
H5	0.903 ± 0.22*	64.8*	96 (23–361)
MetS$^-$	0.841 ± 0.19	52.3	96 (20–336)
MetS$^+$	0.908 ± 0.21*	63.4*	153 (34–413)
Chinese subjects			
Category			
H1	0.814 ± 0.21	47.5	88 (24–186)
H2	0.786 ± 0.14	40.1	91 (33–151)
H3	0.797 ± 0.17	44.4	43 (14–155)
H4	0.820 ± 0.16	51.0	51 (15–147)
H5	0.864 ± 0.17†	56.7	34 (13–93)
MetS$^-$	0.802 ± 0.17	44	62 (16–159)
MetS$^+$	0.853 ± 0.17*	59.7*	49 (19–151)
Black subjects			
Category			
H1	0.867 ± 0.21	39.8	71 (23–196)
H2	0.902 ± 0.20	40.7	41 (19–170)
H3	0.894 ± 0.19	41.1	62 (17–257)
H4	0.911 ± 0.19	41.1	70 (22–205)
H5	0.896 ± 0.17	41.3	65 (14–216)
MetS$^-$	0.885 ± 0.19	38.8	58 (19–232)
MetS$^+$	0.924 ± 0.19*	46.5†	68 (21–195)
Hispanic subjects			
Category			
H1	0.859 ± 0.25	42.5	89 (20–357)
H2	0.815 ± 0.18	40.5	70 (13–167)
H3	0.845 ± 0.19	35.2	85 (25–246)
H4	0.826 ± 0.19	37.8	67 (19–285)
H5	0.860 ± 0.16‡	50.3†	50 (16–175)
MetS$^-$	0.826 ± 0.19	38.3	65 (14–238)
MetS$^+$	0.871 ± 0.18*	48.8†	65 (19–216)
Women			
Category			
H1	0.810 ± 0.18	36.9	67 (19–179)
H2	0.834 ± 0.18	33.8	66 (17–169)
H3	0.847 ± 0.18	37.9	50 (15–200)
H4	0.852 ± 0.19	38.9	58 (19–199)
H5	0.869 ± 0.18*	43.1‡	46 (11–154)
MetS$^-$	0.824 ± 0.18	34.1	50 (13–165)
MetS$^+$	0.881 ± 0.19*	46.8*	62 (19–201)
Men			
Category			
H1	0.859 ± 0.23	57.5	108 (26–362)
H2	0.862 ± 0.19	56.7	93 (22–301)
H3	0.877 ± 0.19	57.5	133 (24–393)
H4	0.895 ± 0.20	60.3	113 (30–416)
H5	0.902 ± 0.19*	63.2	88 (25–319)
MetS$^-$	0.867 ± 0.20	56.4	95 (23–332)
MetS$^+$	0.923 ± 0.20*	67.9*	130 (35–411)

Data are means ± SD unless otherwise indicated. H, HOMA quintiles 1–5. *P* value from ANOVA (test for mean difference) is also provided. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Table 3—*Association between HOMA-IR quintile and CC IMT (mm) in multivariable models in the MESA, 2000–2002*

