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Metabolic Syndrome and 10-Year Cardiovascular Disease Risk in the Hoorn Study

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Background—Different definitions of the metabolic syndrome have been proposed. Their value in a clinical setting to assess cardiovascular disease (CVD) risk is still unclear. We compared the definitions proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP), World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), and American College of Endocrinology (ACE) with respect to the prevalence of the metabolic syndrome and the association with 10-year risk of fatal and nonfatal CVD.

Methods and Results—The Hoorn Study is a population-based cohort study. The present study population comprised 615 men and 749 women aged 50 to 75 years and without diabetes or a history of CVD at baseline in 1989 to 1990. The prevalence of the metabolic syndrome at baseline ranged from 17% to 32%. The NCEP definition was associated with about a 2-fold increase in age-adjusted risk of fatal CVD in men and nonfatal CVD in women. For the WHO, EGIR, and ACE definitions, these hazard ratios were slightly lower. Risk increased with the number of risk factors. Elevated insulin levels were more prevalent in subjects with multiple risk factors, but metabolic syndrome definitions including elevated insulin level were not more strongly associated with risk.

Conclusions—The metabolic syndrome, however defined, is associated with an approximate 2-fold increased risk of incident cardiovascular morbidity and mortality in a European population. In clinical practice, a more informative assessment can be obtained by taking into account the number of individual risk factors. (*Circulation*. 2005;112:666-673.)

Key Words: risk factors ■ insulin resistance ■ cardiovascular diseases ■ prognosis ■ glucose

The global increase in overweight and obesity has been shown to result in a dramatic increase of type 2 diabetes and is expected to lead to an increase in cardiovascular disease (CVD) as well.[1] Obesity and the subsequent clustering of insulin resistance–related CVD risk factors result in a state of high risk for diabetes and CVD.[2,3] To enable international comparison of studies, the World Health Organization (WHO) in 1999 published a working definition of the metabolic syndrome.[4] Alternative definitions have subsequently been proposed by the European Group for the Study of Insulin Resistance (EGIR),[5] the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP),[6] and the American College of Endocrinology (ACE).[7] All definitions include a measure of blood pressure, triglycerides, HDL cholesterol, and fasting glucose. They differ with respect to the selection of cutoff points and a measure of obesity. In contrast to the WHO and EGIR definitions, in which the presence of hyperinsulinemia as an indicator of insulin resistance is the starting point, the NCEP definition is based on the number of abnormalities only, whereas the ACE definition considers the number of abnormalities in selected subjects with high risk of insulin resistance.

So far, there is limited information about the agreement between these different definitions and about the magnitude of their association with fatal and nonfatal CVD. Several population studies have reported an approximately 2-fold increased risk of CVD in the presence of the metabolic syndrome using one of the proposed definitions.[8–17] No previous study reported the results for fatal and nonfatal CVD separately, nor compared all 4 proposed definitions for men and women. Here, we present the agreement of the 4 definitions of the metabolic syndrome in Dutch men and women and their predictive value for total mortality and for fatal and nonfatal CVD.

Methods

Population

The Hoorn Study is a Dutch cohort study of diabetes and diabetes complications in the general population that began in 1989. The cohort and baseline measurements have been described in detail previously.[18] Briefly, a random selection of 3553 men and women 50

TABLE 1.   Metabolic Syndrome Definitions of NCEP, WHO, EGIR, and ACE

	NCEP	WHO	EGIR	ACE
Required	...	Required: Insulin in top 25%; glucose ≥6.1 mmol/L [110 mg/dL]; 2-hour glucose ≥7.8 mmol/L [140 mg/dL]	Required: Insulin in top 25%	High risk*; BMI >25 kg/m² or waist ≥102 cm (men) or ≥88 cm (women)
No. of abnormalities	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	≥6.1 mmol/L [110 mg/dL]		≥6.1 mmol/L [110 mg/dL]	≥6.1 mmol/L [110 mg/dL]; 2-hour glucose ≥7.8 mmol/L [140 mg/dL]
HDL cholesterol	<1.0 mmol/L [40 mg/dL] (men); <1.3 mmol/L [50 mg/dL] (women)	<0.9 mmol/L [35 mg/dL] (men); <1.0 mmol/L [40 mg/dL] (women)	<1.0 mmol/L [40 mg/dL]	<1.0 mmol/L [40 mg/dL] (men); <1.3 mmol/L [50 mg/dL] (women)
		or	or	
Triglycerides	≥1.7 mmol/L [150 mg/dL]	≥1.7 mmol/L [150 mg/dL]	≥2.0 mmol/L [180 mg/dL]	≥1.7 mmol/L [150 mg/dL]
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women); BMI ≥30 kg/m²	Waist ≥94 cm (men) or ≥80 cm (women)	
Hypertension	≥130/85 mm Hg	≥140/90 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg

