diagnosis of multiple sclerosis is potentially more dangerous than a false negative one because it implies unnecessary successive tests and treatments, or needless anxiety and psychological distress for the patient. Multiple sclerosis remains predominantly a clinical diagnosis.

Contributors: See bmj.com.

Funding: This work was supported by the Medical Research Council Health Services Research Collaboration. The authors' work was independent of the funders. JJD is funded by a senior research fellowship in evidence synthesis from the UK Department of Health.

Competing interests: None declared.

Ethical approval: Not required.

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(Accepted 2 February 2006)

doi 10.1136/bmj.38771.583796.7C

Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study

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BMJ 2006;332:878–82

Abstract

Objectives To find out if the presence of the metabolic syndrome increases the risk of subsequent total and cardiovascular mortality, taking into account established risk factors for cardiovascular disease.
Design Prospective cohort study.
Setting General population.
Participants A community based sample of 2322 men followed since 1970 for a maximum of 32.7 years, investigated at ages 50 and 70.
Main outcome measures The relations of the metabolic syndrome defined by the national cholesterol education programme (NCEP) of the US National Heart, Lung, and Blood Institute or criteria of the World Health Organization (WHO) to subsequent total and cardiovascular mortality.
Results When adding the metabolic syndrome to models with established risk factors for cardiovascular disease (smoking, diabetes, hypertension, and serum cholesterol) at age 50, presence of the metabolic syndrome as defined in the NCEP significantly predicted total and cardiovascular mortality (Cox proportional hazard ratios 1.36, 95% confidence interval 1.17 to 1.58; and 1.59, 1.29 to 1.95, respectively). The metabolic syndrome added prognostic information to that of the established risk factors for cardiovascular disease (likelihood ratio tests, $P < 0.0001$ for both outcomes). Similar results were obtained in a subsample without diabetes or manifest cardiovascular disease.
Conclusions In a large, community based sample of middle aged men, the presence of the metabolic syndrome according to the definition of the NCEP gave long term prognostic information regarding

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This is the abridged version of an article that was posted on bmj.com on 20 March 2006: http://bmj.com/cgi/doi/10.1136/bmj.38766.624097.1F

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Table 1 Definitions for metabolic syndrome used in the study

	US national cholesterol education programme, adult treatment panel III*	World Health Organization†
Definition	**Three or more of the following criteria**	**Presence of impaired glucose metabolism and two or more other criteria**
Impaired glucose metabolism	Fasting plasma glucose ≥6.1 mmol/l	Glucose intolerance, impaired fasting glucose or diabetes mellitus, or insulin resistance (WHO_{CLAMP} definition: lowest fourth of clamp insulin sensitivity, age 70; WHO_{HOMA} definition: highest fourth of homeostasis model assessment-insulin resistance, age 50 and 70)
Hypertension	Blood pressure ≥130/85 mm Hg or treatment	Blood pressure ≥140/90 mm Hg or treatment
Dyslipidaemia	Triglycerides ≥1.7 mmol/l HDL cholesterol <1.04 mmol/l	Triglycerides ≥1.7 mmol/l or high density lipoprotein cholesterol <0.91 mmol/l
Central obesity	$NCEP_{WAIST}$ definition: waist circumference >102 cm (age 70) $NCEP_{BMI}$ definition: BMI>29.4 kg/m^2 (ages 50 and 70)	Waist to hip ratio >0.9 (WHO_{CLAMP} definition, age 70) or BMI >30 kg/m^2
Target organ damage	—	Microalbuminuria: urinary albumin excretion rate ≥20 μg/min (WHO_{CLAMP} definition, age 70)

Reference limits given only for men.
*Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final report. *Circulation* 2002;106:3143-421.
†World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation.* Geneva, WHO, 1999. Part 1: Diagnosis and classification of diabetes mellitus.

total and cardiovascular mortality if the status of established risk factors for cardiovascular disease was known. If confirmed this may indicate clinical value in diagnosing the metabolic syndrome.

Introduction

The metabolic syndrome denotes a clustering of risk factors for cardiovascular disease in certain individuals. Its pathophysiology is believed to include insulin resistance[1]; but its definition and clinical importance are under debate.[2] Recent guidelines for the prevention of cardiovascular disease have encouraged identification of the metabolic syndrome in clinical practice.[3 4]

Our hypothesis was that prevalence of the metabolic syndrome increases the risk of subsequent total and cardiovascular mortality, taking into account established risk factors for cardiovascular disease. We also assumed that the prognostic impact of the metabolic syndrome may vary with age and that the predictive capacities of the National Heart, Lung, and Blood Institute's national cholesterol education programme (NCEP)[3] and definitions of the syndrome from the World Health Organization (WHO)[5] may differ. We therefore investigated the prognostic impact of both versions of the metabolic syndrome, at ages 50 and 70, using a large community based cohort of men followed for a maximum of 32.7 years.

