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ORIGINAL ARTICLE

The metabolic syndrome and cardiovascular risk in the British Regional Heart Study

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Objective: To evaluate the metabolic syndrome as an overall risk assessment tool for cardiovascular disease (CVD) and diabetes in middle-aged British men.
Design: Prospective study.
Subjects: A total of 5128 men aged 40–59 years with no history of CVD or diabetes drawn from general practices in 24 British towns and followed up for 20 years.
Results: The metabolic syndrome (National Cholesterol Expert Panel definition) is associated with a significant increase in risk of total CHD (myocardial infarction, angina or CHD death) (relative risk (RR), 95% CI: 1.57, 1.39–1.97), stroke (1.61, 95% CI: 1.26–2.06) and type 2 diabetes (3.57, 95% CI: 2.83–4.50) and is a far stronger predictor of diabetes than of total CHD and stroke in middle-aged men. The metabolic syndrome was inferior to the Framingham Risk Score in predicting total CHD or major CVD over 20 years (area under the curve (AUC) 0.58 vs 0.66 for both CHD and CVD; $P<0.0001$ for difference) but was superior in predicting diabetes (AUC 0.70 vs 0.60; $P<0.001$). However, absolute risk of developing CVD or diabetes over 20 years in those with three or more abnormalities was very high, ranging from 41.8% in those with three abnormalities to over a 50% chance in those with four of five abnormalities, comparable to the absolute incidence rates in the top 2 fifths of the Framingham distribution.
Conclusion: While the initial aim to use the metabolic syndrome to improve risk prediction of CHD has been disappointing, the syndrome identifies patients at high risk of both diabetes and CVD who may derive benefit from lifestyle intervention.
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Keywords: metabolic syndrome; cardiovascular disease; type 2 diabetes

Introduction

The metabolic syndrome, whether defined on the basis of the National Cholesterol Education Program (NCEP) Expert Panel[1] criteria or WHO criteria,[2,3] is associated with increased risk of developing diabetes and cardiovascular disease (CVD)[4,5] and has been proposed as a possible global risk assessment tool for CVD.[6,7] There is growing debate on the use of the metabolic syndrome as an assessment tool for coronary heart disease risk in clinical practice.[8–10] In the few studies that have assessed whether the syndrome is a better predictor of coronary heart disease (CHD) risk than other risk assessments such as the Framingham Risk Score (FRS), there is indication that the metabolic syndrome is inferior to the FRS in predicting CHD and to established rules for the prediction of either type 2 diabetes or CVD.[6,11–13] Furthermore, several investigators have pointed out that the individual components of the syndrome are more important determinants of CHD than either of the WHO or NCEP definitions.[14,15] Thus, the use of the metabolic syndrome as a focus of screening for metabolic risk modification has become questionable.[10] In a previous article[13] from the British Regional Heart Study, the metabolic syndrome was evaluated as a risk assessment for CHD (nonfatal myocardial infarction or CHD death) and type 2 diabetes, and the question whether the metabolic syndrome is a better predictor of CHD and diabetes than the FRS was addressed. In this paper, I have extended CHD outcome to include nonfatal angina to assess the metabolic syndrome as a global risk assessment tool for CVD and diabetes in middle-aged British men.

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The British Regional Heart Study

The British Regional Heart Study (BRHS) is a large prospective study of CVD comprising 7735 men aged 40–59 years

drawn from general practices in each of 24 towns in England, Wales and Scotland with a 78% response rate.[16] Research nurses administered a standard questionnaire that included questions on lifestyle factors and medical history. Physical measurements including height and weight were made and venous nonfasting blood samples were obtained for measurement of biochemical and haematologic variables. Triglyceride measurements were only available for men in the 7–24th towns visited ($n = 5663$). All men have been followed up for all-cause mortality, cardiovascular morbidity and development of type 2 diabetes from the initial screening in January 1978 to July 1980.[17] All major CHD (nonfatal myocardial infarction and angina) and stroke events (fatal and nonfatal) have been recorded, and follow-up has been achieved for 99% of the cohort.