*For the ACE definition, high risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, or acanthosis nigricans; family history of type 2 diabetes, hypertension, or CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI ≥25 kg/m² or waist circumference ≥94 cm for men and ≥80 cm for women; and age>40 years.

to 75 years of age was taken from the population register. A total of 2540 (71.5%) agreed to participate, and after exclusion of 56 nonwhite participants, the Hoorn Study population consisted of 2484 men and women. For the present study, we excluded 612 subjects with missing information on morbidity during follow-up (because they did not give written permission to access their hospital files or moved out of Hoorn) and 72 subjects with missing information on metabolic syndrome variables. Another 90 patients with known diabetes (based on treatment with glucose-lowering medication or diet), 120 subjects with diabetic fasting plasma glucose values (≥7.0 mmol/L, American Diabetes Association 1997), and 470 subjects with self-reported history of CVD were excluded for analysis of the predictive value of the metabolic syndrome, which left 615 men and 749 women. All participants gave their written informed consent. The study was approved by the Ethics Committee of the VU University Medical Center.

Baseline Examination

At the baseline medical examination, a blood sample was taken from all participants after overnight fasting. Weight and height were measured, and body mass index (BMI) was calculated as the ratio of weight and height squared. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer (Hawksley-Gelman Ltd). A standard 75-g oral glucose tolerance test was performed in all subjects, except those using glucose-lowering medication. Plasma glucose was determined with a glucose dehydrogenase method (Merck). Fasting insulin was determined with an insulin-specific double-antibody radioimmunoassay (antibody: Linco SP21). Fasting triglycerides and total and HDL cholesterol were determined by enzymatic techniques (Boehringer-Mannheim). LDL cholesterol was estimated with the Friedewald formula, except in subjects with triglycerides >8.0 mmol/L. Information about use of medication, including antihypertensive medication, smoking status (nonsmokers, ex-smokers, and current smokers), and history of CVD (assessed by Rose Questionnaire) were determined by self-administered questionnaire.

Follow-Up

The cohort is being followed up with respect to morbidity and mortality. Vital status is obtained from the population register of the city of Hoorn. Information on morbidity and mortality is obtained

from the medical records of the general practitioners and the local hospital. Causes of death were coded according to the International Classification of Diseases, Injuries and Causes of Death, ninth revision (ICD-9).

CVD was defined as documented angina pectoris (chest pain followed by coronary artery bypass surgery or angioplasty, or in the presence of >50% stenosis, or ECG changes or positive exercise test), myocardial infarction (in the presence of at least 2 of the following: typical pain, elevated enzymes, or ECG changes), congestive heart failure (in the presence of at least 2 of the following: shortness of breath, cardiomegaly, or dilated neck veins, or 1 of the former in the presence of edema or tachycardia), stroke or transient ischemic attack (sudden onset of symptoms, neurological symptoms, or change of consciousness), peripheral disease (by procedure, or typical pain accompanied by stenosis, ankle-arm blood pressure ratio <0.90, or positive vascular stress test). In fatal cases, CVD was defined with ICD codes 390 to 459 (diseases of the circulatory system) or 798 (sudden death, cause unknown), because sudden death in general is of CVD origin. Data on nonfatal outcomes were complete until 2000. Until January 2000, 271 subjects died, 309 had at least 1 nonfatal CVD event, and 383 had at least 1 fatal and/or nonfatal CVD events. Follow-up time was calculated as the time between the date of baseline physical examination and the date of the first event or January 1, 2000.

