

# The Metabolic Syndrome in Older Individuals: Prevalence and Prediction of Cardiovascular Events

## The Cardiovascular Health Study\*

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**OBJECTIVE** — The prevalence of the metabolic syndrome, a potent risk factor for cardiovascular diseases (CVDs), has not been adequately explored in older individuals. Moreover, two sets of criteria have been proposed for the definition of metabolic syndrome, one by the World Health Organization (WHO) and one by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). We therefore investigated the prevalence of this syndrome in a subgroup of older participants from the Cardiovascular Health Study (CHS) who were free of CVD at baseline. We also compared the prognostic significance of the two definitions of the metabolic syndrome.

**RESEARCH DESIGN AND METHODS** — A total of 2,175 subjects from the CHS who were free of CVD at baseline and not taking antihypertensive or lipid-lowering medications were studied. Prevalence of the metabolic syndrome was assessed with both the WHO and ATP III criteria. The incidence of coronary or cerebrovascular disease was ascertained during a median follow-up time of 4.1 years.

**RESULTS** — Prevalence of the metabolic syndrome was 28.1% by ATP III criteria and 21.0% by WHO criteria. The two sets of criteria provided concordant classification for 80.6% of participants. Multivariate Cox proportional hazard models showed that the metabolic syndrome defined with the ATP III criteria, but not with the WHO criteria, was an independent predictor of coronary or cerebrovascular events and was associated with a 38% increased risk (hazard ratio 1.38 [95% CI 1.06–1.79],  $P < 0.01$ ).

**CONCLUSIONS** — Prevalence of the metabolic syndrome in older individuals is ~21–28% (depending on the definition used). The two sets of criteria have 80% concordance in classifying subjects. As defined by the ATP III criteria, the metabolic syndrome yields independent prognostic information, even after adjusting for traditional cardiovascular risk factors and the individual domains of the metabolic syndrome.

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\*A complete list of the participating Cardiovascular Health Study investigators and institutions can be found in the APPENDIX.

**Abbreviations:** AUC, area under the curve; CeVD, cerebrovascular disease; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CVD, cardiovascular disease; IMT, intima-media thickness; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization.

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

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The metabolic syndrome is increasingly recognized as a risk factor for cardiovascular diseases (CVDs) (1) and cardiovascular mortality (2). Because older individuals are at high risk for CVD (3), an understanding of the scope of the metabolic syndrome in this segment of the population is necessary for the rational allocation of health care and research resources. However, the prevalence of the metabolic syndrome in older individuals has not been well defined, in part, because these individuals have traditionally been underrepresented in most large epidemiological studies.

Two differing sets of criteria have been put forth for the definition of the metabolic syndrome by international committees: one by the World Health Organization (WHO) (4) and, more recently, a related but not identical definition from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (NCEP ATP III) (5).

Therefore, the goals of the present analyses were: 1) to investigate the prevalence of the metabolic syndrome in a subgroup of older participants in the Cardiovascular Health Study (CHS) who were free of CVD at baseline, 2) to evaluate whether the two definitions of the metabolic syndrome (WHO and ATP III) yield different estimates for the prevalence of this syndrome, 3) to compare the degree of concordance in the classification of metabolic syndrome by these two definitions, and 4) to prospectively evaluate the prognostic value of each of these two definitions of the metabolic syndrome.

## RESEARCH DESIGN AND METHODS

The study subjects were participants in the CHS, a prospective multicenter study of men and women 65 years of age or older, sponsored by the National Heart, Lung, and Blood Institute (6). A detailed description of the recruit-

ment methods has been published previously (7). The original cohort was recruited between June 1989 and May 1990 and comprised 5,201 individuals, 94% of whom were Caucasian. An additional 687 African-American participants were enrolled into the study between June 1992 and May 1993.

The baseline examination for both cohorts included medical history, physical examination, laboratory testing, and assessment of CVD status. The study design, quality-control procedures, laboratory methods, and blood pressure measurements have been reported previously (6–8). Prevalent CVD at first visit (prevalent CVD) was defined as a history of myocardial infarction, angina, coronary artery bypass surgery, coronary artery angioplasty, stroke, transient ischemic attack, or carotid endarterectomy, confirmed by review of medical records. The cohort used for the present analyses excluded all subjects with prevalent CVD, as well as subjects receiving antihypertensive and/or lipid-lowering medications at baseline.

