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Arterial structure and function in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study

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Aims To study the relations between the metabolic syndrome (MS) and subclinical atherosclerosis in young adults.

Methods and results International Diabetes Federation (msIDF), National Institute of Health Adult Treatment Panel III (msNCEP), and European Group for the Study of Insulin Resistance (msEGIR) definitions of MS were related to carotid artery intima–media thickness (cIMT), brachial flow-mediated dilatation (FMD), and carotid artery compliance (CAC) in 2163 Finnish adults (aged 32 ± 5years). All definitions associated with increased cIMT and decreased CAC in both sexes. The cIMT values (mean ± SD) were 0.576 ± 0.088 mm in subjects without the syndrome, 0.615 ± 0.102 mm in msIDF, 0.617 ± 0.104 mm in msNCEP, and 0.607 ± 0.097 mm in msEGIR ($P < 0.0001$). Corresponding CAC values were 2.26 ± 0.72, 1.76 ± 0.66, 1.73 ± 0.66, 1.72 ± 0.66%/10 mmHg ($P < 0.001$). Impaired brachial FMD was not related to MS but it modified the relations between MS and cIMT: MS correlated with increased cIMT in subjects with an impaired FMD response ($P = 0.003$) but not in subjects with an enhanced FMD response ($P = 0.75$).

Conclusion All current definitions of MS identify a population of young adults with evidence of increased subclinical atherosclerosis. Impaired brachial endothelial response is not a hallmark of MS in young adults, but the status of endothelial function modifies the association between metabolic risk factors and atherosclerosis.

Keywords Metabolic syndrome • Carotid intima-media thickness • Carotid compliance • Brachial flow-mediated dilatation • Atherosclerosis

Introduction

The metabolic syndrome (MS) is a cluster of cardiovascular risk factors including obesity, impaired glucose tolerance, hypertension, and dyslipidaemia.[1] MS is associated with increased risk of developing diabetes and cardiovascular diseases.[2,3] Previous reports have suggested that young adults with MS may have increased subclinical atherosclerosis, indicated as increased intima–media thickness[4] and pulse wave velocity.[5] The development of atherosclerosis in response to risk factor exposure begins in early life.[6,7] Therefore, diagnosing MS in young subjects may be helpful in identifying a population at risk for increased subclinical atherosclerosis.

Carotid artery intima–media thickness (cIMT), carotid artery compliance (CAC), and brachial artery flow-mediated dilatation (FMD) are markers of arterial health that can be measured non-invasively by ultrasound. Increased cIMT correlates with vascular risk factors,[6,7] relates to coronary artery disease,[8] and predicts cardiovascular events.[9] Similarly, decreased carotid artery compliance is associated with risk factors,[10] and has been implicated as a predictor for cardiovascular events.[11] Brachial FMD is a marker of

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endothelial function that reflects nitric oxide release from vascular endothelial cells.[12] Impaired brachial FMD has been shown to predict cardiovascular events in patients with coronary disease.[13] Furthermore, brachial FMD status may modify the relations between risk factors and atherosclerosis.[14,15]

We examined the relations of MS to cIMT, CAC, and brachial FMD in young adults and used 3 recently published guidelines to diagnose MS: the International Diabetes Federation guideline (msIDF),[16] the National Institute of Health Adult Treatment Panel III guideline (msNCEP),[17] and the European Group for the Study of Insulin Resistance guideline (msEGIR).[18]

Methods

Subjects

The Cardiovascular Risk in Young Finns Study is a multi-centre study of atherosclerotic risk factors of children and young adults. The baseline study in 1980 included 3596 (83.2% of those invited) children and adolescents, aged 3–18 years.[19] In 2001, we re-examined 2285 individuals aged 24–39. Complete data in this analysis included 2163 subjects (999 men and 1164 women; mean age 32 ± 5 years). None had established cardiovascular disease, 35 subjects (1.6%) had antihypertensive and seven subjects (0.3%) had lipid-lowering medication. The analysis of the study was restricted to non-diabetic (type 1) and non-pregnant subjects.

