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Metabolic Syndrome and Early-Onset Coronary Artery Disease

Is the Whole Greater Than Its Parts?

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OBJECTIVES We sought to examine the association between the metabolic syndrome (MetS) (defined both by the 2001 National Cholesterol Educational Program Adult Treatment Panel III [ATP-III] definition and the American Heart Association/National Heart, Lung and Blood Institute [AHA/NHLBI] revision incorporating the lower threshold for impaired fasting glucose [IFG]) and early-onset coronary artery disease (CAD).

BACKGROUND The impact of MetS on premature CAD has not been studied extensively. Lowering the threshold to define the IFG component (from 110 to 100 mg/dl) and the value of the syndrome as a whole versus its individual components are subjects of intense debate.

METHODS We performed a case-control study with 393 early-onset CAD subjects (acute myocardial infarction, angina with ≥50% stenosis, or coronary revascularization) in men under age 46 years or women under age 56 years and 393 control subjects individually matched for gender, age, and race/ethnicity.

RESULTS By conditional logistic regression, presence of ATP-III MetS without diabetes (adjusted odds ratio [adj-OR] 4.9; 95% confidence interval [CI] 3.4 to 8.0) and with diabetes (adj-OR 8.0, 95% CI 4.39 to 14.6) was a strong independent determinant of early-onset CAD. Using the AHA/NHLBI revision, these ORs became slightly stronger. However, neither definition of MetS remained significantly associated with early-onset CAD in multivariate models adjusting for individual components.

CONCLUSIONS The presence of MetS imparts a high risk of early-onset clinical CAD, but the prognostic information associated with the syndrome is not greater than the sum of its parts. (J Am Coll Cardiol 2006;48:1800–7) © 2006 by the American College of Cardiology Foundation

In 2001, the National Cholesterol Educational Program Adult Treatment Panel III (NCEP-ATP-III) defined the metabolic syndrome (MetS) as a clustering of 3 or more vascular risk factors, including abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose (1). Subsequent studies have shown that the MetS defined using the ATP-III imparts an increased risk of type 2 diabetes mellitus as well as clinical (2–9) and subclinical (10–13) coronary artery disease (CAD) in older populations. Because the prevalence of MetS is increasing alarmingly among adolescents and young adults because of adverse physical activity and dietary patterns (14), it is important to quantify its relation with clinical CAD occurring early in life.

A recent American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) report (15) recommends lowering the threshold for impaired fasting glucose (IFG) from 110 to 100 mg/dl, following the recently modified American Diabetes Association (ADA) criteria for IFG (16). However, the impact of changing the glucose threshold for IFG has not been rigorously evaluated and has been called into question because it could expand the population with MetS by about 20% (17).

Besides the IFG controversy, the clinical utility of the MetS above and beyond its individual components remains uncertain and has led to a critical appraisal of the syndrome (18,19). The present study was undertaken to: 1) evaluate the association between MetS (defined using both the ATP-III criteria and the new AHA/NHLBI criteria) and early-onset CAD; and 2) ascertain whether the MetS (defined with both criteria) adds beyond the contribution of the component risk factors.

METHODS

Study population and design. The ADVANCE (Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology) study is a case-control investigation of genetic and nongenetic determinants of CAD and mode of CAD presentation. All study participants have been identified and recruited from the membership of Kaiser Permanente of Northern California (KPNC), a

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Abbreviations and Acronyms

ADA	= American Diabetes Association
ADVANCE	= Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology
AHA/NHLBI	= American Heart Association/ National Heart, Lung, and Blood Institute
CAD	= coronary artery disease
CARDIA	= Coronary Artery Risk Development in Young Adults
HOMA-IR	= homeostasis model assessment of insulin resistance
IFG	= impaired fasting glucose
KPNC	= Kaiser Permanente of Northern California
MetS	= metabolic syndrome
NCEP-ATP-III	= National Cholesterol Educational Program Adult Treatment Panel III

large integrated health care delivery system in the San Francisco Bay area and surrounding counties.

