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Metabolic Syndrome Amplifies the Age-Associated Increases in Vascular Thickness and Stiffness

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OBJECTIVES We sought to evaluate whether the clustering of multiple components of the metabolic syndrome (MS) has a greater impact on these vascular parameters than individual components of MS.

BACKGROUND Intima-media thickness (IMT) and vascular stiffness have been shown to be independent predictors of adverse cardiovascular events. The MS is defined as the clustering of three or more of the cardiovascular risk factors of dysglycemia, hypertension, dyslipidemia, and obesity.

METHODS Carotid IMT and stiffness were derived via B-mode ultrasonography in 471 participants from the Baltimore Longitudinal Study on Aging, who were without clinical cardiovascular disease and not receiving antihypertensive therapy.

RESULTS The MS conferred a disproportionate increase in carotid IMT (+16%, $p < 0.0001$) and stiffness (+32%, $p < 0.0001$), compared with control subjects. Multiple regression models, which included age, gender, smoking, low-density lipoprotein, as well as each individual component of MS as continuous variables, showed that MS was an independent determinant of both IMT ($p = 0.002$) and stiffness ($p = 0.012$). The MS was associated with a greater prevalence of subjects whose values were in the highest quartiles of IMT, stiffness, or both.

CONCLUSIONS Even after taking into account each individual component of MS, the clustering of at least three of these components is independently associated with increased IMT and stiffness. This suggests that the components of MS interact to synergistically impact vascular thickness and stiffness. Future studies should examine whether the excess cardiovascular risk associated with MS is partly mediated through the amplified alterations in these vascular properties. (J Am Coll Cardiol 2004;43:1388–95) © 2004 by the American College of Cardiology Foundation

The metabolic syndrome (MS), also referred to as the insulin resistance syndrome, is defined as the clustering of several cardiovascular risk factors in an individual, including impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity (1–3). Epidemiologic studies have shown that MS is quite common, affecting 24% of the U.S. population between the ages of 20 and 70 years (4). There is increasing evidence that this syndrome is a predictor of adverse cardiovascular events (4–7).

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The independent association between vascular structure and function and the individual components of MS—namely, hypertension (8–12), high-density lipoprotein (HDL) cholesterol (13), triglycerides (8,14), waist circumference (9), fasting glucose (14), and hemoglobin A_{1C} (9)—has previously been reported.

Alterations in vascular structure and function, including increased arterial wall thickness, as indexed by intima-media thickness (IMT) and increased vascular wall stiffness, are also increasingly recognized as significant independent predictors of adverse cardiovascular outcomes (15–24).

We therefore undertook a cross-sectional study, using data from the Baltimore Longitudinal Study of Aging (BLSA), to examine the relationship between MS and large artery structure (thickness) and function (stiffness). We sought to evaluate whether the clustering of multiple components of MS has a greater impact on these vascular parameters than individual components of MS.

METHODS

Study population. The BLSA is a prospective study of community-dwelling volunteers, largely from the Baltimore/Washington area, conducted by the National Institute on Aging since 1958. The BLSA participants are healthy volunteers (age 21 to 96 years) who have agreed to return at regular intervals to the Gerontology Research Center in Baltimore, Maryland, for 2.5 days of medical, physiological, and psychological examinations (25). Carotid ultrasonography was performed on a subset of the BLSA population

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Abbreviations and Acronyms

AGEPs = advanced glycation end products
BLSA = Baltimore Longitudinal Study of Aging
BP = blood pressure
CCA = common carotid artery
DBP = diastolic blood pressure
HDL = high-density lipoprotein
IMT = intima-media thickness
LDL = low-density lipoprotein
MS = metabolic syndrome
SBP = systolic blood pressure

chosen in a non-systematic yet random fashion. Of those, 471 subjects were free of preexisting coronary artery disease as defined by a history of angina pectoris, documented myocardial infarction, or major Q waves on the resting electrocardiogram (Minnesota Code 1:1 or 1:2) (26).

Variables measured. BLOOD PRESSURE. Blood pressure (BP) determinations were performed in the morning, after a light breakfast, with subjects in the seated position, and after a quiet resting period of 5 min. Blood pressure was measured in both arms with a mercury sphygmomanometer using an appropriately sized cuff. The BP values used in this study are the average of the second and third measurements on both the right and left arms. Values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined by Korotkoff phases I and V, respectively. Pulse pressure was computed as PP = (SBP − DBP); and mean BP was computed as MBP = DBP + (PP/3).