Clinical characteristics

Height, weight, waist, and hip circumferences were determined for all participants. Blood pressure was measured using a random zero sphygmomanometer. Venous blood samples were taken after fasting for 12 h. Lipid determinations were done using standard methods. Details of analytical procedures have been reported previously.[20] LDL-cholesterol concentration was calculated by the Friedewald formula.[21] Glucose concentrations were analyszed enzymatically and serum insulin was measured by microparticle enzyme immunoassay kit.[11]

Carotid artery ultrasound imaging

Ultrasound studies were performed for 2264 subjects using a high-resolution ultrasound system (Sequoia 512, Acuson, CA, USA). cIMT was measured from the left common carotid artery.[22,23] The between visit coefficient of variation of cIMT measurements was 6.4%.[6]

Ultrasound and brachial blood pressure measurements were used to calculate the carotid artery compliance, $CAC=[(D_s-D_d)/D_d)]/(P_s-P_d)$, where D_s is the systolic diameter, D_d, the diastolic diameter, P_s, systolic blood pressure, and P_d, diastolic blood pressure. CAC measures the ability of the arteries to expand as the response to pulse pressure caused by cardiac contraction and relaxation.[11]

To assess brachial FMD, the left brachial artery diameter was measured both at rest and during the reactive hyperaemia, induced by inflation of a pneumatic tourniquet placed around the forearm, followed by release. The vessel diameter after reactive hyperaemia was expressed as the percentage relative to the resting scan. The 3 month between-visit CV was 3.2% for brachial artery diameter measurements and 26.0% for FMD measurements.[15]

Diagnostic criteria of metabolic syndrome

msIFD is diagnosed as: waist ≥94 cm in men and ≥80 cm in women, fasting glucose ≥5.6 mmol/L, hypertriglyceridaemia ≥1.695 mmol/L, and HDL-cholesterol <1.036 mmol/L in men and <1.295 in women, and blood pressure ≥130/≥85 mmHg or treatment. A diagnosis requires abdominal obesity and ≥2 of the four criteria. msNCEP is diagnosed as three or more of the following conditions: waist ≥102 cm in men and ≥88 cm in women, serum triglycerides ≥1.695 mmol/L (150 mg/dl), HDL-cholesterol <1.036 mmol/L (40 mg/dl) in men and <1.295 mmol/l (50 mg/dl) in women, blood pressure ≥130 or ≥85 mmHg or treated, and glucose ≥5.6 mmol/L (100 mg/dl). According to the EGIR criteria, subjects with MS were defined as the presence

Table 1 Population characteristics and characteristics of study subjects defined by IDF, NCEP, and EGIR metabolic syndrome

Variable	All	No syndrome	IDF	NCEP	EGIR
n	2163	1766	323	279	211
Sex (% men)	46.2	43.1	56.4	60.6	60.2
Age (years)	31.7 ± 5.0	31.4 ± 5.0	33.4 ± 4.6	33.0 ± 4.7	32.6 ± 4.9
BMI (kg/m^2)	25.0 ± 4.4	23.9 ± 3.5	30.7 ± 4.5	30.8 ± 4.9	31.3 ± 4.8
Waist (mm)	841 ± 122	808 ± 100	1000 ± 108	1006 ± 111	1019 ± 114
Systolic blood pressure (mmHg)	117 ± 13	115 ± 12	127 ± 14	129 ± 14	128 ± 15
Diastolic blood pressure (mmHg)	71 ± 11	69 ± 9	80 ± 12	82 ± 12	81 ± 12
Total cholesterol (mmol/L)	5.1 ± 1.0	5.0 ± 0.9	5.6 ± 1.1	5.7 ± 1.1	5.7 ± 1.1
LDL-cholesterol (mmol/L)	3.3 ± 0.8	3.2 ± 0.8	3.6 ± 0.9	3.6 ± 0.9	3.6 ± 0.9
HDL-cholesterol (mmol/L)	1.28 ± 0.31	1.34 ± 0.30	1.04 ± 0.25	1.00 ± 0.23	1.03 ± 0.26
Triglycerides (mmol/L)	1.32 ± 0.84	1.11 ± 0.50	2.24 ± 1.19	2.35 ± 1.20	2.45 ± 1.46
Glucose (mmol/L)	5.0 ± 0.5	4.9 ± 0.4	5.4 ± 0.8	5.5 ± 0.8	5.4 ± 0.7
Insulin (mU/L)	7.7 ± 5.5	6.4 ± 3.5	13.4 ± 8.9	14.0 ± 9.1	16.9 ± 9.1
Smoking (%)	24.6	24.3	25.1	23.9	21.9

