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The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns

Jianjun Wang[1†], Sanna Ruotsalainen[1†], Leena Moilanen[2], Päivi Lepistö[1], Markku Laakso[1], and Johanna Kuusisto[1*]

[1]*Department of Medicine, University of Kuopio and Kuopio University Hospital, PO Box 1777, FI-70211 Kuopio, Finland; and* [2]*Department of Clinical Nutrition, University of Kuopio and Kuopio University Hospital, PO Box 1777, FI-70211 Kuopio, Finland*

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Aims The metabolic syndrome (MetS) is defined as a clustering of cardiovascular risk factors characterized by insulin resistance. We investigated the relationship of the MetS and its single components, defined by all six different criteria, with coronary heart disease (CHD), cardiovascular disease (CVD), and all-cause mortality in a prospective population-based study.
Methods and results The MetS was defined according to the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP), the American College of Endocrinology (ACE), the International Diabetes Federation (IDF), and the American Heart Association (updated NCEP) criteria. We investgated the relationship of the MetS defined by aforementioned six criteria with CHD, CVD, and all-cause mortality with Cox regression analyses in a non-diabetic Finnish population of 1025 subjects, aged 65–74 years, during the 13-year follow-up. The MetS defined by all aforementioned criteria was associated with a statistically significant risk for CVD mortality when adjusted for all confounding variables (Hazards Ratios, HRs from 1.31 to 1.51). The MetS defined by the WHO, ACE, and IDF criteria was associated with an increased risk of CHD mortality (HRs from 1.42 to 1.58). There was no association between the MetS by any criteria and all-cause mortality. Of the single components of the MetS, the following predicted CVD mortality in multivariable models: impaired fasting glucose by the WHO, NCEP, and ACE criteria (HR 1.34) and by the IDF and updated NCEP criteria (HR 1.29); impaired glucose tolerance by the WHO and ACE criteria (HR 1.55); low HDL cholesterol by the EGIR criteria (HR 1.50) and by the NCEP, IDF, and updated NCEP criteria (HR 1.29); and microalbuminuria according to the WHO definition (HR 1.86).
Conclusion The MetS defined by all six current criteria predicts CVD mortality in elderly subjects. However, of the single components of the MetS, IFG, IGT, low HDL cholesterol, and microalbuminuria predicted CVD mortality with equal or higher HRs when compared with the different definitions of the MetS. Therefore, our study suggests that the MetS is a marker of CVD risk, but not above and beyond the risk associated with its individual components.

Introduction

The metabolic syndrome (MetS), or insulin resistance syndrome, refers to the clustering of cardiovascular risk factors, insulin resistance, hyperinsulinemia, central obesity, glucose intolerance, dyslipidemia, and hypertension.[1–4] During the last few years, six criteria for the MetS have been presented. The World Health Organization (WHO) Consultation for the classification of diabetes and its complications first published its definition for the MetS.[5] Subsequently, the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP) Expert Panel, American College of Endocrinology (ACE), and the International Diabetes Federation (IDF) presented their definitions for the MetS.[6–9] Recently, the American Heart Association and the National Heart, Lung, and Blood Institute updated the NCEP criteria.[10]

One of the main purposes of the definitions for the MetS has been to establish a useful tool to identify individuals at a high risk for cardiovascular disease (CVD).[7–9] Indeed, several prospective studies have shown that the MetS defined by the WHO and NCEP criteria is associated with the risk of coronary heart disease (CHD), CVD, and all-cause mortality.[11–24] However, most of these studies have used modified definitions,[11–14,16] or only the NCEP definition for the MetS.[15,17,18,20,23] No study has assessed the ability of

* Corresponding author. Tel: +358 17-173949; fax: +358 17-173959.
E-mail address: johanna.kuusisto@kuh.fi
† The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

the MetS, defined by the IDF and updated NCEP, to predict CHD, CVD, and all-cause mortality. Consequently, it is unclear which one of the six definitions is most useful in predicting cardiovascular events. There is also a relative lack of studies on the importance of the MetS as a cardiovascular risk factor in elderly subjects, although these individuals are at a particularly high risk of CVD.