Metabolic Syndrome Definitions

Table 1 summarizes the 4 criteria. The NCEP definition[6] considers the syndrome to be present with at least 3 of the following: elevated fasting glucose, elevated triglycerides, low HDL, high blood pressure, or large waist circumference. The WHO definition[4] defines the syndrome with insulin resistance in the upper quartile of the population and/or impaired glucose regulation in combination with at least 2 of dyslipidemia (elevated triglycerides or low HDL), high blood pressure, or obesity (high waist-to-hip ratio or high BMI). Because information on the presence of microalbuminuria is not generally available in clinical practice and was available only for a subset of the present study population, this component was not used in the present study, which followed the WHO modified definition in a prior study.[16] Insulin resistance was estimated by fasting insulin (75th percentile: 94.95 pmol/L) or by the HOMA equation[19] (homeostasis model assessment of insulin resistance=fasting insulin [IU/L]×fasting glucose [mmol/L]/22.5; 75th percentile: 3.91). The

TABLE 2.   Baseline Characteristics in 615 Men and 749 Women Without Diabetes or Prevalent CVD, According to the Presence of the NCEP Metabolic Syndrome Definition

Characteristic	Women		Men	
	NCEP	No NCEP	NCEP	No NCEP
No.	193	556	117	498
Age, y	62.8±7.6	60.3±7.2	62.2±7.1	60.4±7.1
Current smoking, %	35	26	34	35
Former smoker, %	20	24	50	46
Systolic blood pressure, mm Hg	146.4±20.4	129.1±18.9	146.1±18.0	131.9±18.6
Diastolic blood pressure, mm Hg	84.8±10.7	79.4±9.9	87.3±9.1	82.5±10.0
Antihypertensive medication use, %	26.4	10.4	21	6.2
Total cholesterol, mmol/L	7.14±1.18	6.69±1.12	6.55±1.09	6.28±1.09
LDL cholesterol, mmol/L	4.98±1.12	4.57±1.06	4.52±1.02	4.41±1.01
Triglycerides, mmol/L	2.13±0.77	1.18±0.43	2.28±1.03	1.39±0.63
HDL cholesterol, mmol/L	1.20±0.26	1.59±0.34	1.00±0.24	1.26±0.31
Fasting glucose, mmol/L	5.63±0.58	5.22±0.47	5.86±0.59	5.42±0.45
Fasting insulin, pmol/L	102.7±54.6	74.1±38.4	103.2±45.8	84.4±62.1
BMI, kg/m^2	29.0±3.3	25.6±3.2	28.0±3.0	25.3±2.5
Waist circumference, cm	93±8	83±9	102±9	92±8
Waist-to-hip ratio	0.89±0.06	0.82±0.06	0.99±0.06	0.93±0.06
Framingham CHD risk score	9.7±6.4	4.3±3.9	21.3±7.0	15.1±7.1

Data are mean±SD or percentage of subjects.

EGIR definition[5] considers the syndrome to be present in subjects with fasting insulin in the upper quartile of the population distribution, in the presence of at least 2 of these risk factors: elevated fasting glucose, dyslipidemia (elevated triglycerides or low HDL), high blood pressure, or high waist circumference. The ACE definition[7] considers the syndrome to be present with 2 or more abnormalities (of elevated fasting or postload glucose, elevated triglycerides, low HDL, or high blood pressure) in subjects who have high risk of being insulin resistant (see Table 1 for definition). In the present study, all subjects were older than 40 years, and thus, all were part of the high-risk group. Because the oral glucose tolerance is not performed in usual clinical care, the information on the 2-hour glucose values was not used for the WHO and ACE definitions in the present study, except for additional analyses.

Statistical Analyses

The agreement between the definitions was determined by the kappa statistic (κ).[20] The level of agreement is considered poor with κ=0.20, fair with κ =0.21 to 0.40, moderate with κ=0.41 to 0.60, substantial with **κ**=0.61 to 0.80, and very good with κ>0.80.[20] The age-adjusted hazard ratios of the alternative definitions of the syndrome and their components with nonfatal CVD morbidity, CVD morbidity and mortality combined, and CVD mortality and total mortality were estimated with Cox proportional hazards analysis. To study the additional value of the metabolic syndrome definitions over risk factors that are already taken into account in usual clinical practice, we also adjusted for current smoking and LDL cholesterol and separately for 10-year risk categories (10% to 20%, and >20% relative to <10%) as estimated by the Framingham score.[21] Furthermore, we studied the number of abnormalities in relation to the proportion of subjects with hyperinsulinemia and the hazard ratio of increasing number of abnormalities for risk of fatal and nonfatal CVD.