Methods

Study samples

In 1970-3, all (2841) 50 year old men resident in Uppsala county received an invitation to a health survey aimed at identifying risk factors for cardiovascular disease. Eighty two per cent (2322/2841) of the invited men participated. At a re-examination of the cohort in 1991-95, at age 70, 73% (1221/1681) of invited men participated. We used both examinations as baselines in separate analyses. We fitted all models to the total samples and to "primary preventive" samples, excluding people with a myocardial infarction (9 before age 50; 470 before age 70) or a stroke (3 before age 50; 181 before age 70) before baseline or who had diabetes at baseline (103 at age 50; 182 at age 70). This left 2207 men in the "primary preventive" sample at age 50 and 845 at age 70.

Baseline examinations

At the examination at age 50, researchers used enzyme assays to measure fasting cholesterol and triglyceride concentrations of serum and high density lipoproteins (HDL). Coding of smoking was based on interview reports. Hypertension was defined as any one listed item: supine systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medication. Diabetes was defined according to current guidelines from the American Diabetes Association. We used a formula—fasting insulin×fasting glucose/22.5—to define the homeostasis model assessment-insulin resistance (HOMA-IR).

At the examination at age 70, in addition to the mentioned analyses, researchers determined urinary albumin excretion rate and insulin sensitivity with the euglycaemic insulin clamp technique (see bmj.com).

Metabolic syndrome definitions

We used modified NCEP and WHO definitions of the metabolic syndrome (table 1).[3 5] As waist circumference was measured in only 480 men in the examination at age 50, we modified the NCEP definition for use at age 50 by using a cut-off point for BMI instead of the given criterion of a waist circumference of more than 102 cm. In this subsample, a waist circumference of 102 cm corresponded to a BMI of 29.4 in a linear regression analysis. We denoted this definition $NCEP_{BMI}$ (see bmj.com). For analyses using the age 70 baseline, we used the original NCEP definition ($NCEP_{WAIST}$) and the modified $NCEP_{BMI}$ definition. For the WHO definition, we used two criteria for insulin resistance, in separate definitions: the lowest fourth of clamp insulin sensitivity (WHO_{CLAMP}), and the highest fourth of homeostasis model assessment-insulin resistance (WHO_{HOMA}). We included the microalbuminuria and waist to hip ratio criteria only in the WHO_{CLAMP} definition at the age 70 baseline only.

Follow-up and outcome measures

In the analysis of middle aged men, follow-up was from the examination at age 50 (in 1970-73) to 31 December 2002, with a maximum of 32.7 years of follow-up (median 29.8 years, 60 347 person years at risk). In the analysis of elderly men, follow-up was from the examination at age 70 (in 1991-5) to 31 December 2002, with a maximum of 11.4 years of follow-up (median 9.1 years, 10 455 person years at risk).

Table 2 Baseline characteristics at ages 50 and 70 in the total sample. Values are numbers (percentages) of participants unless otherwise indicated

Baseline	Age 50	Age 70
No of individuals	2322	1221
Smoking	1185 (51)	245 (21)
Diabetes	106 (5)	233 (19)
Hypertension	990 (43)	911 (75)
Mean (SD) total cholesterol in mmol/l	6.9 (1.3)	5.8 (1.0)
$NCEP_{BMI}$	405 (17)	282 (23)
$NCEP_{WAIST}$	—	294 (24)
WHO_{HOMA}	270 (12)	258 (21)
WHO_{CLAMP}	—	520 (43)

NCEP=national cholesterol education programme; WHO=World Health Organization; BMI=body mass index; HOMA=homeostasis model assessment.

We used the Swedish national register recording cause of death to define end points, so we had minimal loss to follow-up. We defined the primary end points a priori: cardiovascular death and death from any cause.

Statistical analyses

We used Cox proportional hazards models to examine relations of baseline variables to the incidence of endpoints. For each sample, baseline and end point, we examined unadjusted models (with only the metabolic syndrome variables, each in a separate model) and multivariable adjusted models (adjusting for established risk factors for cardiovascular disease: smoking, diabetes, hypertension, and total cholesterol measurements). To test the primary hypothesis, we fitted Cox models incorporating these four established risk factors to the total and primary preventive samples for each baseline and end point. Thereafter we added the variable of the metabolic syndrome. We then used likelihood ratio tests to compare the Cox models with a metabolic syndrome variable and risk factors for cardiovascular disease with models with only the risk factors for cardiovascular disease.