As part of the overall design, the study included "early-onset" CAD subjects and age-matched control subjects. The definition of early-onset CAD is presented in Figure 1. In short, it included men aged 18 through 45 years and women aged 18 through 55 years who were hospitalized for acute myocardial infarction (AMI), angina, or a coronary revascularization procedure between January 1, 1999, and December 12, 2003. Because the case subjects had to survive the index event and up to the clinic visit, we were unable to enroll out-of-hospital sudden cardiac death or fatal cardiac arrest in the hospital. The combination of primary discharge code 410.x of the ninth revision of the International Classification of Diseases plus evidence of peak cardiac troponin I of 4 ng/dl or combination of creatine kinase (CK)-MB fraction of 5.6 ng/ml and CK-MB percentage of 3.3 during hospital admission has 96% specificity using chart review as the "gold standard" (4). The sequence of exclusions for medical or residential reasons, the number of participant refusals before or after the screening interview, and the number of case subjects excluded after completion of the clinic visit are detailed in Figure 2. Briefly, after initial electronic exclusions, there were 1,820 eligible patients with early-onset CAD; 1,418 (78%) were contacted by recruiters, and, of those, 566 (40%) were deemed eligible and agreed to participate. Clinic visits ended when the target recruitment of 500 case subjects was reached.

The selection of young control subjects was done in 2 steps. About two-thirds of the control subjects (n = 479; 65%) were participants in the year 15 examination of the CARDIA (Coronary Artery Risk Development in Young Adults) study in 2000 to 2001 at the Oakland CARDIA clinic. These CARDIA participants were not re-examined; rather, we used previously collected DNA and risk factor data. CARDIA is a longitudinal study funded by the NHLBI to examine coronary heart disease (CHD) risk factors in black and white young adults (20). The CARDIA subjects were first enrolled in 1985 and 1986 when they were between 18 and 30 years old. Among the 1,005 CARDIA Oakland participants at the year 15 visit, 4 were excluded owing to history of CAD, 1 for being transgender, and 189 for having insufficient DNA stored. Out of these 811, we randomly selected (in gender and race strata) 479 subjects as control subjects for young case subjects of white or black race. The remaining young control subjects (n = 264; 35%) were recruited de novo from the KPNC membership. An initial pool of KPNC members was assembled consisting of 57,988 men between the ages of 18 and 45 years and women between the ages of 18 and 55 years (as of June 30, 2003) who lived in the San Francisco Bay area and had continuous health plan membership between January 1998 and June 30, 2003. We then excluded subjects with a history of diagnosed cardiovascular disease, systemic cancer, end-stage renal disease, cirrhosis, dementia, and bone marrow or organ

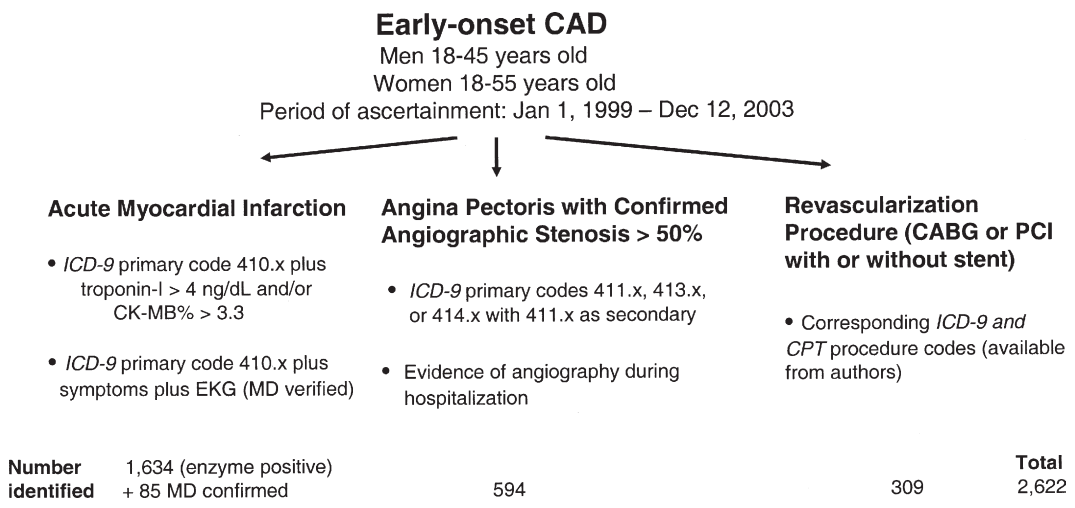

Figure 1. Early-onset coronary artery disease (CAD) definition criteria in the ADVANCE Study. CABG = coronary artery bypass graft; CK-MB = creatine kinase-MB fraction; CPT = current procedural terminology; EKG = electrocardiogram; ICD-9 = ninth revision of the International Classification of Diseases; MD = metabolic syndrome; PCI = percutaneous coronary intervention.

