Carotid Atherosclerosis and Coronary Heart Disease in the Metabolic Syndrome

Prospective data from the Bruneck Study

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OBJECTIVE — The present study aimed at prospectively evaluating carotid atherosclerosis and coronary heart disease (CHD) in subjects with the metabolic syndrome.

RESEARCH DESIGN AND METHODS — Within a prospective population-based survey examining 888 subjects aged 40–79 years, 303 subjects were identified as fulfilling World Health Organization (WHO) criteria and 158 as fulfilling the National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP)-III criteria for diagnosing the metabolic syndrome. The 5-year change in carotid status, as assessed by echo-duplex scanning, and incident fatal and nonfatal CHD, as assessed by medical history and death certificates, were compared in subjects with the metabolic syndrome and in the rest of the sample (control subjects).

RESULTS — Compared with the control subjects, subjects with the metabolic syndrome by WHO criteria had an increased 5-year incidence and progression of carotid atherosclerosis: 51 vs. 35% developed new plaques ($P = 0.021$) and 34 vs. 19% developed carotid stenosis >40% ($P = 0.002$) after adjusting for several confounders. Subjects with the metabolic syndrome by these criteria also had an increased incidence of CHD during follow-up: 8 vs. 3% in control subjects ($P = 0.012$). Similar results were found when the NCEP-ATPIII criteria were used.

CONCLUSIONS — Subjects with the metabolic syndrome are at increased risk for both progressive carotid atherosclerosis and CHD.

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An aggregation of several metabolic and nonmetabolic abnormalities within the single individual was described repeatedly over the last decade (1–3) and was termed with several names, including "syndrome X" (4), "insulin resistance syndrome" (5) or "metabolic syndrome" (6).

A few years ago a committee of experts from the World Health Organization (WHO) suggested that the appropriate name should be "metabolic syndrome" and indicated a set of diagnostic criteria (7). Another set of criteria was indicated by the experts of the National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP)-III (8). Most recently, the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services attributed a specific code to the "dysmetabolic syndrome" (ICD #277.7), providing it with a clinical dignity it never had in the past. The metabolic syndrome is expected to be diagnosed in millions of subjects in the near future worldwide by either WHO or NCEP-ATPIII criteria.

Currently, there are very few data in the literature clearly documenting that subjects with the metabolic syndrome have an increased cardiovascular risk. Thus, the aim of the present study was to assess the development/progression of carotid atherosclerosis and the incidence of coronary heart disease (CHD) in subjects with the metabolic syndrome.

RESEARCH DESIGN AND METHODS

Subjects

The Bruneck Study is a prospective population-based survey on atherosclerosis and its risk factors. It is being carried out in Bruneck, a small town of ~13,500 people, located in Northeastern Italy. As reported previously (9), the baseline evaluation was performed between July and November 1990 on subjects aged 40–79 years. Among the 1,000 randomly selected men and women aged 40–79 years, 936 volunteered after the purposes and modalities of the study had been carefully presented. Altogether, 2 subjects who were insulin treated, 17 subjects with incomplete data collection, and 29 subjects with no serum available for the measurement of insulin were excluded, which left 888 subjects (450 men and 438 women) for the current analysis.

From July to October 1995, a reeval-

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Abbreviations: ATP, Adult Treatment Panel; CHD, coronary heart disease; HOMA, homeostasis model assessment; HOMA-IR, HOMA for insulin resistance; ECG, electrocardiogram; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

uation of the cohort was performed (10). Of the original population sample, 62 subjects were deceased, 1 had moved away and could not be traced, and 30 declined to participate in the follow-up study. Thus, the latter was 96.5% complete among survivors (n = 826 of 856).

The protocol was approved by the Ethics Committee of the University of Verona. All subjects gave an informed consent.

Clinical data

The following demographic and clinical data were collected with a standardized questionnaire: sex, age, cigarette smoking, alcohol consumption, physical activity, socioeconomic status, previous diseases, and drug consumption. Details on the methodology were previously reported (10). BMI, waist-to-hip ratio (WHR), and blood pressure were assessed with standard techniques.