Results

Baseline characteristics in subjects with and without the metabolic syndrome according to the NCEP definition are shown in Table 2. For both men and women, approximately half of the subjects with the syndrome had insulin levels in the upper quartile of the population, and 15% of the women and 21% of the men without the syndrome reached these levels. The prevalence of the metabolic syndrome according to the NCEP definition was 19% in men and 26% in women. For the WHO, EGIR, and ACE definitions, the prevalences were 32%, 19%, and 41%, respectively, in men, and 26%, 17%, and 35%, respectively, in women. The agreement between the definitions ranged from a κ of 0.28 between EGIR and ACE definitions in men (fair agreement) to 0.78 (substantial agreement) between NCEP and ACE definitions in women (Table 3).

The NCEP definition was associated with an approximately 2-fold risk of all end points in men and of nonfatal CVD in women, after adjustment for age only (Table 4). The hazard ratios of the WHO, EGIR, and ACE definitions for all end points were just slightly lower. In men, the highest hazard ratio of the constituent risk factors and metabolic syndrome definitions were generally observed for fatal CVD, whereas in women, the associations were stronger for nonfatal CVD. The estimated risk for metabolic syndrome was not greater than for the individual components of the syndrome. Adjustment for current smoking and LDL cholesterol attenuated the associations with fatal and nonfatal CVD combined only for ACE in men and NCEP and ACE in women (Table 5). After adjustment for the 10-year coronary heart disease risk, as estimated with the Framingham risk score, the hazard ratios associated with the WHO and EGIR definitions did not change markedly. The hazard ratio of the NCEP and ACE metabolic syndrome definitions were reduced to 1.6 and 1.1 in men, and in women, the hazard ratios were reduced to 1.2 to 1.3 and not statistically significant (Table 5).

TABLE 3.   Agreement (κ) Between 4 Definitions of Metabolic Syndrome for Men and Women

Men					
		NCEP	WHO	EGIR	ACE
	NCEP	. . .	0.37 (0.29–0.45)	0.39 (0.30–0.48)	0.51 (0.44–0.57)
Women	WHO	0.46 (0.37–0.52)	. . .	0.66 (0.59–0.72)	0.39 (0.32–0.47)
	EGIR	0.44 (0.36–0.51)	0.74 (0.68–0.79)	. . .	0.28 (0.21–0.35)
	ACE	0.78 (0.73–0.82)	0.41 (0.34–0.47)	0.36 (0.29–0.43)	. . .

Agreement is shown as Cohen's κ (95% CI).

Numbers in the upper right corner are results for men; under the diagonal, for women.

The overlap between the definitions for men/women were: NCEP-WHO 75 %/79%, NCEP-EGIR 81%/81%, NCEP-ACE 78%/90%, WHO-EGIR 87%/91%, WHO-ACE 72%/74%, and EGIR-ACE 68%/74%; a total of 9%/12% had metabolic syndrome for all definitions, and 49%/56% did not have the metabolic syndrome with regard to any definition.

Number of Risk Factors

The presence of 1 or 2 risk factors was also associated with enhanced risk of CVD, particularly in women. The Figure shows the age-adjusted hazard ratios of incident fatal and nonfatal CVD according to the number of abnormalities with the NCEP definitions. In these analyses, subjects with baseline diabetes or history of CVD were included as separate categories. Men with the metabolic syndrome according to the NCEP definition had similar risk as men with diabetes but less than men with prevalent CVD. Women with the metabolic syndrome had lower risk than diabetic women, whose risk approached that of those with prevalent CVD. When the number of risk abnormalities was included as a linear variable, the age-adjusted hazard ratio of fatal and nonfatal CVD was 1.29 (1.11 to 1.50) per risk factor, and this was identical for men and women. With increasing number of abnormalities, the proportion of subjects with insulin $\geq$95.0 pmol/L (the upper quartile) increased, ranging from 10% in men and 6% in women with no abnormalities to >50% with 4 or 5 abnormalities according to the NCEP definition.

Additional Analyses

When the HOMA estimate for insulin sensitivity was used instead of fasting insulin for the WHO and EGIR definitions, this increased the hazard ratios for all end points in men but not in women (data not shown). The WHO and ACE definitions originally also included elevated 2-hour glucose levels. Inclusion of the 2-hour glucose levels barely affected the prevalence of the syndrome, because most subjects with impaired glucose tolerance had several other abnormalities, and the hazard ratios did not change markedly (data not shown). We then repeated analyses without using the fasting glucose criterion. Importantly, this had very little impact and did not differ between the 4 definitions. The prevalence of the syndrome according to the NCEP definitions was reduced to 14% in men and 22% in women. The hazard ratio of fatal and nonfatal CVD combined was identical in men (1.91, 95% CI 1.27 to 2.87), and even slightly higher in women (1.88, 95% CI 1.23 to 2.86).