As a measure of subclinical cardiovascular disease, carotid intima-media thickness (IMT) was evaluated with high-resolution B-mode ultrasonography (9). One longitudinal image of the common carotid artery was acquired. Measurements were made at a central reading center by readers blinded to all clinical information. The same readers were used for all readings. The maximal IMT of the common carotid artery was defined as the mean of the maximal IMT of the near and far walls on both the left and right sides.

### Two definitions of the metabolic syndrome

A WHO report (4) provided a “working definition” of the metabolic syndrome by establishing five domains to be considered: glucose/insulin metabolism, blood pressure, plasma lipids, obesity/body fat distribution, and microalbuminuria. The WHO definition of metabolic syndrome has been modified for use in epidemiological studies (10), as proposed, in part, by the European Group for the Study of Insulin Resistance (11), which excluded microalbuminuria from the definition. Thus, the modified WHO definition is defined as an alteration in the glucose domain with at least two alterations among the other three domains (blood pressure, plasma lipids, and obesity/body fat distri-

bution). Alterations are defined as follows. Glucose domain: 2-h post-oral glucose load plasma glucose  $\geq 140$  mg/dl or clinical diabetes (therapy with oral hypoglycemic agents or insulin). Blood pressure domain: systolic  $\geq 140$  mmHg or diastolic  $\geq 90$  mmHg. Plasma lipids domain: triglycerides  $>150$  mg/dl or HDL cholesterol  $<35$  mg/dl in men and  $<39$  mg/dl in women. Body composition domain: waist-to-hip ratio  $>0.9$  in men and  $>0.85$  in women or BMI  $>30$  kg/m<sup>2</sup>.

The ATPIII (5) provided an alternative definition of the metabolic syndrome, requiring an alteration in three or more of the following five domains: abdominal obesity, triglycerides, HDL cholesterol, blood pressure (systolic or diastolic), and fasting glucose. According to this definition, the following cut-off values to define alterations are used: waist circumference  $>102$  cm for men and  $>88$  cm for women, triglycerides  $\geq 150$  mg/dl, HDL cholesterol  $<40$  mg/dl for men and  $<50$  mg/dl for women, blood pressure  $\geq 130/ \geq 85$  mmHg, and fasting glucose  $\geq 110$  mg/dl.

### Outcomes

Incidence of coronary heart disease (CHD) was defined as the occurrence of angina pectoris, myocardial infarction, coronary artery angioplasty, or aorto-coronary bypass surgery. Incidence of cerebrovascular disease (CeVD) was defined by the occurrence of stroke or transient ischemic attack. New myocardial infarctions and strokes were adjudicated according to published algorithms (12). Incidence of CVD was the primary end point for the outcomes analyses and was defined as the composite of CHD or CeVD.

### Statistical analysis

All analyses were performed with SAS statistical software (version 8.1). Cox proportional hazards models were used to describe the time to the primary end point (CVD) and the secondary end points (CHD and CeVD). Independent variables in the models included age, sex, the metabolic syndrome (ATPIII or WHO definition), the individual domains of metabolic syndrome, LDL cholesterol, current smoking, and family history of myocardial infarction. Additional models were run that also included IMT as an independent variable. Multiple logistic regression analyses, which included the

same variables as in the Cox analyses, were used to estimate receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) was calculated for each model and was used as a measure of how well a model is able to predict the outcome of interest, with an AUC value equal to 0.50 indicating no accuracy and an AUC value equal to 1.00 indicating maximal accuracy. Values are expressed as means  $\pm$  SD. Statistical significance was inferred for  $P < 0.05$ .

**RESULTS** — In the entire CHS cohort free of prevalent CVD at baseline (including those subjects who were receiving antihypertensive or lipid-lowering medication), the prevalence of metabolic syndrome was 35.1% by the ATPIII criteria (32.1% in men and 37.4% in women) and 27.6% by the WHO criteria (32.4% in men and 23.9% in women).