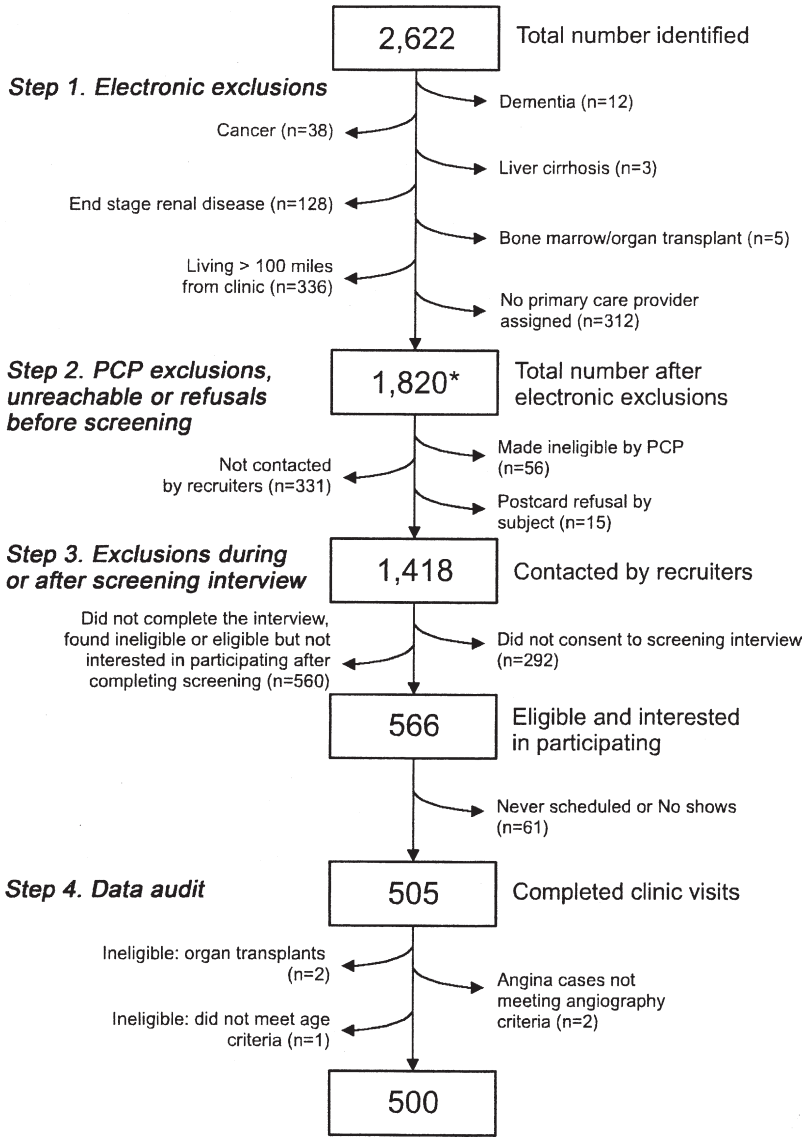

Figure 2. Schematic representation of the recruitment process for early-onset coronary artery disease subjects in the ADVANCE study. PCP = primary care provider. *Numbers do not add up because electronic exclusions are not mutually exclusive.

transplants, as well as those who previously requested not to be contacted for research studies or who did not have a regular primary care physician, leaving an eligible pool of 50,507. Age, gender, and race strata were created, and we selectively recruited persons with the aim of frequency matching to the young case subjects on age, gender, and race/ethnicity.

We then excluded 31 case subjects and 82 control subjects in whom 1 or more components of the metabolic syndrome were missing or values for glucose or triglycerides were nonfasting, leaving 469 case subjects and 661 control subjects. To ensure optimal case-control balance by gender and race (non-Hispanic white, non-Hispanic black, Hispanic/Latino, Asian/Pacific Islander, other, or mixed), we assembled a subset of case subjects and control subjects using 1:1 matching on gender and race. This resulted in 393 matched pairs.

Race/ethnicity was based on the subjects' self-identification and by grandparents' country of origin. Educational attainment, cigarette smoking status, and average consumption of beer, wine, and liquor over the last 12 months were collected by self-administered questionnaires. Height, weight, and waist circumference were measured at the clinic visit by certified personnel using standard instruments and protocols. Before the measurement of blood pressure, subjects were fasting and instructed to avoid heavy physical activity, smoking, and caffeine. Before measuring blood pressure, subjects were seated for 5 min with feet flat on the floor and told to relax and to avoid talking. The blood pressure cuff size was based on the individual's arm circumference, and all readings were taken in the right arm by an automated digital vital signs monitor from Welch Allyn (Skaneateles Falls, New York), model 5200. A total of 3 readings were taken with a 1-min rest period between assessments, and the average of second