Discussion

The NCEP definition was associated with an approximately 2-fold elevation in risk of fatal CVD in men and nonfatal CVD in women, after adjustment for age only, compared with patients without the NCEP criteria. For the WHO, EGIR, and ACE definitions, the hazard ratios were somewhat lower. Risk of CVD was strongly associated with the number of risk factors. Although the number of risk factors was associated with insulin level, definitions that required elevated fasting insulin were no better predictors of CVD.

Previous Studies

Previous prospective studies reported associations between metabolic syndrome definitions and risk of CVD that ranged between 1.5 for fatal and nonfatal myocardial infarction or stroke for the NCEP definition in high-risk subjects with elevated cholesterol[15] and 3.7 for fatal and nonfatal coronary heart disease for the WHO definition in the general Italian population.[11] The present results are quite similar given that these studies differ with respect to absolute risk of CVD, definitions of the end points, gender, age, and cultural aspects, including diet and physical activity. Furthermore, because these studies used data already collected, the definitions were mostly modified to accommodate the data. The predictive value of the NCEP and WHO definitions was compared previously.[9,11,16] In the San Antonio Heart Study, the NCEP definition was associated with a 2-fold higher risk of CVD in subjects without diabetes or prevalent CVD, whereas the WHO definition was not.[16] In contrast, in 3 previous European studies, the WHO definition was associated with more than 2-fold risk.[8,9,11] In 2 of these 3 studies, the WHO definition included the presence of microalbuminuria, which was a strong risk factor in both studies.[8,11] This may explain the difference from the present study, in which information on microalbuminuria was not used for the WHO definition. In the combined data from 7 European cohort studies reported by the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study, the hazard ratio of CVD mortality for the presence of 3 or more abnormalities (of obesity, dyslipidemia, impaired glucose regulation, or hypertension) was lower than with 2 or more abnormalities, with hyperinsulinemia included as a prerequisite.[12] However, because several studies did not measure waist circumference, obesity was defined as BMI >30 kg/m^2. As also observed in the present study, a high waist circumference is more strongly associated with CVD than high BMI, and this may explain the difference, at least in

TABLE 4.   CVD Risk Factors, Metabolic Syndrome Definitions, and Hazard Ratios of Fatal and Nonfatal CVD and All-Cause Mortality