Recently, more criticism for MetS has been presented because of its imprecise definition, uncertain pathogenisis, and ambiguous value as a CVD risk marker.[25,26] Particularly, it is unclear whether the MetS predicts CVD beyond and above its individual components, and whether all risk factors included in the definition of the MetS are equally important in predicting CVD risk.[25] Therefore, the aim of the present study was to investigate whether the MetS and its single components, defined by all six current criteria, predict CHD, CVD, and all-cause mortality in an elderly cohort of Finnish subjects during a 13-year follow-up.

Methods

Baseline study

The formation[27] and representativeness[28] of the study population have been described in detail previously. Briefly, the study was conducted in Kuopio, east Finland, in 1986–1988. Altogether 1910 subjects born between 1912 and 1921 were randomly selected from the population register including all inhabitants of Kuopio. This random sample covered 35% of all residents in the age group of 65–74 years. The overall participation rate was 71%. All subjects with a previous history of diabetes or newly diagnosed diabetes at the baseline study were excluded from the present analyses. The WHO criteria[5] for impaired glucose tolerance (IGT) and diabetes mellitus were used in the classification of subjects without previously known diabetes based on fasting plasma glucose (FPG) and 2-h post glucose load (2-h PG) values at baseline. Thus, a total of 1025 non-diabetic subjects aged 65–74 years were included in the current study.

Weight, height, waist, and hip circumference, and blood pressure were measured. Waist-to-hip ratio (WHR) was defined as waist circumference to hip circumference. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres. Smoking status was defined as current smoking. With respect to alcohol consumption, subjects were classified as alcohol users or nonusers. Physical activity during leisure time was classified as physically inactive (little and occasional activity) and physically active (regular exercise at least once a week and at least 30 min per time).

ECGs were classified according to the Minnesota code.[29] Previous verified definite and possible myocardial infarction (MI) prior the baseline study were defined according to the WHO MONICA project criteria[30] as modified by the FINMONICA AMI Register Study Group.[31] WHO criteria for definite and possible stroke were used in the ascertainment of the previous stroke.[32]

Blood samples were taken in the morning after a 12 h overnight fast. All subjects underwent an oral glucose tolerance test (75 g glucose). Plasma glucose and insulin, serum lipids and lipoproteins, and urinary albumin were determined as previously described.[27,33] Ratio of urinary albumin (mg/L) to urinary creatinine (mmol/L) (ACR) was used as a measure of albumin excretion.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Kuopio University Hospital. All study subjects gave informed consent.

Follow-up study

Medical records of all study subjects who participated in the baseline study in 1986–1988 were reviewed by 2 of the authors (S.R, J.K.). Copies of death certificates of all those who had died during the 13-year follow-up were obtained from medical records or from the files of the Central Statistical Office in Finland and reviewed (S.R., J.K.). Deaths were recorded until the end of June, 2001, and they were coded according to the 9th revision of the International Classification of Disease (ICD-9). CHD death during the follow-up was defined as a death resulting from CHD (ICD-9 codes 410 to 414). ICD-9 codes 390 to 459 were classified as CVD deaths.

Definitions of the MetS

In the present study, each component of the six definitions of the MetS was defined according to the original criteria. Criteria for all current definitions of the MetS, including the WHO, the EGIR, the NCEP, the ACE, the IDF, and the updated NCEP definitions are shown in *Table 1*.

Statistical analyses

All statistics were performed with the SPSS 11.5 statistical programs. Because of the skewed distribution of fasting insulin, triglyceride concentrations, and ACR, these variables were log transformed for statistical analyses. Univariable Cox proportional regression models were used to estimate the effect of risk factors listed in *Table 1* on the risk of CHD, CVD, and all-cause mortality. The variables not included in the definitions of MetS, showing a statistically significant association with CVD, CHD, or all-cause mortality in the univariable Cox models, were added into the multivariable Cox regression models as confounders. The multivariable Cox regression analyses were applied to investigate the association of the MetS defined by the six criteria with CHD, CVD, and all-cause mortality in confounder adjusted models (Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, history of MI and stroke, current smoking, consumption of alcohol, physical activity at leisure time, and total cholesterol). A product term of gender by each of six definitions was added to the model to represent interaction. The null hypothesis of no interaction was tested using the change in -2 log likelihoods between Cox models with and without the product term. The effect of the single components of the MetS on CVD mortality was tested by the multivariable Cox regression models adjusted for confounding factors. A *P*-value <0.05 (two-sided) was considered statistically significant. Exact *P*-values and confidence intervals (CI) are given in tables.