Our study population comprised the 2,175 subjects from the CHS who were free of CVD at baseline and who were not receiving antihypertensive or lipid-lowering medication. The baseline characteristics of the study population are shown in Table 1. Subjects concordantly classified by both sets of criteria as not having the metabolic syndrome and those concordantly classified as having the metabolic syndrome did not significantly differ in age, sex, smoking status, family history of myocardial infarction, and LDL cholesterol levels.

By applying the ATPIII criteria, 28.1% of the participants were classified as having metabolic syndrome. By applying the WHO criteria, 21.0% were classified as having it. The two sets of criteria provided concordant classification for 80.6% of participants: 13.2% of subjects were classified as having the metabolic syndrome by the ATPIII but not by the WHO criteria; conversely, 6.2% were classified as having the metabolic syndrome by the WHO but not by the ATPIII criteria. The ATPIII and WHO criteria yielded similar estimates for the prevalence of metabolic syndrome in men (25.6 and 26.2%, respectively) but yielded markedly different estimates for the prevalence of metabolic syndrome in women (26.2 and 16.6%, respectively). The prevalence of the metabolic syndrome was different between Caucasians (27.6%) and African Americans regardless of the criteria used to define metabolic syndrome (27.6 vs. 32.7% by the ATPIII

Table 1—Baseline characteristics of the study population

	Entire cohort	No metabolic syndrome by either ATP III or WHO criteria	Metabolic syndrome by both ATP III and WHO criteria
n	2,175	1,430	323
African American (%)	9.9	5.93	2.11
Age (years)	73 ± 5	73 ± 5	73 ± 5
Male sex (%)	57.6	58.7	55.3
Current smoking (%)	13.9	13.5	14.9
Family history of MI (%)	29.0	27.9	32.5
Waist (cm)*	92.7 ± 11.6	89.9 ± 11.1	101.8 ± 9.8
Hip (cm)*	100.8 ± 8.0	99.4 ± 7.5	106.4 ± 7.9
Waist-to-hip ratio*	0.92 ± 0.08	0.90 ± 0.08	0.96 ± 0.07
BMI (kg/m <sup>2</sup> )*	26.0 ± 3.8	25.1 ± 3.5	29.0 ± 3.6
SBP (mmHg)*	136.4 ± 18.9	133.9 ± 18.9	143.8 ± 18.4
DBP (mmHg)*	71.2 ± 9.8	70.4 ± 9.7	73.7 ± 10.2
Pulse pressure (mmHg)*	65.2 ± 16.7	63.6 ± 16.7	70.0 ± 17.1
Fasting plasma glucose (mg/dl)*	104.9 ± 26.9	96.3 ± 8.1	141.2 ± 48.0
Triglycerides (mg/dl)*	129.6 ± 65.9	110.7 ± 42.7	181.3 ± 100.0
HDL cholesterol (mg/dl)*	56.5 ± 16.0	60.4 ± 15.6	47.4 ± 13.1
LDL cholesterol (mg/dl)	129.8 ± 35.1	128.7 ± 33.8	130.1 ± 36.6
CCA IMT (mm)*	0.99 ± 0.23	0.97 ± 0.23	1.06 ± 0.24
CCA diameter (mm)*	9.06 ± 0.94	8.96 ± 0.94	9.34 ± 0.95

Data are means ± SD. \*P < 0.001 for no metabolic syndrome vs. metabolic syndrome. CCA, common carotid artery; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure.

criteria and 20.8 vs. 28.9% by the WHO criteria; P < 0.001 for both comparisons).

To better understand where the two metabolic syndrome definitions differed in our elderly population, the distribution of each individual component of the metabolic syndrome by ATP III and WHO criteria was analyzed according to the number of altered components. As shown in Table 2, elevated blood pressure was one of the most frequently altered components in elderly subjects with metabolic syndrome by either criteria. However, abdominal obesity was most frequently altered in subjects with meta-

bolic syndrome by ATP III criteria, whereas glucose domain was the most prevalent altered component in those with metabolic syndrome by WHO criteria. Of note, among those elderly subjects classified as having no altered component by the WHO criteria, 32.9% presented altered blood pressure domain and 30.1% altered abdominal obesity domain by ATP III criteria (with 27.9% having both alterations) (data not shown).