Values are mean ± SD or percentage of subjects. In all pairwise comparisons $P < 0.003$ (NCEP vs. no syndrome, EGIR vs. no syndrome, and IDF vs. no syndrome), except for smoking $P > 0.4$ in all comparisons.
IDF, International Diabetes Federation; NCEP, National Institute of Health Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance.

of hyperinsulinaemia (defined as non-diabetic subjects having fasting insulin level in the highest quartile, the cut-off point of our study was 9 mU/L), and at least two of the following conditions: fasting glucose $\geq$6.1 mmol/L, blood pressure $\geq$140/$\geq$90 mmHg or current use of antihypertensive medication, serum triglyceride level $>$2.0 mmol/L or HDL-cholesterol $<$1.0 mmol/L, and waist at least 94 cm in men and 80 cm in women.

Statistical methods

Results are expressed as mean and standard deviation (SD). Mean cIMT, CAC, and FMD for each MS definition was compared between groups using ANOVA. Values for fasting insulin and triglycerides were log transformed due to skewed distribution. Linear regression models were used to examine the association of MS and its components to ultrasound variables. The three definitions of MS were intercorrelated: $r = 0.760$ between IDF and NCEP, $r = 0.594$ between NCEP and EGIR, $r = 0.619$ between IDF and EGIR. These associations were considered not to be high enough to cause multicollinearity in regression analysis. There was no interaction between sexes in MS definitions and ultrasound variables, indicating that the effects of MS definitions on ultrasound markers were similar between sexes. Therefore, analyses were performed sexes combined by including sex as a covariate in regression models. For the linear regression models, the model assumptions of constant variance were assessed by drawing absolute and predicted values of residuals into the co-ordinates. The normality assumptions of the residuals were assessed by examining histograms of the residuals and normal probability plots. All analyses were repeated after excluding subjects taking lipid-lowering or antihypertensive medications, with essentially similar results. Statistical tests were performed with SAS version 8.1 and statistical significance was inferred at a two-tailed *P*-value $<$0.05.

Results

Characteristics of study participants are shown in *Table 1*. MS was associated with higher cIMT in both sexes using all three definitions. *Figure 1A* shows the age- and sex-adjusted mean values of cIMT in various groups. Lowest cIMT values were observed in subjects without MS by any criteria (0.576 $\pm$ 0.088 mm). Higher cIMT values were measured in individuals with msIDF (0.615 $\pm$ 0.102 mm), msNCEP (0.617 $\pm$ 0.104 mm), or msEGIR (0.607 $\pm$ 0.097 mm). Similarly, subjects having MS by any criteria had lower CAC and higher FMD than subjects without MS (*Figure 1B* and *C*).

All three definitions were significantly associated with cIMT and CAC in regression models adjusted for age and sex (*Table 2*). When msEGIR was included in the same model with msIDF or msNCEP criteria, the effect of the msEGIR definition became non-significant. All the definitions correlated equally well with CAC. MS explained CAC more strongly than cIMT by all three criteria ($R^2 = 0.16$ vs. 0.11-0.12).

Table 3 shows the age- and sex- adjusted regression coefficients between each of the components of MS and cIMT, CAC, and FMD. In the msIDF and msNCEP definitions, all the individual components, except low HDL-cholesterol, correlated significantly with cIMT. In addition, hyperinsulinaemia, which is the key component of msEGIR, did not correlate with cIMT. All components correlated significantly with CAC. Obesity and hyperinsulinaemia correlated directly with FMD.