Results

The median follow-up was 13.5 years (the 25th and the 75th quartiles were 9.7 and 14.2 years, respectively). Of the 1025 non-diabetic subjects who participated in the baseline study, 629 subjects were alive on 30 June 2001. There were 443 deaths during the follow-up. A total of 250 individuals died of CVD, including 148 deaths due to CHD. Men had higher CHD, CVD, and all-cause mortality than women (*Table 2*). In multivariable Cox regression analyses, male sex, age, previous MI and stroke, current smoking, physical inactivity, SBP, and ACR were associated with increased CHD, CVD, and all-cause mortality. High total cholesterol was associated with mortality from CHD. Fasting insulin was related to CVD mortality (*Table 2*).

Table 3 shows hazard ratios (HRs) of the MetS defined by the six different criteria to predict CHD, CVD, and all-cause mortality during the 13-year follow-up. The prevalence of the MetS at baseline depended on the MetS criteria, varying from 22.5 (EGIR criteria) to 66.4% (ACE criteria). When adjusted for age and gender (Model 1), the MetS by the WHO, ACE, and updated NCEP criteria was associated with a 1.40- to 1.72-fold risk for CHD mortality. The MetS

Table 1 Definitions of the MetS by the WHO, EGIR, NCEP, ACE, IDF, and updated NCEP criteria

	WHO	EGIR	NCEP	ACE	IDF	Updated NCEP
Required	Fasting insulin in top 25%; fasting glucose $\geq$ 6.1 mmol/L; 2 h glucose $\geq$ 7.8	Fasting insulin in top 25%	—	High risk of being insulin resistant[a]	For Europeans: Waist $\geq$ 94 cm in men or $\geq$ 80 cm in women	—
	and $\geq$2 of:	and $\geq$2 of:	$\geq$3 of:	and $\geq$2 of:	and $\geq$2 of:	$\geq$3 of:
Fasting glucose		$\geq$ 6.1 mmol/L	$\geq$ 6.1 mmol/L	$\geq$ 6.1 mmol/L	$\geq$ 5.6 mmol/L	$\geq$ 5.6 mmol/L
HDL cholesterol	$<$0.9 mmol/L in men or $<$1.0 mmol/L in women	$<$1.0 mmol/L	$<$1.03 mmol/L in men or $<$1.29 mmol/L in women	$<$1.03 mmol/L (men) or $<$1.29 mmol/L (women)	$<$1.03 mmol/L (men) or $<$1.29 mmol/L (women)	$<$1.03 mmol/L (men) or $<$1.29 mmol/L (women)
	or	or				
Triglycerides	$\geq$ 1.7 mmol/L	$>$2.0 mmol/L	$\geq$ 1.7 mmol/L	$\geq$ 1.7 mmol/L	$\geq$ 1.7 mmol/L	$\geq$ 1.7 mmol/L
Obesity	Waist/hip ratio $>$0.90 in men or $>$0.85 in women; BMI $\geq$30 kg/m^2	Waist $\geq$ 94 cm in men or $\geq$ 80 cm in women	Waist $\geq$ 102 cm in men or $\geq$ 88 cm in women		Waist $\geq$ 94 cm in men or $\geq$ 80 cm in women (for Europeans)	Waist $\geq$ 102 cm in men or $\geq$ 88 cm in women
Hypertension	$\geq$140/90 mmHg or drug treatment	$\geq$140/90 mmHg or drug treatment	$\geq$130/85 mmHg or drug treatment	$\geq$130/85 mmHg or drug treatment	$\geq$130/85 mmHg or drug treatment	$\geq$130/85 mmHg or drug treatment
Microalbuminuria	Urinary albumin/urinary creatinine ratio $\geq$3.39 mg/mmol (30 mg/g)					

[a]In this study 2 h plasma glucose from 7.8 to 11.0 mmol/L.

