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The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects—a population-based study comparing three different definitions

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Abstract

Aims Between 1998 and 2005, a number of definitions of the metabolic syndrome (MetS) have been proposed. The aim of this population-based cohort study was to compare prevalence rates and the prediction of cardiovascular disease (CVD) using different definitions of MetS.

Methods A total of 5047 non-diabetic subjects (66% women), from the city of Malmö, Sweden, were followed. The incidence of fatal and non-fatal CVD (cardiac events, n = 176, and stroke, n = 171) was monitored over 11 years of follow-up. MetS was defined in three different ways [by International Diabetes Federation (IDF), National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATPIII), or European Group for the study of Insulin Resistance (EGIR) criteria] based on data on waist circumference, blood pressure, serum triglycerides, High-density lipoprotein cholesterol and fasting blood glucose. The IDF definition identified 21.9% of the subjects having the MetS. Corresponding figures for the NCEP-ATPIII and EGIR definitions were 20.7 and 18.8%, respectively.

Results After taking age, gender, low-density lipoprotein cholesterol and lifestyle factors into account, the hazard ratio (HR) for CVD event according to the IDF, NCEP-ATPIII and EGIR definitions were HR 1.11 (95% CI: 0.86–1.44), 1.59 (1.25–2.03) and 1.35 (1.05–1.74), respectively. The results were largely similar for cardiac and stroke events.

Conclusions The prevalence of Mets according to the IDF definition was higher in comparison with NCEP-ATPIII and EGIR definitions, but the IDF definition was not superior to these definitions for prediction of CVD events. This was true for both genders and questions the usefulness of the current IDF criteria of MetS in a North-European, Caucasian population. In addition, single risk factors such as smoking had an equal prediction as the metabolic syndrome.

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Keywords cardiovascular, diabetes, hypertension, lipids, metabolic syndrome

Abbreviations CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; EGIR, European Group for the study of Insulin Resistance; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; HR, hazard ratio; IDF, International Diabetes Federation; LTAI, leisure time activity index; MDC, Malmö Diet and Cancer; MetS, metabolic syndrome; MI, myocardial infarction; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III; WHO, World Health Organization

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Introduction

The clustering of cardiovascular risk factors in association with disturbances of glucose and lipid metabolism is often referred to as the metabolic syndrome (MetS), the definition, pathophysiological background and treatment options of which are currently intensively debated [1–5]. Although the outlines of this syndrome have been known for more than 80 years, based on some early observations by Karl Hitzenberger, Austria [6] and Eskil Kylin, Sweden [7], it was not until 1988 that Gerald Reaven sparked a growing interest in the syndrome [8] and its link to insulin resistance [8,9].

Of the present candidate definitions of MetS, the first proposal made by the World Health Organization (WHO) in 1998 [10] has developed into the new definition put forward by the International Diabetes Federation (IDF) in 2005 [11]. This builds upon some important aspects of the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATPIII) definition from 2001 [12], updated in 2005 [13]. The core variables in the current definitions include abdominal obesity, blood pressure elevation, dyslipidaemia and hyperglycaemia, with varying cut-off levels. One scientific dilemma is that the criteria should provide a useful and practical definition of the MetS. This should not only be simple but also a valid predictor of cardiovascular disease (CVD), which is the main health consequence of the MetS. Previous reports have shown that subjects with the MetS, using different definitions, are at increased risk of CVD, based on data from different Caucasian populations [14–18]. No population-based study has, however, compared the predictive power for both fatal and non-fatal CVD events by use of the most updated definitions from IDF [11] and NCEP-ATPIII [12,13]. This is important as the prevalence rates of MetS may differ according to which definition has been used. In one study based on follow-up of elderly women, it was shown that the IDF definition predicted equally well as the NCEP-ATPIII definition, but data in men were not available [19].

Recent studies from the USA [20] and Greece [21] have reported that the prevalence of MetS is higher using the IDF than the NCEP-ATPIII definition. Whether the prediction of CVD events in middle-aged subjects is better using this definition is, however, still not clear, even if one recent publication from the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) project in 10 269 subjects suggested that the WHO definition [10] had higher hazard ratios for CVD mortality in men than other definitions [22]. However, no data on prediction of non-fatal events were included.

Our aim therefore was to compare three definitions of the metabolic syndrome, the IDF, the NCEP-ATPIII and the European Group for the study of Insulin Resistance (EGIR) definitions, respectively, for prediction of both fatal and non-fatal cardiovascular events in a large Caucasian population of urban middle-aged, non-diabetic subjects followed for a mean of 11 years.