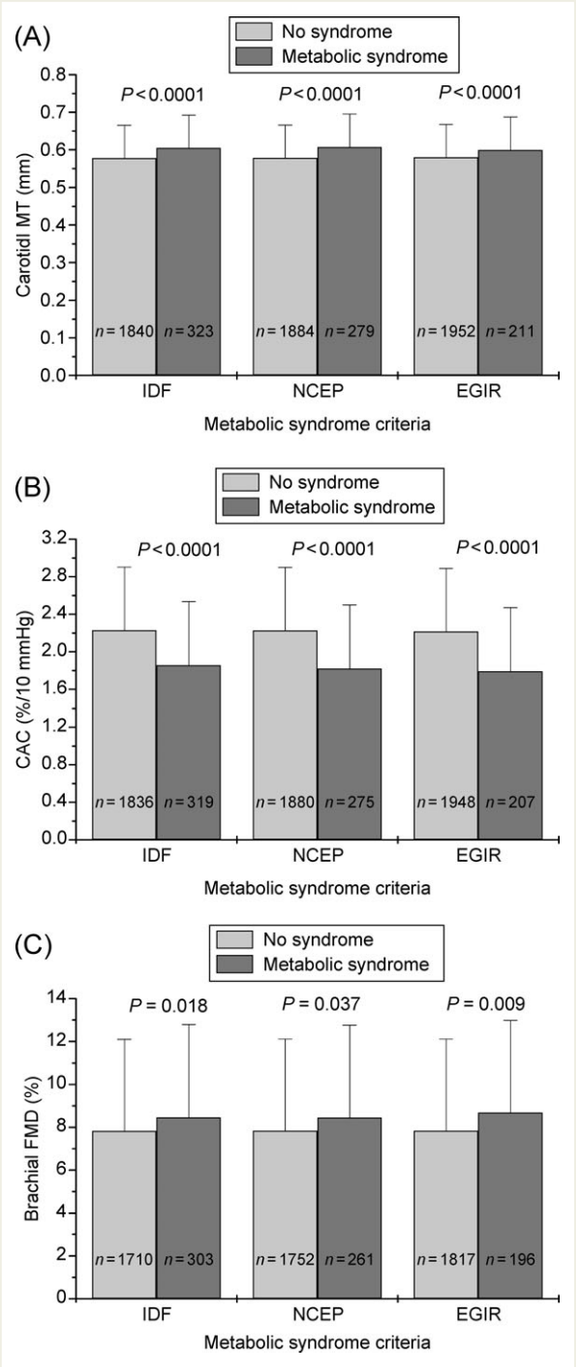

Figure 1 Comparison of age- and sex-adjusted mean ($\pm$SD) values of (*A*), (*B*), and (*C*) brachial between subjects without MS and subjects fulfilling International Diabetes, Federation carotid artery intima-media thickness, criteria, European Group for the Study of Insulin Resistance carotid artery compliance criteria, or National Institute of Health Adult Treatment Panel III flow-mediated dilatation criteria. *P*-values are age- and sex-adjusted

Table 2 IDF, NCEP, and EGIR definitions as determinants of cIMT and CAC in 2163 men and women aged 24–39[a]

		Beta ± SE	*P*-value	R^2
cIMT				
Model 1	IDF	0.0265 ± 0.0053	<0.0001	0.116
Model 2	NCEP	0.0289 ± 0.0057	<0.0001	0.117
Model 3	EGIR	0.0193 ± 0.0064	0.0025	0.110
Model 4	IDF	0.0265 ± 0.0113	0.0002	0.116
	EGIR	−0.0001 ± 0.0135	0.99	
Model 5	NCEP	0.0287 ± 0.0070	<0.0001	0.117
	EGIR	0.0004 ± 0.0079	0.96	
CAC				
Model 1	IDF	−0.3727 ± 0.0415	<0.0001	0.159
Model 2	NCEP	−0.4047 ± 0.0440	<0.0001	0.161
Model 3	EGIR	−0.4236 ± 0.0497	<0.0001	0.156
Model 4	IDF	−0.2496 ± 0.0521	<0.0001	0.165
	EGIR	−0.2416 ± 0.0624	0.0001	
Model 5	NCEP	−0.2808 ± 0.0539	<0.0001	0.167
	EGIR	−0.2395 ± 0.0608	<0.0001	

IDE, International Diabetes Federation; NCEP, National Intstitute of Health Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; CAC, Carotid artery compliance; cIMT, carotid artery intima–media thickness.
IDF: abdominal obesity (waist ≥94 cm in men and ≥80 cm in women) and ≥2 of the four criteria: hypertriglyceridaemia ≥1.695 mmol/L, HDL-cholesterol <1.036 mmol/L in men and <1.295 in women, blood pressure ≥130/≥85 mmHg or treatment for hypertension, and glucose ≥5.6 mmol/L.
NCEP: ≥3 of the following: waist ≥102 cm in men and ≥88 cm in women, serum triglycerides ≥1.695 mmol/L, HDL-cholesterol <1.036 mmol/L in men and 1.295 mmol/l in women, blood pressure ≥130 or ≥85 mmHg or treatment for hypertension, and glucose ≥5.6 mmol/L.
EGIR: hyperinsulinaemia (fasting insulin in the highest quartile), and ≥2 of the following: waist ≥94 cm in men and ≥80 cm in women, serum triglycerides >2.0 mmol/L or HDL-cholesterol <1.0 mmol/L, blood pressure ≥140/≥90 mmHg or treatment, and fasting glucose ≥6.1 mmol/L.
[a]All models are adjusted for age and sex.

