Published in final edited form as:

Int J Stroke. 2010 June ; 5(3): 138–144. doi:10.1111/j.1747-4949.2010.00421.x.

METABOLIC SYNDROME INCREASES CAROTID ARTERY STIFFNESS: THE NORTHERN MANHATTAN STUDY

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Abstract

Background—Arterial Stiffness, an intermediate pre-clinical marker of atherosclerosis, has been associated with an increased risk of stroke and cardiovascular disease (CVD). The metabolic syndrome and its components are established CVD risk factors and may also increase arterial stiffness, but data on this potential relationship is limited. The goal of this study was to determine the association between the metabolic syndrome (MetSyn) and carotid artery stiffness (STIFF) in an elderly multi-ethnic cohort.

Methods—STIFF was assessed by carotid ultrasound as part of the Northern Manhattan Study (NOMAS), a prospective population-based cohort of stroke-free individuals. STIFF was calculated as $[\ln(\text{systolicBP}/\text{diastolicBP})/\text{Strain}]$, where Strain was $[(\text{Systolic Diameter} - \text{Diastolic Diameter})/\text{Diastolic Diameter}]$. MetSyn was defined by the National Cholesterol Education Program: Adult Treatment Panel III (NCEP ATP III) criteria. LogSTIFF was analyzed as the dependent variable in linear regression models, adjusting for demographics, education, current smoking, presence of carotid plaque and intima-media thickness.

Results—STIFF was analyzed in 1133 NOMAS subjects (mean age 65 ± 9 years; 61% women; 58% Hispanic, 22% Black, 20% White). The prevalence of MetSyn was 49%. The mean LogSTIFF was 2.01 ± 0.61 among those with and 1.90 ± 0.59 among those without MetSyn ($p=0.003$). MetSyn was significantly associated with increased logSTIFF in the final adjusted model (parameter estimate $\beta=0.100$, $p=0.01$). Among individual MetSyn components, waist circumference and elevated blood pressure were most significantly associated with a mean increase in logSTIFF ($p<0.01$).

Conclusion—MetSyn is significantly associated with increased carotid artery stiffness in a multiethnic population. Increased carotid artery stiffness may, in part, explain a high risk of stroke among individuals with the metabolic syndrome.

Keywords

metabolic syndrome; arterial stiffness; atherosclerosis; elderly; race-ethnicity

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Conflict of interest: All authors report no conflicts of interest.

Introduction

The prevalence of the Metabolic Syndrome (MetSyn) is estimated to be 30% of the US population. Data from the National Health and Nutrition Examination Survey (NHANES) III have shown that more than 47 million people in the US have the MetSyn (1). According to the National Cholesterol Education Program: Adult Treatment Panel III (NCEP ATP III) criteria MetSyn is defined by the presence of three or more of following traits: central obesity, low high density protein (HDL) cholesterol, hypertriglyceridemia, elevated blood pressure (BP), and impaired glucose metabolism (2).

Individuals with the MetSyn may have a higher burden of subclinical carotid atherosclerosis irrespective of age, sex and race-ethnicity (3). Moreover, it is well known that MetSyn is strongly associated with an increased risk of cardiovascular diseases (CVD) and stroke (4,5). In the Northern Manhattan Study (NOMAS), comprised of predominantly Caribbean Hispanics, MetSyn was associated with a significant increased risk of ischemic stroke with differential effects by sex and race-ethnicity (6). Similarly, MetSyn was associated with an increased risk of stroke in predominately white cohorts such as NHANES III (4), Framingham (5), ARIC (7), a cohort of elderly Finnish people (8), and different components of MetSyn were analyzed in subjects with insulin resistance (9).

Carotid stiffness (STIFF) is a measure of arterial ability to expand and contract with cardiac pulsation and relaxation (10). Increased stiffness is a common pathological precursor that leads to CVD and stroke (11). Recently, arterial stiffness has been measured from the carotid arteries using high-resolution B-mode ultrasound (12) and introduced as a novel risk factor for vascular events (13). Increased carotid stiffness has been observed in patients with type 2 diabetes, and a marginal increase has also been reported in patients with MetSyn (14).

Information regarding the association between MetSyn and arterial stiffness among women and men from diverse race-ethnic backgrounds is limited. The objective of our study was to investigate this association in an elderly multi-ethnic cohort of stroke-free individuals.