Subjects and methods

Study design

The Malmö Diet and Cancer (MDC) study was a population-based cohort which was established between 1991 and 1996 (n = 28 466). The overall participation rate was approximately 40%. Characteristics of all participants and non-participants have been reported separately, including a detailed flow chart [23]. It has been shown that the cohort, in spite of suboptimal participation rate, was representative with respect to the prevalence of overweight and smoking for example [23]. However, the mortality rate was higher in non-participants [23].

A random 50% of those who entered the MDC cohort between 7 November 1991 and 28 February 1994, and who were born between 1926 and 1945 (n = 12 445), were invited to take part in a study on the epidemiology of carotid artery disease [24]. Age range was 46–68 years (mean 57.5, SD 5.9). While attending the first visit in the MDC study [24], 6103 subjects were recruited for the ultrasound examination. In order to arrange for blood sampling under standardized conditions, these individuals had to be rescheduled for a second visit that took place a mean of 8 months later. Of the 6103 subjects, 9.3% did not return for blood sampling. Subjects with history of myocardial infarction or stroke (n = 144), diabetes mellitus (n = 136) and subjects with fasting whole blood glucose > 6.1 mmol/l (i.e. plasma glucose > 7.0 mmol/l, n = 308) or currently using oral glucose-lowering drug therapy, were excluded. A further 378 individuals were excluded because of incomplete data for variables defining the MetS. Finally, after all exclusions, 5047 subjects remained for the present analyses. Data on lifestyle habits were based on a self-administered questionnaire and data on educational level and occupation on national censuses. The Ethics Committee at Lund University approved the project.

Lifestyle habits

Assessment of smoking habits, leisure time physical activity and alcohol consumption has been previously described in detail [24]. In short, smoking habits of individuals were categorized into 'never smokers', 'former smokers' and 'current smokers'. Assessment of leisure time physical activity included questions on 17 predefined activities and an open-ended question. The modified Minnesota leisure time activity (LTA) questionnaire [25] was used to create an activity index taking into account differences in intensity between activities. Each activity was categorized according to type and mean value for the specific activity and was multiplied by an intensity factor ranging from 4 to 8 for different activities. The leisure time activity index (LTAI) comprised the added sum of all reported activities adjusted for intensity. The distribution of LTAI was divided into quintiles and physical activity categorized as 'low' (lower quintile), 'moderate' (quintiles 2–4), or 'high' (upper quintile).

Average daily alcohol consumption (g) is based on the subjects' own recording of foods and beverages consumed during seven consecutive days [26]. The information was collapsed into a five-category variable. Those subjects who reported zero consumption in the menu book, and who indicated in the self-administered questionnaire that they had not consumed any

alcohol during the previous 30 days or previous year, were considered as 'zero' consumers. Subjects who reported that they had consumed alcohol during the previous 30 days but reported zero alcohol consumption in the menu book were considered 'occasional' consumers. The other subjects were categorized on the basis of assumed biological risk [27]. Category ranges were, for men and women, respectively, < 20 g and < 15 g alcohol per day ('low'), 20–40 g and 15–30 g alcohol per day ('moderate') and > 40 g and > 30 g alcohol per day ('high').

Physical examination

Blood pressure (mmHg) was measured once after 10 min rest. Weight (kg) and height (m) were measured with the subjects wearing light indoor clothing and without shoes. The waist circumference (cm) was measured at the level of the umbilicus.

Laboratory analyses

After an overnight fast, blood samples were drawn for the determination of serum lipids, serum insulin and whole blood glucose. Samples were analysed by standard methods at the Department of Clinical Chemistry, Malmö University Hospital, which is attached to a recurrent standardized system. Insulin levels were measured by radioimmunoassay (detection limit 3 mIU/l, and the intra- and interassay coefficients of variation were 5 and 8%, respectively) [28]. Blood glucose was determined by a routine hexokinase method. Triglycerides and total cholesterol were determined on a DAX 48 automatic analyser with use of reagents and calibrators from the supplier of the instrument (Bayer AB, Gotëborg, Sweden). High-density lipoprotein (HDL) cholesterol was determined by the same procedure as used for total cholesterol but after precipitation of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) with dextran–sulphate [29]. LDL cholesterol was calculated from the values for triglycerides, total cholesterol and HDL cholesterol according to the Friedewald formula: LDL = total cholesterol—HDL—(triglycerides/2.2) [30]. Individuals with a fasting whole blood glucose ≥ 5.6 mmol/l (i.e. plasma glucose ≥ 6.1 mmol/l) were classified to have hyperglycaemia. HDL cholesterol values < 0.9 mmol/l and triglycerides > 2.0 mmol/l alone or in combination were used as criteria for dyslipidaemia.