Table 3 Age- and sex-adjusted relationships between components of MS and cIMT, CAC, and brachial FMD in men and women aged 24–39

	Criteria	Beta ± SE	*P*-value
cIMT			
Hypertension	(IDF, NCEP)	0.0270 ± 0.0048	<0.0001
Hypertension	(EGIR)	0.0453 ± 0.0070	<0.0001
Hyperglycaemia	(EGIR)	0.0279 ± 0.0126	0.0270
Hyperglycaemia	(IDF, NCEP)	0.0156 ± 0.0061	0.0105
Obesity	(NCEP)	0.0247 ± 0.0051	<0.0001
Obesity	(IDF, EGIR)	0.0227 ± 0.0040	<0.0001
Dyslipidaemia (TG)	(IDF, NCEP)	0.0093 ± 0.0046	0.0452
Dyslipidaemia (HDL-c)	(IDF, NCEP)	0.0065 ± 0.0039	0.0934
Dyslipidaemia (HDL-c/TG)	(EGIR)	0.0054 ± 0.0046	0.24
Hyperinsulinaemia	(EGIR)	0.0055 ± 0.0004	0.22
CAC			
Hypertension	(IDF, NCEP)	−0.4409 ± 0.0367	<0.0001
Hypertension	(EGIR)	−0.5041 ± 0.0544	<0.0001
Hyperglycaemia	(EGIR)	−0.2728 ± 0.0997	0.0063
Hyperglycaemia	(IDF, NCEP)	−0.1779 ± 0.0476	0.0002
Obesity	(NCEP)	−0.3459 ± 0.0395	<0.0001
Obesity	(IDF, EGIR)	−0.2709 ± 0.0312	<0.0001
Dyslipidaemia (TG)	(IDF, NCEP)	−0.1909 ± 0.0360	<0.0001
Dyslipidaemia (HDL-c)	(IDF, NCEP)	−0.0636 ± 0.0305	0.0374
Dyslipidaemia (HDL-c/TG)	(EGIR)	−0.1825 ± 0.0360	<0.0001
Hyperinsulinaemia	(EGIR)	−0.3283 ± 0.0350	<0.0001
FMD			
Hypertension	(IDF, NCEP)	0.2045 ± 0.2443	0.40
Hypertension	(EGIR)	−0.3425 ± 0.3583	0.34
Hyperglycaemia	(EGIR)	0.2838 ± 0.6570	0.67
Hyperglycaemia	(IDF, NCEP)	0.4350 ± 0.3125	0.16
Obesity	(NCEP)	0.8729 ± 0.2571	0.0007
Obesity	(IDF, EGIR)	1.0675 ± 0.2027	<0.0001
Dyslipidaemia (TG)	(IDF, NCEP)	0.2861 ± 0.2337	0.22
Dyslipidaemia (HDL-c)	(IDF, NCEP)	0.1155 ± 0.1970	0.56
Dyslipidaemia (HDL-c/TG)	(EGIR)	0.3348 ± 0.2331	0.15
Hyperinsulinaemia	(EGIR)	0.7365 ± 0.2284	0.0013

IDE, International Diabetes Federation; NCEP, National Intstitute of Health Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; CAC, Carotid artery compliance; cIMT, carotid artery intima–media thickness; HDL-c, high density lipoprotein cholesterol; TG, triglycerides.

Table 4 shows the multiple regression models for the three criteria, exploring the independent effects of the individual components on cIMT, CAC and FMD. Hypertension and obesity were associated significantly with cIMT in all models. Obesity, hypertension and hyperinsulinemia were inversely correlated with CAC in multivariable models. Obesity correlated directly with FMD, and hypertension defined by the EGIR criteria correlated inversely with FMD.

Figure 2 shows the mean cIMT, CAC and FMD (age- and sex-adjusted) values for subjects with various number of MS components (0, 1, 2, 3 and ≥4) by the IDF criteria. There was an increasing trend in cIMT and a decreasing trend in CAC across the groups with increasing number of MS components. There was also a direct trend between the number of MS components and FMD (*Figure 2c*).