Laboratory data

In the morning after an overnight fast, venous blood was sampled for the measurement of plasma concentrations of glucose and serum concentrations of total and HDL cholesterol, triglycerides, and insulin. A spot urine collection was used for quantifying the albumin-to-creatinine ratio. A 75-g oral glucose load (oral glucose tolerance test [OGTT]) was administered to all subjects except known diabetic patients in order to establish glucose tolerance. During the test, blood was withdrawn at 120 min for the measurement of plasma glucose and serum insulin. Details on analytical procedures were previously reported (10).

Diagnostic criteria of the metabolic syndrome

The metabolic syndrome was diagnosed according to WHO criteria (7), with the exception that insulin resistance was assessed by the homeostasis model assessment (HOMA) instead of the glucose clamp because use of the latter is not feasible in epidemiological settings and HOMA seems to be a reliable alternative (11).

Diagnostic criteria of the metabolic syndrome by the most recent WHO criteria (7) are impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 diabetes or insulin resistance with two or more of the following abnormalities: *1*) IFG (fasting plasma glucose ≥6.1 mmol/l), IGT (2-h OGTT plasma glucose 7.8–11.0 mmol/l), or type 2 diabetes (fasting plasma glucose ≥7.0 mmol/l, 2-h OGTT plasma glucose ≥11.1 mmol/l, or known diabetes); *2*) insulin resistance (see below for the definition); *3*) hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg and/or antihypertensive treatment); *4*) dyslipidemia (triglycerides ≥1.7 mmol/l and/or HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women); *5*) central obesity (WHR >0.90 in men and >0.85 in women and/or BMI >30 kg/m^2); and *6*) microalbuminuria (urinary albumin-to-creatinine ratio ≥30 mg/g).

As an alternative, the metabolic syndrome was diagnosed with the criteria indicated by the NCEP-ATPIII (8). According to these criteria, subjects with the metabolic syndrome are those with any combination of three or more of the following risk determinants: fasting plasma glucose ≥6.1 mmol/l, blood pressure ≥130/≥ 85 mmHg or antihypertensive treatment, plasma triglycerides ≥1.7 mmol/l, plasma HDL cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women, and waist circumference >102 cm in men or >88 cm in women.

Assessment and definition of insulin resistance

The degree of insulin sensitivity was determined by HOMA according to the method described by Matthews et al. (12). In the present study, insulin resistance was defined by a HOMA for insulin resistance (HOMA-IR) value equal or higher than the lower limit of the top quartile of HOMA-IR distribution values in the whole sample, as suggested by the WHO (7). In a recent article (13), we reported on the good reliability of HOMA.

Assessment of carotid atherosclerosis

At baseline and 5 years later, carotid atherosclerosis was determined by high-resolution B-mode ultrasound (ATL UM8; Advanced Technology Laboratories, Bothel, WA), as previously described (9). All measurements were carried out and read by a single specialist physician (J.W.), who was blind to all clinical and laboratory characteristics and who, at follow-up, had absolutely no information on the results of the baseline evaluation. Images were recorded on a videotape. The scanning protocol included imaging of the common and internal carotid arteries in multiple longitudinal and transverse planes. The near and far walls at each of four well-defined imaging sites of both carotid arteries were explored: the proximal common carotid artery (15–30 mm proximal to the carotid bulb), the distal common carotid artery (<15 mm to the carotid bulb), the proximal internal carotid artery (carotid bulb and the initial 10 mm of the vessel), and the distal carotid artery (>10 mm above the flow divider). Atherosclerotic lesions were defined by two ultrasound criteria: wall surface (protrusion into the lumen or roughness of the arterial boundary) and wall texture (echogenicity). In all eight regions of interest the maximum axial diameter of plaques, if any, were measured (in millimeters) and the measurements summed to obtain an atherosclerosis score. This method was successfully used by other investigators (14).