C-reactive protein (CRP) was analysed in frozen plasma in a subsample (n = 4886), gathered at the baseline examination using Tina-quant CRP latex high-sensitivity assay (Roche Diagnostics, Basel, Switzerland) on an ADVIA 1650 Chemistry System (Bayer Healthcare, Tarrytown, NY, USA).

Definitions of the metabolic syndrome

According to the IDF 2005 definition [11], for a person to be defined as having the metabolic syndrome they must have central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women) plus any two other risk factors (Table 1). The NCEP-ATPIII definition from 2001 [12] was revised in 2005 [13] and is based on any three risk factors (Table 1). Finally, as comparison, the EGIR proposed a definition in 1999 [31] in non-diabetic individuals based on the presence of insulin resistance with hyperinsulinaemia as a marker (> 75th percentile), plus any two risk factors (Table 1).

Table 1 Criteria for three definitions of the metabolic syndrome (IDF, NCEP-ATPIII and EGIR)

	NCEP-ATPIII	EGIR	IDF
Insulin resistance		> 75th percentile in non-diabetic population of hyperinsulinaemia	
Waist circumference	≥ 102 cm (men), ≥ 88 cm (women)	≥ 94 cm (men), ≥ 80 cm (women)	≥ 94 cm (men), ≥ 80 cm (women)
Triglycerides	≥ 150 mg/dl (1.7 mmol/l) or treatment	Plasma triglycerides ≥ 2.0 mmol/l and/or HDL cholesterol < 1.0 mmol/l	≥ 150 mg/dl (1.7 mmol/l) or treatment
HDL cholesterol	< 40 mg/dl (1.03 mmol/l) (men) or < 50 mg/dl (1.29 mmol/l) (women)	Plasma triglycerides ≥ 2.0 mmol/l and/or HDL cholesterol < 1.0 mmol/l	< 40 mg/dl (1.03 mmol/l) (men) and < 50 mg/dl (1.29 mmol/l) (women)
Blood pressure	≥ 130/85 mmHg, or treatment of previously diagnosed hypertension	≥ 140/90 mmHg, or treatment of previously diagnosed hypertension	Systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension
Glucose	Raised fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l)	Raised fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l)	Raised fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l), or previously diagnosed Type 2 diabetes

The NCEP-ATPIII definition is based on any three of the risk factors. The EGIR definition in non-diabetic individuals is based on the presence of insulin resistance with hyperinsulinaemia as a marker (> 75th percentile), plus any two risk factors. According to the IDF 2005 definition, for a person to be defined as having the metabolic syndrome, he/she must have central obesity plus any two risk factors. BP, blood pressure; EGIR, European Group for the study of Insulin Resistance; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IDF, International Diabetes Federation; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III.

Homeostatic model assessment (HOMA) was used to estimate insulin sensitivity from fasting insulin and glucose concentrations (i.e. fasting insulin × fasting glucose/22.5) in non-diabetic subjects [32]. Result from the HOMA model are known to correlate well with estimates obtained by the hyperinsulinaemic–euglycemic clamp, and with intravenous tests, and predicts unique values of insulin resistance, HOMA-IR, in non-diabetic subjects [33]. Subjects whose HOMA values exceeded the 75th percentiles (i.e. > 2.09, based on the distribution of all non-diabetic subjects in the cardiovascular cohort) were considered to have insulin resistance. The correlation between fasting insulin and HOMA was $r = 0.98$ in our cohort.

Follow-up, definition of end points

All subjects were followed from the baseline examination until the first cardiovascular event, death or 31 December 2003. Mean follow-up was 10.7 ± 1.4 years. A cardiovascular event was defined as fatal or non-fatal myocardial infarction (MI; ICD-9 code 410), fatal or non-fatal stroke (ICD-9 codes 430, 431, 434, 436), or death from ischaemic heart disease (ICD 410–414), whichever came first. In 176 cases, the first event was a fatal ($n = 48$) or non-fatal ($n = 128$) MI, and in 171 cases the first CV event was a stroke. The end points were retrieved by data linkage with the national Swedish Hospital Discharge register and the local stroke register of Malmö.