Definition of the metabolic syndrome

The metabolic syndrome was based on the modified NCEP definition.[3] In this paper, body mass index (BMI) $\geqslant 28.8\,kg/m^2$ was used as a proxy for abdominal adiposity in conformity with other studies that have used BMI to replace waist circumference.[18] As triglycerides were based on nonfasting levels that are on average 20–30% higher than fasting levels,[19] a higher threshold was used for high triglyceride defined as being above 200 mg per 100 ml ($\geqslant 2.28\,mmol\,l^{-1}$). Thus, in this study the metabolic syndrome includes any three of the following: (1) hypertension (SBP (systolic blood pressure) $\geqslant 130$ or DBP (diastolic blood pressure) $\geqslant 85$ mm Hg or on antihypertensive treatment); (2) high blood glucose ($\geqslant 110$ mg per 100 ml; $\geqslant 6.1\,mmol\,l^{-1}$); (3) hypertriglyceridaemia (>200 mg per 100 ml; $\geqslant 2.28\,mmol\,l^{-1}$); (4) low HDL (high-density lipoprotein) <1.036 (<40 mg per 100 ml; $<1.036\,mmol\,l^{-1}$); and (5) elevated BMI ($\geqslant 28.8\,kg/m^2$).[13]

The metabolic syndrome and risk of CVD and diabetes

The analysis was restricted to 5128 men with no prevalent CVD or diabetes in whom there were 1263 total CHD events (720 angina events and 763 myocardial infarction/CHD death), 291 major stroke events and 299 incident cases of type 2 diabetes during the 20-year follow-up for each man. In all, 1526 men developed major CVD events (myocardial infarction, angina, stroke and all CVD death) or diabetes.

The metabolic syndrome was present in about a quarter of the British men (26.0%) comparable to the prevalence of the metabolic syndrome in the West of Scotland Study.[18] In agreement with other studies,[4,5,20] the metabolic syndrome was associated with a significant increase of total CHD and stroke outcome and, in particular, with type 2 diabetes, after adjustment for age, social class, smoking, physical activity and alcohol (Table 1). Over 44% of men with the syndrome had developed either CVD or diabetes during the 20 years compared with about 30% in those without the syndrome. Those with the syndrome had a 70% increase in risk of CVD or diabetes after adjustment for lifestyle factors compared with those without.

Some studies have suggested that the individual components are stronger determinants of CHD than the metabolic syndrome.[14,15] In the BRHS, the syndrome was associated with greater magnitude of association (relative risk) with CHD than any of the individual components with the exception of hypertension, which showed larger associations than the metabolic syndrome (Table 2). For diabetes, obesity showed stronger associations than the metabolic syndrome. However, the vast majority of men with elevated BMI had

Table 1 The metabolic syndrome and cumulative incidence and adjusted RR of CVD outcomes and diabetes in 5128 men aged 40–59 years with no history of CHD, stroke or diabetes

	No (3895)	*Yes (1333)*
Total CHD events		
Cumulative incidence (%)	21.9	32.4
Adjusted RR	1.00	1.57 (1.39, 1.97)
Major stroke events		
Cumulative incidence (%)	5.0	7.6
Adjusted RR	1.00	1.61 (1.26, 2.06)
All CVD events		
Cumulative incidence (%)	26.8	33.3
Adjusted RR	1.00	1.53 (1.37, 1.70)
Type 2 diabetes		
Cumulative incidence (%)	3.7	12.1
Adjusted RR	1.00	3.57 (2.83, 4.50)
CVD or diabetes		
Cumulative incidence (%)	29.5	44.6
Adjusted RR	1.00	1.70 (1.54, 1.89)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; RR, relative risk. Adjusted for age, smoking, social class, physical activity and alcohol intake. British Regional Heart Study. Data on type 2 diabetes and stroke extracted from Wannamethee *et al.*[13]

Table 2 Individual components of the NCEP: the metabolic syndrome and adjusted RR of CHD and diabetes