and third readings were used in analysis. Serum lipid levels (low-density lipoprotein cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) were measured in fasting serum at the Stanford Hospital and Clinics Laboratory, which is certified by the Centers for Disease Control/NHLBI Lipid Standardization Program. Fasting blood glucose was determined with a hexokinase reagent kit (Washington University, Saint Louis, Missouri). Diabetes mellitus was defined as self-report of a physician diagnosis of diabetes mellitus, use of insulin, oral hypoglycemic, or insulin sensitizing agents, or fasting blood glucose ≥126 mg/dl at the study visit. Plasma C-reactive protein (CRP) was measured using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Indiana), using reagents and calibrators from Denka Seiken (Niigata, Japan). Data collection methods for the CARDIA study year 15 examination have been described elsewhere (21). Whenever possible (i.e., educational attainment, personal medical history, smoking, alcohol consumption, anthropometry), the survey instruments and the clinic procedures used for the case subjects and the non-CARDIA control subjects were the same as those used in the CARDIA study.

The presence of MetS was determined using 2 definitions: the 2001 NCEP-ATP-III definition (1) (waist circumference ≥102 cm in men or ≥88 cm in women, fasting triglycerides ≥150 mg/dl, HDL-cholesterol <40 mg/dl in men or <50 mg/dl in women, hypertension defined as blood pressure ≥130/85 mm Hg or use of blood pressure medication, and IFG ≥110 mg/dl) and the revised AHA/NHLBI definition (15) incorporating the lower threshold for IFG (≥100 mg/dl). Fasting blood glucose of ≥126 mg/dl was considered diagnostic of diabetes. We then categorized case subjects and control subjects (according to both ATP-III and AHA/NHLBI criteria) into the following mutually exclusive groups: MetS without diabetes, diabetes without MetS, diabetes with MetS, and neither of these conditions. We did not implement the World Health Organization criteria (22) for MetS because it requires oral glucose tolerance testing, which was not performed in our study subjects.

Statistical analysis. All analyses were conducted using SAS statistical software version 9 (SAS Institute, Cary, North Carolina). Univariate case-control comparisons were performed using appropriate tests for paired data, including the paired *t* test for normally distributed continuous variables, the Wilcoxon matched pairs signed rank test for non-normally distributed continuous variables, the McNemar test for 2 × 2 categoric variables and the generalized Mantel-Haenzel test for 2 × n categoric variables (where n >2). For assessing normality, we relied on graphic methods, including box plots and normal probability plots. Conditional logistic regression was then applied to quantify the relative odds of early-onset CAD associated with MetS without diabetes, with diabetes without MetS, and with diabetes with MetS relative to having neither of these conditions. Two sequential models were fitted: first a model with no adjustment for covariates (gender and race are adjusted for by design), and second a model adjusting for covariates external to MetS including age, educational attainment, body mass index, any use of alcohol consumption in the past year, and cigarette smoking status. Next, we assessed the strength of association of each of the 5 individual components categorically defined (i.e., all components included in the same model) with early-onset CAD. To ascertain the prognostic importance of the MetS above and beyond its components, we then added a dichotomous term representing MetS to the model already including the 5 categoric components. Because the cut points to define the components are somewhat arbitrary, the same analysis was repeated entering the individual components as continuous variables, divided by their gender-specific standard deviation.

RESULTS

Overall, 59% of early-onset CAD subjects (n = 230) were acute myocardial infarction, 26% (n = 101) had a revascularization procedure, and 16% (n = 62) had a diagnoses of angina with ≥50% stenosis on coronary angiography. By gender, these percentages were 60%, 29%, and 11% in men and 57%, 24%, and 19% in women. The baseline characteristics of case and control subjects are presented in Table 1. Mean age was 46 years in early-onset CAD subjects and 45 years in control subjects; gender (61% female) and the race/ethnicity distribution (61% white) were identical in case subjects and control subjects by design. Compared with control subjects, case subjects had lower education attainment and were more likely to be former or current smokers and less likely to report any alcohol use in the past year. By beverage type, case subjects who reported alcohol use in the past year (compared with control subjects who also reported alcohol use in the past year) tended to consume less wine, but no significant differences were noted for beer or liquor. Also compared with control subjects, case subjects had higher systolic blood pressure, higher prevalence of hypertension, lower HDL cholesterol, and higher levels of fasting triglycerides, CRP, glucose, insulin, and homeostasis model assessment of insulin resistance. Body mass index and waist circumference were greater among case subjects, with 54% of case subjects being obese compared with 27% of control subjects. The LDL cholesterol was lower in case subjects than in control subjects, owing to the fact that a substantially higher proportion of case subjects (89% vs. 6%) were using lipid-lowering medication. By both criteria, the presence of MetS without diabetes, diabetes without MetS, and diabetes with MetS was significantly higher in case subjects than in control subjects. By using the AHA/NHLBI criteria, the prevalence of MetS without diabetes increased to 32% from 28% (i.e., by 14%) among case subjects and to 11% from 10% (i.e., by 1%) among control subjects. In turn, adopting the AHA/NHLBI criteria resulted in very little change in the prevalence of MetS with diabetes (to 26% from 25%, a 4% increase) among case subjects and no change (5%) among control subjects.