Statistical methods

SPSS (version 11.0) was used for all statistical analyses. One-way ANOVA and Pearsons' χ^2 test was used to compare risk factors between groups. For variables with skewed distributions (CRP, triglycerides, HOMA), log-normalized values were used in the analysis. Age-, sex- and risk factor-adjusted Cox regression analyses were used to study the relationships between the MetS by three definitions (IDF, NCEP-ATPIII, EGIR) and cardiovascular events. The follow-up time (in years) was used as time variable. The fit of the proportional hazards model was confirmed by plotting the crude incidence of cardiovascular events over time in different categories of risk factors. Social background characteristics (educational level, occupation) were also adjusted for. Hazard ratios (HR) and 95% confidence interval (CI) were calculated. To estimate the global cardiovascular risk burden in different categories of MetS, a cardiovascular risk score was computed from age, diabetes, smoking, blood pressure, total cholesterol and LDL cholesterol, based on the risk equation from the Framingham Heart Study [34].

Sex-specific effects were assessed in the Cox models by introducing interaction terms (sex × MetS). Finally, the predictive power of individual risk factors was calculated. A P-value less than 0.05 was considered significant.

Results

Baseline findings

The baseline clinical characteristics of subjects fulfilling the three definitions (NCEP-ATPIII, EGIR, IDF) of MetS are shown in Table 2. Except for smoking, all risk factors were significantly different ($P < 0.05$) when comparing those with and without MetS. The proportion of cases fulfilling each of the MetS criteria is presented in Table 3.

Figure 1 illustrates the overlap between the different definitions of MetS. The proportion of subjects who fulfilled all three definitions was 10.7%. In addition, 4.1% had MetS according to the IDF definition only, while 3.7% had MetS according to the NCEP-ATPIII definition only.

Risk of cardiovascular disease according to MetS

Adjusted for age and sex, subjects with MetS according to the NCEP-ATPIII definition had significantly higher prospective risk for CVD, with HR 1.95 (95% CI 1.56–2.47), compared with those without MetS by the same definition (Table 4). The corresponding HRs for the EGIR and IDF definitions were HR 1.55 (95% CI 1.23–1.95) and HR 1.37 (95% CI 1.09–1.72), respectively. The increased HR associated with MetS by NCEP-ATPIII remained significant even after additional adjustments for confounding factors. The relationships were largely consistent in both men and women, Table 4.

Myocardial infarction and stroke risk showed similar relationships with MetS. The age, sex and risk factor adjusted hazard ratios associated with NCEP-ATPIII were 1.40 (0.99–2.0) and 1.82 (1.3–2.6), for MI and stroke, respectively. The corresponding HRs for the EGIR definition were 1.31 (0.92–1.9) and 1.40 (0.97–2.0), respectively. The IDF definition was associated with HRs of 1.04 (0.7–1.5) and 1.20 (0.8–1.7) for MI and stroke, respectively.

Table 5 presents the relationships between MetS and incidence of CVD in the subgroup with additional information on CRP ($n = 4886$). Adjustments for CRP levels weakened the relationships between MetS and CVD. However, MetS according to the NCEP-ATPIII definition was still significantly predictive of CVD after adjustments for age, sex and other confounding factors.

There was no evidence of any sex-specific risk effects. The P-values for the sex × MetS interaction terms were all > 0.80, irrespectively of MetS definition.

Modification of waist circumference criteria in IDF definition

In order to further explore the reasons for the lower CVD risk in subjects with MetS according to the IDF definition, these criteria were modified using a higher cut-off for abdominal obesity. If waist circumference > 102 cm for men and > 88 cm for women was required (the same criteria as in NCEP-ATPIII definition 2005) instead of > 94/> 80 cm in the current IDF definition, 523 subjects had MetS. Based on this modification of the IDF criteria, the age- and sex-adjusted HR was 2.10 (95% CI 1.6–2.7), the risk factor adjusted HR was 1.77 (95% CI 1.3–2.4) and the risk factor plus CRP-adjusted HR was 1.72 (95% CI 1.3–2.4).

