Does a diagnosis of the metabolic syndrome provide additional prediction of cardiovascular disease and total mortality in the elderly? The Dubbo Study

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ABSTRACT

Objective: To assess whether a diagnosis of the metabolic syndrome (MetS) improves the prediction of cardiovascular disease or total mortality beyond that already provided by conventional risk factors.

Design and setting: A longitudinal cohort study conducted in Dubbo, New South Wales.

Participants: 2805 men and women aged 60 years and older living in the community, first assessed in 1988–1989 and followed for 16 years.

Main outcome measures: Coronary heart disease (CHD) events, ischaemic stroke events, and total mortality.

Results: MetS was present in 31% of men and 34% of women. Crude CHD, ischaemic stroke, and total mortality rates were higher in the presence of MetS in men and women. In proportional hazards models that included conventional risk factors, but excluded variables used to define the presence of MetS, MetS was a significant predictor of CHD, stroke and total mortality. In men, the respective hazard ratios were 1.64 (95% CI, 1.37–1.96), 1.31 (95% CI, 0.97–1.77), and 1.53 (95% CI, 1.30–1.79). In women, the respective hazard ratios were 1.70 (95% CI, 1.43–2.02), 1.37 (95% CI, 1.04–1.82), and 1.35 (95% CI, 1.15–1.59). The use of MetS variables on an ordinal scale produced broadly similar conclusions.

Conclusions: A diagnosis of MetS provides additional prediction of CHD events, stroke events, and total mortality beyond that provided by other conventional risk factors.

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The metabolic syndrome (MetS) is a grouping of related metabolic factors that together predict an increased risk of cardiovascular disease and diabetes mellitus.[1-4] There has been controversy as to what constitutes a universally acceptable definition of MetS,[5,6] and whether a diagnosis of MetS offers any better prediction of cardiovascular disease than that provided by its component parts.[5,6] A recent study from Sweden of middle-aged men reported that presence of MetS gave additional long-term prognostic information on total and cardiovascular mortality if the status of conventional risk factors was known.[7] Other studies have suggested that MetS offers no additional prediction beyond its component parts.[3,8]

Central abdominal obesity and, to a lesser extent, insulin resistance are felt to be key factors in the pathogenesis of MetS.[9,10] The most recent definition of MetS from the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) in 2005 proposes a clinical diagnosis based on the presence of at least three of the following five features: elevated waist circumference, elevated plasma triglyceride level, reduced high-density lipoprotein cholesterol (HDL-C) level, elevated blood pressure, and elevated fasting plasma glucose level.[11] An earlier definition proposed by the International Diabetes Federation is similar, but mandates elevated waist circumference *plus* any two of the other features.[12]

The ongoing study of healthy ageing in Dubbo, in western New South Wales,[13-15] has afforded the opportunity to address the question: does a diagnosis of MetS improve the prediction of cardiovascular disease or total mortality beyond that provided by its component parts and by other conventional risk factors? This article presents a longitudinal analysis of the role of MetS in predicting coronary heart disease (CHD) events, ischaemic stroke events, and total mortality in a cohort of Australians aged 60 years and older.

METHODS

Participants and baseline examinations

The Dubbo Study cohort was first examined in 1988–1989. All non-institutionalised residents of Dubbo born before 1930 were eligible to participate. The participation rate was 73% (1233 men and 1572 women). Methods and measures have been described in detail previously.[13-15]

Briefly, the baseline examinations comprised demographic, psychosocial and standard cardiovascular risk assessments. The medical examination included anthropometry, blood pressure, resting electrocardiogram (ECG), peak expiratory flow rate, and collection of 12-hour fasting blood samples for measurement of plasma lipid, lipoprotein and glucose levels. A questionnaire explored alcohol and tobacco use, medical history, medications, myocardial infarction and chest pain. Prior CHD was defined as previous myocardial infarction or angina reported in the questionnaire, or ECG changes; diabetes mellitus was defined on prior history or medication for diabetes or fasting plasma glucose $\geq$ 7.8 mmol/L. There was no follow-up medical examination.