	%	All-Cause Mortality	Fatal CVD	Nonfatal CVD	Fatal and Nonfatal CVD
Men					
No. of cases		94	39	107	132
Insulin ≥95.0 pmol/L	26.5	1.26 (0.82–1.94)	1.35 (0.70–2.61)	1.56 (1.05–2.32)	1.50 (1.04–2.14)
HOMA-IR ≥3.91	27.2	1.41 (0.93–2.15)	1.86 (0.98–3.51)	1.62 (1.09–2.40)	1.64 (1.15–2.34)
FPG ≥6.1 mmol/L	13.5	2.16 (1.36–3.45)	2.18 (1.06–4.48)	1.24 (0.74–2.09)	1.44 (0.93–2.25)
Waist >102 cm	15.3	2.01 (1.28–3.16)	2.25 (1.13–4.49)	1.74 (1.11–2.73)	1.81 (1.21–2.71)
Waist/hip ratio >0.9	67.3	1.10 (0.69–1.71)	1.52 (0.70–3.33)	1.37 (0.88–2.12)	1.49 (0.99–2.23)
Waist ≥94 cm	47.2	1.32 (0.87–2.00)	1.48 (0.77–2.85)	1.43 (0.97–2.11)	1.45 (1.02–2.06)
BMI ≥30 kg/m²	6.8	1.92 (1.02–3.61)	1.61 (0.57–4.53)	1.20 (0.58–2.46)	1.21 (0.64–2.31)
TG ≥1.7 mmol/L	32.4	0.99 (0.64–1.53)	0.99 (0.50–1.96)	1.24 (0.84–1.84)	1.08 (0.75–1.56)
TG >2 mmol/L	21.8	1.04 (0.60–1.80)	1.33 (0.65–2.72)	1.36 (0.88–2.09)	1.18 (0.79–1.76)
HDL <1.0 mmol/L	25.5	1.46 (0.95–2.24)	2.17 (1.15–4.09)	1.06 (0.69–1.64)	1.25 (0.86–1.82)
HDL <0.9 mmol/L	13.2	1.89 (1.14–3.14)	2.56 (1.25–5.25)	1.49 (0.90–2.48)	1.64 (1.05–2.56)
BP ≥130/85 mm Hg or HTN medication	65.2	2.08 (1.22–3.53)	3.07 (1.19–7.39)	1.60 (1.03–2.49)	1.82 (1.21–2.75)
BP ≥140/90 mm Hg or HTN medication	44.9	1.86 (1.21–2.89)	2.37 (1.19–4.74)	1.70 (1.15–2.50)	1.83 (1.29–2.60)
NCEP	19.0	1.98 (1.28–3.05)	2.25 (1.16–4.34)	1.88 (1.24–2.87)	1.91 (1.31–2.79)
WHO	32.4	1.29 (0.85–1.95)	1.45 (0.77–2.74)	1.43 (0.97–2.11)	1.45 (1.02–2.05)
EGIR	19.0	1.58 (1.01–2.47)	1.86 (0.95–3.64)	1.48 (0.96–2.29)	1.49 (1.01–2.21)
ACE	41.0	1.53 (1.02–2.29)	1.80 (0.96–3.40)	1.20 (0.82–1.76)	1.30 (0.92–1.83)
Women					
No. of cases		70	26	75	95
Insulin ≥95.0 pmol/L	23.8	0.90 (0.53–1.53)	1.04 (0.45–2.40)	1.48 (0.92–2.40)	1.31 (0.85–2.02)
HOMA-IR ≥3.91	23.1	0.84 (0.49–1.44)	0.88 (0.37–2.11)	1.52 (0.94–2.46)	1.34 (0.87–2.07)
FPG ≥6.1 mmol/L	9.0	1.29 (0.69–2.44)	0.76 (0.22–2.57)	1.36 (0.71–2.61)	1.19 (0.65–2.15)
Waist >88 cm	38.7	1.13 (0.70–1.81)	0.57 (0.25–1.28)	1.68 (1.06–2.68)	1.31 (0.87–1.97)
Waist/hip ratio >0.85	50.0	1.15 (0.70–1.87)	0.69 (0.32–1.49)	1.37 (0.85–2.21)	1.20 (0.79–1.82)
Waist >80 cm	70.0	1.19 (0.67–2.12)	1.04 (0.41–2.60)	1.92 (1.03–3.57)	1.64 (0.96–2.78)
BMI ≥30 kg/m²	16.8	0.90 (0.49–1.65)	0.69 (0.24–2.01)	1.07 (0.60–1.89)	0.97 (0.58–1.69)
TG ≥1.7 mmol/L	26.0	1.22 (0.74–2.02)	2.27 (1.05–4.91)	1.83 (1.15–2.92)	1.92 (1.27–2.96)
TG ≥2.0 mmol/L	17.1	0.92 (0.50–1.72)	1.06 (0.40–2.81)	1.88 (1.14–3.12)	1.62 (1.02–2.58)
HDL <1.3 mmol/L	31.0	1.55 (0.96–2.49)	2.06 (0.95–4.46)	1.99 (1.26–3.15)	1.91 (1.27–2.87)
HDL <1.0 mmol/L	6.4	1.26 (0.51–3.12)	1.41 (0.33–5.98)	2.34 (1.16–4.64)	2.28 (1.22–4.28)
BP ≥130/85 mm Hg or HTN medication	62.2	0.76 (0.45–1.27)	0.87 (0.36–2.11)	1.52 (0.87–2.66)	1.31 (0.81–2.13)
BP ≥140/90 mm Hg or HTN medication	44.5	1.04 (0.64–1.68)	1.64 (0.71–3.82)	1.61 (0.99–2.61)	1.64 (1.06–2.53)
NCEP	25.8	1.18 (0.72–1.94)	0.76 (0.32–1.83)	2.05 (1.29–3.26)	1.68 (1.11–2.55)
WHO	26.3	1.01 (0.61–1.67)	0.98 (0.43–2.21)	1.48 (0.92–2.37)	1.31 (0.85–2.00)
EGIR	17.2	0.87 (0.49–1.55)	0.90 (0.36–2.26)	1.53 (0.92–2.56)	1.34 (0.85–2.14)
ACE	32.4	1.29 (0.80–2.07)	1.57 (0.72–3.42)	1.98 (1.25–3.15)	1.84 (1.22–2.78)

HOMA-IR indicates insulin resistance estimated by homeostasis model assessment; FPG, fasting plasma glucose; TG, triglycerides; BP, blood pressure; and HTN, hypertension.