Table 2 Baseline characteristics of subjects who died of CHD, CVD or any cause, and risk factors for CHD, CVD, and all-cause mortality during the 13-year follow-up in 1025 non-diabetic subjects (univariable Cox regression analysis)

	Died of CHD ($n = 148$)	Died of CVD ($n = 250$)	Died of any cause ($n = 443$)
Male/Female, No.	85/63*	126/124*	218/225*
Age (y)	70.0 ± 2.7*	69.8 ± 2.8*	69.6 ± 2.9*
Previous MI, no. (%)	32 (21.6)*	46 (18.4)*	62 (14.0)*
Previous stroke, no. (%)	14 (9.5)*	22 (8.8)*	26 (5.9)*
Current smokers, no. (%)	22 (14.9)**	31 (12.4)**	59 (13.3)***
Alcohol user, no. (%)	51 (34.5)	82 (32.8)	147 (33.2)
Physically inactive at leisure time, no. (%)	44 (29.7)**	75 (30.0)***	134 (30.2)*
Body mass index (kg/m^2)	27.3 ± 3.8	26.9 ± 3.7	26.8 ± 3.8
Waist circumference (cm)	93.1 ± 10.9***	91.8 ± 11.0**	91.1 ± 10.7
Waist circumference (cm) in men	96.0 ± 10.2	95.6 ± 9.8	93.7 ± 10.4
Waist circumference (cm) in women	89.4 ± 10.9	88.0 ± 10.8	88.6 ± 10.5
Waist–to-hip ratio	0.95 ± 0.08*	0.94 ± 0.08*	0.93 ± 0.08*
Waist–to-hip ratio in men	0.99 ± 0.07	0.99 ± 0.06	0.98 ± 0.07
Waist–to-hip ratio in women	0.89 ± 0.07	0.89 ± 0.07	0.89 ± 0.07
Systolic blood pressure (mmHg)	161 ± 26**	160 ± 26**	158 ± 25
Urinary albumin to urinary creatinine ratio (mg/mmol)	6.9 ± 22.1*	5.7 ± 17.8*	5.2 ± 20.0*
Total cholesterol (mmol/L)	6.58 ± 1.25	6.52 ± 1.35	6.51 ± 1.33
Triglycerides (mmol/L)	1.85 ± 1.07**	1.81 ± 0.98**	1.73 ± 0.87
Triglycerides (mmol/L) in men	1.70 ± 0.67	1.69 ± 0.73	1.64 ± 0.70
Triglycerides (mmol/L) in women	2.04 ± 1.43**	1.92 ± 1.17**	1.82 ± 1.00
HDL cholesterol (mmol/L)	1.21 ± 0.33*	1.23 ± 0.34*	1.27 ± 0.35***
HDL cholesterol (mmol/L) in men	1.11 ± 0.29**	1.13 ± 0.31**	1.16 ± 0.31
HDL cholesterol (mmol/L) in women	1.34 ± 0.34	1.34 ± 0.34	1.37 ± 0.35
Fasting insulin (pmol/l)	97.8 ± 53.8***	96.7 ± 51.5***	90.8 ± 45.4
Fasting plasma glucose (mmol/L)	5.7 ± 0.5**	5.7 ± 0.5**	5.7 ± 0.5
2-h postload glucose (mmol/L)	6.7 ± 1.7	6.7 ± 1.7**	6.6 ± 1.7

Data are means ± SD or No. (percentages) (*P*-value for variables significantly predicting CHD, CVD, or total mortality).
*$P < 0.001$.
**$P < 0.05$.
***$P < 0.01$.