The study population was broadly representative of the Australian population born before 1930 by sex, age, employment, socioeconomic status, housing tenure, tobacco use, mean blood pressure, and other variables.[13,14]

Definition of the metabolic syndrome

The Dubbo Study database does not contain information on waist circumference, but body mass index (BMI, weight/height^2) was available, and this showed a similar distribution in men and women. We arbitrarily selected the 80th percentile of BMI (29.3 kg/m^2) as a reference point for central obesity. MetS was defined according to the AHA/NHLBI proposal,[11] but substituting BMI for waist circumference. MetS was coded as present if subjects manifested at least three of the following five criteria: BMI $\geq$ 29.3 kg/m^2; fasting plasma triglyceride level $\geq$ 1.7 mmol/L; HDL-C level < 1.03 mmol/L in men and < 1.30 mmol/L in women; blood pressure $\geq$ 130 mmHg systolic or 85 mmHg diastolic, or on antihypertensive treatment; fasting plasma glucose level $\geq$ 5.6 mmol/L or on hypoglycaemic treatment or with his-

1 Crude event rates* during 16 years, by age and metabolic syndrome status in men and women

	60–69 years		70–79 years		⩾ 80 years		All ages	
	MetS +	MetS –	MetS +	MetS –	MetS +	MetS –	MetS +	MetS –
Men	(*n* = 232; 32%)	(*n* = 504; 68%)	(*n* = 129; 31%)	(*n* = 281; 69%)	(*n* = 23; 26%)	(*n* = 64; 74%)	(*n* = 384; 31%)	(*n* = 849; 69%)
CHD	51 (118)	34 (171)	62 (80)	44 (124)	57 (13)	41 (26)	55 (211)	38 (321)
Ischaemic stroke	16 (36)	10 (51)	23 (30)	24 (66)	13 (3)	27 (17)	18 (269)	16 (134)
Total mortality	54 (125)	36 (180)	84 (108)	74 (207)	100 (23)	95 (61)	67 (256)	53 (448)
Women	(*n* = 262; 31%)	(*n* = 587; 69%)	(*n* = 212; 39%)	(*n* = 337; 61%)	(*n* = 62; 36%)	(*n* = 112; 64%)	(*n* = 536; 34%)	(*n* = 1036; 66%)
CHD	37 (98)	20 (115)	57 (121)	38 (128)	65 (40)	48 (54)	48 (259)	29 (297)
Ischaemic stroke	11 (29)	7 (38)	23 (48)	16 (55)	23 (14)	30 (33)	17 (91)	12 (126)
Total mortality	30 (78)	23 (136)	68 (143)	50 (169)	87 (54)	92 (103)	51 (275)	39 (408)

*Event rates are shown per 100 subjects (number of events). MetS + = metabolic syndrome present. MetS – = metabolic syndrome not present. CHD = coronary heart disease. ◆

tory of diabetes. A separate computation was made of the number of these factors present, for use in an analysis of the outcome in ordinal scale. Only 1% of men and 2% of women were using lipid medications at study entry, and this was ignored in the coding.

Outcome studies

Cardiovascular disease events and deaths from any cause over 16 years from September 1988 until September 2004 were included. Hospitalisation and NSW death records were monitored continuously, with postal surveys conducted every 2 years to confirm vital status. More than 95% of surviving participants were traceable at the most recent survey. Records were coded according to the International classification of diseases, 9th revision (clinical modification) (ICD-9) and 10th revision (Australian modification) (ICD-10). CHD was defined by ICD-9 codes 410–414 and ICD-10 codes I20–I25. Ischaemic stroke was defined by ICD-9 codes 433–436 and ICD-10 codes I63–I66 and G45–G46.

The independent contribution of MetS and other factors to the outcomes was examined in Cox proportional hazards models. Point estimates and 95% confidence intervals for the relative hazard of an outcome were calculated from the regression coefficients (presented as hazard ratios). For categorical variables, the lowest or opposite category served as the reference group. The proportional hazards model assumes constant relative hazard over the length of follow-up, and this was confirmed by a log-minus-log hazard plot demonstrating parallel curves over all categories for various predictors. Statistical analysis was conducted using SPSS version 14.0 (SPSS Inc, Chicago, Ill, USA).

Ethics approval

The study has been approved by institutional ethics committees at St Vincent's Hospital, Sydney, the University of New South Wales, and the University of Western Sydney. All subjects gave informed, written consent.