A total of 134 subjects (94 men and 40 women) were excluded because of concurrent antihypertensive therapy at the time of their first vascular measurement. These subjects were excluded because BP influences the values of the variables measured in the present study (8–12) and because of the potential effects of specific antihypertensive drug classes on these parameters (27–31). However, secondary analyses were performed, including treated hypertensive subjects, to exclude a potential hypertension selection bias.

ANTHROPOMETRY AND SMOKING STATUS. Height, weight, and waist circumference were determined for all participants. Body mass index was determined as kg/m^2. Smoking status was ascertained by a questionnaire that classified each subject as a non-smoker, former smoker, or current smoker. For the purpose of the present study, "ever-smoker" status (former or current) was used.

PLASMA LIPIDS AND FASTING BLOOD GLUCOSE. Blood samples were drawn from the antecubital vein between 7 and 8 AM after an overnight fast. Subjects were not allowed to smoke, engage in significant physical activity, or take medications before the sample was collected. Concentrations of plasma triglycerides and total cholesterol were determined by an enzymatic method (Abott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, Texas). The concentration of HDL cholesterol was determined by a dextran sulfate-magnesium precipitation procedure (32). Low-density lipoprotein (LDL) cholesterol concentrations were estimated by using the Friedewald formula. According to the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) (1), subjects with LDL ≥160 mg/dl were classified as having high LDL.

The fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments, Inc., Fullerton, California).

Carotid ultrasonography. High-resolution B-mode carotid ultrasonography was performed with a linear-array, 5- to 10-MHz transducer (Ultramark 9 HDI, Advanced Technology Laboratories, Inc., Seattle, Washington). The subject lay in the supine position in a dark, quiet room. Blood pressure was measured at 5-min intervals (Critikon 1846SX/P, version 085, Dinamap, Critikon, Tampa, Florida). The stabilized BP after 15 min from the onset of testing was used for subsequent analyses. The right common carotid artery (CCA) was examined with the head tilted slightly upward in the mid-line position. The transducer was manipulated so that the near and far walls of the CCA were parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1.5 cm proximal to the carotid bifurcation was identified, and the IMT of the far wall was evaluated as the distance between the lumen-intima interface and the media-adventitia interface. The IMT was measured on the frozen frame of a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail. The IMT measurement was obtained from five contiguous sites at 1-mm intervals, and the average of the five measurements was used for analyses. All measurements were performed by a single sonographer. The intrarater correlation between repeated IMT measurements from 10 subjects was 0.96 ($p < 0.001$), with similar averages for the two sets of readings (0.47 ± 0.13 vs. 0.45 ± 0.12 mm, p = NS) (33).

Stiffness of the CCA was evaluated by the stiffness index (no unit) that has been validated by Kawasaki et al. (34) and Hirai et al. (35):

$$\text{Stiffness index} = (\ln[\text{SBP}/\text{DBP}])/(\Delta d/D)$$

where Δd is the difference between the systolic and diastolic right CCA diameter, and D is the diastolic diameter. The intrarater correlation between repeated stiffness measurements from 10 subjects was 0.96 ($p < 0.01$), with similar averages for the two sets of readings (6.37 ± 2.59 vs. 6.43 ± 2.58, p = NS).

Definition of MS. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (1) provided a working definition of MS, defined as an alteration in three or more of the following five components: abdominal obesity, triglycerides, HDL cholesterol, BP (systolic or diastolic), and fasting glucose. We employed this definition, which uses the following cut-off values to define alterations: waist

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Table 1. Anthropomorphic, Metabolic, and Vascular Profiles by Metabolic Syndrome Status

	Control Subjects (n = 376)	MS Patients (n = 95)	p Value
Age (yrs)	57 ± 17	62 ± 15	0.01
Male gender (%)	39.9	52.6	0.05
Current smoker (%)	6.9	7.4	NS
BMI (kg/m^2)	25.0 ± 3.5	29.4 ± 4.2	0.0001
Waist circumference (cm)	83.9 ± 11.2	98.3 ± 9.8	0.0001
Fasting glucose (mg/dl)	94.5 ± 13.6	110.7 ± 32.4	0.0001
Triglycerides (mg/dl)	83.0 ± 43.7	168.3 ± 83.0	0.0001
HDL cholesterol (mg/dl)	51.8 ± 13.9	39.4 ± 10.0	0.0001
SBP (mm Hg)	127 ± 21	142 ± 17	0.0001
DBP (mm Hg)	78 ± 10	87 ± 10	0.0001
Total cholesterol (mg/dl)	176.6 ± 34.7	188.3 ± 37.8	0.01
LDL cholesterol (mg/dl)	106.6 ± 31.7	114.0 ± 32.1	0.05
Carotid IMT (mm)	0.51 ± 0.14	0.59 ± 0.17	0.0001
Carotid stiffness index	6.49 ± 2.90	8.55 ± 4.99	0.0001

Data are presented as the mean value ± SD or percentage of subjects.
BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; IMT = intima–media thickness; LDL = low-density lipoprotein; MS = metabolic syndrome; NS = not significant; SBP = systolic blood pressure.

circumference of >102 cm for men and >88 cm for women for abdominal obesity, triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl for men and <50 mg/dl for women, BP ≥130/≥85 mm Hg, and fasting glucose ≥110 mg/dl.