Table 3 HRs and their 95% CI (in parentheses) of the MetS defined by the WHO, EGIR, NCEP, ACE, IDF, and updated NCEP criteria for CHD, CVD, and all-cause mortality during the 13-year follow-up in 1025 non-diabetic subjects (percentage in parentheses after each definition is the prevalence of the MetS)

	Models	HR (95% CI) CHD mortality	CVD mortality	All-cause mortality
No. of deaths		148	250	443
WHO definition (42.6%)	1	1.61 (1.16–2.23)*	1.56 (1.22–2.00)**	1.21 (1.01–1.46)***
	2	1.58 (1.14–2.18)*	1.51 (1.17–1.93)*	1.16 (0.97–1.41)
EGIR definition (22.5%)	1	1.32 (0.92–1.90)	1.40 (1.06–1.84)***	1.08 (0.86–1.34)
	2	1.31 (0.91–1.89)	1.34 (1.01–1.77)***	1.02 (0.82–1.27)
NCEP definition (42.7%)	1	1.35 (0.98–1.88)	1.43 (1.12–1.84)*	1.13 (0.93–1.37)
	2	1.30 (0.94–1.81)	1.35 (1.05–1.74)***	1.08 (0.89–1.31)
ACE definition (66.4%)	1	1.72 (1.19–2.50)*	1.52 (1.15–2.01)*	1.17 (0.96–1.43)
	2	1.54 (1.06–2.24)***	1.38 (1.04–1.82)***	1.09 (0.89–1.34)
IDF definition (55.9%)	1	1.37 (0.99–1.91)	1.32 (1.02–1.70)***	1.09 (0.90–1.31)
	2	1.42 (1.01–1.99)***	1.33 (1.03–1.72)***	1.08 (0.89–1.31)
Updated NCEP definition (51.3%)	1	1.40 (1.01–1.94)***	1.37 (1.07–1.77)***	1.10 (0.91–1.33)
	2	1.35 (0.97–1.88)	1.31 (1.02–1.69)***	1.08 (0.88–1.28)

Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, history of MI and stroke, current smoking, consumption of alcohol, physical activity at leisure time, and total cholesterol.
*$P < 0.01$.
**$P < 0.001$.
***$P < 0.05$.

by all six definitions was associated with a statistically significant 1.32- to 1.56-fold risk for CVD mortality. Only the WHO definition was predictive of all-cause mortality (HR: 1.21, 95%CI 1.01–1.46). After further adjustment for history of MI and stroke, current smoking, consumption of alcohol, physical activity at leisure time, and total cholesterol (Model 2), the MetS defined by the WHO, ACE, and the IDF criteria was associated with a statistically significant 1.42- to 1.58-fold risk for CHD mortality. The MetS by all six criteria was associated with a 1.31- to 1.51-fold risk for CVD mortality when adjusted for all aforementioned confounding factors. None of the definitions predicted all-cause mortality when adjusted for all confounders. Of the six criteria for the MetS, only the WHO and ACE definitions predicted both CHD and CVD mortality in both of the aforementioned two models.

Interaction terms between the gender and the MetS by the WHO and ACE definitions were significant for CHD and CVD mortality ($P < 0.05$). Therefore, we investigated the association of the MetS by all six definitions with the risk for CHD, CVD, and all-cause mortality separately in men and women (*Table 4*). In men, the MetS defined by the WHO (HR 1.97), ACE (HR 2.23), and IDF criteria (HR 1.58) was associated with a statistically significant risk for CHD mortality. The MetS defined by the WHO (HR 1.70) and ACE criteria (HR 1.71) were associated with an increased risk for CVD mortality in men. In women, the MetS did not predict CHD or CVD mortality by any criteria. None of the definitions predicted all-cause mortality in men or women.

We also repeated statistical analyses excluding subjects with CVD at baseline ($n = 213$). The HRs of the MetS by different criteria for CHD mortality were very similar to those in the whole study population (Table 3), with the exception of the MetS defined by the ACE and IDF criteria which did not predict CHD mortality [adjusted HRs in Model 2: 1.57 (0.96–2.56); 1.55 (0.98–2.45), respectively]. The associations of the MetS by different criteria with CVD mortality were quite similar to those presented in *Table 2*, with the exception of the MetS defined by the EGIR, which was not predictive of CVD mortality in any of the models. No association of any definitions of the MetS with all-cause mortality was found (data not shown).

We also investigated if the MetS defined by the IDF, NCEP, and updated NCEP criteria predicted CVD and CHD mortality in non-diabetic subjects without microalbuminuria or IGT at baseline. After excluding subjects with microalbuminuria, the MetS by IDF criteria (HR 1.51 and 1.37, respectively), but not by NCEP and updated NCEP criteria, predicted CHD, and CVD mortality ($n = 827$). After excluding study subjects with IGT, the MetS did not predict CHD and CVD mortality by any criteria ($n = 809$), and the HRs were lower (1.03–1.24).