RESULTS

MetS was present in 31% of men and 34% of women, with similar prevalence in each age group. Crude event rates are presented in Box 1. All outcomes were more frequent in the presence of MetS, except in the ⩾ 80-years age group, but subject numbers in this group were relatively few.

After controlling for age alone, MetS was a significant predictor of CHD events in men (hazard ratio [HR], 1.70; 95% CI, 1.43–2.02) and women (HR, 1.91; 95% CI, 1.62–2.26). After including conventional risk factors, but excluding those used to define MetS, MetS remained a significant predictor of CHD events (men: HR, 1.64; 95% CI, 1.37–1.96; women: HR, 1.70; 95% CI, 1.43–2.02) (Box 2). Another model that included variables used to define MetS was discarded because of multicollinearity between MetS and some of its component variables. Other major predictors of CHD were age, hypertension, smoking, diabetes (women only), total cholesterol, HDL-C,

2 Coronary heart disease (CHD) prediction over 16 years, by the metabolic syndrome in Cox proportional hazards models

	Men		Women	
	Model 1*	Model 2†	Model 1*	Model 2†
Metabolic syndrome		1.64 (1.37–1.96)		1.70 (1.43–2.02)
Age	1.04 (1.02–1.05)	1.04 (1.02–1.05)	1.06 (1.05–1.08)	1.07 (1.06–1.08)
High BP therapy	1.88 (1.55–2.29)		1.92 (1.56–2.37)	
BP ⩾ 200/100 mmHg	1.10 (0.77–1.56)		1.49 (1.07–2.07)	
Smoker, current	1.27 (0.97–1.66)	1.11 (0.85–1.44)	1.21 (0.91–1.62)	1.22 (0.92–1.63)
Diabetes	1.09 (0.82–1.44)		1.94 (1.47–2.56)	
Body mass index	1.02 (1.00–1.05)		0.99 (0.97–1.01)	
Total cholesterol	1.11 (1.02–1.20)	1.04 (0.97–1.12)	1.10 (1.02–1.18)	1.05 (0.99–1.12)
HDL cholesterol	0.63 (0.45–0.88)		0.57 (0.42–0.78)	
Log triglycerides	0.89 (0.72–1.10)		1.05 (0.82–1.34)	
Peak expiratory flow, tertile I	1.49 (1.19–1.88)	1.43 (1.14–1.80)	1.33 (1.05–1.68)	1.41 (1.12–1.78)
Alcohol, any	0.81 (0.66–1.00)	0.82 (0.67–1.01)	0.87 (0.73–1.04)	0.82 (0.69–0.98)
Prior CHD	2.55 (2.11–3.09)	3.08 (2.57–3.69)	1.83 (1.50–2.23)	2.27 (1.88–2.74)

Values are hazard ratios (95% CI). Age, body mass index, and lipids were entered as continuous variables, the remainder as categorical variables, with the "nil", lowest or opposite category as the reference value (eg, no BP therapy, the lowest of four BP categories at ⩽ 140/90 mmHg, never smoked, peak expiratory flow tertile III, nil alcohol). *Model 1 includes all variables except the metabolic syndrome. †Model 2 includes all variables except those used to define the metabolic syndrome. BP = blood pressure. HDL = high-density lipoprotein. ◆

3 Total mortality prediction over 16 years, by the metabolic syndrome in Cox proportional hazards models

	Men		Women	
	Model 1*	Model 2†	Model 1*	Model 2†
Metabolic syndrome		1.53 (1.30–1.79)		1.35 (1.15–1.59)
Age	1.10 (1.09–1.11)	1.10 (1.09–1.11)	1.10 (1.09–1.12)	1.11 (1.09–1.12)
High BP therapy	1.55 (1.31–1.83)		1.43 (1.19–1.72)	
BP ⩾ 200/100 mmHg	1.63 (1.21–2.19)		1.45 (1.08–1.95)	
Smoker, current	2.08 (1.64–2.64)	1.83 (1.46–2.30)	1.69 (1.31–2.18)	1.75 (1.36–2.26)
Diabetes	1.59 (1.26–2.02)		1.80 (1.37–2.36)	
Body mass index	1.01 (0.98–1.03)		0.98 (0.96–1.00)	
Total cholesterol	0.99 (0.91–1.06)	0.98 (0.92–1.05)	0.97 (0.90–1.03)	0.98 (0.92–1.04)
HDL cholesterol	0.97 (0.74–1.30)		1.07 (0.82–1.41)	
Log triglycerides	1.03 (0.86–1.25)		1.36 (1.08–1.72)	
Peak expiratory flow, tertile I	1.54 (1.25–1.90)	1.56 (1.27–1.92)	2.15 (1.70–2.73)	2.29 (1.81–2.89)
Alcohol, any	0.76 (0.64–0.92)	0.77 (0.65–0.92)	0.75 (0.64–0.88)	0.75 (0.64–0.87)
Prior CHD	1.36 (1.14–1.62)	1.53 (1.30–1.81)	1.09 (0.90–1.32)	1.25 (1.05–1.51)