Table 2 Baseline characteristics in relation to presence of the metabolic syndrome, by three definitions (NCEP-ATPIII, EGIR and IDF)

	NCEP-ATPIII		EGIR		IDF	
	No	Yes	No	Yes	No	Yes
n	4004	1043	4098	949	3942	1105
Age (years)	57.2 (5.9)	58.5 (5.8)	57.2 (5.9)	58.8 (5.7)	57.3 (6.0)	58.3 (5.9)
Men (%)	1508 (38)	531 (51)	1518 (37)	521 (55)	1471 (37)	568 (51)
Body mass index (kg/m^2)	24.9 (3.3)	28.8 (4.2)	24.8 (3.2)	29.5 (4.0)	24.6 (3.2)	29.5 (3.5)
Waist, men (cm)	90 (8)	100 (10)	90 (8)	101 (10)	89 (8)	102 (8)
Waist, women (cm)	75 (8)	88 (11)	75 (8)	90 (10)	74 (8)	90 (9)
Homeostatic model assessment—index*	1.23 (1.7)	2.54 (1.9)	1.16 (1.6)	3.48 (1.6)	1.21 (1.8)	2.58 (1.9)
HbA_{1c} (%)	4.77 (0.43)	5.06 (0.86)	4.77 (0.44)	5.08 (0.82)	4.78 (0.45)	5.02 (0.77)
Glucose (mmol/l)	4.86 (0.57)	5.62 (1.3)	4.84 (0.51)	5.77 (1.2)	4.87 (0.57)	5.55 (1.2)
Systolic blood pressure (mmHg)	139 (19)	149 (17)	139 (19)	150 (18)	139 (19)	148 (18)
Diastolic blood pressure (mmHg)	86 (9)	91 (9)	86 (9)	92 (9)	86 (9)	91 (9)
Triglycerides* (mmol/l)	1.04 (1.5)	2.04 (1.5)	1.095 (1.5)	1.75 (1.6)	1.07 (1.5)	1.79 (1.6)
High-density lipoprotein(mmol/l)	1.47 (0.35)	1.06 (0.25)	1.44 (0.37)	1.15 (0.3)	1.46 (0.36)	1.11 (0.25)
Low-density lipoprotein (mmol/l)	4.1 (1.0)	4.4 (1.1)	4.1 (1.0)	4.3 (1.0)	4.1 (1.0)	4.4 (1.0)
Smokers (%)	875 (22)	250 (25)	931 (23)	194 (21)	877 (23)	248 (23)
C-reactive protein* (mg/l)	1.25 (2.8)	1.98 (3.1)	1.23 (2.8)	2.24 (3.1)	1.22 (2.8)	2.10 (3.1)
Risk score†						
All	7.7 (3.2)	10.6 (3.2)	7.9 (3.3)	10.1 (3.1)	7.74 (3.3)	10.2 (3.1)
Men	6.8 (2.5)	8.7 (2.3)	6.9 (2.6)	8.6 (2.1)	6.9 (2.6)	8.5 (2.2)
Women	8.21 (3.5)	12.5 (3.1)	8.4 (3.5)	12.0 (3.2)	8.3 (3.5)	12.0 (3.0)

Values are means (SD) or proportions (%).
*Geometrical means. Except for smoking, all risk factors are significantly ($P < 0.05$) higher in the MetS group (irrespective of definition) than in the corresponding non-MetS group.
†Framingham Risk Score [34].
EGIR, European Group for the study of Insulin Resistance; IDF, International Diabetes Federation; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III.

Table 3 Proportion of individuals with MetS (NCEP-ATPIII, EGIR or IDF) fulfilling each criteria of the syndrome

	NCEP-ATPIII	EGIR	IDF
n	1043	949	1105
MetS criteria:			
Hypertension, *n* (%)	1015 (97)	841 (89)	1061 (96)
Hyperglycaemia, *n* (%)	452 (43)	442 (47)	422 (38)
Low HDL cholesterol, *n* (%)	816 (78)	494 (52)*	763 (69)
Hypertriglyceridaemia, *n* (%)	785 (75)		662 (60)
Waist increased, *n* (%)	524 (50)	820 (86)	1105 (100)
High HOMA-index, *n* (%)		949 (100)	

The definitions of risk factors vary between the definitions of the MetS. See Subjects and methods.
*According to EGIR, 52% had dyslipidaemia, 39% had triglycerides > 2.0 mmol/l and 34% had HDL cholesterol < 1.0 mmol/l.
EGIR, European Group for the study of Insulin Resistance; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III.

Prediction by the components of the syndrome

Although it was not the primary aim of our study, we also included analyses of prediction of CVD events based on individual risk factors in the syndrome, Table 6. These hazard ratios were similar to the highest prediction based on the syndrome itself.