Table 5 shows HRs for the single components of the MetS definitions for CVD mortality in multivariable Cox regression models after the adjustment for confounding factors in all subjects and by gender. Of the single components of the MetS, the following predicted CVD mortality in all subjects: IFG (FPG >6.1 mmol, HR 1.34) according to the WHO, NCEP, and ACE criteria; IGT (2-h PG 7.8–11.0 mmol/L, HR 1.55) according to the WHO and ACE criteria; low HDL cholesterol according to the EGIR criteria (HDL cholesterol <1.0 mmol, HR 1.50); and microalbuminuria (ACR >3.39 mg/mmol, HR 1.86) according to the WHO definition. Of the single components of the MetS, only microalbuminuria (HR 1.75 for men, HR 1.99 for women) and IGT (HR 1.61 for men, HR 1.40 for women) predicted CVD mortality in both sexes when adjusted for confounding variables. In men, IGT (HR 1.61), upper quartile of insulin (HR 1.48), BMI over 30 kg/m^2 (HR 1.63), low HDL cholesterol according to the EGIR criteria (HDL cholesterol < 1.0 mmol, HR 1.71), and according to the NCEP, IDF, and updated NCEP criteria (HDL cholesterol <1.03 mmol/L in men, HR 1.57) were predictive of CVD mortality.

Discussion

In the present study, the MetS defined by all six current criteria predicted CVD mortality in the elderly population. Moreover, the MetS defined by the WHO, ACE, and IDF criteria predicted CHD mortality. None of the MetS definitions predicted all-cause mortality. The MetS, however, did not predict CVD mortality beyond and above of four of its single components, namely IFG, IGT, low HDL cholesterol, and microalbuminuria. Of the single components of the

Table 4 HRs of the MetS defined by the WHO, EGIR, NCEP, ACE, IDF and updated NCEP criteria for CHD, CVD, and all-cause mortality during the 13-year follow-up in 377 non-diabetic men and 648 non-diabetic women

	HR (95% CI)[a] Men ($n = 377$) CHD mortality	CVD mortality	All-cause mortality	Women ($n = 648$) CHD mortality	CVD mortality	All-cause mortality
No. of deaths	85	126	218	63	124	225
WHO definition	1.97 (1.27–3.05)*	1.70 (1.19–2.43)*	1.21 (0.93–1.58)	1.11 (0.67–1.83)	1.32 (0.93–1.89)	1.20 (0.92–15.6)
EGIR definition	1.48 (0.92–2.38)	1.45 (0.98–2.13)	0.93 (0.67–1.29)	1.06 (0.59–1.91)	1.26 (0.84–1.89)	1.13 (0.87–1.48)
NCEP definition	1.39 (0.90–2.14)	1.43 (1.00–2.03)	1.08 (0.82–1.42)	1.13 (0.69–1.87)	1.27 (0.89–1.82)	1.08 (0.83–1.40)
ACE definition	2.23 (1.31–3.80)*	1.71 (1.14–2.57)**	1.21 (0.91–1.61)	0.92 (0.53–1.60)	1.13 (0.76–1.68)	1.04 (0.78–1.39)
IDF definition	1.58 (1.02–2.44)**	1.34 (0.94–1.92)	1.09 (0.83–1.43)	1.14 (0.67–1.93)	1.32 (0.90–1.94)	1.11 (0.84–1.46)
Updated NCEP definition	1.29 (0.84–1.98)	1.32 (0.93–1.87)	1.05 (0.80–1.37)	1.32 (0.78–2.23)	1.29 (0.89–1.87)	1.09 (0.83–1.43)

[a]Adjusted for age, gender, history of MI and stroke, current smoking, consumption of alcohol, physical activity at leisure time, and total cholesterol.
*$P < 0.01$.
**$P < 0.05$.