Results

Baseline characteristics including prevalences of metabolic syndrome and its components in the total sample at ages 50 and 70 are presented in table 2 and table A on bmj.com.

During follow-up from the examination at age 50 to 31 December 2002, 1078 men died (rate 17.9/1000 person years at risk), of which 502 died from cardiovascular disease (rate 8.3/1000 person years at risk) in the total sample. During follow-up from the examination at age 70 to 31 December 2002, 302 men died (rate 28.9/1000 person years at risk), of whom 133 died from cardiovascular disease (rate 12.7/1000 person years at risk) in the total sample.

Predictive value of the metabolic syndrome at age 50

In unadjusted analyses, the presence of the metabolic syndrome according to $NCEP_{BMI}$ or WHO_{HOMA} criteria at age 50 increased the risk by 1.7 times to 2.2 times for total and cardiovascular mortality in the total sample (table 3).

When presence is added compared with absence of the metabolic syndrome to models with established risk factors for cardiovascular disease at age 50, both definitions of the metabolic syndrome were significant predictors of both total and cardiovascular mortality. The highest hazard ratios were associated with the $NCEP_{BMI}$ metabolic syndrome (table 3 and bmj.com), whereas the WHO_{HOMA} metabolic syndrome was a borderline significant risk factor. We obtained similar results in the primary preventive sample (see bmj.com).

Predictive value of the metabolic syndrome at age 70

In unadjusted analyses, the presence of the metabolic syndrome according to NCEP or WHO criteria at age 70 increased the risk by 1.5 times to 2.3 times for total and cardiovascular mortality in the total sample (table 3). In this age group, some of the versions of the metabolic syndrome were borderline significant risk factors

Table 3 Predictive value of the metabolic syndrome at ages 50 and 70 in the total sample. Values are Cox proportional hazard ratios (95% confidence intervals), and likelihood ratio test P values, comparing models with established cardiovascular disease risk factors (smoking, diabetes, hypertension, and total cholesterol) to models with these variables plus a metabolic syndrome variable

	Age 50		Age 70	
Baseline	**Total mortality**	**Cardiovascular mortality**	**Total mortality**	**Cardiovascular mortality**
Metabolic syndrome (*v* no metabolic syndrome), unadjusted				
$NCEP_{WAIST}$	—	—	1.58 (1.24 to 2.01)	2.01 (1.41 to 2.85)
$NCEP_{BMI}$	1.67 (1.45 to 1.93)	2.21 (1.82 to 2.68)	1.52 (1.19 to 1.94)	2.11 (1.49 to 3.00)
WHO_{CLAMP}	—	—	1.54 (1.23 to 1.93)	2.12 (1.50 to 2.99)
WHO_{HOMA}	1.66 (1.41 to 1.96)	2.24 (1.80 to 2.79)	1.72 (1.35 to 2.21)	2.34 (1.64 to 3.33)
Established risk factors, adjusted for each other				
Smoking (*v* not smoking)	1.92 (1.69 to 2.17)	1.97 (1.64 to 2.37)	1.81 (1.40 to 2.33)	2.16 (1.48 to 3.14)
Diabetes (*v* no diabetes)	1.64 (1.28 to 2.10)	1.79 (1.28 to 2.51)	1.75 (1.34 to 2.30)	1.82 (1.22 to 2.73)
Hypertension (*v* no hypertension)	1.55 (1.37 to 1.75)	2.34 (1.95 to 2.80)	1.46 (1.08 to 1.98)	2.18 (1.28 to 3.70)
Total cholesterol (per SD)	1.10 (1.04 to 1.16)	1.16 (1.07 to 1.26)	0.97 (0.86 to 1.09)	0.96 (0.80 to 1.16)
Metabolic syndrome (*v* no metabolic syndrome), adjusted for established risk factors above				
$NCEP_{WAIST}$	—	—	1.26 (0.95 to 1.66) P=0.11	1.43 (0.95 to 2.17) P=0.10
$NCEP_{BMI}$	1.36 (1.17 to 1.58) P<0.0001	1.59 (1.29 to 1.95) P<0.0001	1.20 (0.90 to 1.59) P=0.23	1.55 (1.02 to 2.35) P=0.04
WHO_{CLAMP}	—	—	1.16 (0.87 to 1.53) P=0.31	1.53 (1.01 to 2.34) P=0.05
WHO_{HOMA}	1.26 (1.05 to 1.52) P=0.02	1.35 (1.06 to 1.73) P=0.02	1.37 (1.03 to 1.83) P=0.03	1.70 (1.12 to 2.59) P=0.01