After a median follow-up of 4.1 years (maximum 5.1), 464 (21.3%) CVD events occurred. Of these, 360 were CHD events and 104 were CeVD events. As

summarized in Table 3, subjects who developed a CVD event were older and more likely to be men than those who remained free of a CVD event. Levels of traditional cardiovascular risk factors (blood pressure, plasma lipids, and fasting glucose) differed between the two groups, with the exception of BMI and current smoking status. The prevalence of the metabolic syndrome, defined by the WHO or ATP III criteria, as well as most of its individual components, was higher in subjects who developed a CVD event (Table 3).

The incidence of CVD was 17.8% in those without metabolic syndrome by both definitions, 27.5% in those with metabolic syndrome by ATP III only, 26.6% in those with metabolic syndrome by WHO only, and 34.8% in those with metabolic syndrome according to both WHO and ATP III (P < 0.0001 for each metabolic syndrome group vs. no metabolic syndrome group). The ATP III criteria had a slightly higher sensitivity than the WHO criteria (38.7 vs. 29.3%) but lower specificity (76.0 vs. 82.7%). The two sets of criteria had essentially similar positive predictive values (31.3 and 32.4%) and negative predictive values (81.5 and 80.6%).

The ability of metabolic syndrome to predict future CVD events was analyzed with Cox proportional hazard models (Table 4). The first model only included metabolic syndrome and showed that metabolic syndrome by either set of criteria was a significant predictor of CVD. Specifically, the hazard ratio (HR) for the ATP III definition was 1.90 (95% CI 1.60–2.26, P < 0.0001) and for WHO definition was 1.89 (1.57–2.28, P < 0.0001). These HRs remained significant after adjusting for age and sex (model 2) and after adjusting for age, sex, family history of myocardial infarction, current smoking,

Table 2—Distribution of altered domains of the metabolic syndrome by ATP III and WHO criteria

	ATP III criteria (%)					WHO criteria (%)			
	Glucose	Blood pressure	HDL cholesterol	Triglycerides	Abdominal obesity	Glucose	Blood pressure	Lipid	Obesity
ATP III-defined metabolic syndrome	55.8	82.6	63.4	68.9	77.6	55.8	61.1	71.7	57.5
Three altered components	44	77.1	55.1	54.5	69.4	44	59.7	58.4	57.7
Four altered components	65.7	88.6	68.6	89.5	87.6	65.7	64.3	91	58.1
Five altered components	100	100	100	100	100	100	61.3	100	54.7
WHO-defined metabolic syndrome	100	78.5	38.1	44.7	56.4	100	62.7	47.9	66.8
Three altered components	65.9	84.1	42.5	64.5	57.0	65.9	79.2	69.6	85.3
Four altered components	100	96.2	57.0	89.9	69.6	100	100	100	100

**Table 3—Baseline characteristics and prevalence of the metabolic syndrome and its components in subjects who developed and did not develop a CVD event**