Table 5 HRs of individual components of the MetS for CVD mortality based on the WHO, EGIR, NCEP, ACE, IDF, and updated NCEP criteria in 1025 non-diabetic subjects

	HR (95% CI)[a]		
	All subjects ($n = 1025$)	Men ($n = 377$)	Women ($n = 648$)
Fasting plasma glucose $\geq$ 6.1 mmol/L	1.34 (1.02–1.77)*	1.39 (0.97–2.00)	1.32 (0.85–2.04)
Fasting plasma glucose $\geq$ 5.6 mmol/L	1.29 (0.99–1.66)	1.28 (0.88–1.86)	1.29 (0.90–1.84)
2-h postload glucose 7.8–11.0 mmol/L	1.55 (1.17–2.05)**	1.61 (1.08–2.42)*	1.40 (1.00–2.21)*
Upper quartile of fasting insulin	1.30 (0.99–1.71)	1.48 (1.01–2.16)*	1.14 (0.76–1.70)
Blood pressure $\geq$ 130/85 mmHg or medication use	0.89 (0.60–1.33)	1.00 (0.60–1.68)	0.71 (0.38–1.33)
Blood pressure $\geq$ 140/90 mmHg or medication use	1.08 (0.79–1.49)	1.06 (0.71–1.59)	1.07 (0.63–1.82)
Waist circumference $\geq$ 94 cm (women: $\geq$ 80 cm)	1.12 (0.85–1.48)	1.21 (0.85–1.73)	1.01 (0.64–1.58)
Waist circumference $\geq$ 102 cm (women: $\geq$ 88 cm)	1.05 (0.79–1.38)	1.30 (0.86–1.96)	0.89 (0.62–1.28)
Waist–to-hip ratio $>$ 0.90 (women: $>$ 0.85)	1.23 (0.88–1.72)	1.32 (0.68–2.55)	1.21 (0.81–1.80)
BMI $\geq$ 30 kg/m^2	1.22 (0.89–1.68)	1.63 (1.01–2.62)*	0.99 (0.65–1.52)
Triglycerides $\geq$ 1.7 mmol/L	1.19 (0.92–1.54)	1.16 (0.80–1.69)	1.21 (0.84–1.75)
Triglycerides $>$ 2.0 mmol/L	1.27 (0.97–1.67)	1.18 (0.79–1.76)	1.34 (0.92–1.96)
HDL cholesterol $<$1.0 mmol/L	1.50 (1.12–2.01)**	1.71 (1.17–2.49)**	1.22 (0.74–2.01)
HDL cholesterol $<$0.9 mmol/L (women: $<$1.0 mmol/L)	1.26 (0.92–1.73)	1.30 (0.85–1.99)	1.22 (0.75–2.01)
HDL cholesterol $<$1.03 mmol/L (women: $<$1.29 mmol/L)	1.29 (0.99–1.67)	1.57 (1.09–2.26)*	1.03 (0.71–1.50)
Urinary albumin: urinary creatinine $\geq$ 3.39 mg/mmol	1.86 (1.40–2.47)***	1.75 (1.15–2.66)**	1.99 (1.35–2.94)**

[a]Adjusted for age, gender, history of MI and stroke, current smoking, consumption of alcohol, physical activity at leisure time, and total cholesterol.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

MetS, IGT and microalbuminuria had the highest HRs for CVD mortality. Accordingly, the WHO and ACE criteria for the MetS, which include IGT and microalbuminuria in their definitions, predicted most consistently CVD and CHD mortality.

Several prospective studies have evaluated the value of the NCEP and WHO definitions to predict CHD, CVD, and all-cause mortality.[11–15] However, most of these studies have used modified definitions other than those originally proposed. Moreover, these studies have varied with respect to characteristics of the baseline population, number of deaths, and statistical analyses. The Kuopio Ischemic Heart Disease Risk Factor Study[11] reported that both the NCEP and WHO criteria predicted all-cause, CHD, and CVD mortality after the adjustment for age, examination year, low-density lipoprotein cholesterol, smoking, and family history of CHD in 1209 men aged 42–60 years without initial diabetes and CVD. However, an oral glucose tolerance test was not performed. In contrast, the San Antonio Heart Study[12] including 2372 participants, aged 25–64 years, without initial diabetes and CVD showed that after the adjustment for age, gender, and ethnic group, neither the modified WHO definition (microalbuminuria excluded) nor the NCEP definition predicted all-cause mortality, but the latter was associated with a 2-fold risk of CVD mortality. The Hoorn study[16] investigated whether the EGIR, NCEP, WHO (microalbuminuria excluded), and ACE definitions predicted 10-year risk of fatal and nonfatal CVD in 615 men and 749 women without diabetes and self-reported CVD at baseline. The results showed that the NCEP, EGIR, and ACE definitions predicted all-cause mortality, and only the NCEP definition was predictive of CVD mortality in men, whereas among women, there was no association of the MetS defined by any definition with mortality from all-cause and CVD. Clearly, the modification of the definition, differences in covariates, and the number of study subjects and outcomes have resulted in inconsistent findings with respect to the importance of the MetS as a cardiovascular risk factor.