	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* trend
White subjects					
Model 1	0.03 (0.01–0.05)	0.03 (0.01–0.05)	0.05 (0.02–0.07)	0.08 (0.06–0.10)	<0.001
Model 2	0.03 (0.01–0.05)	0.02 (0.01–0.05)	0.03 (0.01–0.05)	0.06 (0.03–0.08)	<0.001
Model 3	0.02 (−0.01 to 0.03)	0.01 (−0.02 to 0.03)	0.01 (−0.02 to 0.03)	0.03 (0.00–0.05)	0.3
Chinese subjects					
Model 1	−0.01 (−0.05 to 0.02)	0.00 (−0.04 to 0.04)	0.03 (−0.01 to 0.07)	0.08 (0.04–0.13)	<0.001
Model 2	−0.01 (−0.05 to 0.03)	0.00 (−0.03 to 0.04)	0.03 (−0.01 to 0.07)	0.08 (0.03–0.12)	<0.01
Model 3	−0.02 (−0.06 to 0.01)	−0.02 (−0.06 to 0.01)	0.00 (−0.05 to 0.04)	0.02 (−0.02 to 0.08)	0.1
Black subjects					
Model 1	0.03 (0.01–0.06)	0.03 (0.004–0.06)	0.04 (0.02–0.07)	0.04 (0.02–0.07)	0.01
Model 2	0.03 (0.00–0.06)	0.03 (0.00–0.05)	0.04 (0.00–0.06)	0.03 (0.00–0.06)	0.1
Model 3	0.02 (−0.01 to 0.05)	0.01 (−0.01 to 0.04)	0.02 (−0.01 to 0.05)	0.01 (−0.02 to 0.04)	0.7
Hispanic subjects					
Model 1	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.02)	0.0 (−0.04 to 0.03)	0.01 (−0.02 to 0.05)	0.3
Model 2	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.02)	−0.01 (−0.05 to 0.02)	0.00 (−0.04 to 0.04)	0.6
Model 3	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.01)	−0.02 (−0.06 to 0.01)	−0.03 (−0.07 to 0.01)	0.6
Women					
Model 1	0.03 (0.01–0.04)	0.03 (0.01–0.05)	0.03 (0.02–0.05)	0.06 (0.04–0.07)	<0.001
Model 2	0.03 (0.01–0.04)	0.02 (0.01–0.04)	0.03 (0.01–0.04)	0.04 (0.02–0.06)	<0.01
Model 3	0.02 (0.00–0.03)	0.01 (−0.01 to 0.03)	0.01 (−0.01 to 0.03)	0.01 (−0.01 to 0.03)	0.4
Men					
Model 1	0.01 (−0.01 to 0.03)	0.02 (0.00 to 0.04)	0.05 (0.02–0.07)	0.06 (0.04–0.08)	<0.001
Model 2	0.01 (−0.01 to 0.03)	0.02 (−0.01 to 0.04)	0.04 (0.01–0.06)	0.05 (0.02–0.07)	<0.001
Model 3	0.00 (−0.02 to 0.02)	0.00 (−0.03 to 0.02)	0.01 (−0.01 to 0.04)	0.01 (0.01–0.04)	0.6

Data are β-coefficient in millimeters (95% CI) compared with HOMA-IR quintile 1. For race/ethnicity-stratified results, model 1 adjusts for age (years), sex, clinical site, education, smoking status, and LDL cholesterol (mg/dl). For sex-stratified results, model 1 adjusts for race. Model 2: model 1 + MetS (dichotomous). Model 3: model 1 + nonglucose MetS components (hypertension medication and continuous HDL, triglycerides, systolic and diastolic blood pressure, and waist circumference).

tween HOMA-IR and race/ethnicity (*P* value for interaction term 0.01 in model 1) but not for an interaction between HOMA-IR and sex (*P* value for interaction term 0.4 in model 1).

In each race/ethnic group except black subjects and in both sexes, a linear association between HOMA-IR and CAC prevalence was observed after adjusting for model 1 variables (Table 4). Among black participants, however, those in the highest HOMA-IR quintile were significantly more likely to have a CAC score more than zero compared with the reference category. The association was attenuated by adjustment for MetS. When adjusting for MetS components (model 3), the association between HOMA-IR and CAC was no longer significant in most groups; even in Hispanic subjects, the 5th quintile was not significantly more likely to have CAC than quintile 1. There was no evidence of an interaction between HOMA-IR and race/ethnicity (interaction term $P = 0.2$) or sex (interaction term $P = 0.8$) with regard to CAC prevalence. HOMA-IR was not associated with meaningful differences in the amount of CAC among those with CAC scores more than zero in any model (data not shown).

In model 2, the association between MetS (dichotomous) and CC IMT after adjusting for demographic factors, LDL, smoking, and HOMA-IR was consistent in both men (+0.031; $P < 0.01$) and women (+0.026; $P < 0.001$). Similarly, the association between MetS and CAC after adjustment for the same variables was similar in both men (relative risk 1.07; $P = 0.02$) and women (1.11; $P = 0.01$). There was some variability in the association between MetS and carotid IMT by race/ethnicity (CC IMT increment 0.035, $P < 0.01$ in white subjects; 0.013, $P = 0.4$ in Chinese subjects; 0.028, $P = 0.01$ in black subjects; and 0.023, $P = 0.05$ in Hispanic subjects). The association between MetS and CAC was more variable (relative risk 1.09, $P < 0.001$ in white subjects; 1.12, $P = 0.1$ in Chinese subjects; 1.07, $P = 0.2$ in black subjects; and 1.11, $P = 0.06$ in Hispanic subjects).