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Table 1. Characteristics of Early-Onset Coronary Artery Disease (CAD) Cases and Controls

Variable	Early-Onset CAD Subjects (n = 393)	Control Subjects (n = 393)	p Value
Age, yrs	45.8 ± 6.5	45.2 ± 5.6	0.06
Women	239 (61%)	239 (61%)	Matching factor
White race	238 (61%)	238 (61%)	Matching factor
Black race	43 (11%)	43 (11%)	
Hispanic/Latino race	42 (11%)	42 (11%)	
Asian race	35 (9%)	35 (9%)	
Other/mixed race	35 (9%)	35 (9%)	
Education level			
Less than high school	30 (8%)	13 (3%)	<0.0001
High school graduate or some college	258 (66%)	144 (37%)	
College graduate	82 (21%)	133 (34%)	
Post-graduate degree	21 (5%)	103 (26%)	
Unknown	2 (0.5%)	0 (0%)	
Current cigarette smoking*	95 (24%)	52 (13%)	<0.0001
Former cigarette smoking	139 (35%)	82 (21%)	
Never cigarette smoking	156 (40%)	258 (65%)	
Unknown smoking status	3 (0.8%)	1 (0.3%)	
Use of any alcohol in past 12 months	267 (68%)	335 (85%)	<0.0001
Beer, drinks/week among drinkers	1.3 ± 3.5	1.9 ± 7.5	0.29
Wine, drinks/week among drinkers	1.5 ± 3.1	2.4 ± 4.4	0.05
Liquor, drinks/week among drinkers	0.8 ± 2.5	0.6 ± 1.6	0.92
Systolic blood pressure	118.6 ± 18.6	114.5 ± 14.6	0.0004
Diastolic blood pressure	73.1 ± 10.5	74.4 ± 10.0	0.05
Hypertension	308 (78%)	115 (29%)	<0.0001
ATP-III MetS			<0.0001
Neither MetS nor diabetes	153 (39%)	325 (83%)	
MetS without diabetes	109 (28%)	38 (10%)	
Diabetes without MetS	31 (8%)	10 (3%)	
MetS with diabetes	100 (25%)	20 (5%)	
AHA/NHLBI MetS			<0.0001
Neither MetS nor diabetes	136 (35%)	318 (81%)	
MetS without diabetes	126 (32%)	45 (11%)	
Diabetes without MetS	27 (7%)	10 (3%)	
MetS with diabetes	104 (26%)	20 (5%)	
HDL cholesterol, mg/dl	45.0 ± 13.2	53.7 ± 14.8	<0.0001
LDL cholesterol, mg/dl	100.4 ± 28.7	119.1 ± 31.6	0.0001
Triglycerides, mg/dl¶	128 ± 115	93 ± 71	<0.0001
C-reactive protein, mg/dl¶	2.36 ± 4.3	0.94 ± 2.3	<0.001
Fasting glucose, mg/dl¶	99.0 ± 29	88.0 ± 15	<0.0001
Fasting insulin, iU/ml¶	12.4 ± 13.3	9.0 ± 8.3	<0.0001
HOMA-IR, mol × iU/l¶	3.24 ± 4.5	1.94 ± 1.8	<0.0001
Use of cholesterol-lowering agents	351 (89%)	25 (6%)	<0.0001
Body mass index, kg/m^2	31.4 ± 7.0	27.8 ± 6.7	<0.0001
Waist circumference, cm	96.7 ± 16.0	87.2 ± 14.8	<0.0001

For non-normally distributed variables, median ± interquartile range is shown. *As of index date.

AHA = American Heart Association; ATP-III = Adult Treatment Panel III; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein; MetS = metabolic syndrome; NHLBI = National Heart, Lung, and Blood Institute.