Since one of the main purpose of the working definitions for the MetS has been to establish a useful clinical tool to identify individuals at high risk for CVD, it is important to investigate whether the current six definitions for the Met predict CVD morbidity and mortality, and compare their ability to predict mortality in one study population, as we have done in the present study. Compared with the previous studies, the present study has several advantages. First, to our knowledge, this is the first prospective population-based study investigating the relationship between CHD, CVD, and all-cause mortality and the MetS defined by all the six current criteria and including all components of each definition. Second, our study has a large number of deaths (445 deaths) due to a long follow-up, which ensures an adequate power of statistical analyses. Third, as diabetes is a powerful predictor of mortality independently of the MetS, an oral glucose tolerance test was used to exclude all diabetic subjects from our study. Fourth, we also investigated the MetS as a predictor of mortality in subjects without CVD at baseline. Fifth, when we studied the MetS as a predictor of CHD, CVD, and all-cause death, mortality rates were adjusted for confounding variables showing a statistically significant association with CVD or CHD mortality. Finally, our study was performed in a population of elderly subjects, in whom most events of cardiovascular disease occur.

In the present study, we also studied the MetS as a predictor of CHD, CVD, and all-cause mortality separately in men and women. The MetS predicted CHD, CVD, and all-cause mortality only in men, not in women. However, mortality rates were significantly lower in women than in men, suggesting that the lack of statistical power may explain this gender difference. Also a previous study, based on 11 prospective European cohorts, found that the relative risk

of CVD and all-cause mortality associated with the MetS was similar in men and women.[14]

It has remained unclear whether the MetS predicts CVD mortality better than its single components. In the present study, we found that of the single components of the MetS, particularly IGT and microalbuminuria, but also IFG and low HDL cholesterol were predictive of CVD mortality. Accordingly, the WHO and ACE criteria for the MetS, which include IGT and microalbuminuria in their definitons, most consistently predicted CVD and CHD mortality and had the highest HRs in different statistical models. In contrast, when subjects with microalbuminuria or IGT were excluded, the predictive power of the MetS was significantly attenuated. Our findings support the findings of previous prospective studies, including our study,[33] which have shown that microalbuminuria predicts CHD and CVD morbidity and mortality and all-cause mortality independently of other risk factors,[34,35] and that subjects with IGT have markedly higher risk for all-cause and CVD mortality than subjects with IFG.[36] As the MetS did not have higher HRs for CVD mortality than its single components, our study suggests that the MetS does not predict CHD and CVD above and beyond its components. Our findings are in concordance with a recent case-control study showing that the MetS defined by the NCEP and updated NCEP criteria was not associated with a greater risk of early-onset coronary artery disease than individual components of the MetS, such as low HDL cholesterol, hypertension, and IFG.[37]

A limitation of our study is the absence of middle-aged individuals in the cohort. Our study included only elderly subjects which may lead to survival bias. In addition, there was a limited number of CHD and CVD deaths when analyses were done separately for men and women. Furthermore, because of several definitions of the MetS, multiple testing increases the likelihood of false positive *P*-values.

In conclusion, the MetS defined by all six current criteria predicts CVD mortality in the elderly. However, four single components of the MetS, namely IFG, IGT, low HDL cholesterol, and microalbuminuria predicted CVD mortality with equal or higher HRs when compared with the MetS. Therefore, our study gives support for the notion that the MetS is a marker of CVD risk, but not above and beyond the risk associated with its individual components.

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