Values are hazard ratios (95% CI). Age, body mass index, and lipids were entered as continuous variables, the remainder as categorical variables, with the "nil", lowest or opposite category as the reference value (eg, no BP therapy, the lowest of four BP categories at ⩽ 140/90 mmHg, never smoked, peak expiratory flow tertile III, nil alcohol). * Model 1 includes all variables except the metabolic syndrome. † Model 2 includes all variables except those used to define the metabolic syndrome. BP = blood pressure. CHD = coronary heart disease. HDL = high-density lipoprotein. ◆

reduced peak expiratory flow, and prior CHD (Box 2).

After controlling for age alone, MetS was a significant predictor of ischaemic stroke events in men and women (men: HR, 1.43; 95% CI, 1.07–1.92; women: HR, 1.53; 95% CI, 1.17–2.01). In the multivariate model, MetS was a borderline predictor in men (HR, 1.31; 95% CI, 0.96–1.77) and a significant predictor in women (HR, 1.37; 95% CI, 1.04–1.82).

Box 3 presents the models for prediction of total mortality. After controlling for age, MetS was a significant predictor of mortality in men (HR, 1.60; 95% CI, 1.37–1.86) and women (HR, 1.43; 95% CI, 1.23–1.67). MetS remained a significant predictor of mortality in men and women in the multivariate model (men: HR, 1.53; 95% CI, 1.30–1.79; women: HR, 1.35; 95% CI, 1.15–1.59). Other significant predictors of total mortality were age, hypertension, current cigarette smoking, diabetes, peak expiratory flow, alcohol intake, and prior CHD (Box 3).

The models were recalculated to include an interaction term between MetS and age. This term was non-significant for all outcomes and both sexes. Models were also recalculated using a lower cut-point for BMI (70th percentile, 27.7 kg/m^2). Hazard ratios for prediction of all outcomes by MetS status were not materially changed by this step. For example, the hazard ratios for CHD in men and women became 1.65 (95% CI, 1.38–1.97) and 1.66 (95% CI, 1.39–1.97), respectively.

The dichotomous variable MetS was replaced in the multivariate model by the number of factors contributing to MetS, and the findings are summarised in Box 4. With respect to CHD and total mortality, the risk attached to the number of components increased in an approximately continuous and graded manner. In the prediction of stroke, only the presence of four or five component variables approached significance.

DISCUSSION

Previous studies highlight the role of MetS in the genesis of atherosclerotic cardiovascular disease.[1-4] We have clearly demonstrated that a diagnosis of MetS in older people provides prediction of CHD events, stroke events, and total mortality beyond that provided by conventional risk factors. The use of the MetS variables on an ordinal scale produced broadly similar conclusions.

The evidence summarising risk of mortality and cardiovascular disease in MetS was recently reviewed.[16] The combined relative risks of cardiovascular disease and total mortality were 2.60–2.99 and 1.27–1.37, respectively, depending on the definition of MetS. These findings are broadly consistent with our study, but the analyses did not specify the outcome for CHD, nor for men and women separately.

A study of CHD events over 5 years in middle-aged Scottish men found a significant hazard ratio for MetS (HR, 1.30).[3] This was observed in a Cox model that included conventional risk factors, but the hazard ratio was not significant when the model included individual components of MetS. We made a similar observation in models discarded because of multicollinearity between MetS and its component variables.