Subjects and Methods

Study Population

The Northern Manhattan Study (NOMAS) is a prospective cohort study of stroke risk factors in a multi-ethnic, urban population of northern Manhattan. In 2000 the population numbered almost 260,000 according to the US census, and 40% were aged >39 years 20% were black, 63% Hispanic, and 15% white. NOMAS is strongly representative of the underlying ethnic mix in this community. Methodology for the NOMAS study has been described previously (15). The study was approved by the Institutional Review Board at Columbia University Medical Center (CUMC), and written consent was obtained. Standardized questions were adapted from the validated Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System (16). The validity of these questions in the northern Manhattan cohort have been described previously (16).

The NOMAS cohort consists of 3298 stroke-free subjects who were enrolled between 1993 and 2001. Carotid ultrasound imaging was initiated after standardization of the procedure and limited to a sample of those who were not enrolled at home (11%). High-resolution carotid ultrasonography imaging for carotid stiffness was performed in 1133 individuals. Sensitivity analyses using imputed data for the entire cohort (n=3298) did not show a significant selection bias.

Exposure Assessment: Metabolic Syndrome

The primary exposure of interest was MetSyn as diagnosed by the Third Report of the NCEP ATP III (2). A working definition of MetSyn includes at least 3 of the following abnormalities: (1) Waist circumference > 40.8" in men and > 35.2" in women; (2) Serum triglycerides level of at least 150 mg/dL; (3) HDL cholesterol level of less than 40 mg/dL in men and 50 mg/dL in women; (4) BP of at least 130/85 mmHg or previously-diagnosed hypertension; and (5) Serum glucose level of at least 110 mg/dL.

BP was obtained from the right brachial artery after a 10 minute rest in a supine position (Dinamap Pro100, Critikon Inc). BP was measured twice, before and after each examination, and averaged.

Fasting blood specimens were analyzed at the Core Laboratory to determine glucose, HDL and triglycerides as described previously (16). The inter-assay coefficients of variation in our laboratory were 2% for total cholesterol, 4% for triglycerides, and 3% for HDL (17). Fasting serum glucose was measured according to standard procedures using a glucose dehydrogenase method (18).

Outcome Assessment: Carotid Stiffness

Carotid Ultrasound Imaging—High resolution carotid ultrasonography was performed on a GE LOGIQ 700 system (GE Healthcare, Milwaukee, WI) with a multifrequency 9/13-MHz linear array transducer. Both internal and common carotid arteries as well as bifurcations were imaged in transverse (short axis) and longitudinal planes (anterior, lateral, and posterior views) using standardized scanning and reading protocols (19). The 2 independent study sonographers (who were also the readers) performed the scans on all subjects under standardized conditions. Our carotid IMT reliability study demonstrated a high reproducibility (19). In a sample of 88 stroke-free community subjects, mean absolute difference of carotid IMT between 2 readers was 0.19 ± 0.36 mm, with a variation coefficient of 7.5%, a correlation coefficient of 0.77, and a percent error of 10.6%. Intrareader mean absolute IMT difference was 0.07 ± 0.04 mm, with a variation coefficient of 5.4%, a correlation coefficient of 0.94, and a percent error of 5.6%.

Ultrasound Image Acquisition—Carotid images were divided into 3 segments using the lateral extent of each carotid segment as defined relative to the tip of the flow divider, the most clearly defined anatomic reference where blood flow divides in the carotid bifurcation. The segments were as follows: segment 1, the near and far walls of the arterial segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery (CCA); segment 2, the near and far walls of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and segment 3, the near and far walls of the proximal 10 mm of the internal carotid artery. STIFF was measured as a part of the carotid intima-media thickness (IMT) protocol (19). The intraluminal diameters of 10 mm of the right CCA below the origin of the carotid bulb (segment 1) were analyzed. Both the near and the far wall interfaces defining the blood-intima boundaries were maximized and clearly depicted on B-mode images (Fig. 1A). M-mode images were obtained in orientations perpendicular to the arterial walls and were adjusted for the clearest representation of the CCA walls throughout the cardiac cycles (Fig. 1B).

Image Processing and Reading Protocol—The offline measurement of STIFF was performed using Image Pro image analysis software (Microsoft Corporation, Redmond, WA) on a specially designed reading station. The best visualized blood-intima boundaries from up to 10 M-mode cardiac cycles were traced and the systolic diameter (SD) and diastolic diameter (DD) were automatically computed, averaged and stored in a data file. The high reliability of

the SD and DD measurements between the two readers in our laboratory was reported previously (12). The inter-reader correlation coefficients were 0.96 for SD and 0.95 for DD.