Statistical analysis. All analyses were performed using the SAS package (Cary, North Carolina). Data are presented as the mean value ± SD, unless otherwise specified. Differences in mean values for each of the measured variables in subjects with and without MS were compared by the *t* test for continuous variables and by the chi-square test for categorical variables. A comparison of different age quartiles with or without MS was made by analysis of variance, followed by Bonferroni's test for all two-way comparisons, or by chi-square analysis, as appropriate. Geometric mean values of vascular end points were calculated across categorized features of MS by means of Proc GLM (SAS). Analysis of co-variance (ANCOVA) was used to ascertain interactions between variables.

To evaluate the independent determinants of IMT and stiffness, multiple regression models were constructed, which included age, gender, smoking, and each individual's risk factor component of MS (fasting glucose, SBP, DBP, triglycerides, HDL cholesterol, and waist circumference as continuous variables) as independent variables. A second set of models was constructed, which also included LDL as a co-variate. Both models yielded similar results; thus, only the latter set is presented subsequently. Stepwise regression analysis was used to calculate the contribution of the significant determinants of vascular indexes. To evaluate whether MS was independently associated with vascular stiffness and thickness, we ran the models again, after adding in MS as a dummy variable. To confirm the significance of MS, we constructed another set of models that included the individual components of MS (but without MS) as well as all of the possible interactions among these components. To illustrate the contribution of MS to the values of IMT and stiffness, these values were calculated with the least-squares method after adjusting for: 1) age and gender; 2) age, gender, and LDL; and 3) age, gender, LDL, smoking, and the individual components of MS. For each adjustment, the values were computed in the absence and in the presence of MS in the model, and they were compared by ANCOVA.

Logistic regression analysis was used to test whether MS was associated with a greater prevalence of outliers in carotid IMT, stiffness, or both after adjusting for age, gender, and each component of MS. Outliers were defined as values of IMT or stiffness that were in the highest quartile.

RESULTS

Our study population consisted of 471 subjects (200 men and 271 women; mean age 59 ± 16 years) free of clinical overt cardiovascular disease at baseline. Table 1 shows the clinical characteristics of the study population. As expected, the values of all the anthropometric, metabolic, and BP variables were higher in patients with MS than in control subjects. Patients with MS were, on average, five years older ($p < 0.01$) and more likely to be men (52.6% vs. 39.9%, $p < 0.05$) than those without MS. No difference in the prevalence of current smokers was observed between the two groups. Carotid IMT was, on average, 16% higher, and stiffness was, on average, 32% higher in MS patients than in controls.

Table 2. Prevalence of Individual Components and Clusters of Components of the Metabolic Syndrome by Age Quartiles

	First Quartile (n = 118)	Second Quartile (n = 117)	Third Quartile (n = 118)	Fourth Quartile (n = 118)	p Value*
Age (yrs)	37 ± 7	51 ± 2	64 ± 4	79 ± 6	
Altered waist circumference component (%)	15.4	24.1	24.3	21.8	NS
Altered glucose component (%)	11.1	15.2	22.3	21.8	0.08
Altered triglyceride component (%)	9.4	11.6	18.5	9.1	NS
Altered HDL component (%)	42.7	41.1	35.9	38.2	NS
Altered BP component (%)	25.6	39.3	48.5	70.9	0.001
High LDL cholesterol (%)	3.4	1.8	9.7	10.0	0.05
MS† (%)	10.2	18.8	28.0	23.7	0.01

*By chi-square analysis. †Alteration in three or more components. Data are presented as the mean value ± SD or percentage of subjects.
BP = blood pressure; other abbreviations as in Table 1.