Data are baseline prevalence and age-adjusted hazard ratios (95% CI).

part. The observed gradually increasing risk with increasing number of abnormalities is in line with the observations in population studies in the United States[13,14] and in subjects with elevated cholesterol levels.[10,15]

Insulin Resistance or Obesity

The main purpose of the working definitions was standardization. The working definitions of the WHO and subsequently the EGIR group in fact defined the "insulin resistance syndrome." These definitions are based on the premise that insulin resistance is the causal factor. Therefore, insulin levels, as a proxy for insulin resistance were included in the definition. Insulin resistance is indeed associated with atherosclerosis, as measured by carotid intima thickness[22] or coronary calcification.[23] Although fasting insulin is an accepted proxy for insulin resistance in population studies, the agreement between these parameters in the general population is only moderate. In the EGIR database of 1308 nondiabetic

TABLE 5.   Metabolic Syndrome Definitions and Hazard Ratios of Risk of Fatal and Nonfatal CVD, With Adjustment for Other CVD Factors and for 10-Year Framingham Risk*

Adjusted for:	NCEP	WHO	EGIR	ACE
Men				
Age	1.91 (1.31–2.79)	1.45 (1.02–2.05)	1.49 (1.01–2.21)	1.30 (0.92–1.83)
Age, LDL cholesterol, current smoking	1.88 (1.28–2.76)	1.48 (1.04–2.12)	1.69 (1.13–2.54)	1.16 (0.82–1.65)
10-Year Framingham risk category	1.64 (1.11–2.44)	1.44 (1.01–2.04)	1.48 (0.99–2.19)	1.06 (0.74–1.53)
Women				
Age	1.68 (1.11–2.55)	1.31 (0.85–2.00)	1.34 (0.87–2.14)	1.84 (1.22–2.78)
Age, LDL cholesterol, current smoking	1.44 (0.95–2.19)	1.32 (0.86–2.01)	1.33 (0.84–2.11)	1.52 (1.01–2.30)
10-Year Framingham risk category	1.17 (0.73–1.87)	1.31 (0.85–2.02)	1.21 (0.75–1.95)	1.31 (0.81–2.10)

Data are age-adjusted hazard ratios (95% CI).

*Framingham risk score and metabolic syndrome definitions both include information on HDL cholesterol and hypertension. There was considerable variation in the presence of the metabolic syndrome over 10-year Framingham risk categories, and the models that included both variables did not become unstable, as might be indicated by large changes in the estimate.

subjects who had a euglycemic hyperinsulinemic clamp to measure insulin sensitivity, the overlap between hyperinsulinemia and insulin resistance, defined as the upper 25% of the distributions in 700 lean subjects, was only slightly more than 50%.[24] Furthermore, in studies with directly measured insulin resistance in nondiabetic subjects, the NCEP definition and also the WHO definition of the metabolic syndrome identified fewer than half of the insulin-resistant subjects.[25,26] Finally, the causal relationship between insulin resistance and CVD still needs to be established.

The other mechanism leading to the clustering of cardiovascular risk factors may be obesity per se. In a study of 314 nondiabetic volunteers who had a modified insulin suppression test to measure insulin sensitivity, BMI explained only 22% of the variation in insulin sensitivity.[27] In this study and in the EGIR data, the majority of obese people are not insulin resistant.[27,28] Furthermore, obesity leads to hyperinsulinemia even after adjustment for insulin resistance,[28] and it precedes changes in components of the metabolic syndrome.[29] In the Insulin Resistance in Atherosclerosis Study (IRAS), a high waist circumference was a better predictor of the incidence of

the metabolic syndrome than directly measured insulin resistance.[30] In line with this, in the present study, definitions that included information on fasting insulin level were no better predictors of CVD risk.