Carotid Stiffness Calculation—Stiffness of an artery segment is a reflection of the mechanical stress affecting the arterial wall during the cardiac cycle (10). Strain was defined as the amount of deformation relative to the unstressed state and expressed as percent change in the arterial diameter: $\text{Strain} = (\text{SD} - \text{DD}) / \text{DD}$. STIFF was calculated using the following formula: $\text{Stiffness} (\beta) = \text{Ln} (\text{SBP} / \text{DBP}) / \text{Strain}$, where SBP and DBP were brachial systolic and diastolic BP (10,11).

Covariate Assessment

All subjects completed a comprehensive in-person assessment of sociodemographics, vascular risk factors, medical history, and medication use including lipid-lowering agents, insulin, oral hypoglycemic agents, and antihypertensive agents. Race-ethnicity was defined by self-identification, and categorized as Hispanic, Non-Hispanic White, and Non-Hispanic Black. Smoking was assessed by self-report and categorized as never, former and current (within past year). Education level (completed high school) was used to define socioeconomic status.

Presence of carotid plaque and IMT were determined at the time of STIFF assessments. Plaque was defined as an area of focal wall thickening or protrusion in the lumen at least 50% greater than surrounding wall thickness (20). Data were collected on presence of plaque (yes or no), locations of plaques (internal carotid artery, carotid bifurcation and common carotid artery), and number of plaques at any of carotid artery segments and categorized as 0, 1, or >1. Carotid IMT is expressed as a composite measure of the mean IMT measured in 12 specified carotid segments (the near and the far wall of the right and left common carotid artery, carotid bifurcation and internal carotid artery).

Statistical Analyses

The mean and standard deviation (SD) values for continuous variables and the proportions for categorical variables were calculated and stratified by the MetSyn status. T-tests and χ^2 tests were used to examine the associations between MetSyn and the continuous and categorical variables, respectively.

STIFF was log transformed to satisfy normality assumptions, and analyzed as the dependent variable. Two multiple linear regression models were conducted to examine the association between STIFF and (1) the MetSyn (presence vs. absence); and (2) the MetSyn components entered simultaneously as independent variables. Multivariate models were adjusted for sociodemographics (age, sex, and race-ethnicity), high school education, current smoking, presence of carotid plaque and IMT. The results were considered significant at $\alpha=0.05$. SAS version 9.1 (SAS institute, Cary, NC) was used for all statistical analyses.

Results

In the cohort of 1133 subjects, the mean age was 65 ± 9 years; 61% were women; 58% were Hispanics, 22% blacks, and 20% whites. The prevalence of MetSyn was 49%, and differed by sex (39% in men, 55% in women, $p<0.0001$) as well as race-ethnicity (56% in Hispanics, 41% in blacks, and 39% in whites, $p<0.0001$). Table 1 shows demographics of the study population overall and stratified by MetSyn. There were differences in the use of lipid-lowering agents (17% MetSyn vs 9% without MetSyn), insulin (5% MetSyn vs. 1% without MetSyn), oral hypoglycemic agents (15% MetSyn vs. 4% without MetSyn); and antihypertensive agents (49% MetSyn vs. 29% without MetSyn) between the two groups.

The MetSyn components (overall and by sex) are presented in Figure 2A. Women were more likely to have wider (sex-specific) waist circumference value ($p<0.0001$). No other sex differences among the MetSyn components were found (Fig. 2A). Whites were least likely to have elevated BP and high levels of serum glucose compared to Hispanics and blacks (Fig. 2B). Overall, the prevalence of increased waist circumference was highest among blacks and lowest among whites. Moreover, Hispanics presented higher prevalence of high levels of triglycerides and low levels of HDL compared with the other two groups.

The carotid artery diameters, stiffness, presence of carotid plaque and IMT are presented in Table 2. Diastolic diameter and logSTIFF were positively associated with MetSyn ($p<0.05$). In the multivariate model, MetSyn remained significantly associated with increased logSTIFF after adjustment for age, sex, race-ethnicity, current smoking, high school education, presence of carotid plaque and IMT and medications (parameter estimate $\beta=0.100$, $p=0.01$). Age was the only other covariate independently associated with STIFF ($\beta=0.012$, $p<0.0001$). No other covariates such as current smoking, male sex, high school education, carotid plaque, carotid IMT and race-ethnicity were significant associated with STIFF. No significant interaction was also observed between MetSyn and sex, or between MetSyn and race-ethnicity (data not shown).

In the adjusted multiple linear regression model of the individual MetSyn components (Table 3), wider waist circumference and increased BP were significantly associated with a mean increase in logSTIFF of 0.130 ($p=0.002$) and 0.185 ($p=0.0003$), respectively.