	Total CHD Adjusted RR	*Type 2 diabetes Adjusted RR*
Metabolic syndrome	1.57 (1.39, 1.97)	3.57 (2.83, 4.50)
Components		
Obesity	1.37 (1.18, 1.59)	3.66 (2.87, 4.66)
Hypertension	1.68 (1.43, 1.97)	1.96 (1.38, 2.79)
High triglyceride	1.45 (1.29, 1.63)	2.19 (1.74, 2.77)
Low HDL-C	1.38 (1.23, 1.55)	1.92 (1.52, 2.44)
High glucose	1.18 (1.03, 1.35)	2.70 (2.13, 3.45)

Abbreviations: CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; RR, relative risk. Adjusted for age, smoking, social class, physical activity and alcohol intake. British Regional Heart Study.

the metabolic syndrome (71.6%). This compared with only 32% among those with hypertension. These findings are consistent with previous studies, which have indicated that the magnitude of the associations for individual components of the syndrome is similar or larger than that seen for the metabolic syndrome.[14,15]

The risk of CHD and diabetes increased significantly and progressively with increasing number of metabolic abnormalities (Table 3) as has been reported in other studies;[17,21–23] less consistent relationships were seen with stroke risk.

Comparisons between the Framingham Risk Score and the metabolic syndrome

The predictive power for CHD of the number of metabolic abnormalities was compared with the FRS equation[24,25] over 20 years. The top fifth of the FRS showed a higher probability of developing total CHD than even the presence of four or more abnormalities (Figure 1). The FRS was a significantly better predictor of CHD than the number of metabolic abnormalities as indicated by the ROC area under the curve (AUC) but less predictive for diabetes than the metabolic syndrome ($P<0.001$ for differences) (Table 4). This was largely due to the FRS being a far better predictor of nonfatal myocardial infarction or CHD death. The FRS and the metabolic syndrome showed similar prediction for nonfatal angina. The FRS was also a significant better discriminator for stroke than the number of metabolic abnormalities. Thus, the metabolic syndrome was a stronger predictor of diabetes than of CHD as observed in previous studies;[17,26] but less effective at predicting CHD than the FRS, consistent with reports from the United States.[6,11,12] It is not surprising that the FRS is a better predictor of CHD as the metabolic syndrome does not contain several well-established risk factors for CHD such as serum total cholesterol and smoking. However, the metabolic syndrome was a far better predictor of diabetes than the FRS. This is likely to be due to the inclusion of established risk factors for diabetes such as waist circumference (BMI) and high blood glucose levels (short of diabetes), which are not included in the FRS.

Since CVD is more common than diabetes, the FRS was a better discriminator and more sensitive in identifying total events (total CHD, stroke or diabetes) than the metabolic syndrome (AUC 0.66, 95% CI (confidence interval): 0.64–0.68 vs 0.60, 0.58–0.62; $P<0.001$, sensitivity 41.2 vs 34.7%), but absolute risk of developing CVD or diabetes over 20 years in those with three or more metabolic abnormalities was very high ranging from 41.8 to 50.8% chance, comparable with the absolute incidence rates in the top 2 fifths of the Framingham distribution over 20 years. The probability of developing heart attacks, angina, stroke or diabetes over 20 years increased markedly with increasing number of components from 18.5% in those with none to 28.2% with one, 35.1% with two, 41.8% with three and 50.8% with four

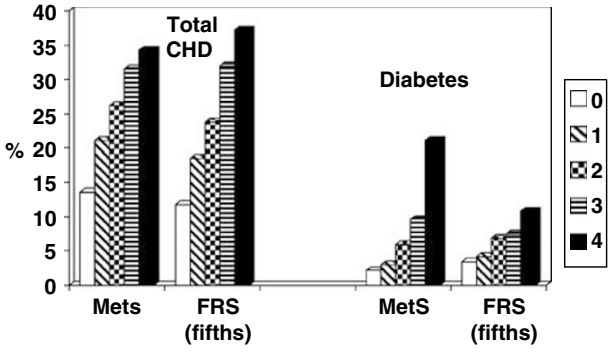

Figure 1 The metabolic syndrome and Framingham Risk Score (FRS), and probability of occurrence of total CHD events and type 2 diabetes over 20 years. Data on diabetes extracted from Wannamethee *et al.*[13]