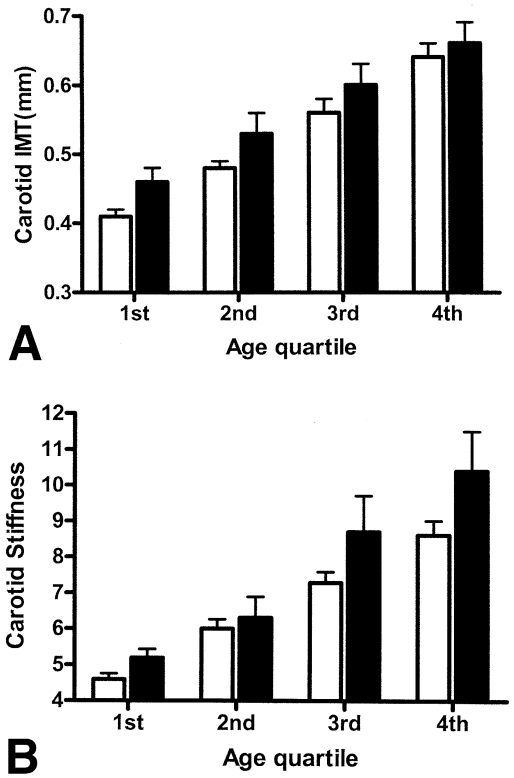

Figure 1. Common carotid intima-media thickness (IMT) **(A)** and stiffness **(B)** by age quartile and metabolic syndrome (MS) status. $p < 0.0001$ for age effect; $p < 0.01$ for MS effect; and p = NS for interaction. **Open bars** = controls; **solid bars** = MS patients.

The prevalence of MS in this study population was 20.2%. Table 2 shows the prevalence of the individual components of MS by quartiles of age, as well as the prevalence of MS itself, defined as the clustering of three or more of these components. The prevalence of hypertension and MS increased with advancing age group quartiles, whereas a trend toward borderline statistical significance was observed for altered glucose homeostasis. Of note, alterations in HDL were more frequent than alterations in LDL in all age groups, which may be partly related to the levels used as cut-off values. The prevalence of elevated LDL increased with advancing age groups.

Figure 1A shows that carotid IMT increased with advancing age quartiles in both MS patients and controls, and that in each age group, IMT was higher in MS patients than in controls. Figure 1B shows that CCA stiffness increased with advancing age quartiles in controls, and that in each group, stiffness was higher in MS patients than in controls. The interaction between age quartile and MS was not statistically significant, suggesting that the effects of MS on CCA thickness and stiffness do not significantly change across age groups.

Effects of MS on CCA thickness and stiffness. Multiple regression models were constructed to evaluate the independent contributions of factors on carotid IMT and stiffness. A first set of models included age, gender, smoking, LDL, and each individual's component of MS, but excluded the variable of MS (i.e., clustering of MS components). As shown in Table 3, age, male gender, LDL, and fasting blood glucose were each independently associated with IMT (model $R^2 = 0.406$, $p < 0.001$). Age, fasting blood glucose, SBP, and DBP (negative coefficient) were each independently associated with stiffness (model $R^2 = 0.440$, $p < 0.001$). When the first set of models was run again after adding MS as a dummy variable (second set), the variables remained independently associated with IMT and stiffness, respectively (Table 3). However, MS was also found to be independently associated with both IMT ($p = 0.002$) and stiffness ($p = 0.01$) (Tables 3 and 4), independent of the individual components of MS, which were also in the model, and accounting for 1.3% and 1.4% of the variability in IMT and stiffness, respectively.

Thus, the clustering of three or more of these components (i.e., MS) was independently associated with IMT or stiffness, even though several of the individual components of MS were not, suggesting that the clustering of these components interacted to exert synergistic effects on vascular structure and function. To explore this idea, an additional set of multiple regressions models were constructed for both IMT and stiffness. These models included age, gender, LDL, smoking, the individual components of MS, and interaction terms representing all of the possible interactions among these components as independent variables.

Table 3. Multiple Regression Models Evaluating the Independent Determinants of Carotid Intima-Medial Thickness

MS Not Added to Model			MS Added to Model		
	Coefficient	p Value		Coefficient	p Value
Age	0.0050	0.0001	Age	0.0050	0.0001
Female gender	−0.0343	0.001	Female gender	−0.0328	0.001
LDL cholesterol	0.0005	0.01	MS	0.0319	0.01
Fasting glucose	0.0009	0.01	LDL cholesterol	0.0005	0.01
			Fasting glucose	0.0007	0.05
Model R^2	0.406	0.0001	Model R^2	0.415	0.0001

The metabolic syndrome was defined according to the Adult Treatment Panel III criteria. All the models included age, gender, smoking, LDL cholesterol, and each individual's risk factor component of MS (fasting glucose, SBP, DBP, triglycerides, HDL cholesterol, and waist circumference as continuous variables) as independent variables. Only those variables that remained significant after backward stepwise elimination are shown in Tables 3 and 4.

Abbreviations as in Table 1.