A study of middle-aged and older Swedish men found that MetS was a significant predictor of total (HR, 1.36) and cardiovascular (HR, 1.59) *mortality* in 50-year-old subjects).[7] This was observed in a Cox

4 Event prediction by number of component variables of the metabolic syndrome in Cox proportional hazards models

Number of components	Men			Women		
	CHD	Stroke	Mortality	CHD	Stroke	Mortality
0 (97, 128)	1.00	1.00	1.00	1.00	1.00	1.00
1 (395, 501)	1.84 (1.12–3.01)	0.94 (0.50–1.78)	1.41 (0.96–2.06)	1.55 (0.93–2.59)	2.14 (0.92–4.95)	1.03 (0.70–1.53)
2 (357, 407)	1.85 (1.13–3.05)	1.07 (0.57–2.01)	1.50 (1.02–2.20)	1.97 (1.18–3.28)	1.97 (0.84–4.64)	1.26 (0.85–1.87)
3 (237, 319)	2.83 (1.71–5.04)	1.01 (0.51–2.00)	2.15 (1.45–3.19)	2.42 (1.45–4.04)	2.12 (0.90–5.03)	1.23 (0.82–1.84)
4 or 5 (147, 217)	3.00 (1.79–5.04)	1.78 (0.91–3.48)	2.14 (1.42–3.23)	3.68 (2.19–6.20)	3.84 (1.61–9.15)	2.06 (1.37–3.11)

Values are hazard ratios (95% CI). The number of men and women in each group is indicated in parentheses after the number of components. This is the multivariate Model 2 in Box 2 and Box 3. CHD= coronary heart disease. ◆

model including other conventional risk factors but not the components of MetS. A later report suggested that MetS did not add significant predictive value (of the same outcomes) when a Cox model included component parts of MetS.[8] We discarded such models because of a perceived problem with multicollinearity between MetS and its component variables.

Our study has a number of strengths and weaknesses. We followed a well defined community sample and chose not to exclude diabetic subjects, in contrast to some other studies,[7] on the grounds that glucose intolerance is an essential component of MetS. We subdivided cardiovascular disease into CHD and ischaemic stroke, and did not confine these outcomes to fatal events. Our models controlled for the simultaneous effect of conventional risk factors. Given the apparent multicollinearity between MetS and its components in the models, it has not been possible to define whether MetS provides additional prediction of events beyond its component parts.

The most serious limitation in our study is the lack of data on waist circumference. The AHA/NHLBI definition uses a cut-point for waist circumference of 102 cm for men and 88 cm for women.[11] Other studies have faced a similar problem, and have used BMI instead of waist circumference.[3,7] It is not suggested that BMI is an ideal surrogate for waist circumference, but BMI will continue to be used when waist circumference is unavailable in some research studies. By coincidence, the cut-point for BMI in the Swedish study[7] was 29.4 kg/m^2 (compared with 29.3 kg/m^2 in our study). Lowering our reference point from the 80th to the 70th percentile of BMI made no difference to the outcome predictions.

The lack of prediction of CHD by diabetes in men over 16 years of follow-up was surprising, given that we had already reported significant prediction by diabetes at 5 years of follow-up.[17] Hence, a more detailed analysis was conducted in diabetes. In men aged 60–69 years at study entry, 54/100 with diabetes suffered CHD over 16 years; 37/100 did so without diabetes. The corresponding rates were 55/100 and 49/100 for men aged 70–79 years, and 46/100 and 49/100 for those aged $\geq$ 80 years. It appears that diabetes is not a risk factor for CHD in elderly men followed for a very long time, yet it still has an important effect on survival. This interaction of diabetes, age and CHD risk does not appear to be present in women.

Finally, we performed sensitivity and specificity analyses on the value of MetS as a diagnostic tool. The sensitivity of this diagnosis was around 40% for CHD, stroke or total mortality, but specificity was around 70% for the same outcomes. The positive predictive value of the diagnosis of MetS was around 50% for CHD, 18% for stroke, and 60% for mortality. Although some may argue against the utility of MetS as a clinical tool,[18] a diagnosis of MetS does provide additional prediction of CHD events, stroke events, and total mortality beyond that provided by other conventional risk factors, and this may ultimately prove useful in clinical management.

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COMPETING INTERESTS

None identified.

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