The prevalence of the individual components of MetS is shown in Table 2. Hypertension followed by low HDL cholesterol and large waist circumference were the most common components among case subjects; low HDL cholesterol and hypertension were also the most common components among control subjects. Whereas 31% of case subjects and 8% of control subjects had IFG by ATP-III criteria, 49% and 15%, respectively, did by AHA/NHLBI criteria. The case/control prevalence ratio was highest for ATP-III fasting glucose (3.9) and lowest for high triglycerides (1.9).

In conditional logistic regression adjusting for educational attainment, cigarette smoking, alcohol consumption, and body mass index (with having neither MetS nor diabetes as the reference level) (Table 3), the odds ratios (95% confidence intervals [CI]) for early-onset CAD associated with MetS without diabetes, diabetes without MetS, and MetS with diabetes, respectively, were 4.9 (95% CI 3.4 to 8.0), 7.2 (95% CI 3.2 to 16), and 8.0 (95% CI 4.4 to 14.6) using the ATP-III criteria and 5.7 (95% CI 3.5 to 9.2), 6.3 (95% CI 2.8 to 14.3), and 10.5 (95% CI 5.7 to 19.2) using the AHA/NHLBI criteria. Further adjustment for CRP attenuated only slightly the odds ratio estimates (data not shown). We performed a subset analysis to determine whether the associations of interest were similar when

Table 2. Prevalence of Metabolic Syndrome Components by Case-Control Status

Metabolic Syndrome Component	Cases (n = 393)	Controls (n = 393)	Prevalence Ratio
Waist circumference 102 cm (men); 88 cm (women)	55%	28%	2.0
Triglycerides 150 mg/dl	39%	21%	1.9
HDL cholesterol <40 mg/dl (men); <50 mg/dl (women)	59%	30%	2.0
Hypertension	78%	29%	2.7
ATP-III fasting glucose 110–125 mg/dl	31%	8%	3.9
AHA/NHLBI fasting glucose 100–125 mg/dl	49%	15%	3.3

Abbreviations as in Table 1.

restricting the analysis to AMI (n = 230) and corresponding matched control subjects (n = 230). Compared with the "composite case" definition, there was a weakening of the effect of MetS with diabetes (particularly when using the ATP-III MetS definition), but the AMI estimates were all well within the 95% CI of the composite case definition estimates (data not shown).

Next, we assessed the prognostic value of MetS above and beyond its individual components. In conditional logistic regression adjusting for educational attainment, cigarette smoking, alcohol consumption, body mass index, and diabetes, MetS by the ATP-III criteria was associated with 3.70 (95% CI 2.41 to 5.68) increased odds of early-onset CAD; MetS by the AHA/NHLBI criteria was associated with 4.57 (95% CI 2.98 to 7.01) increased odds of early-onset CAD. In a model containing the previously mentioned external covariates plus the 5 components defined according to the ATP-III definition (Table 4), low HDL cholesterol, hypertension, and IFG were significantly associated with early-onset CAD, and the strongest association by far was with hypertension. Similar overall results were obtained in the model with AHA/NHLBI MetS components, although the association with IFG was stronger using the AHA/NHLBI threshold of 100 to 125 mg/dl (adjusted odds ratio 4.1) than the ATP-III threshold of 110 to 125 mg/dl (adjusted odds ratio 2.7). After all 5 components plus external variables and diabetes were in the model, MetS was no longer significantly associated with early-onset CAD, and this was true regardless of the definition used.

We also performed supplementary analysis to address the issue of whether MetS without diabetes, diabetes without MetS, or diabetes with MetS is still associated with CAD after adjustment for the MetS components as categoric variables. After adjusting for the components, the odds ratios were 1.63 (95% CI 0.55 to 4.82) for MetS without diabetes, 9.02 (95% CI 2.50 to 32.49) for diabetes without MetS, and 2.02 (95% CI 0.51 to 8.08) for MetS with diabetes when using the ATP-III MetS definition. Corresponding estimates using the AHA/NHLBI MetS definition were 1.38 (95% CI 0.64 to 2.97) for MetS without diabetes, 3.75 (95% CI 1.48 to 9.51) for diabetes without MetS, and 1.65 (95% CI 0.63 to 4.33) for MetS with diabetes.

Table 3. Adjusted* Association Between Joint Categories of Metabolic Syndrome (MetS) and Diabetes and Early-Onset Coronary Artery Disease

	ATP-III MetS	AHA/NHLBI MetS
MetS without diabetes	4.95 (3.4–8.05)	5.70 (3.55–9.16)
Diabetes without MetS	7.21 (3.24–16.0)	6.31 (2.78–14.3)
MetS with diabetes	8.00 (4.39–14.6)	10.5 (5.70–19.2)

*Adjusted for age, educational attainment, cigarette smoking, alcohol consumption, and body mass index.
Abbreviations as in Table 1.