Table 4. Multiple Regression Models Evaluating the Independent Determinants of Carotid Stiffness

MS Not Added to Model			MS Added to Model		
	Coefficient	p Value		Coefficient	p Value
Age	0.0658	0.0001	Age	0.0635	0.0001
Fasting glucose	0.0447	0.01	Fasting glucose	0.0348	0.01
SBP	0.0650	0.01	SBP	0.0652	0.01
DBP	−0.1115	0.001	DBP	−0.1226	0.001
			MS	1.0660	0.01
Model R^2	0.440	0.0001	Model R^2	0.457	0.0001

The metabolic syndrome was defined according to the Adult Treatment Panel III criteria. All the models included age, gender, smoking, LDL cholesterol, and each individual's risk factor component of MS (fasting glucose, SBP, DBP, triglycerides, HDL cholesterol, and waist circumference as continuous variables) as independent variables. Only those variables that remained significant after backward stepwise elimination are shown in Tables 3 and 4.
Abbreviations as in Table 1.

For IMT and stiffness, we found that several terms representing the interaction of three or more components of MS were independently associated with these vascular parameters. This confirms that interactions among the individual components of MS exert synergistic effects on IMT and stiffness. Overall, the model R^2 (0.48 for both) was modestly increased by the addition of these interaction terms (R^2 = 0.40 for IMT and R^2 = 0.44 for stiffness in the absence of the interaction terms). This is likely due to the dominant effect of age in accounting for the variance in IMT and stiffness (~35% for both).

To illustrate the contribution of MS to the values of IMT and stiffness, these values were calculated with the least-squares method after adjusting for: 1) age and gender; 2) age, gender, and LDL; and 3) age, gender, LDL, smoking, and the individual components of MS (Table 5). For each adjustment, the values were calculated in the absence and in the presence of MS in the model. By ANCOVA, the addition of MS to the models significantly increased the values of IMT and stiffness for all three adjustments. As noted earlier, the magnitude of the change attributed to MS was relatively small, because age was responsible for the largest part of the total variance.

Log transformation of IMT yielded similar results. When treated and untreated hypertensive patients were combined, the significance of the same predictors persisted on multiple regression analyses, and the model R^2 were reduced by only 1%. These findings exclude a hypertension selection bias.

Effects of MS on combined CCA thickness and stiffness. In unadjusted analyses, IMT and stiffness are significantly ($p < 0.001$), albeit weakly ($R^2 = 0.11$), correlated with each other. We investigated whether MS was independently associated with simultaneous increases in the combined end point of carotid thickness and stiffness. Stiffness and IMT were divided into quartiles, and subjects were classified as outliers for each or both parameters if their values fell in the highest quartile of the parameters. As shown in Figure 2, the MS group included a significantly greater percentage of subjects classified as outliers for either IMT or stiffness, compared with controls. Furthermore, the MS group included a significantly greater percentage of subjects classified as outliers for both IMT and stiffness, compared with controls. The increased risk of having excessive alterations in one or both of these vascular parameters remained significant even after adjusting for age, gender, and each individual's component of MS in a multivariable logistic

Table 5. Mean Adjusted Values of Carotid Intima–Media Thickness and Stiffness, Calculated by the Least Mean Squares Method, in the Absence or Presence of the Metabolic Syndrome

	Adjusted for Age and Gender	Adjusted for Age, Gender, and LDL Cholesterol	Multivariate Model*
IMT (mm)			
No	0.522 ± 0.006	0.522 ± 0.006	0.525 ± 0.007
Yes	0.561 ± 0.012	0.559 ± 0.012	0.562 ± 0.016
p Value	0.005	0.009	0.04
Stiffness index			
No	6.61 ± 0.17	6.60 ± 0.16	6.51 ± 0.15
Yes	7.83 ± 0.34	7.59 ± 0.33	7.70 ± 0.36
p Value	0.002	0.008	0.005

*The multivariate model included age, gender, LDL cholesterol, smoking, waist circumference, fasting blood glucose, HDL cholesterol, triglycerides, SBP, and DBP. Data are presented as the mean value ± SE.
Abbreviations as in Table 1.

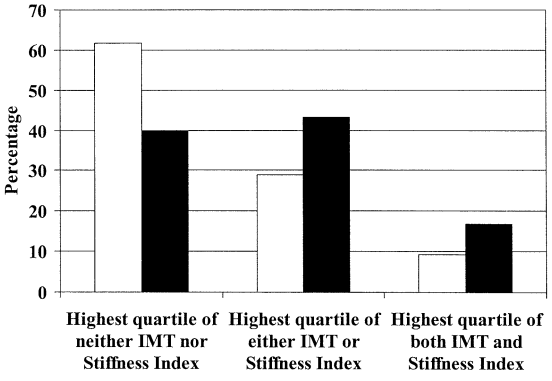

Figure 2. Ratio of the prevalence of outliers for carotid intima-media thickness (IMT) and/or stiffness between metabolic syndrome patients **(solid bars)** and controls **(open bars)**. Outliers for IMT or stiffness are defined as subjects having values for IMT or stiffness that exceed the 75th percentile levels in the study population. $p < 0.001$ across high quartile status by analysis of variance.

model (odds ratio 2.39, 95% confidence interval 1.09 to 5.08; p = 0.03).