CONCLUSIONS — In this cohort of adults free of CVD, we demonstrated that HOMA-IR is associated with subclinical atherosclerosis as measured by either coronary calcium or carotid IMT. There was only evidence of a significant interaction between race/ethnicity and HOMA-IR for CC IMT; otherwise, the patterns observed were consistent by race/ethnicity and sex. Our results suggest that the association between insulin resistance and CC IMT is not independent of the MetS components. We demonstrate an attenuation of the observed HOMA-IR associations when adjusting for MetS as a categorical variable, whereas MetS remained significant in most strata. When further adjusting for the MetS component factors, there was no longer an independent effect of HOMA-IR on either carotid IMT or coronary calcification.

The strengths of this analysis include the use of a large, diverse, and well-characterized population-based sample and the consideration of two subclinical atherosclerosis measures. The measure of insulin resistance utilized in this study, HOMA-IR, has a strong correlation with the more precise determination via the euglycemic clamp (15). We acknowledge limitations to our approach as well. There is potentially some overadjustment when both HOMA-IR and MetS are modeled, as impaired fasting glucose is a MetS criterion.

Table 4—*Association between HOMA-IR quintile and relative risk of coronary artery calcification in multivariable models in the MESA, 2000–2002*

	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* trend
White subjects					
Model 1	0.98 (0.90–1.06)	1.05 (0.96–1.14)	1.05 (0.96–1.14)	1.19 (1.09–1.30)	<0.001
Model 2	0.97 (0.89–1.06)	1.03 (0.94–1.12)	1.01 (0.93–1.11)	1.13 (1.03–1.25)	0.03
Model 3	0.96 (0.88–1.04)	1.00 (0.91–1.09)	0.96 (0.0.88–1.06)	1.07 (0.96–1.19)	0.1
Chinese subjects					
Model 1	1.02 (0.81–1.28)	0.98 (0.77–1.25)	1.23 (1.01–1.52)	1.36 (1.06–1.75)	0.01
Model 2	1.00 (0.79–1.27)	0.94 (0.74–1.21)	1.19 (0.96–1.47)	1.28 (0.99–1.66)	0.03
Model 3	0.91 (0.72–1.14)	0.84 (0.67–1.06)	0.96 (0.77–1.20)	1.04 (0.79–1.38)	0.4
Black subjects					
Model 1	1.07 (0.91–1.25)	1.10 (0.94–1.29)	1.07 (0.90–1.26)	1.21 (1.04–1.41)	0.1
Model 2	1.06 (0.90–1.24)	1.09 (0.93–1.28)	1.04 (0.88–1.24)	1.17 (0.99–1.38)	0.4
Model 3	1.07 (0.91–1.26)	1.11 (0.94–1.32)	1.05 (0.87–1.27)	1.18 (0.99–1.41)	0.4
Hispanic subjects					
Model 1	1.19 (1.0–1.41)	0.98 (0.81–1.19)	1.13 (0.95–1.34)	1.33 (1.13–1.56)	<0.001
Model 2	1.18 (0.99–1.40)	0.97 (0.80–1.17)	1.08 (0.91–1.29)	1.26 (1.07–1.49)	<0.01
Model 3	1.16 (0.97–1.38)	0.92 (0.75–1.12)	1.02 (0.84–1.24)	1.16 (0.96–1.40)	0.02
Women					
Model 1	1.01 (0.91–1.13)	1.02 (0.91–1.15)	1.06 (0.95–1.19)	1.25 (1.12–1.40)	<0.001
Model 2	1.01 (0.91–1.13)	0.99 (0.88–1.12)	1.02 (0.91–1.15)	1.18 (1.05–1.33)	0.02
Model 3	1.01 (0.90–1.12)	0.97 (0.86–1.09)	0.98 (0.87–1.11)	1.12 (0.98–1.27)	0.1
Men					
Model 1	1.02 (0.94–1.10)	1.01 (0.93–1.09)	1.05 (0.97–1.14)	1.16 (1.08–1.26)	<0.001
Model 2	1.01 (0.93–1.10)	0.99 (0.91–1.08)	1.02 (0.94–1.11)	1.12 (0.03–1.22)	0.04
Model 3	1.00 (0.92–1.09)	0.97 (0.89–1.06)	0.99 (0.91–1.08)	1.07 (0.97–1.18)	0.2

Data are relative risks (95% CI) compared with HOMA-IR quintile 1. For race/ethnicity-stratified results, model 1 adjusts for age (years), sex, clinical site, education, smoking status, and LDL cholesterol (mg/dl). For sex-stratified results, model 1 adjusts for race. Model 2: model 1 + MetS (dichotomous). Model 3: model 1 + nonglucose MetS components (hypertension medication and continuous HDL, triglycerides, systolic and diastolic blood pressure, and waist circumference).