	Free of CVD events	Incident CVD events	P
n	1,711	464	
Age (years)	73 ± 5	75 ± 5	<0.001
Male sex (%)	38.9	64.7	<0.001
Current smoking (%)	13.2	15.6	0.18
Family history of MI (%)	27.9	35.6	<0.01
Waist (cm)	92.2 ± 11.7	95.5 ± 10.1	<0.001
BMI (kg/m <sup>2</sup> )	26.0 ± 3.8	26.2 ± 3.2	0.22
SBP (mmHg)	135.3 ± 18.0	142.3 ± 17.4	<0.001
DBP (mmHg)	70.9 ± 9.5	72.4 ± 9.3	<0.01
Pulse pressure (mmHg)	64.4 ± 16.4	69.9 ± 16.0	<0.001
Fasting plasma glucose (mg/dl)	103.5 ± 23.6	112.6 ± 38.5	<0.001
Triglycerides (mg/dl)	127.5 ± 62.3	145.8 ± 75.5	<0.001
HDL cholesterol (mg/dl)	57.5 ± 15.5	50.1 ± 13.6	<0.001
LDL cholesterol (mg/dl)	129.8 ± 33.6	134.3 ± 37.5	<0.05
CCA IMT (mm)	0.97 ± 0.21	1.10 ± 0.28	<0.001
Alterations by ATPIII criteria			
Glucose domain (%)	19.1	31.4	<0.001
Blood pressure domain (%)	59.6	77.8	<0.001
HDL cholesterol domain (%)	22.3	33.1	<0.001
Triglycerides domain (%)	25.1	33.7	<0.001
Abdominal obesity domain (%)	42.2	40.2	0.43
Metabolic syndrome (%)	24.0	38.7	<0.001
Alterations by WHO criteria			
Glucose domain (%)	19.1	31.4	<0.001
Blood pressure domain (%)	43.7	60.9	<0.001
Lipid domain (%)	26.8	35.3	<0.001
Obesity domain (%)	43.7	60.0	<0.001
Metabolic syndrome (%)	17.2	29.3	<0.001

CCA, common carotid artery; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure.

and LDL cholesterol (model 3), but their values were higher than those in model 1 with the ATPIII criteria and lower than those in model 1 with the WHO criteria. When individual components of the metabolic syndrome were also introduced as independent variables (model 4), age, male sex, current smoking, higher systolic blood pressure, and higher LDL and lower HDL cholesterol were independently associated with an increased risk of CVD. However, only the metabolic syndrome defined with the ATPIII criteria, not with the WHO criteria, was an independent predictor of CVD events and was associated with a 38% increased risk of CVD (HR 1.38 [95% CI 1.07–1.79],  $P < 0.01$ ). AUC calculated for each of the four models indicated that after adjusting for age and sex, the addition of traditional cardiovascular risk factors, including the individual components of the metabolic

syndrome, did not dramatically improve the accuracy of the predictive models for incident CVD events in this cohort. Similar results were obtained when IMT was added to the models (1.39 [1.07–1.81],  $P < 0.01$ , for the ATPIII definition; 1.13 [0.85–1.50],  $P = 0.39$ , for the WHO definition).

**Table 4—Metabolic syndrome as a predictor of subsequent CVD in elderly subjects**

	ATPIII-defined metabolic syndrome				WHO-defined metabolic syndrome			
	HR	95% CI	P	AUC	HR	95% CI	P	AUC
Model 1	1.90	1.60–2.26	0.0001	0.57	1.89	1.57–2.28	0.0001	0.56
Model 2	2.12	1.77–2.52	0.0001	0.70	1.64	1.36–1.98	0.0001	0.68
Model 3	2.04	1.69–2.46	0.0001	0.71	1.63	1.33–2.01	0.0001	0.71
Model 4	1.38	1.07–1.79	0.01	0.74	1.15	0.88–1.50	0.32	0.74

Independent variables included in the models are as follows: model 1: metabolic syndrome only; model 2: metabolic syndrome, age, and sex; model 3: metabolic syndrome, age, sex, family history of myocardial infarction, current smoking, and LDL cholesterol; model 4: metabolic syndrome, age, sex, family history of myocardial infarction, current smoking, LDL cholesterol, and individual components of the metabolic syndrome. HRs and 95% CIs analyzed by Cox regression analysis. AUC determined by logistic regression analysis.

Secondary analyses were performed with the same independent variables described above but with CHD or CeVD as the dependent variables. Once again, after adjusting for each individual domain of the metabolic syndrome, the metabolic syndrome defined according to the ATPIII criteria, but not the WHO criteria, was an independent predictor of CHD and was associated with a 40% increased risk (HR 1.40 [95% CI 1.04–1.89],  $P = 0.02$ ). The metabolic syndrome defined according to both the ATPIII and the WHO criteria were associated with a 68 and 80%, respectively, higher risk for CeVD (1.68 [0.98–2.89],  $P = 0.06$ , for the ATPIII definition; 1.80 [0.99–1.29],  $P = 0.054$ , for WHO definition). The marginal significance of these statistical associations is likely due to the limited number of CeVD events.