DISCUSSION

The main findings of this study are that: 1) MS increases carotid arterial thickness and stiffness across all age groups; and 2) MS exerts its effects on carotid structure and function independent of its individual components and other cardiovascular risk factors.

To our knowledge, only one previous study has investigated the relationship between MS and vascular stiffness. In studying a cohort of 180 non-diabetic, healthy, middle-aged women, van Popele et al. (36) found that carotid arterial distensibility was associated with several variables of MS, as well as with clustering of variables of MS, even after adjusting for mean BP. Our study confirms these findings and extends them insofar as: 1) we used a different index of stiffness that has been previously shown to be associated with insulin resistance in non-insulin-dependent diabetic subjects (37); 2) our study population included men and women; 3) was across a broad age range; and 4) showed that the association between MS and vascular stiffness was significant across all age groups. Furthermore, we found that MS, defined as the clustering of any three or more altered components, was itself an independent predictor of stiffness. Importantly, arterial stiffness is increasingly recognized as a potent and independent predictor of adverse cardiovascular outcomes (15–24).

The IMT increases with advancing age in humans (33) and in animal models of aging (38,39). In this study, we found that MS was associated with higher vascular wall thickness, compared with controls, across all age groups. A few previous studies have evaluated the association between MS and IMT (40–42). In a cross-sectional population-based study in Sweden, Hedblad et al. (40) found that age- and gender-adjusted IMT was significantly higher in MS patients than in controls. Hulthe et al. (41) studied clinically healthy 58-year-old men. They found that patients with MS had a significantly higher common carotid, carotid bulb, and femoral IMT than did subjects without risk factors. On the other hand, they did not find any significant differences in these IMT variables between MS patients and those with only one risk factor. Of note, they used the World Health Organization (2) definition of MS, which uses components and cut-off values for defining alterations in these components that are somewhat different from those of the ATP III.

A novel finding of our study is that MS conferred increased odds of having both thicker and stiffer large arteries. In fact, a significantly greater percentage of subjects with extremely high IMT and stiffness was observed in the MS group than in the control group.

There is increasing interest in the relevance of multiple risk factors, as well as the existence of thresholds in the relationships between the levels of known risk factors and the risk of disease (42–44). The presence of a dose-response relation between the levels of known risk factors and the risk of cardiovascular disease, whether measured by incident cardiovascular event or "intermediate phenotypes" such as subclinical vascular disease, indicates that there is value in modifying risk factors in people at high risk, irrespective of the reason for the high risk and regardless of the level of the risk factor.

Potential mechanisms. It is conceivable that one of the mechanisms by which MS exerts its well-documented deleterious effects is by adversely affecting the structural and functional properties of the vasculature (such as thickness and stiffness). Interestingly, MS was associated with a higher prevalence of alterations in both vascular parameters. Alternatively, it is possible that a common pathogenic factor could underlie both the arterial structural changes and the alterations in the components that comprise MS.

Circumferential wall stress and flow-mediated shear stress are considered to be important determinants of arterial wall structure and function during development and their remodeling during aging or in response to disease in adults (45–49). Blood pressure and blood flow are major determinants of these mechanical stresses that act on the arterial wall and lumen. Of note, we have previously demonstrated that in the context of an increased circumferential wall stress, specific alterations in carotid geometry were associated with differing levels of flow-mediated shear stress and resulted in specific patterns of alterations in carotid function (50).

Another potential mechanism by which MS can alter large-artery structure and function might be the glycation of matrix proteins. Alterations in matrix proteins within the vessel wall can be derived from nonenzymatic cross-links between glucose (or other reducing sugars) and amino groups that generate advanced glycation end products (AGEPs) (51,52). The AGEPs accumulate slowly on long-lived proteins, such as collagen and elastin, and lead to increased stiffening of both arteries and the heart (51). In animal models, decreasing these cross-links enhances vascular and cardiac compliance (53–56). Of note, we recently showed in a randomized, double-blinded, placebo-controlled study that a novel medication that cleaves the AGEPs cross-links favorably impacts measures of vascular stiffness in older human subjects (57).