Discussion

In this cross-sectional study, we have demonstrated a significant association between metabolic syndrome and carotid artery stiffness in a multi-ethnic population-based cohort. This relationship is independent of sex and race-ethnicity. In addition, it was independent of presence of carotid plaque and IMT, and lipid lowering and blood pressure lowering agents that could have had an effect on artery wall function (21,22). Our results indicate that individuals with the MetSyn have increased STIFF which may be an important early marker of subclinical atherosclerosis associated with an increased risk of vascular events.

The functional impairment of the arterial wall may occur in an early stage of the atherosclerotic process before structural wall changes become detectable and before the occurrence of clinical symptoms (23). Arterial wall stiffness also may be a distinct phenotype of atherosclerosis and completely independent of presence of atherosclerotic plaque or increased IMT (24). In the present study, the association between MetSyn and STIFF is independent of presence of carotid plaque and IMT suggesting that these subclinical markers may indeed be distinct phenotypes of subclinical atherosclerosis. In addition, carotid plaque and IMT may represent a later stage in the evolution of atherosclerotic disease than stiffness.

The relationship between arterial stiffness and risk of ischemic stroke has been shown previously (25,26). However, the number of prospective studies on the association of arterial stiffness and vascular disease is limited and mainly confined to individuals with manifest arterial disease or to patients with end stage renal disease. We will have an opportunity to investigate the relationship of STIFF and risk of stroke in a stroke-free population in the prospective part of our study after accumulating a sufficient number of follow-up years.

We have also demonstrated an association between MetSyn and ischemic stroke risk in NOMAS (6). Recently, we have also reported an independent association between MetSyn and subclinical carotid atherosclerosis as measured by carotid plaque presence and thickness (3). The current study extends our previous results by showing that MetSyn is not only associated with impairment of arterial wall structure but also with wall function, independent of plaque

presence and arterial wall thickness. Individuals with the MetSyn had a higher burden of subclinical carotid atherosclerosis, suggesting that markers of subclinical carotid atherosclerosis are intermediate conditions before occurrence of overt vascular diseases. We also have shown that subjects with both MetSyn and endothelial dysfunction, evaluated by brachial artery flow-mediated dilatation, were at the higher risk for CVD than those with either one alone (27).

There is no consensus on the gold standard for measuring arterial stiffness. Several methods, including ultrasound, applanation tonometry, and pulse wave velocity (PWV) have been recommended by the First International Consensus Conference on the Clinical Applications of Arterial Stiffness (28) and by the European Network for Non-invasive Investigation of Large Arteries (29). Using ultrasound, an association between MetSyn and arterial stiffness have been reported in selected populations with type 2 diabetes, patients with clinical manifestations of arterial disease, those with high-normal blood pressure and impaired glucose regulation, and in untreated hypertensive patients (14,30). Using PWV, an increase in arterial stiffness was demonstrated in the presence of the MetSyn independent of advanced age, elevated BP, and accelerated heart rate (31). MetSyn was shown to be associated with an increased progression of arterial stiffness with age (32). The rate of PWV increased with age 4.7 times greater among those with MetSyn (33). Although study populations, designs, and methods used in these reports have been inconsistent, increased arterial stiffness has been associated with an increased risk of vascular disease despite different methods used to measure arterial stiffness.

We found that wider waist circumference and elevated blood pressure were MetSyn components most significantly associated with STIFF. In a previous study high blood pressure was also suggested to be an important MetSyn component associated with an increase in arterial stiffness, as well as high fasting glucose (34). Considerable evidence shows that sustained elevations in blood pressure accelerate atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increases arterial stiffness. Increased stiffness appears however to be the effect of distending pressure rather than structural changes in the carotid artery wall at least in an early stage of atherosclerosis (35). Our results support this hypothesis. Obesity may also exert adverse affects on the vascular system by increasing arterial stiffness (36). Excess body fat, abdominal visceral fat, and larger waist circumference have been identified as risk factors for accelerated arterial stiffening (37). The mechanism behind these associations may be the link between excess body fat, insulin resistance, inflammation, and the hormone leptin which, much like insulin, has been shown to promote smooth muscle cell proliferation and angiogenesis leading to an arterial stiffening (36). Given the increasing prevalence of obesity in the population and augmented arterial stiffness in obese individuals these data may have great public health implications. The degree to which vascular stiffening may be reduced with weight loss is unknown and it may be important for prevention of stroke and other vascular diseases.