Because the use of categoric variables has been disputed on the basis that risk is really a progressive function, we repeated the analysis of components using continuous variables for waist circumference, triglycerides, HDL cholesterol, and fasting glucose. In agreement with the categoric analysis, the effect of MetS (both by ATP-III and by AHA/NHLBI criteria) was greatly attenuated and lost statistical significance after adjustment for the individual components (Table 5).

DISCUSSION

The prevalence of MetS is increasing at an alarming rate in young people (14). However, very few studies have quantified the impact of MetS on CAD occurring early in life. We also focused on 2 critical issues: 1) what are the repercussions of adopting the newly proposed threshold for IFG (100 to 125 mg/dl) in terms of the prevalence of the syndrome and its association with early-onset CAD; and 2) is MetS associated or not with greater risk of atherosclerotic cardiovascular disease more so than any of its individual components? It has been argued that the concept of syndrome implies that the risk associated with having the syndrome ought to be greater than the sum of its parts, and that all the factors should have a common underlying physiology which is responsible for their clustering (18).

In the present study, after adjusting for external risk factors, the presence of the MetS by ATP-III criteria in the absence of diabetes conferred an almost 5-fold increase in the odds of early-onset CAD; combined with diabetes, the odds ratio was 8. The AHA/NHLBI definition resulted in a slightly better prediction of outcome: the odds ratios were almost 6 and 10, respectively, for MetS without diabetes and with diabetes. However, in multivariate analysis, MetS (regardless of the definition used) conveyed no additional predictive information beyond its components, casting doubt on the clinical utility of MetS. A logical interpretation of this finding is that clinicians would be better off addressing the individual risk factors rather than "treating the

Table 4. Adjusted* Odds Ratios (95% Confidence Intervals) of Early-Onset Coronary Artery Disease Associated With Categorically Defined Components of the Metabolic Syndrome (MetS) and With the Syndrome Above and Beyond Its Components

Component	ATP-III MetS	AHA/NHLBI MetS	ATP-III Components + ATP-III MetS	AHA/NHLBI Components + AHA/NHLBI MetS
Waist circ. 102 (men), 88 cm (women)	1.29 (0.74–2.26)	1.15 (0.65–2.04)	1.26 (0.69–2.28)	1.10 (0.59–2.05)
Triglycerides 150 mg/dl	0.78 (0.50–1.23)	0.81 (0.52–1.28)	0.75 (0.44–1.28)	0.77 (0.46–1.31)
HDL cholesterol <40 (men), <50 mg/dl (women)	2.91 (1.96–4.31)	3.09 (2.07–4.63)	4.82 (1.80–4.42)	2.97 (1.87–4.69)
Hypertension	7.26 (4.92–10.70)	7.27 (4.88–10.83)	7.10 (4.67–10.79)	7.06 (4.60–10.82)
Fasting glucose 110–125 mg/dl	2.71 (1.60–4.57)		2.63 (1.50–4.62)	
Fasting glucose 100–125 mg/dl		4.06 (2.59–6.38)		3.91 (2.38–6.41)
ATP-III MetS			1.11 (0.53–2.31)	
AHA/NHLBI MetS				1.15 (0.55–2.41)

*All components entered into the same model and adjusted for age, educational attainment, cigarette smoking, alcohol consumption, and body mass index.
circ. = circumference; other abbreviations as in Table 1.

syndrome." We recognize, however, that the identification of a condition like MetS, even if it does not provide incremental value over its components, may better motivate physicians to treat the condition and its accompanying risk factors.

Previous investigators have reached similar conclusions. For example, blood pressure, HDL cholesterol, and diabetes, but not presence of MetS, were significant multivariate predictors of prevalent CHD in a recent analysis of the Third National Health and Nutrition Examination Survey (23). In the Caerphilly and Speedwell population studies, the excess of ischemic heart disease risk associated with MetS was no greater than can be explained by individual effects of the defining variables in a multiple logistic model (24).

We found that the components of MetS more strongly associated with early-onset CAD were hypertension, low HDL cholesterol, and IFG. Notably, IFG defined by the lower AHA/NHLBI threshold was more strongly associated with the outcome than IFG defined by the ATP-III criteria. Waist circumference and triglycerides were not independently related to early-onset CAD. This is most likely due to the fact that the effect of visceral adiposity is largely mediated by the other factors, and by the high correlation between triglycerides and HDL cholesterol (Spearman $r = -0.53$ combining case and control subjects).