We also tested whether the predictive role of either metabolic syndrome definition differed in older Caucasian and African-American subjects. However, given the few cardiovascular events (6.9% of 216 African Americans vs. 23.7% of Caucasians) and the small African-American population free of CVD at baseline, the limited statistical power did not allow any conclusion from the Cox analysis stratified by ethnicity.

**CONCLUSIONS**— In this cohort of older individuals who were free of CVD at baseline, approximately one-quarter met the criteria for the metabolic syndrome by either the ATPIII or WHO definitions. These two sets of criteria classified subjects concordantly in 80.6% of cases. Our results showed that the metabolic syndrome is an independent predictor of CVD, over and above its individual components, only when it is defined accord-

ing to the ATPIII and not the WHO criteria.

This is the first report of the prevalence of the metabolic syndrome in a cohort of older individuals. Meigs et al. (13) found a similar prevalence of the metabolic syndrome in middle-aged adults from the San Antonio Heart Study (23% by ATPIII and 21% by WHO criteria in non-Hispanic whites and ~30% in Hispanic whites with both definitions) and in the Framingham Offspring Study (24% by both metabolic syndrome definitions). In the NHANES III (National Health and Nutrition Examination Survey III) cohort (14), the age-adjusted prevalence of metabolic syndrome was 23.9% using the ATPIII definition and 25.1% using the WHO definition; the two definitions concordantly classified subjects in 86.2% of cases. In contrast, Bonora et al. (15) observed a higher prevalence of metabolic syndrome when it was defined according to the WHO criteria (34.1%) as compared with the ATPIII criteria (17.8%) in a population-based survey of Northern Italian subjects aged 40–79 years. Lakka et al. (16) also reported a higher prevalence of WHO-defined than of ATPIII-defined metabolic syndrome (14.3 vs. 8.8%) in a middle-aged cohort of Finnish men free of CVD and diabetes at baseline. A similar trend was observed in a cohort of 1,529 Italian subjects with type 2 diabetes (17).

The metabolic syndrome, as well as each of its domains, was found to be significantly associated with resting electrocardiographic evidence of ischemic heart disease in 2,300 elderly subjects enrolled in the Rancho Bernardo Study (18). Of note, even though this cross-sectional study used factor analysis to investigate the cluster of risk factors that constitute the metabolic syndrome (19–20), the cluster of variables constituting metabolic syndrome was not included in their statistical models.

Several studies have recently evaluated the ability of metabolic syndrome to predict CVD. In the Botnia Study (21), WHO-defined metabolic syndrome was a significant independent predictor of cardiovascular and overall mortality in middle-aged subjects with prevalent CVD at baseline. In the Kuopio Ischemic Heart Disease Risk Factor Study, which included middle-aged Finnish men, the WHO-defined but not the ATPIII-defined metabolic syndrome was an independent predictor of higher cardiovascular and

overall mortality (16). Conversely, in middle-aged individuals from the San Antonio Heart Study, both metabolic syndrome definitions were predictive of cardiovascular mortality, and the ATPIII-defined metabolic syndrome was a stronger predictor in low-risk subjects (22). Our study strengthens the evidence that the metabolic syndrome is an independent predictor of morbid cardiovascular events, even after accounting for its individual components, and extends it to older individuals.

Although both sets of criteria for the definition of the metabolic syndrome encompass similar domains, namely alterations in fasting glucose, blood pressure, adiposity, and lipids, they differ in the weights accorded to each domain. For example, the threshold for elevated blood pressure is higher in the WHO definition, thus less subjects have alterations in this domain by the WHO criteria than by the ATPIII criteria. Conversely, the WHO criteria do not distinguish between alterations in triglycerides and HDL cholesterol, as opposed to the ATPIII criteria, which recognize each one of these lipid abnormalities as a separate domain. As a matter of fact, we observed that elevated blood pressure and increased abdominal obesity were the most frequent altered components in those subjects with metabolic syndrome determined by the ATPIII criteria, whereas glucose domain was the most frequent in those with metabolic syndrome determined by the WHO criteria. In addition, ~28% of those older subjects with no altered component by the WHO criteria presented elevated blood pressure and abdominal obesity by the ATPIII criteria. Whether these differences indicate that ATP criteria capture other cardiovascular factors not measured by WHO criteria or they explain why ATPIII-defined but not WHO-defined metabolic syndrome remained an independent predictor of CVD in our cohort, after adjusting for the individual domains, remains an unresolved issue.