Study limitations. Certain limitations of this study should be recognized, including its cross-sectional nature. Longitudinal observations are required in order to more fully address the relationships and potential mechanistic links between MS and vascular structure and function. Furthermore, the study population is relatively small, predominantly Caucasian and well educated, which limits the generalizability of our findings, even though the prevalence of MS in our study was similar to that observed by others (58). Future studies that include more racially and socioeconomically diverse populations are needed to further

investigate the relationship between MS and vascular structure and function.

An additional limitation is that the BP values used to calculate the carotid stiffness index were measured over the brachial artery, which tends to overestimate carotid pressures due to central to peripheral BP amplification (59). Central (carotid) BPs measured on the same visit as the carotid Doppler studies were available for 26 subjects. As anticipated, brachial SBP (116 ± 14 mm Hg) exceeded central SBP (103 ± 14 mm Hg). However, the correlation between central and brachial measurements of ln (SBP/DBP), the numerator of the stiffness index, was 0.92. These findings suggest a fixed difference in ln (SBP/DBP), which should lead to a fixed, systematic error in the stiffness index.

Conclusions. Our analyses indicate that MS is independently associated with increased thickness and stiffness of the carotid artery. Because increased arterial stiffness and thickness are well established as age-associated processes, this suggests that MS can be perceived as accelerating vascular aging. The excess alteration in carotid structure and function conferred by MS over and above the risk associated with abnormalities in each single component of this syndrome raises the prospect that integrated preventive or therapeutic strategies that target multiple components of MS may yield synergistically improved outcomes, as compared with those that are aimed at the individual components.

Future studies should investigate the mechanistic links between MS and vascular aging, and whether strategies to reduce vascular stiffness or thickness can attenuate the deleterious outcomes of MS.

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REFERENCES

1. The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
2. Alberti KGMM, Zimmet PZ, for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
3. Meigs JB, D'Agostino RB Sr., Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. Diabetes 1997;46:1594–600.
4. Meigs JB. Epidemiology of the metabolic syndrome, 2002. Am J Manag Care 2002;8 Suppl:S283–92.
5. Hedblad B, Nilsson P, Engstrom G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470–5.
6. Arnlov J, Lind L, Zethelius B, et al. Several factors associated with the insulin resistance syndrome are predictors of left ventricular systolic dysfunction in a male population after 20 years of follow-up. Am Heart J 2001;142:720–4.
7. Kuusisto J, Lempiainen P, Mykkanen L, Laakso M. Insulin resistance syndrome predicts coronary heart disease events in elderly type 2 diabetic men. Diabetes Care 2001;24:1629–33.
8. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension 2001;38:429–33.
9. Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, et al. Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. Am J Hypertens 2002;15:16–23.
10. Muiesan ML, Pasini G, Salvetti M, et al. Cardiac and vascular structural changes. Prevalence and relation to ambulatory blood pressure in a middle-aged general population in northern Italy: the Vobarno Study. Hypertension 1996;27:1046–52.
11. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–7.
12. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr., the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14–22.
13. Havlik RJ, Brock D, Lohman K, et al. High-density lipoprotein cholesterol and vascular stiffness at baseline in the activity counseling trial. Am J Cardiol 2001;87:104–7.
14. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non–insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 1995;91:1432–43.
15. Liao D, Arnett DK, Tyroler HA, et al. Arterial stiffness and the development of hypertension: the ARIC study. Hypertension 1999;34:201–6.
16. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–41.
17. de Simone G, Roman MJ, Koren MJ, Mensah GA, Ganau A, Devereux RB. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. Hypertension 1999;33:800–5.
18. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension 2001;38:434–8.
19. Darne B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension 1989;13:392–400.
20. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension 1994;23:395–401.
21. Mitchell GF, Moye LA, Braunwald E, et al., the Survival And Ventricular Enlargement (SAVE) Investigators. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Circulation 1997;96:4254–60.
22. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. JAMA 1999;281:634–9.
23. Fagard RH, Pardaens K, Staessen JA, Thijs L. The pulse pressure-to-stroke index ratio predicts cardiovascular events and death in uncomplicated hypertension. J Am Coll Cardiol 2001;38:227–31.
24. Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol 1999;33:951–8.
25. Shock NW, Greulich RC, Andres RA, et al. Normal human aging: the Baltimore Longitudinal Study of Aging. NIH publication no. 84-2450. Washington, DC: U.S. Government Printing Office, 1984:45.
26. Rose GA, Blackburn H. Cardiovascular Survey Methods. Geneva: World Health Organization, 1968.
27. Zanchetti A, Bond MG, Hennig M, et al., the European Lacidipine Study on Atherosclerosis Investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: prin-