Discussion

The prevalence of MetS ranged from 18.8% based on the EGIR definition to 21.9% for the IDF definition. As many as 31.3% had MetS by any definition, while only 10.7% fulfilled all three definitions criteria. Hence, the identified risk groups were quite different for the three definitions used. The associated

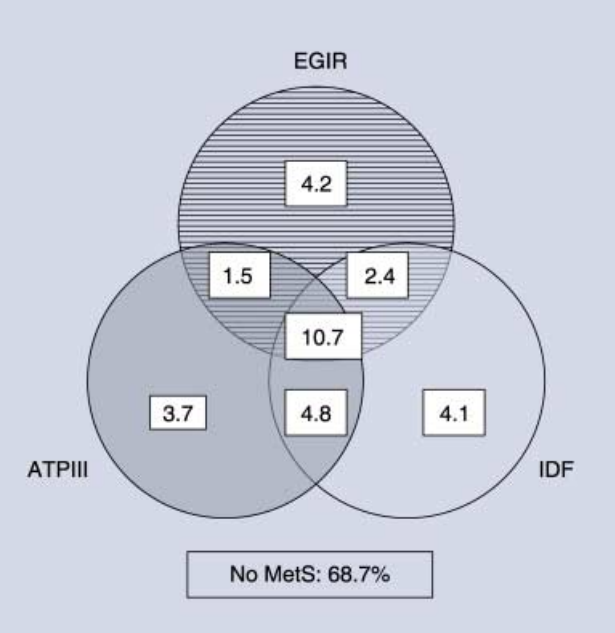

FIGURE 1 Prevalence (%) of the metabolic syndrome (MetS) according to the three definitions used [European Group for the study of Insulin Resistance (EGIR), International Diabetes Federation (IDF) and National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATPIII)].

risk for fatal and non-fatal CVD was also very different. For the NCEP-ATPIII definition, the risk of CVD remained significant after adjustments for several confounding factors, while the new IDF definition was not associated with any increased cardiovascular risk after these adjustments. The results suggest that the cut-off for waist circumference used in the IDF definition may be too low in this Caucasian population, in spite of the fact that it is by itself a well-documented risk factor [35].

In a similar study, based on 3589 elderly British women [19], it was concluded that MetS, defined by any of the three methods (WHO, NCEP-ATPIII and IDF), is only modestly associated with coronary heart disease (CHD) risk. The authors suggested that life-course socio-economic position appeared to be an important confounder in the association of MetS with CHD risk [19]. In the present study, however, adjustments for educational achievement had very small effects on the relationships between MetS and CVD, regardless of which definition was used. The results were virtually unchanged after further adjustments for occupation (data not shown). There are important differences between the two studies, e.g. with respect to populations and end-point definitions that could possibly explain the different results. In our study both men and women of younger age groups were included, thus making the results more easy to generalize for middle-aged subjects of both sexes, but we could not adjust for social characteristics over the life course [19] because of lack of

Table 4 Incidence of fatal and non-fatal cardiovascular events in non-diabetic subjects with MetS according to three definitions (NCEP-ATPIII, EGIR and IDF)

	NCEP-ATPIII		EGIR		IDF	
	No	Yes	No	Yes	No	Yes
All						
n	4004	1043	4098	949	3942	1105
Incident MI/stroke (*n*/*n*)	220 (116/104)	127 (60/67)	241 (124/117)	106 (52/54)	239 (122/117)	108 (54/54)
Events/1000 person years	5.2	12.0	5.6	11.0	5.8	9.5
Age- + sex-adjusted HR	Reference	1.95 (1.56–2.47)	Reference	1.55 (1.23–1.95)	Reference	1.37 (1.09–1.72)
Risk-factor-adjusted* HR	Reference	1.59 (1.25–2.03)	Reference	1.35 (1.05–1.74)	Reference	1.11 (0.86–1.44)
Men						
n	1508	531	1518	521	1471	568
Incident MI/stroke (*n*/*n*)	120 (70/50)	83 (46/37)	131 (75/56)	72 (41/31)	131 (75/56)	72 (41/31)
Age-adjusted HR	Reference	2.00 (1.51–2.64)	Reference	1.50 (1.13–2.01)	Reference	1.37 (1.03–1.82)
Risk-factor-adjusted* HR	Reference	1.71 (1.26–2.31)	Reference	1.33 (0.97–1.82)	Reference	1.17 (0.85–1.60)
Women						
n	2496	512	2580	428	2471	537
Incident MI/stroke (*n*/*n*)	100 (46/54)	44 (14/30)	110 (49/61)	34 (11/23)	108 (47/61)	46 (12/23)
Age-adjusted HR	Reference	1.88 (1.32–2.69)	Reference	1.63 (1.11–2.40)	Reference	1.37 (0.94–2.01)
Risk-factor-adjusted* HR	Reference	1.45 (0.97–2.17)	Reference	1.42 (0.92–2.18)	Reference	1.05 (0.68–1.62)

Hazard ratio (HR) with 95% confidence intervals (CI).
*Adjustment for age, sex, low-density lipoprotein cholesterol, current smoking, former smoking, high alcohol intake, low education and low physical activity.
EGIR, European Group for the study of Insulin Resistance; IDF, International Diabetes Federation; MI, myocardial infarction; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III.