Based on the follow-up examination, we assessed 5-year changes in the vascular status. In particular, we evaluated the change in the atherosclerosis score during follow-up. In addition, the scanning protocol permitted a differentiation of two main stages of atherogenesis, termed "incident nonstenotic atherosclerosis" (early atherogenesis) and "incident stenotic atherosclerosis" (advanced atherogenesis). As extensively discussed in previous articles (15,16), the former was defined as the occurrence of new plaques in previously normal vessel segments and was assessed in subjects with and without preexisting carotid atherosclerosis. Thresholds of 0.7 mm (common carotid artery) and 1.0 mm (internal carotid artery) were introduced in the definition of incident nonstenotic atherosclerosis as a minimum plaque diameter requirement because smaller lesions were difficult to distinguish from focal/diffuse wall thickening. Incident stenotic atherosclerosis was defined by the finding of a relative increase in the maximum axial diameter of a preexisting plaque that exceeded twice the measurement error of the method and a narrowing of the lumen >40%. As detailed elsewhere, the cutoff of 40% appeared to be a biological threshold in our population, at which marked changes in the growth kinetics of plaques (continuous, slow, and diffuse growth versus occasional and focal prominent lesion expansion), risk profiles (conventional versus procoagulant), and vascular remodeling process (com-

pensatory or overcompensatory versus insufficient or even absent) occurred as indicative of a switch in the underlying pathogenetic mechanisms from conventional atherogenesis to atherothrombosis (15,16). This person-based progression model is an unique feature of the Bruneck Study and has been presented in several previous reports (10,17–21).

Validity and reproducibility of the ultrasound method we used have been described in detail elsewhere (15,16). Briefly, intraobserver coefficients of variation (CVs) for the measurement of maximum axial diameter of plaques varied from 10 to 15%, depending on the vessel segment. CV of the atherosclerosis score was 13.5%. CV for change of atherosclerosis score during follow-up was 27%. Reproducibility of the ultrasound categories (incident plaques or incident stenosis) was "near perfect" (k coefficient >0.8), as derived from two independent measurements performed by the same sonographer in a reproducibility sample of 100 subjects. Maximum efforts were made to avoid drifts in ultrasound assessments between 1990 and 1995. These included special training courses, continuous analyses for time trends in ultrasound assessments, and performance of all scans with the same equipment and by the same experienced sonographer.

Assessment of CHD

In all subjects a 12-lead electrocardiogram (ECG) was recorded at the baseline and at the follow-up. All the ECGs were subsequently read by the same cardiologist, who interpreted them according to the Minnesota Code (22). The presence of CHD at baseline was regarded as "definite" when an ECG showed alterations typical of myocardial ischemia (codes 1.1, 4.1, 5.1, and 7.1) and/or when the proband had a medical history positive for myocardial infarction or angina pectoris, as ascertained by examining the medical records of local general practitioners and/or Bruneck Hospital, as "probable" when an ECG showed alterations strongly suggestive of ischemia (codes 1.2, 4.2, and 5.2), and as "possible" when an ECG showed alterations suggesting ischemia (codes 1.3, 4.3, and 5.3) and when the patient experienced several episodes of chest pain. Assessment of incident (fatal and nonfatal) definite CHD during follow-up was based on medical history and detailed review of the files of the Bruneck Hospital, including clinical examinations and results of laboratory exams and ECGs. Myocardial infarction was deemed confirmed when WHO criteria for definite disease status (23) were met, including compatible symptoms (24), ECG changes, and elevated cardiac enzymes. Angina pectoris was deemed confirmed when the proband had typical effort-dependent chest pain, and myocardial ischemia was confirmed by exercise-positive ECG and/or angiography.

In subjects who died during the follow-up, death certificates and medical records were carefully examined in order to define the cause of death and, in particular, whether it could be attributed to CHD (myocardial infarction or sudden cardiac death).

Statistical analysis

Statistical analysis was performed with SPSS-X and BMDP software. Skewed variables were $\log_e$-transformed to improve the approximation to a Gaussian distribution. Statistics included Student's t test for unpaired data, one-way ANOVA, ANCOVA, and χ^2 test with Yates' correction for continuity. The association between the metabolic syndrome and carotid atherosclerosis or definite (fatal and nonfatal) CHD was evaluated by multiple linear and logistic regression analyses. The former focused on continuous variables (atherosclerosis score and change in atherosclerosis score from 1990 to 1995); the latter focused on categorical variables (incident plaques, incident arterial stenosis, and incident fatal and nonfatal CHD). Separate models were tested with the metabolic syndrome traits considered as independent covariates simultaneously included in the same equation or with the metabolic syndrome considered as a single entity. Sex, age, smoking, alcohol, physical activity, social status, and LDL cholesterol were further covariates in these models. Models on atherosclerosis progression also included baseline atherosclerosis as a covariate, whereas models on CHD incidence included baseline CHD (definite or probable or possible) as a covariate. A further analysis on CHD incidence excluded subjects with CHD (definite, probable, or possible) at baseline.