Strengths and Limitations of the Study

A number of limitations have to be taken into consideration. We excluded subjects with missing information on nonfatal disease because they did not give permission to access their hospital records. To study the possibility of selection bias, we repeated the analyses for mortality using the data from the entire nondiabetic original Hoorn Study cohort, without prevalent CVD, and estimates were almost identical (data not shown). In the Hoorn Study, microalbuminuria has been assessed only in a subsample and therefore could not be studied in the present analyses. In the subsample, microalbuminuria had a strong association with CVD mortality,[31] and it may be speculated that addition of this information for the WHO definition would increase its hazard ratio; however, in general practice, microalbuminuria is not commonly determined.

Not all the components of the metabolic syndrome appeared to predict CVD morbidity and mortality equally within both genders. Furthermore, gender-specific estimates of hazard ratios for each metabolic syndrome definition but without consideration of fasting plasma glucose levels were in the same range for the end points analyzed as those estimated with the full definitions. Possibly, the relative weights and predictive properties of the various components may vary by population studied. Previous studies in different countries have shown widely varying estimates of the prevalences and associations with CVD.[12,32] This has led to a proposed different cutoff point for (abdominal) obesity for subjects of Asian origin.[32]

This is the first study to prospectively study fatal and nonfatal CVD separately in men and women in the general population in relation to the metabolic syndrome. The number of fatal CVD events was rather low in women, and the wide CIs are still compatible with an increased risk of fatal CVD in women. However, the number of cases of nonfatal CVD and the number of cases of fatal and nonfatal CVD combined
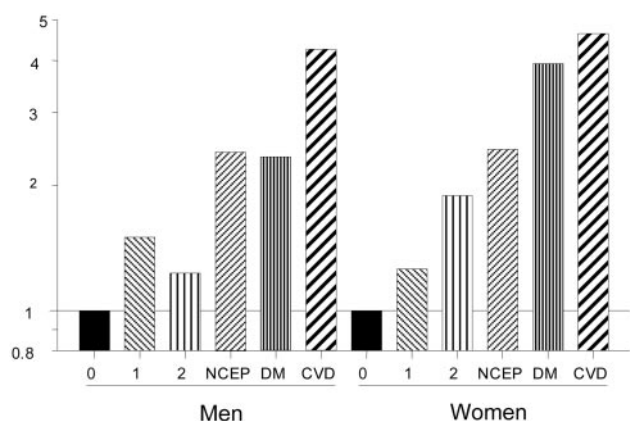
Number of metabolic syndrome abnormalities by NCEP definition, diabetes, and prevalent CVD and hazard ratios of 10-year risk of fatal and nonfatal CVD. Bars show age-adjusted hazard ratios for 0 (reference category), 1, 2, and ≥3 metabolic syndrome abnormalities by NCEP definition, baseline diabetes (DM), and baseline prevalent CVD status.

were sufficient to provide robust estimates in women and men. The data suggest that associations with nonfatal CVD generally were somewhat stronger in women than in men. The presence of the metabolic syndrome is associated with a similar increased risk of CVD in both genders, but in men, cardiovascular events more often have a fatal outcome. This may be important, because European guidelines for risk stratification are based on risk of fatal CVD only.[33] In population studies in the United States, similar[17] or even higher[16] risks of CVD mortality were reported for men and women in the general population, but their analysis included subjects with prevalent CVD and diabetes, and gender differences in CVD risk are abolished by diabetes.[34]

Implications

After adjustment for the Framingham risk score, metabolic syndrome definitions were no longer associated with risk of CVD in women, and in men, the hazard ratios were reduced to ≈1.5, as might be expected given the overlap in components considered in these risk assessments. In AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) and 4S (Scandinavian Simvastatin Survival Study), clinical trials of patients with prior congestive heart disease and hypercholesterolemia or low HDL levels, stratification by Framingham risk score did not abolish the associations with the metabolic syndrome in placebo-treated patients.[15] The difference may be due to the much lower mean CVD risk of the population-based participants of the Hoorn Study, in which hypertension and low HDL, which are both part of the Framingham risk score, were strongly and linearly associated with risk of fatal and nonfatal CVD.

All metabolic syndrome definitions, which are meant to facilitate decision making in clinical practice, are hampered by the loss of information. The cutpoints that define abnormality of the individual risk factor and the presence of the syndrome ignore the gradual relationship with CVD risk of the separate risk factors.

Conclusions

The results of the present study show that the metabolic syndrome, however defined, is associated with increased risk of fatal and nonfatal CVD, but the number of the constituent factors present provides a more informative graded assessment of risk in patients without diabetes or CVD.

Disclosure

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