Table 5 Incidence of fatal and non-fatal cardiovascular events and HR ratios (95% CI) in relation to different combinations of MetS in the subgroup with additional C-reactive protein (CRP) measurements

	NCEP-ATPIII		EGIR		IDF	
	No	Yes	No	Yes	No	Yes
All						
n	3892	994	3983	903	3826	1060
Incident MI/stroke (*n*/*n*)	198 (105/93)	111 (50/61)	216 (112/104)	93 (43/50)	211 (108/103)	98 (47/51)
Age- + sex-adjusted HR	Reference	1.92 (1.52–2.42)	Reference	1.54 (1.20–1.97)	Reference	1.42 (1.11–1.80)
Risk-factor-adjusted* HR	Reference	1.55 (1.20–2.00)	Reference	1.35 (1.03–1.77)	Reference	1.14 (0.87–1.49)
+ C-reactive protein	Reference	1.45 (1.12–1.88)	Reference	1.23 (0.93–1.62)	Reference	1.05 (0.80–1.38)
Men						
n	1463	505	1473	495	1422	546
Incident MI/stroke (*n*/*n*)	109 (65/44)	71 (38/33)	117 (69/48)	63 (34/29)	116 (68/48)	64 (35/29)
Age-adjusted HR	Reference	1.91 (1.41–2.57)	Reference	1.49 (1.10–2.03)	Reference	1.37 (1.01–1.87)
Risk-factor-adjusted* HR	Reference	1.62 (1.17–2.24)	Reference	1.33 (0.95–1.86)	Reference	1.15 (0.82–1.61)
+ C-reactive protein	Reference	1.55 (1.12–2.16)	Reference	1.25 (0.89–1.76)	Reference	1.10 (0.78–1.54)
Women						
n	2429	489	2510	408	2404	514
Incident MI/stroke (*n*/*n*)	89 (40/49)	40 (12/28)	99 (43/56)	30 (9/21)	95 (40/55)	34 (12/22)
Age-adjusted HR	Reference	1.93 (1.32–2.81)	Reference	1.62 (1.07–2.44)	Reference	1.50 (1.01–2.22)
Risk-factor-adjusted* HR	Reference	1.45 (0.95–2.22)	Reference	1.41 (0.89–2.22)	Reference	1.16 (0.74–1.81)
+ C-reactive protein	Reference	1.27 (0.82–1.95)	Reference	1.15 (0.72–1.85)	Reference	0.97 (0.61–1.54)

*Adjustment for age, sex, low-density lipoprotein cholesterol, current smoking, former smoking, high alcohol intake, low education and low physical activity.
EGIR, European Group for the study of Insulin Resistance; HR, hazard ratio; IDF, International Diabetes Federation; MI, myocardial infarction; NCEP-ATPIII, National Cholesterol Education Program—Adult Treatment Panel III.

Table 6 Prevalence of MetS and its components according to three definitions (NCEP-ATPIII, EGIR and IDF), and risk of fatal or non-fatal CVD events with hazard ratio (HR) and 95% confidence intervals (CI)

	Prevalence (%)	HR* (95% CI)
MetS NCEP-ATPIII	21	1.95 (1.56–2.43)
MetS EGIR	19	1.55 (1.23–1.95)
MetS IDF	22	1.37 (1.09–1.72)
Hypertension (A, I)	79	2.97 (1.90–4.63)
Hypertension (E)	63	2.22 (1.67–2.95)
Obesity (A)	15	1.81 (1.42–2.31)
Obesity (E, I)	37	1.20 (0.97–1.48)
Low high-density lipoprotein (A, I)	30	2.01 (1.63–2.49)
Dyslipidemia (E)	21	1.65 (1.31–2.07)
Hypertriglyceridaemia (A, I)	22	1.37 (1.09–1.73)
Hyperglycemia (A, E, I)	14	1.39 (1.07–1.81)
Insulin resistance (E)	25	1.45 (1.16–1.81)
Current smoking	23	1.95 (1.55–2.45)

*RR adjusted for age and sex compared with those without the risk factor.
Variables included in the definition of metabolic syndrome (MetS): A, Adult Treatment Panel III (ATPIII); E, European Group for the study of Insulin Resistance (EGIR); I, International Diabetes Federation (IDF); based on criteria.

data. In another paper the NCEP-ATPIII definition of MetS was superior to the IDF definition for prediction of vascular events in 750 patients with established coronary artery disease [36], but this study was not population based. Correspondingly, in a study of 20 789 well-educated (75% college graduates), non-Hispanic white American males visiting a health screening clinic, the long-term prediction of total and CVD mortality was equal by use of the IDF and NCEP-ATPIII definitions of MetS, but differed according to waist circumference cathegory [37]. Recently, the DECODE study published data to support the use of the WHO definition for prediction of CVD mortality, particularly in men [22].