RESULTS — In the whole sample, the prevalence of the various components of the metabolic syndrome were as follows: impaired glucose regulation (IFG or IGT) or type 2 diabetes 22.6% (n = 201), central obesity 73.6% (n = 654), dyslipidemia 30.8% (n = 274), hypertension 62.0% (n = 551), and microalbuminuria 12.0% (n = 107). A total of 72 (8.1%) subjects had none of the clinical traits of the metabolic syndrome as defined by WHO, and 208 (23.4%) had only one trait. In addition, 264 (29.7%), 178 (20.0%), 102 (11.5%), 52 (5.8%), and 12 (1.3%), had two, three, four, five, or six traits simultaneously present, respectively, and 303 (34.1%) subjects fulfilled the WHO diagnostic criteria for the metabolic syndrome. The main baseline clinical and biochemical data of these subjects are summarized in Table 1. As compared with the rest of the sample (the control subjects), these subjects had higher age, BMI, WHR, glucose, insulin, HOMA-IR, triglycerides, blood pressure, and microalbuminuria and lower HDL cholesterol, physical activity score, and social status.

At baseline, the prevalence of plaques of any size was 42.3%, whereas the prevalence of carotid stenosis >40% was 5.2%. The baseline prevalence of definite or probable CHD was 10.3%, and that of possible CHD was 10.0%.

Subjects with the metabolic syndrome according to WHO criteria showed a significantly increased risk of development or progression of carotid atherosclerosis during the 5-year follow-up. In fact, changes in the atherosclerosis score (sum of all plaques, if any) in 1995 compared with baseline, as well as the percent of subjects who developed new plaques (early atherogenesis) or arterial stenosis >40% (advanced atherogenesis) from 1990 to 1995, were higher in subjects with the metabolic syndrome than in control subjects. All of these differences were significant after adjusting for sex, age, smoking, alcohol, physical activity, social status, LDL cholesterol, and baseline atherosclerosis (Table 2). The multiple-adjusted odds ratios (ORs) for incident plaques and for incident stenosis in subjects with the metabolic syndrome compared with control subjects were 1.5 (95% CI 1.1–2.1, P = 0.02) and 2.4 (1.3–4.1, P = 0.01), respectively (Table 3, model 2).

Subjects with the metabolic syndrome according to WHO criteria also showed an increased incidence of definite (fatal and nonfatal) CHD during the

Table 1—*Metabolic and nonmetabolic clinical and biochemical features in subjects with the metabolic syndrome by WHO criteria and in the control subjects*

	Control subjects	Metabolic syndrome	*P*
n	585	303	
Sex (% men)	52	49	NS
Age (years)	57.0 ± 11.1	62.6 ± 11.2	<0.001
Smoking (cigarette/day)	4.2 ± 8.0	4.0 ± 8.1	NS
Alcohol (% >50 g/day)	23	21	NS
Physical activity (score)	4.5 ± 1.5	3.9 ± 1.6	<0.001
Social status (% low)	60	68	0.020
BMI (kg/m^2)	24.1 ± 3.3	26.6 ± 4.2	<0.001
WHR	0.91 ± 0.07	0.93 ± 0.07	<0.001
Fasting glucose (mmol/l)	5.2 ± 0.4	6.3 ± 1.5	<0.001
2-h glucose (mmol/l)	4.7 (3.8–5.7)	7.2 (4.9–9.2)	<0.001
Fasting insulin (pmol/l)	59 (44–86)	134 (88–204)	<0.001
2-h insulin (pmol/l)	194 (122–313)	448 (282–730)	<0.001
HOMA-IR	1.9 (1.4–2.8)	5.1 (3.7–8.1)	<0.001
LDL cholesterol (mmol/l)	3.5 ± 0.9	3.6 ± 1.2	NS
HDL cholesterol (mmol/l)	1.5 ± 0.3	1.4 ± 0.4	<0.001
Triglycerides (mmol/l)	1.2 (0.8–1.6)	1.7 (1.2–2.5)	<0.001
Systolic blood pressure (mmHg)	141 ± 20	154 ± 22	<0.001
Diastolic blood pressure (mmHg)	87 ± 10	92 ± 10	<0.001
Albumin-to-creatinine ratio (mg/g)	6.0 (3.7–134)	7.5 (4.1–178)	0.002

Data are means ± SD, geometric mean (interquartile range), and %. *P* for sex, age, smoking, alcohol, physical activity, and social status are unadjusted. All other *P* values are adjusted for sex, age, smoking, alcohol, physical activity, and social status.