One of the mechanisms through which the metabolic syndrome may exert its well-documented deleterious effects is by adversely affecting the structural and functional properties of the vasculature, such as arterial wall stiffness and thickness (IMT, which is sometimes regarded as a marker of subclinical atherosclerosis). In this regard, we recently described that the clustering of the components of

the metabolic syndrome has a synergistic detrimental effect on carotid IMT and stiffness (23); furthermore, the metabolic syndrome conferred increased odds of having both thicker and stiffer large arteries. Similarly, in a longitudinal study of 888 subjects aged 40–79 years, Bonora et al. (15) observed that the metabolic syndrome, defined according to the WHO criteria, conferred a significantly increased risk for developing new carotid plaques (HR 1.5), new carotid stenosis (2.5), and new coronary events (2.3). A similar effect was observed for the metabolic syndrome defined according to the ATPIII criteria.

Several limitations to our analytical approach deserve discussion. We excluded subjects taking antihypertensive or lipid-lowering medications from our analyses. Although the definition of the metabolic syndrome could have been adapted to include these individuals, we selected not to do this in order to avoid the confounding effects of medications. Moreover, we chose to include both the metabolic syndrome and its individual components as independent variables in the Cox models (Table 3) because of one of the goals of this study was to test whether the metabolic syndrome added prognostic information in elderly subjects, over and above its individual components. Of note, using a similar analytical approach, we recently showed that even after adjusting for these individual components, the metabolic syndrome remained an independent predictor of arterial stiffness and thickness in participants from the Baltimore Longitudinal Study of Aging (23).

In conclusion, we observed that the two definitions of the metabolic syndrome yielded roughly similar estimates for the prevalence of the metabolic syndrome (approximately one-quarter of older individuals) and had a concordance rate of 80.6%. In addition, we noted that the metabolic syndrome defined according to the ATPIII criteria was a significant predictor of cardiovascular events in older individuals, independent of the individual components of the metabolic syndrome and of other traditional cardiovascular risk factors. This finding should be interpreted with caution, as the incidence of cardiovascular events was similar with both definitions of the metabolic syndrome, and they both had similar positive and negative predictive values.

Nonetheless, the advantages of the ATPIII over the WHO criteria are that they yield independent prognostic information and are easier to apply in clinical practice and in epidemiological studies.

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## APPENDIX

### Participating CHS investigators and institutions

(All investigators here listed have provided signed permission to be acknowledged.) Wake Forest University School of Medicine, Steering Committee Chairman: Curt D. Furberg, MD, PhD. NHLBI Project Office: Jean Olson, MD, MPH. Wake Forest University School of Medicine: Gregory L. Burke, MD. Wake Forest University—ECG Reading Center: Pentti M. Rautaharju, MD, PhD. University of California, Davis: John Robbins, MD, MHS. The Johns Hopkins University: Linda P. Fried, MD, MPH. The Johns Hopkins University—MRI Reading Center: Nick Bryan, MD, PhD, and Norman J. Beauchamp, MD. University of Pittsburgh: Lewis H. Kuller, MD, DrPH. University of California, Irvine—Echocardiography Reading Center (baseline): Julius M. Gardin, MD. Georgetown Medical Center—Echocardiography Reading Center (follow-up): John S. Gottdiener, MD. New England Medical Center, Boston—Ultrasound Reading Center: Daniel H. O'Leary, MD. University of Vermont—Central Blood Analysis Laboratory: Russell P. Tracy, PhD. University of Arizona, Tucson—Pulmonary Reading Center: Paul Enright, MD. University of Wisconsin—Retinal Reading Center: Ronald Klein, MD. University of Washington—Coordinating Center: Richard A. Kronmal, PhD.

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