One aspect of the diagnostic procedure in general is labelling. This may interfere with the quality of life in subjectively healthy people, living with a number of risk factors. However, it may also be seen as an alarm signal for the need of lifestyle

improvement. Ideally, improved eating habits and physical exercise, as well as smoking cessation, should be the expected consequence of this diagnostic procedure. However, if too many people are labelled with a diagnosis of MetS this may lead to great difficulties for the health-care system to handle this large number of patients, as resources are always limited. Therefore, a diagnosis of MetS should be used in order to find high-risk individuals to motivate for lifestyle changes, not to label low-risk individuals. It might therefore be questioned, according to the most recent definition by IDF from 2005 [11], in spite of good intentions, whether the cut-off for waist circumference, for the purpose of identifying high-risk individuals for CVD is accurate or not. In itself, without concomitant risk factors, obesity is a rather weak cardiovascular risk, and the same is true for triglyceridaemia alone, as previously shown in the Malmö data [38]. However, elevated blood pressure seems to be a stronger risk factor [39].

Quite a different ambition is to use different definitions of MetS to target risk individuals for the development of Type 2 diabetes [40]. Even if this is similar to finding risk individuals for CVD, the target groups are not completely identical. The different MetS definitions should therefore also be compared for prediction of Type 2 diabetes, in a similar way as for the prediction of CVD.

Many studies have reported that established Type 2 diabetes is a stronger CVD risk factor in women, with about 50% higher relative risk in women than in men with diabetes [41]. MetS is a risk factor for diabetes and could be regarded as a precursor of established diabetes. It is therefore noteworthy that men and women with MetS had largely the same relative risk of CVD in this study, with overlapping confidence intervals between genders. However, this study was restricted to non-diabetic subjects.

With a few exceptions, HRs for full definitions of the syndrome were not significantly different from those for their single components (Table 6), as in the DECODE study for prediction of CVD mortality [22]. It should, however, be kept in mind that, for example, smoking is not a component of the metabolic syndrome by any definition, in spite of its highly predictive value for CVD risk, and therefore some comparisons of single risk factors or clusters of risk factors for prediction might be unbalanced.

Limitations of the study

Although the MDC is a large prospective cohort study, our attendance rate was only 40% [23]. The recruitment of more healthy subjects (selection bias) would, however, most likely decrease, not increase, the predictive power for total CVD events. Therefore, we do not think that we have exaggerated our findings. As we only used measurements of variables at one single examination, this may dilute the precision of defining MetS. Ideally we should have used multiple measurements of, for example, blood pressure and blood glucose. However, it can be assumed that this effect on the prevalence of MetS was similar for all definitions. Another limitation is that we have no information on possible treatment effects in this cohort, as it could be expected that a substantial number of risk subjects were offered treatment following screening. However, if such preventive treatment was offered, it would dilute our findings of risk prediction, not strengthen them. It has also been argued that the criteria for MetS should be used not as fixed characteristics, but as continuous variable [42]; however, we did not do this analysis. Finally, we did not have information about proinsulin or inflammatory markers other than CRP which could be useful in order to further explore the nature of the relationships between MetS and CVD, as shown for proinsulin in another Swedish study [43]. The number of events in women was low in comparison with men, thus the statistical power to make comparisons between genders is currently too weak.

However, our study was based on a large cohort of both men and women, followed for 11 years for prediction of both fatal and non-fatal events. We were also able to adjust for CRP levels in relation to MetS and CVD risk, which has not often been carried out previously.

In conclusion, the new IDF 2005 definition of the metabolic syndrome resulted in a higher prevalence rate (labelling) of MetS than previous definitions (NCEP-ATPIII, EGIR), but was not superior for prediction of total cardiovascular events. This was true for both genders and questions the usefulness of the IDF criteria in a North-European, Caucasian population, if cardiovascular risk prediction based on MetS is the main goal.

Competing interests

None declared.

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