5-year follow-up compared with that of control subjects. This difference was significant after adjusting for sex, age, smoking, alcohol, physical activity, social status, LDL cholesterol, and baseline CHD (Table 2). The exclusion of subjects with preexisting CHD (definite, probable, or possible) did not change the results (incident CHD 5 vs. 2%, $P = 0.046$, in subjects with the metabolic syndrome and control subjects, respectively). The multiple-adjusted OR for incident CHD in subjects with the metabolic syndrome was 2.3 (CI 1.2–4.3, $P = 0.01$) (Table 3, model 2).

When we evaluated with separate multiple logistic regression models, the specific risks for carotid atherosclerosis or CHD associated with the various traits composing the metabolic syndrome (i.e., hypertension, dyslipidemia, central obesity, impaired glucose regulation, microalbuminuria, and insulin resistance as categorical variables), we found that: *1*) none of the above-mentioned traits was a significant independent predictor of incident carotid plaques; *2*) impaired glucose regulation/diabetes and dyslipidemia were the only significant independent predictors of incident carotid stenosis; and *3*) hypertension was the only significant independent predictor of incident CHD (Table 3, model 1). Most importantly, when we excluded from the analysis subjects with diabetes and/or definite hypertension (treatment and/or systolic blood pressure >160 and/or diastolic blood pressure >95 mmHg) and focused on subjects with mild abnormalities (IFG/IGT, mild hypertension, along with dyslipidemia, central obesity, microalbuminuria, and insulin resistance), we found that none of the individual components of the metabolic syndrome was an independent predictor of carotid atherosclerosis or CHD (Table 3, model 3). In this analysis, restricted to subjects without diabetes or definite hypertension, a separate model confirmed that the metabolic syndrome was associated with an increased risk of atherosclerosis and CHD (Table 3, model 4).

When we used a more stringent criterion to define insulin resistance, setting the threshold at the lower limit of the top quintile of HOMA-estimated insulin resistance in lean subjects with no metabolic disorder, as we did in a previous study (25), thus including in the category of the metabolic syndrome ~50% of the sample, the results were not substantially different.

In further analyses we examined the risk associated with the presence of the metabolic syndrome as identified by NCEP-ATPIII criteria. Among subjects diagnosed with the metabolic syndrome using these criteria ($n = 158$), 47% had incident new plaques, 42% had incident stenosis, and 6% had incident CHD. The corresponding figures for the rest of the sample ($n = 730$) were 39% (χ^2 $P = 0.216$), 20% (χ^2 $P = 0.0006$), and 5% (χ^2 $P = 0.32$), respectively. The multiple-adjusted risk of incident new plaques (OR 1.30, P = NS) and incident carotid stenosis (3.1, $P < 0.001$) as well as the multiple-adjusted risk of incident CHD (1.5, P = NS) computed by logistic regression analysis were not superimposable but were similar to those we yielded when using the WHO criteria.

Table 2—*Carotid atherosclerosis and CHD in subjects with the metabolic syndrome by WHO criteria and in the control subjects*

	Control subjects	Metabolic syndrome	*P*
CA score in 1999 (mm)	1.53 ± 2.0	2.31 ± 4.01	NS
n	585	303	
Change in CA score 1990–1995 (mm)	1.21 ± 2.32	2.13 ± 2.78	0.007
n	524	267	
Incident plaques (% of subjects)*	35 (31.8–38.9)	51 (45.4–56.6)	0.022
n	524	267	
Incident stenosis (% of subjects)†	19 (15.8–22.2)	34 (28.7–39.3)	0.003
n	183	130	
Incident CHD in 1990–1995 (% of subjects)‡	3 (2.0–4.0)	8 (4.9–11.1)	0.014
n	585	303	

Data are means ± SD or % (95% CI). *P* values are adjusted for sex, age, smoking, alcohol, physical activity, social status, and LDL cholesterol. *Baseline atherosclerosis was an additional covariate; †analysis restricted to subjects with preexisting plaques; ‡subjects with preexisting CHD were not excluded, but baseline CHD was an additional covariate. CA, carotid atherosclerosis.