Furthermore, the ethnic-specific analyses should be interpreted cautiously due to the smaller and unequal sample size for each. Finally, these cross-sectional analyses do not permit the conclusion that insulin resistance (or MetS) causes subclinical disease.

Our findings are consistent with the observation of increased carotid IMT in young black and white adults (aged 20–38 years) with MetS (8), as well as with reports from European populations (9,18,19). Some recent reports (9,12) have suggested a differential effect of MetS on carotid IMT by sex. In this sample, we did not find a substantial difference in the patterns of association between HOMA-IR or MetS and either carotid IMT or CAC by sex. The association between insulin resistance and carotid IMT has been assessed in several populations, including European, Chinese, Hispanic, and black Americans, using several different indexes of insulin resistance, including HOMA. Several studies (20–23) have found insulin resistance to be positively associated with carotid IMT. Data from the Insulin Resistance Atherosclerosis Study showed that insulin resistance measured by minimal model analysis was associated with carotid IMT in white and Hispanic subjects but not in black subjects (24). In this cohort, HOMA-IR was associated with IMT in black, white, and Chinese subjects in models that did not adjust for MetS. Among Hispanic subjects, we did not demonstrate a significant association between HOMA-IR and carotid IMT. Our results may differ from those seen in the Insulin Resistance Atherosclerosis Study due to the substantial heterogeneity of Hispanic subjects in MESA, which includes individuals with origins in Mexico, Central and South America, and the Caribbean, whereas the Insulin Resistance Atherosclerosis Study sample was Mexican American.

MetS has been demonstrated to be associated with a higher prevalence of CAC in samples of adults free of coronary heart disease, aged 20–79 years, who were primarily referred for CAC screening (6) and in nonreferred adults from the community (7). In the present cohort, the prevalence of CAC among those with MetS, was remarkably similar to that reported by Wong et al. (6) (57.6 vs. 58.8%), although among those without MetS, the prevalence of CAC was lower in our study (45.8 vs. 53.5%). In a cohort of adults without diabetes or CVD but with a family history of CVD (95% white, aged 30–70 years), both MetS and HOMA-IR index were associated with CAC independently of established risk factors and of each other (25).

Our results are not inconsistent with the hypothesis that insulin resistance is a key feature of MetS or that it contributes to atherosclerosis. One interpretation of these results is that the effect of insulin resistance on atherosclerosis may be mediated through hypertension or dyslipidemia. The measurement of insulin (and calculation of HOMA-IR) is not routinely performed in most clinical settings; therefore, these data can be used to ask whether improved risk stratification could be obtained by considering an estimate of insulin resistance in addition to standard risk factors. Our results suggest that HOMA-IR is not especially useful in addition to National Cholesterol Education Program MetS criteria in assessing coronary or carotid subclinical disease. At least one other study (26) has suggested that HOMA-IR in addition to MetS (or individual risk factors) does not provide a greater ability to predict events. In the Fra-

mingham Offspring Study (26), both HOMA-IR and MetS were associated with incident clinical CVD in univariate analyses; however, after adjustment for age, sex, LDL, smoking, and MetS, HOMA-IR levels were not independently related to incident CVD, while MetS was related. Based on our results, we would not advocate the routine measurement of insulin in order to calculate HOMA-IR for the purposes of identifying a population with increased subclinical atherosclerosis. Use of the standard risk factors to determine who has MetS may identify individuals who are more likely to have more significant atherosclerosis. However, MetS does not appear to improve the prediction of CVD over the Framingham Risk Score, suggesting there is no additional benefit to defining MetS (27). Rather than refinement of risk stratification, there is a pressing need for enhanced strategies to control hypertension and dyslipidemia and prevent obesity and physical inactivity, which are the underpinnings of the MetS epidemic.

Acknowledgments— 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.

The authors thank the other investigators, the staff, and the participants of MESA for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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