We acknowledge limitations to this study. This is a cross sectional study, so the effects of MetSyn on STIFF progression, and any treatment response, could not be assessed. In addition, our study is observational, so only assumptions about possible etiological relationships can be made. Furthermore, ATP III criteria were used to diagnose the MetSyn; other definitions (American Association of Clinical Endocrinologists (38) and World Health Organization) (39) exist, which may make comparisons difficult. However, using different definition of MetSyn has not been shown to alter the association with artery stiffness (40). Whether the results from our study can be generalized to other populations is also a possible limitation, particularly because the prevalence of MetSyn and arterial dysfunction among the members our population is high. However, our data provides information on important US minority groups living together as one community, and there is no evidence to suggest that the

physiological processes leading to carotid artery stiffness in our population are any different than those acting on other communities in the United States.

Conclusion

In a multi ethnic urban population of stroke-free individuals, a significant association between metabolic syndrome and carotid arterial stiffness was observed which may, in part, explain a high risk of stroke and CVD. These data may have great public health implications in primary preventive strategies.

Acknowledgments

This work was supported in part by the Gilbert Baum Memorial Grant and the Goddess Fund for Stroke Research in Women (TR), and by grants from the National Institute of Neurological Disorders and Stroke, R01 29993 (RLS, MSVE, TR, BBA), K23 NS42912 (MSVE), AHA (Kathleen Scott Research Fellowship, MSVE) and the General Clinical Research Center (2 M01 RR00645).

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Figure 1.

A. B and M-mode image of the CCA diameter change during the cardiac cycles

B. M-mode tracing of the CCA diameter during the cardiac cycle

Figure 2.

Figure 2A. Metabolic syndrome components and gender

The numbers express in percentage indicate the prevalence of Metabolic Syndrome components in the overall patients.

Figure 2B. Metabolic syndrome components and race-ethnicity

BP indicates blood pressure $\geq 130/85$ mm Hg; FBS indicates fasting blood sugar ≥ 110 mg/dL; Waist indicates waist circumference >40.8 " in men and >35.2 " in women; Trig. Indicates triglycerides ≥ 150 mg/dL; HDL indicates high-density lipoprotein <40 mg/dL in men and <50 mg/dL in women.

Table 1

Demographics of study participants

	Overall n=1133	No MetSyn n=578 (51%)	MetSyn n=555 (49%)	P
Age, years (mean±StD)	65.4 ± 8.8	65.7 ± 9.4	65.0 ± 8.0	0.16
Sex, n(%)				<0.0001
Women	695 (61%)	312 (45%)	383 (55%)	
Men	438 (39%)	266 (61%)	172 (39%)	
Race/ethnicity, n(%)				<0.0001
Hispanic	658 (58%)	292 (44%)	366 (56%)	
Black	254 (22%)	151 (59%)	103 (41%)	
White	221 (20%)	135 (61%)	86 (39%)	

Table 2

Common carotid artery diameters, distensibility parameters, carotid plaque, and IMT by metabolic syndrome status

Mean $\pm$ SD	Overall n=1133	No MetSyn n=578 (51%)	MetSyn n=555 (49%)	P
Systolic Diameter (mm)	6.73 $\pm$ 0.99	6.68 $\pm$ 1.06	6.78 $\pm$ 0.91	0.09
Diastolic Diameter (mm)	6.22 $\pm$ 0.99	6.16 $\pm$ 1.04	6.29 $\pm$ 0.94	0.04
Strain	0.09 $\pm$ 0.14	0.09 $\pm$ 0.05	0.09 $\pm$ 0.19	0.86
Stiffness (LogSTIFF)	1.95 $\pm$ 0.61	1.90 $\pm$ 0.59	2.01 $\pm$ 0.61	0.003
Carotid plaque, n(%)	830 (73.3%)	417 (72.2)	413 (74.4)	0.39
Carotid IMT	0.92 $\pm$ 0.09	0.92 $\pm$ 0.09	0.92 $\pm$ 0.09	0.83

Table 3

Association between metabolic syndrome components and carotid artery stiffness (Multiple linear regression)

<u>LogSTIFFNESS</u>	β	P
Waist >40.8(M), >35.2(W)	0.130	0.002
Serum triglycerides >150mg/Dl	0.007	0.87
HDL < 40mg/dL(M) / <50(W)	- 0.031	0.45
BP > 130/85 mm Hg	0.185	0.0003
Serum glucose > 110mg/dL	0.044	0.31

Adjusted for age, sex, race-ethnicity, education, current smoking, carotid plaque, and IMT