Table 3—*ORs for incident carotid atherosclerosis and CHD associated with the various components of the metabolic syndrome considered separately or with the syndrome (by WHO criteria) considered as a single entity (see legend for description of models)*

	Incident carotid plaques	Incident carotid stenosis	Incident CHD
Model 1			
n	791	313	888
Impaired glucose regulation (IFG, IGT, type 2 diabetes)	1.3 (0.8–1.9)	2.3 (1.2–4.3)*	1.5 (0.7–3.0)
Insulin resistance (top quartile HOMA-IR)	1.4 (0.9–2.0)	0.7 (0.4–1.6)	1.0 (0.5–2.2)
Central obesity	1.0 (0.6–1.6)	0.7 (0.4–1.5)	1.6 (0.7–3.5)
Dyslipidemia	0.9 (0.6–1.3)	2.3 (1.2–4.3)*	1.4 (0.7–2.7)
Hypertension	1.2 (0.8–1.7)	0.9 (0.4–1.8)	3.1 (1.2–8.2)*
Microalbuminuria	1.3 (0.8–2.0)	1.7 (0.8–3.3)	1.1 (0.5–2.5)
Model 2			
n	791	313	888
Metabolic syndrome	1.5 (1.1–2.1)†	2.4 (1.3–4.1)*	2.3 (1.2–4.3)*
Model 3			
n	443	133	491
Impaired glucose regulation (IFG and/or IGT)	1.6 (0.8–3.4)	1.3 (0.3–4.7)	1.7 (0.3–6.1)
Insulin resistance (top quartile HOMA-IR)	1.8 (0.9–4.1)	2.2 (0.6–8.9)	1.4 (0.4–7.8)
Central obesity	0.9 (0.5–1.7)	0.8 (0.2–3.1)	1.1 (0.3–4.4)
Dyslipidemia	0.8 (0.4–1.3)	1.0 (0.3–3.3)	1.3 (0.4–4.7)
Mild hypertension	1.1 (0.6–1.8)	0.5 (0.2–1.6)	2.5 (0.6–11.1)
Microalbuminuria	1.3 (0.6–2.9)	0.5 (0.1–2.1)	2.4 (0.5–10.7)
Model 4			
n	443	133	491
Metabolic syndrome	2.0 (1.2–3.4)*	2.0 (1.0–3.8)†	3.7 (1.2–11.6)†

Data are odds ratio (95% CI). All models include sex, age, smoking, alcohol, physical activity, social status, LDL cholesterol, baseline carotid atherosclerosis, or baseline CHD. Model 1: components of the syndrome considered separately but entered simultaneously into the same equation. Model 2: metabolic syndrome considered as a single entity into the equation. Model 3: components of the syndrome considered separately but entered simultaneously into the same equation. Subjects with diabetes and definite hypertension excluded. Model 4: metabolic syndrome considered as a single entity into the equation. Subjects with diabetes and definite hypertension were excluded. *$P < 0.01$, †$P < 0.05$.

We also examined the risk of atherosclerosis and CHD in subjects positive according to both WHO and NCEP-ATPIII criteria ($n = 117$), to WHO criteria only ($n = 186$), and to NCEP criteria only ($n = 41$). Compared with control subjects, we found that subjects positive according to WHO criteria and not NCEP criteria had a significantly higher risk of incident carotid stenosis (OR 2.17, $P = 0.02$) and incident CHD (2.64, $P = 0.009$). In subjects who were positive according to NCEP criteria and negative according to WHO criteria, the ORs were similar (incident carotid stenosis 2.39 and incident CHD 2.35), but the CIs were large, and the *P* values were not significant due to low statistical power. In subjects positive according to both WHO and NCEP criteria the risk was not substantially higher than in subjects positive by only WHO or NCEP criteria (incident plaques OR 1.72, $P = 0.03$; incident carotid stenosis 5.06, $P < 0.001$; incident CHD 2.08, $P = 0.11$).