We have previously shown in this population that brachial FMD response may modify the association between conventional risk factors and cIMT.[15] Therefore, we analysed whether the relations between MS and cIMT are modified by the magnitude of the FMD response. *Figure 3* shows cIMT values in subjects with and without msIDF categorized according to their FMD response defined in

Table 4 Multivariable relationships between each components of MS and cIMT, CAC, and brachial FMD adjusted for age, sex, and the other MS components in 2163 men and women aged 24–39

	cIMT		CAC		FMD	
	Beta ± SE	*P*-value	Beta ± SE	*P*-value	Beta ± SE	*P*-value
IDF components (absent−present)						
Hypertension	0.0218 ± 0.0049	<0.0001	−0.3793 ± 0.0374	<0.0001	−0.0819 ± 0.2507	0.74
Obesity	0.0180 ± 0.0044	<0.0001	−0.1806 ± 0.0330	<0.0001	1.1085 ± 0.2207	<0.0001
Low HDL-c	0.0017 ± 0.0040	0.68	0.0069 ± 0.0305	0.82	−0.1177 ± 0.2047	0.57
High TG	−0.0016 ± 0.0049	0.74	−0.0663 ± 0.0374	0.076	−0.0739 ± 0.2500	0.77
High glucose	0.0085 ± 0.0061	0.16	−0.0785 ± 0.0465	0.092	0.2170 ± 0.3160	0.49
NCEP components (absent−present)						
Hypertension	0.0223 ± 0.0049	<0.0001	−0.3756 ± 0.0374	<0.0001	0.0010 ± 0.2518	0.997
Obesity	0.0176 ± 0.0054	<0.0001	−0.2339 ± 0.0410	<0.0001	0.8275 ± 0.2752	0.0027
Low HDL-c	0.0021 ± 0.0040	0.68	0.0088 ± 0.0305	0.77	−0.0552 ± 0.2058	0.79
High TG	0.0007 ± 0.0048	0.74	−0.0821 ± 0.0367	0.025	0.1001 ± 0.2473	0.69
High glucose	0.0090 ± 0.0061	0.16	−0.0765 ± 0.0465	0.10	0.2715 ± 0.3176	0.39
EGIR components (absent−present)						
High Insulin	−0.0093 ± 0.0051	0.066	−0.2039 ± 0.0389	<0.0001	0.3709 ± 0.2560	0.15
Hypertension	0.0403 ± 0.0071	<0.0001	−0.3905 ± 0.0549	<0.0001	−0.8209 ± 0.3678	0.026
Obesity	0.0217 ± 0.0045	<0.0001	−0.1430 ± 0.0341	<0.0001	1.0315 ± 0.2257	<0.0001
Dyslipidaemia	−0.0031 ± 0.0048	0.52	−0.0393 ± 0.0371	0.29	0.0003 ± 0.2471	0.999
High glucose	0.0222 ± 0.0126	0.080	−0.0945 ± 0.0975	0.33	0.0252 ± 0.6608	0.97

Regression coefficients indicate the change in cIMT (mm), in CAC (%/10 mmHg), and in FMD (%) for absence or presence of individual MS components.
IDF, International Diabetes Federation; EGIR, European Group for the Study of Insulin Resistance; CAC, Carotid artery compliance; cIMT, carotid artery intima−media thickness; FMD, flow-mediated dilatation; HDL-c, high density lipoprotein cholesterol; TG, triglycerides.

three groups;[15] impaired (lowest age and sex specific decile, $n = 206$, FMD = 1.1 ± 1.4%, mean ± SD), intermediate (values between the 10th and 90th percentiles, $n = 1601$, FMD = 7.8 ± 2.9%), and enhanced (highest age and sex- specific decile, $n = 206$, FMD = 15.9 ± 2.8%). MsIDF was associated with higher cIMT values in subjects with impaired and intermediate FMD response. Whereas subjects with msIDF and enhanced FMD response had cIMT values corresponding to the population mean (*Figure 3*). Similar results were seen with msNCEP and msEGIR (data not shown).

Discussion

We found that young adults with MS had increased cIMT and decreased CAC. All recently proposed diagnostic criteria for MS worked equally well to identify subsets of individuals at risk for increased cIMT and decreased CAC, despite the overlap in their target populations.