NCEP=US national cholesterol education programme; WHO=World Health Organization; BMI=body mass index; HOMA=homeostasis model assessment.

when we had adjusted for established risk factors for cardiovascular disease (likelihood ratio test $P > 0.01$ for all; table 3). The highest hazard ratios were associated with cardiovascular mortality and with the WHO_{HOMA} version of the syndrome.

In the primary preventive sample, none of the versions of the metabolic syndrome was a significant predictor of total or cardiovascular mortality in unadjusted models ($P > 0.10$ for all) or models with established risk factors for cardiovascular disease ($P > 0.37$ for all) at age 70.

Discussion

In a community based cohort of men with long follow-up, the metabolic syndrome (according to the NCEP definition) was an independent risk factor in middle age for total and cardiovascular mortality, when established risk factors for cardiovascular disease were taken into account. The metabolic syndrome did not consistently predict adverse outcomes in elderly men.

Comparisons with other studies

Our observations confirm findings of previous studies. We adjusted for more established risk factors for cardiovascular disease than most previous studies, and had considerably longer follow-up time. This may be of importance, as an apparent lag time of 10-15 years occurred before the mortality curves for men with and without the $NCEP_{BMI}$ metabolic syndrome started to diverge (see bmj.com). In contrast to one previous study,[6] the NCEP metabolic syndrome seemed equally predictive in primary prevention as in the general population in middle age in our study.

Influence of age on risk associated with the metabolic syndrome

The metabolic syndrome added little prognostic information at age 70 in either sample. This may be a result of a smaller sample size at age 70, as the point estimates for the metabolic syndrome are similar at age 50 and 70, but the confidence intervals were wider at age 70. A healthy cohort effect, shorter follow-up, and competing non-cardiovascular causes of death may also account for the lower prognostic impact at age 70.

Influence of definition of the metabolic syndrome on risk

The NCEP definition seemed to predict mortality slightly stronger than the WHO definition in middle aged men in our study. Similar results were obtained in some,[6] but not all, previous studies.[7] Reasons for this may include the fact that the NCEP definition is more weighted towards people with suboptimal blood pressure and dyslipidaemia, and the absence of a compulsory glucose dysregulation criterion in the NCEP definition. At age 70, the WHO_{HOMA} version seemed slightly more predictive than the WHO_{CLAMP} version (see bmj.com).

Limitations and strengths of the study

The modified definitions of the metabolic syndrome led us to refrain from formal statistical comparisons of predictive capacity between the definitions. At the age of 50, a measurement of microalbuminuria was not available for the original WHO definition. We further had to substitute body mass index for abdominal obesity in the NCEP definition at age 50, and did not account for waist to hip ratio in the WHO definition at age 50. Other limitations include the homogeneous sample of men of the same age and ethnic background, limiting generalisability.

In addition to the long follow-up period, strengths of this study include the large population, the availability of two baseline investigations 20 years apart, the minimal loss to follow-up, the reliable endpoint definitions, and the detailed metabolic characterisation of the cohort, including the euglycaemic insulin clamp, which is the gold standard method for assessment of insulin sensitivity.

Conclusions

In this large community based sample of middle aged men, the presence of the metabolic syndrome according to the NCEP definition gave long term prognostic information regarding total and cardiovascular mortality if status of established risk factors for cardiovascular disease was known.

What is already known on this topic

The metabolic syndrome is a risk factor for cardiovascular events

General practitioners know their patients' status regarding established risk factors for cardiovascular disease

It is unknown if diagnosing the metabolic syndrome adds risk information in that setting

What this study adds

The presence of the metabolic syndrome increased the risk for total and cardiovascular mortality by 40-60%, when established cardiovascular disease risk factors were taken into account

It may be meaningful to diagnose the syndrome for risk prediction in primary care

Hans Lithell died on 27 November 2005.

Contributors: see bmj.com

Funding: Thuréus Foundation, the Swedish Heart-Lung Foundation, and the Swedish Society for Medical Research. The funding sources had no involvement in the research.

Competing interests: None declared.

Ethical approval: Uppsala University Ethics Committee.

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(Accepted 2 February 2006)

doi 10.1136/bmj.38766.624097.1F