CONCLUSIONS — To the best of our knowledge, the present study provides the first population-based prospective information on both carotid atherosclerosis and CHD in subjects with the metabolic syndrome, as diagnosed according to the most recent criteria indicated by the WHO (7) or the NCEP-ATPIII (8). We focused on subjects from the general population aged ≥40 years, as they represent the segment of the population with the highest risk of the syndrome.

The unique findings of our study are that subjects with the metabolic syndrome, identified with clinically applicable criteria, had significantly greater incidence/progression of carotid atherosclerosis and greater risk for incident CHD than those without the syndrome. Moreover, most components of the syndrome were not significantly associated with carotid atherosclerosis or CHD when considered individually, whereas the syndrome was a significant predictor of the outcomes we examined. These findings, which need to be confirmed in larger databases with greater statistical power and applied particularly to subjects with a cluster of mild abnormalities (e.g., IFG or IGT rather than diabetes) and/or minor risk factors (e.g., central obesity or microalbuminuria), are pivotal in addressing one of the critical questions about the metabolic syndrome: "What is the value of identifying this phenotype beyond the recognition and treatment of its component traits?" Answering such questions is one of the key advances in the understanding of this syndrome. Our data support the conclusion that a focus on the coexistence of multiple mild abnormalities allows one to identify a large number of subjects at risk of atherosclerosis progression and cardiovascular disease who would be missed with a focus limited to single abnormalities (e.g., definite hypertension, diabetes, and severe dyslipidemia). As a consequence, it seems that there is a clear improvement in vascular risk prediction when using the metabolic syndrome approach.

The results of a study by Isooma et al. (26), which focused on myocardial infarction, stroke, and cardiovascular mortality in a sample of Finnish people, are consistent with ours in reporting an increased cardiovascular risk in subjects with the metabolic syndrome. However, this study was not population-based and focused on highly selected high-risk relatives of type 2 diabetic subjects and did not report data on atherosclerosis, which underlies clinical events.

A different set of diagnostic criteria for identifying subjects with the metabolic syndrome were recently proposed by the NCEP-ATPIII (8). When we used these criteria, subjects with the syndrome were approximately one-half of those identified with the WHO criteria. Al-

though ORs were not superimposable and *P* values were not always significant due to lower statistical power, subjects with the metabolic syndrome by NCEP-ATPIII criteria were also at higher risk of carotid atherosclerosis and CHD. Interestingly, both subjects positive for the metabolic syndrome only by WHO criteria and those positive only by NCEP-ATPIII criteria were at greater risk. Thus, none of these two criteria seems superior to the other in the definition of the cardiovascular risk. However, a greater number of subjects at risk are identified by WHO criteria. In this respect, the latter might be preferred. On the other hand, it is unquestionable that NCEP-ATPIII criteria are easier to apply because they do not require insulin and microalbuminuria assessment or an OGTT.

Our finding of an increased incidence/progression of carotid atherosclerosis and CHD in subjects with the metabolic syndrome is consistent with data obtained with factor analysis of clinical and biochemical characters clustering with hyperinsulinemia in three epidemiological studies carried out in Finland (27–29). These analyses suggested that a putative insulin resistance factor predicts cardiovascular disease in both nondiabetic and diabetic subjects. However, this factor was composed by different sets of variables in the three studies. Most importantly, the results of factor analyses can be applied only to the database from which they were extracted and cannot be transferred to other databases or to the clinical arena. In this respect, it is important to emphasize that in our study clinically applicable criteria to define the metabolic syndrome were able to identify subjects with a proven increase in atherosclerosis and CHD incidence.

In conclusion, the metabolic syndrome, which occurs very frequently in the general population, is burdened by a more frequent incidence and progression of carotid atherosclerosis and a higher incidence of CHD. The identification of subjects with the metabolic syndrome is conceivably useful from a clinical standpoint, as it can be anticipated that these individuals should benefit from interventions aimed at reducing cardiovascular risk. As a corollary, our findings strongly suggest that current risk reduction recommendations, focusing on single risk factor identification and correction, should be replaced by targeting individuals with the cluster and tailoring treatment possibly on the underlying mechanisms, like insulin resistance, responsible for or contributing to the complex of coexisting abnormalities.