The relations between MS definitions and subclinical atherosclerosis in young adults have been previously studied in the Bogalusa Heart Study. Tzou *et al.*[4] performed carotid intima−media measurements in 507 young adults. They reported that MS, defined by either NCEP or WHO guidelines, was associated with increased cIMT. Urbina *et al.*[24] and Li *et al.*[5] reported that MS and its components were associated with increased arterial stiffness in young adults. In the Baltimore Longitudinal Study of Aging, Scuteri *et al.*[25] studied the association between MS and cIMT and stiffness (evaluated by the stiffness index) in 471 subjects and reported that cIMT was 16% higher and stiffness 32% higher in subjects with the msNCEP compared with controls. Our data from a population of over 2000 subjects confirm these findings.

The components of msIDF and msNCEP are easily ascertainable, as the diagnoses do not require the measurement of insulin or oral glucose tolerance test. Insulin resistance is generally considered as the primary underlying abnormality in MS.[1,26] Thus intuitively, the inclusion of a marker of insulin resistance to the diagnostic criteria of MS should increase the power to predict increased cardiovascular risk. However, hyperinsulinemia, which is a required diagnostic component in EGIR definition, did not correlate with cIMT in our study population. Moreover, the correlation between cIMT and msEGIR lost its significance in a multivariable model adjusted for msIDF or msNCEP. Inclusion of a marker of insulin resistance to MS definition may increase the predictive value for diabetes but not necessarily cardiovascular disease. On the other hand, analysis of the NHANES data have suggested that the NCEP criteria may fail to detect a proportion of subjects with insulin resistance.[27] According to the studies by Laaksonen *et al.*,[28] the NCEP definition may be less sensitive than the WHO definition in predicting type 2 diabetes. Interestingly, Meigs *et al.*[29] found that subjects with msNCEP were less insulin resistant but had higher future risk of cardiovascular disease than subjects with MS according to the WHO definition.

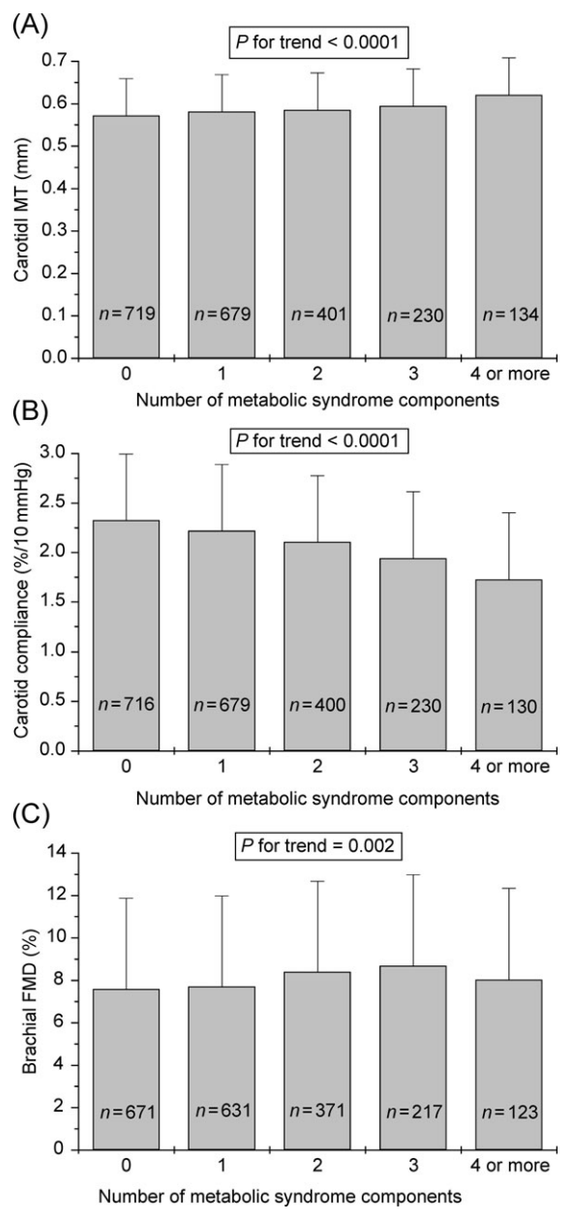

Figure 2 Age- and sex-adjusted mean (±SD) values of (*A*) carotid artery intima-media thickness, (*B*) carotid artery compliance, and (*C*) brachial flow-mediated dilatation across the number of metabolic syndrome components defined by the International Diabetes Federation guideline