Table 4 Comparisons between the metabolic syndrome and Framingham Risk Score

	Metabolic syndrome		*Framingham*	
	AUC	*Sensitivity (%)*	*AUC*	*Sensitivity (%)*
Total CHD	0.58	33.3	0.66	41.6
MI	0.59	35.5	0.68	47.2
Nonfatal angina	0.57	32.9	0.58	32.8
Stroke	0.55	34.7	0.66	44.1
All CVD	0.58	33.3	0.66	40.1
T2DM	0.70	53.9	0.60	35.6
CVD or T2DM	0.60	34.7	0.66	41.2

Abbreviations: AUC, area under the curve; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; T2DM, type 2 diabetes. Data on T2DM and stroke extracted from Wannamethee *et al.*[13]

Table 3 Adjusted relative risk of total CHD, stroke events and diabetes by number of metabolic risk factors in 5128 men aged 40–59 years with no history of CHD, stroke or diabetes

	No of metabolic abnormalities				
	0	*1*	*2*	*3*	*4/5*
No. of men	557	1757	1481	902	431
Total CHD	1.00	1.74 (1.22, 2.39)	2.34 (1.65, 3.32)	2.88 (2.02, 4.11)	3.44 (2.35, 5.03)
Stroke	1.00	1.23 (0.76, 1.57)	1.17 (0.72, 1.90)	2.06 (1.27, 3.36)	1.54 (0.87, 2.73)
Type 2 diabetes	1.00	1.36 (0.70, 2.62)	2.73 (1.45, 5.14)	4.56 (2.48, 8.78)	10.88 (5.77, 20.50)

Abbreviation: CHD, coronary heart disease. Adjusted for age, smoking, social class, physical activity and alcohol intake. Data on stroke and type 2 diabetes extracted from Wannamethee *et al.*[13]

or more abnormalities. The absolute probability was comparable to the probability associated with fifths of the FRS: 16.8, 24.7, 31.9, 42.3 and 51.3% for the five FRS groups. Thus, the metabolic syndrome is a simple tool, which identifies subjects predisposed to either CVD or diabetes.

Caveats

The definition of the metabolic syndrome used in this study was based on NCEP criteria, and it is unclear how the WHO definition, which includes insulin, or the more recent International Diabetes Federation (IDF) definition (2005), would compare against the FRS. However, in most studies NCEP definition has shown to be similar or more predictive for CVD than the WHO definition[27–29] or the IDF definition.[30]

Relative risks associated with many of the components of the metabolic syndrome such as hypertension and blood lipids decrease with increasing age,[31] and the prognostic significance of obesity in the elderly is controversial.[32] The present study was carried out in a middle-aged population followed up for 20 years, and whether these findings are generalizable to an elderly population is not certain. Some have suggested very modest associations between the metabolic syndrome and CVD in the elderly,[14,33] while others suggest the metabolic syndrome to be a strong predictor of CVD.[34]

Conclusion

In middle-aged men, risk of CHD and diabetes increased significantly and progressively with increasing number of metabolic abnormalities. These findings emphasize the importance of intervention even in those with two metabolic abnormalities. The metabolic syndrome (NCEP definition) is associated with a significant increase in risk of CHD, stroke and diabetes and is a far stronger predictor of diabetes than of CHD and stroke in middle-aged men. Although it is inferior to the FRS in predicting total CHD and, in particular, heart attacks, the metabolic syndrome identifies people who are predisposed to either CVD or diabetes. While the initial aim to use the metabolic syndrome to improve risk prediction of CHD has been disappointing, the metabolic syndrome (number of metabolic abnormalities) may still be a useful concept. It may serve as a simple clinical approach to identifying patients at high risk of both diabetes and CVD who may reduce their risk by lifestyle intervention such as weight reduction and improved physical activity.

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Conflict of interest

The author declared no financial interests.

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