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References

1. Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 320:703–706, 1989
2. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin resistance syndrome (syndrome X). *Diabetes* 41: 715–722, 1992
3. Meigs JB, D'Agostino RB, Wilson PWF, Cupples LA, Nathan DM, Singer DE: Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 46:1594–1600, 1997
4. Reaven GM: Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
5. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
6. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991
7. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
8. 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* 285:2486–2497, 2001
9. Willeit J, Kiechl S: Prevalence and risk factors of asymptomatic extra-cranial carotid artery atherosclerosis: a population-based study. *Arterioscl Thromb* 13:661–668, 1993
10. Bonora E, Willeit J, Kiechl S, Oberhollenzer F, Egger G, Bonadonna R, Muggeo M: Relationship between insulin and carotid atherosclerosis in the general population: the Bruneck Study. *Stroke* 28:1147–1152, 1997
11. Balkau B, Charles MA, for the European Group for the Study of Insulin Resistance (EGIR): Comment on the provisional report from the WHO consultation. *Diabet Med* 16:442–443, 1999
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
13. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63, 2000
14. Crouse JR, Harpold GH, Kahl FR, Toole JF, McKinney WM: Evaluation of a scoring system for extra-cranial carotid atherosclerosis extent with B-mode ultrasound. *Stroke* 17:270–275, 1986
15. Kiechl S, Willeit J for the Bruneck Study Group: The natural course of atherosclerosis. Part I. Incidence and progression. *Arterioscl Thromb Vasc Biol* 19:1484–1490, 1999
16. Kiechl S, Willeit J for the Bruneck Study Group: The natural course of atherosclerosis. Part II. Vascular remodeling. *Arterioscl Thromb Vasc Biol* 19:1491–1498, 1999
17. Kiechl S, Willeit S, Poewe S, Egger G, Oberhollenzer F, Muggeo M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross-sectional population study (Bruneck Study). *BMJ* 313:1040–1044, 1996
18. Kiechl S, Muigg A, Santer P, Mitterer M, Egger G, Oberhollenzer M, Oberhollenzer F, Mair A, Gasperi A, Poewe W, Willeit W: Poor response to activated protein C as a prominent risk predictor of advanced atherosclerosis and arterial disease. *Circulation* 99:614–619, 1999
19. Kiechl S, Lorenz E, Reindl M, Wiedermann CJ, Oberhollenzer F, Bonora E, Wileit J, Schwartz DA: Toll-like receptor 4 polymorphisms and atherogenesis in humans. *N Engl J Med* 347:185–192, 2002
20. Bonora E, Kiechl S, Oberhollenzer F,

Egger G, Bonadonna RC, Muggeo M: Impaired glucose tolerance, type 2 diabetes mellitus and carotid atherosclerosis: prospective results from the Bruneck Study. *Diabetologia* 43:156–164, 2000
21. Kiechl S, Egger G, Mayr M, Wiedermann CJ, Bonora E, Oberhollenzer F, Muggeo M, Xu Q, Wick G, Poewe W, Willeit J: Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. *Circulation* 103: 1064–1070, 2001
22. Epstein FH, Ostrander LD, Johnson BC, Payne MW, Hayner NS, Keller JB, Francis T: Epidemiological studies of cardiovascular diseases in a total community, Tecumseh, Michigan. *Ann Intern Med* 62: 1170–187, 1965
23. Ischemic Heart Disease Register: *Report of the Fifth Working Group*. Copenhagen, Denmark, WHO, 1971
24. Rose G, Blackburn H, Gillum R: Cardiovascular survey methods. Geneva, World Health Org., 1982
25. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC, Muggeo M: Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 47:1643–1649, 1998
26. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
27. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J: Insulin resistance syndrome predict coronary heart disease events in elderly nondiabetic men. *Circulation* 100:123–128, 1999
28. Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K: Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-age men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscl Thromb Vasc Biol* 20:538–544, 2000
29. Lehto S, Rønnemaa T, Pyorala K, Laakso M: Cardiovascular risk factors clustering with endogenous hyperinsulinemia predict death from coronary heart disease in patients with type II diabetes. *Diabetologia* 43:148–155, 2000