cipal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002;106:2422–7.
28. Zanchetti A, Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. J Hypertens 1998;16:1667–76.
29. Simon A, Gariepy J, Moyse D, Levenson J. Differential effects of nifedipine and co-amilozide on the progression of early carotid wall changes. Circulation 2001;103:2949–54.
30. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study (BCAPS). Circulation 2001; 103:1721–6.
31. Lonn E, Yusuf S, Dzavik V, et al., the SECURE Investigators. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). Circulation 2001;103:919–25.
32. Warnick G, Benderson J, Albers J. Dextran sulfate-Mg^{2+} precipitation procedure for quantification of high-density-lipoprotein cholesterol. Clin Chem 1982;28:1379–88.
33. Nagai Y, Metter EJ, Earley CJ, et al. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation 1998;98:1504–9.
34. Kawasaki T, Sasayama S, Yagi S, Asakawa T, Hirai T. Non-invasive assessment of the age related changes in stiffness of major branches of the human arteries. Cardiovasc Res 1987;21:678–87.
35. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: a noninvasive method to predict severity of coronary atherosclerosis. Circulation 1989;80:78–86.
36. van Popele NM, Westendorp IC, Bots ML. Variables of the insulin resistance syndrome are associated with reduced arterial distensibility in healthy non-diabetic middle-aged women. Diabetologia 2000;43: 665–72.
37. Emoto M, Nishizawa Y, Kawagishi T, et al. Stiffness indexes beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. Diabetes Care 1998;21:1178–82.
38. Li Z, Froehlich J, Galis ZS, Lakatta EG. Increased expression of matrix metalloproteinase-2 in the thickened intima of aged rats. Hypertension 1999;33:116–23.
39. Asai K, Kudej RK, Shen YT, et al. Peripheral vascular endothelial dysfunction and apoptosis in old monkeys. Arterioscler Thromb Vasc Biol 2000;20:1493–9.
40. Hedblad B, Nilsson P, Engstrom G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470–5.
41. Hulthe J, Wiklund O, Bondjers G, Wikstrand J. The metabolic syndrome, LDL particle size, and atherosclerosis: the Atherosclerosis and Insulin Resistance (AIR) study. Arterioscler Thromb Vasc Biol 2000;20:2140–7.
42. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. BMJ 2002;324:1570–6.
43. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, the CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–7.
44. Wilson PF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
45. Glagov S, Giddens DP, Zarins CK. Micro-architecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress. J Hypertens 1992;10 Suppl:S101–4.
46. Rubanyi GM, Freany ADK, Kauser K, Johns A, Harder DR. Mechanoreception by the endothelium: mediators and mechanisms of pressure and flow-induced vascular response. Blood Vessels 1990;27: 246–57.
47. Laurent S. Arterial wall hypertrophy and stiffness in essential hypertensive patients. Hypertension 1995;26:355–62.
48. Pourageaud F, De Mey JGR. Structural properties of rat mesenteric small arteries after 4-week exposure to elevated or reduced blood flow. Am J Physiol 1997;273:H1699–706.
49. Mulvany JM, Baumbach GL, Aalkjær C, et al. Vascular remodeling. Hypertension 1996;28:505–6.
50. Scuteri A, Chen CH, Yin FCP, Tai TC, Spurgeon HA, Lakatta EG. Functional correlates of central arterial geometric phenotypes. Hypertension 2001;38:1471–5.
51. Lee AT, Cerami A. Role of glycation in aging. Ann NY Acad Sci 1992;663:63–70.
52. Airaksinen KE, Salmela PI, Linnaluoto MK, et al. Diminished arterial elasticity in diabetes: association with fluorescent advanced glycosylation end products in collagen. Cardiovasc Res 1993;27:942–5.
53. Wolffenbuttel BH, Boulanger CM, Crijns FR, et al. Breakers of advanced glycation end products restore large artery properties in experimental diabetes. Proc Natl Acad Sci USA 1998;95:4630–4.
54. Corman B, Duriez M, Poitevin P, et al. Aminoguanidine prevents age-related stiffening and cardiac hypertrophy. Proc Natl Acad Sci USA 1998;95:1301–6.
55. Asif M, Egan J, Vasan S, et al. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. Proc Natl Acad Sci USA 2000;97:2809–13.
56. Vaitkevicius PV, Lane M, Spurgeon H, et al. A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Proc Natl Acad Sci USA 2001;98:1171–5.
57. Kass DA, Shapiro EP, Kawaguchi M, et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation 2001;104:1464–70.
58. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 1991;34:416–22.
59. Nichols WW, O'Rourke M. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 4th ed. London: Arnold, 1998, 54–401.