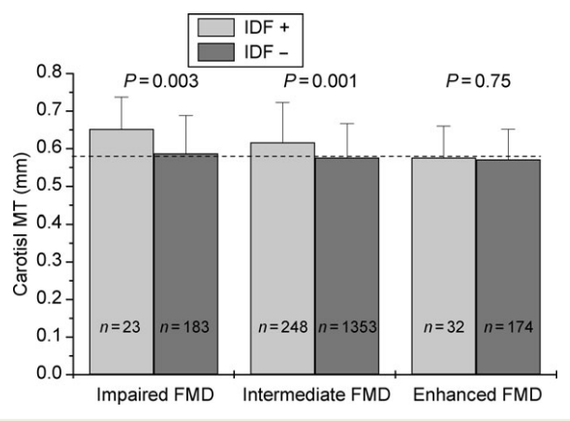

Figure 3 Association between brachial flow-mediated dilatation (impaired, intermediate, or enhanced flow-mediated dilatation response) and carotid artery intima-media thickness (mean ± SD) in young adults with or without International Diabetes Federation. Dashed line indicates the population mean. flow-mediated dilatation response status modified the relation between International Diabetes Federation and carotid artery intima-media thickness (*P*-value for interaction 0.023). This significant interaction indicates that the strength of the association between International Diabetes Federation and carotid artery intima-media thickness is different across the categories of the flow-mediated dilatation response

Type 2 diabetes increases the risk of cardiovascular disease in women to a greater extent than in men.[30] Iglseder *et al.*[31] recently reported that the effects of MS on cIMT were more pronounced in women than in men. However, we found no evidence of interaction by sex on the effects of MS definitions on markers of subclinical atherosclerosis.

Conventional risk factors do not correlate very strongly with brachial FMD in our population.[15] FMD is directly related with HDL-cholesterol and BMI, and inversely with systolic blood pressure when these risk markers are considered as continuous variables.[15] Previously, Yan *et al.*[32] found an inverse correlation between FMD and blood pressure, but no correlations between FMD and other individual risk factors in 1578 healthy middle-aged firefighters in the FATE study. In the present analysis, we found no evidence of impaired FMD response in the individuals with MS. In fact, subjects with MS had slightly higher average FMD responses due to the unexpected direct relation between FMD and body size.[15] We have no plausible explanation for this observation, but it suggests that an increase in body size within the non-obese range in a population of healthy young adults is associated with physiological changes that lead to enhanced FMD responses, and overcome the opposite influences of larger vessel size and increased oxidative stress associated with higher BMI's. One possibility is that the relationship between body size and endothelial function is not linear.[33] In line with this, we have previously shown that the relationship between body size and endothelial function is curvilinear, and that we are observing the upward slope of this relationship in our population of healthy adults.[15]

Although subjects with MS did not have impaired endothelial function, the FMD response modified the relations between MS and subclinical atherosclerosis. MS was associated with higher cIMT in subjects with impaired FMD, whereas subjects with MS and enhanced FMD had normal cIMT values, comparable with the population average. These findings indicate that systemic endothelial function may reflect the propensity of arteries to develop atherosclerotic changes in response to exposure to metabolic risk factors. Arterial endothelial damage or activation may be

required before risk factors can induce atherosclerotic changes in the arterial wall. Conversely preserved endothelial function may offer protection against the development atherosclerosis.

We measured cIMT only from the common carotid artery, which is less sensitive to local atherosclerosis than carotid bifurcation and internal carotid segments.[34] The prognostic value of IMT measurements to predict future cardiovascular events may increase when data from all three segments are combined.[9] Therefore, our present study may underestimate the relationships between MS and carotid atherosclerosis. We measured pulse pressure from the brachial artery to calculate carotid artery compliance. It would be more ideal to measure pulse pressure directly from the carotid artery, because the use of brachial blood pressures can overestimate pulse pressure in central arteries.[35]

In summary, all three recent diagnostic definitions of MS identify subsets of young adults with greater cIMT and lower CAC indicative of increased burden of subclinical carotid atherosclerosis. Although brachial FMD responses are not related to MS, the status of systemic endothelial function seems to modify the relations between metabolic risk and atherosclerosis. Individuals with evidence of enhanced endothelial function may be protected against the development of subclinical atherosclerosis in response to metabolic risk factors.

Conflict of interest: none declared.

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