To our knowledge, this is the first study describing the association between MetS and early-onset clinical CAD using concurrent age-, gender-, and race-matched control subjects. An earlier study in Turkey recruited 582 consecutive patients (496 men, 86 women) with newly diagnosed premature CAD (age ≤45 years), but did not include control subjects (25). The overall prevalence of MetS using ATP-III criteria (but including diabetics) in that study was 37%; the prevalence of MetS without diabetes was not reported.

Previous studies have shown that older individuals with MetS are at 2- to 3-fold increased risk of cardiovascular morbidity and mortality (4,5,7,23,26). The demonstration here of an even stronger effect of the presence of MetS without diabetes on early-onset CAD constitutes important new evidence for primary and secondary prevention of CAD in young adulthood.

Based on the strength of associations observed for the individual components and the fact that the association of the MetS with early-onset CAD was greatly attenuated and no longer significant after adjustment for its components, our data support the view that more intensive efforts should be directed toward prevention and management of the individual risk factors (particularly hypertension, low HDL cholesterol, and IFG) than to "diagnosing" the syndrome. From the standpoint of primary prevention, interventions designed to increase exercise and achieve weight loss have been shown to effectively reduce these risk factors (27). In addition, drug treatment for hypertension is well established, but definitive randomized clinical trial data supporting the use of drugs aimed at increasing HDL cholesterol levels independent of lowering LDL cholesterol levels are still needed.

Table 5. Adjusted* Odds Ratios (95% Confidence Intervals) of Early-Onset Coronary Artery Disease Associated With Continuously Defined Components of the Metabolic Syndrome (MetS) and With the Syndrome Above and Beyond Its Components

Component	Component Only	Component + ATP-III MetS	Component + AHA/NHLBI
Waist circumference, per 1 SD	0.96 (0.82–1.13)	0.95 (0.80–1.12)	0.92 (0.78–1.09)
Triglycerides, per 1 SD	1.01 (0.79–1.28)	0.98 (0.76–1.26)	0.94 (0.74–1.20)
HDL cholesterol, per 1 SD	0.63 (0.52–0.78)	0.65 (0.52–0.81)	0.68 (0.55–0.85)
Hypertension	6.70 (4.58–9.77)	6.40 (4.30–9.52)	5.96 (4.0–8.86)
Fasting glucose, per 1 SD	1.94 (1.43–2.63)	1.90 (1.39–2.58)	1.83 (1.35–2.48)
ATP-III MetS		1.22 (0.71–2.12)	
AHA/NHLBI MetS			1.66 (0.98–2.82)

SD = waist circumference of 13 cm in men, 17 cm in women; triglycerides = 121 mg/dl in men, 107 in women; HDL cholesterol = 11 mg/dl in men, 15 mg/dl in women; glucose = 42 mg/dl in men, 49 mg/dl in women. *All components entered into the same model and adjusted for age, educational attainment, cigarette smoking, alcohol consumption, and body mass index.
Abbreviations as in Table 1.

Study limitations. First, our case definition excluded fatal CAD, because subjects were identified and invited to attend a clinic visit after being discharged alive from the hospital. Thus, we could not ascertain whether MetS or its components are more or less relevant for fatal versus nonfatal CAD. Second, the majority of case subjects (~90%) received treatment for dyslipidemia (vs. 6% of control subjects) and therefore had therapeutically lowered LDL cholesterol. Consequently, we were unable to statistically adjust for lipid-lowering medication and LDL cholesterol as external variables to the syndrome.

Although triglycerides remained significantly higher in early-onset CAD subjects compared with control subjects, the high prevalence of lipid-lowering use may have contributed also to weakening the association of triglycerides with early-onset CAD in our study. Finally, participants were all insured (CARDIA control subjects also were recruited from KPNC), and therefore our findings may not apply to uninsured populations.

The strengths of the study include the availability of a unique large set of very well characterized case subjects with early-onset clinical CAD, which is a relatively rare event that requires very large source populations. We also recruited young adults free of cardiovascular disease for ideally matched control subjects. Second, our sample was ethnically diverse and recruited directly from the communities covered by a large integrated health care delivery system, which increases the generalizability of the findings.

Conclusions. The present results provide new evidence that the presence of MetS without and with diabetes is a strong independent determinant of early-onset CAD. Moreover, the AHA/NHLBI revision to the ATP-III criteria appeared to better predict outcome. However, the results of our analysis suggest that MetS does not constitute a syndrome that is more prognostic than the sum of its parts.

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