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Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes

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Abstract *Aims/hypothesis:* We investigated the prognostic implication of metabolic syndrome according to modified National Cholesterol Education Program criteria and the implication of individual features of metabolic syndrome on cardiovascular disease (CVD) and CHD in a 5-year community-based study of people with newly diagnosed type 2 diabetes. *Methods:* We entered 562 participants, aged 30–74 years, into a cross-sectional analysis and 428 participants (comprising those who were CVD-free at study entry) into a prospective analysis. In both analyses, the association of metabolic syndrome features with CVD/CHD was studied. Binary logistic regression, a Cox regression model and Fisher's exact test were used for statistical analyses. *Results:* At diagnosis of type 2 diabetes, metabolic syndrome was independently associated with CVD (odds ratio [OR] 2.54; p=0.006) and CHD (OR 4.06; p=0.002). In the 5-year follow-up, metabolic syndrome at baseline was an independent predictor of incident CVD (hazard ratio [HR] 2.05; p=0.019). An increase in the number of individual features of the metabolic syndrome present at the time of diagnosis of type 2 diabetes was associated with a linear increase in incident CVD risk (trend p=0.044) with an almost five-fold increase when all five features were present, compared with hyperglycaemia alone (HR 4.76; p=0.042). Increasing age (HR 1.07; p<0.001), female sex (HR 0.62; p=0.032), total cholesterol (HR 1.43; p=0.01) and lipid-lowering therapy (HR 0.32; p<0.001) were also independent predictors of risk. *Conclusions/interpretation:* Metabolic syndrome at baseline is associated with an increased risk of incident CVD in the 5 years following diagnosis of type 2 diabetes. CVD-free survival rates declined incrementally as the presence of metabolic syndrome features increased. Thus, identifying the features of metabolic syndrome at diagnosis of type 2 diabetes is potentially a useful prognostic tool for identifying individuals at increased risk of CVD.

Keywords Cardiovascular disease · Cardiovascular risk · Coronary heart disease · Metabolic syndrome · Type 2 diabetes

Abbreviations ATP III: Adult Treatment Panel III · CVD: cardiovascular disease · HR: hazard ratio · NCEP: National Cholesterol Education Program · NHANES: National Health and Nutrition Exam Survey · OR: odds ratio · UKPDS: UK Prospective Diabetes Study · WOSCOPS: West of Scotland Prevention Study

Introduction

The metabolic syndrome, a concurrence of several cardiovascular risk factors (obesity and its central distribution, increased plasma glucose, increased plasma triglycerides, decreased HDL cholesterol and increased blood pressure) has become a subject of great interest because of its association with the development of type 2 diabetes and atherosclerotic cardiovascular disease (CVD). Two related but slightly differing definitions of metabolic syndrome, which can be used in people with diabetes, have been formulated by expert groups: by the World Health Organization Consultation in 1999 [1] and by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2001 [2]. The European Group for Study of Insulin Resistance definition [3] was developed for use in people without diabetes. In 2005, the International Diabetes Federation consensus definition (available at http://www.idf.org/webdata/

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docs/IDF_Metasyndrome_definition.pdf [Accessed 8 August 2005]) was released. It differs from the NCEP definition in that it has lower thresholds for waist circumference and fasting glucose. In non-diabetic populations, metabolic syndrome has been shown to be associated with an increased risk of major coronary events and cardiovascular mortality [4–8].

The NCEP ATP III provides a definition of the metabolic syndrome that is pragmatic, applicable to routine clinical practice and uses variables that are easily measurable. In the West of Scotland Prevention Study (WOSCOPS),the presence of metabolic syndrome according to modified NCEP-criteria increased the risk of a CHD event and predicted CHD events in a multivariate model incorporating conventional risk factors [9]. Men with four or five features of the syndrome had a 3.7-fold increase in risk of CHD and a 24.5-fold increase in risk of diabetes compared with men who had none of the features.

Alexander et al. [10] described the association between NCEP metabolic syndrome and the prevalence of CHD using cross-sectional data drawn from participants aged over 50 years in the National Health and Nutrition Exam Survey III (NHANES III). They showed that the prevalence of metabolic syndrome in diabetes was very high and that the prevalence of CHD markedly increased in the presence of metabolic syndrome. Their study also demonstrated that participants with diabetes and without metabolic syndrome have a similar prevalence of CHD to those with neither and that participants with both diabetes and metabolic syndrome had the highest prevalence of CHD. However, the impact of these metabolic syndrome features on cardiovascular risk in people with diabetes has not been demonstrated within the setting of a prospective study. For informative comparisons to be made, it would be desirable to have results of studies in which cross-sectional and prospective data are available in people with diabetes.

We investigated the association of the presence of metabolic syndrome according to the modified NCEP definition, and its individual features on CVD and CHD both in a cross-sectional analysis and in a prospective, 5-year community-based study of people with newly diagnosed type 2 diabetes.

Subjects and methods

Subjects

The members of the study cohort were drawn from the Poole Diabetes Study; a community-based prospective study of people with newly diagnosed type 2 diabetes that has been previously described [11, 12]. In brief, 24 general practices whose registered patients live within the Poole Hospital catchment area participated in the Poole Diabetes Study. The background population consisted of all the patients, 186 889, registered with the 24 primary-care practices in the Poole area and representing 78% of the hospital's total catchment population. Between 1 May 1996 and 30 June 1998, a surveillance programme identified 571 cases of type 2 diabetes in the population aged between 30 and 74 years at diagnosis. Nine (1.6%) were unable to participate. Hence, 562 (332 male, 230 female) individuals entered the cross-sectional analysis, and after exclusion of those who had pre-existing CVD (n=112) or were registered outside the Dorset Health Authority during the course of the study (n=22), the remaining 428 (241 male, 187 female) participants were entered into the prospective analysis.

Study design

Metabolic syndrome was identified largely according to NCEP criteria (triglycerides ≥1.7 mmol/l, HDL cholesterol [men<1.03 mmol/l; women<1.29 mmol/l], blood pressure ≥135/≥85 mmHg, and fasting glucose ≥6.1 mmol/l), with the exception of waist circumference, where an equivalent BMI value was used. The BMI cut-off values were: men: >28.8 kg/m^2 (based on values used in the WOSCOPS [9]); women: >26.7 kg/m^2, as in the Women's Health Initiative Study [13]. People on antihypertensive drug therapy were included in the category with raised blood pressure, as recommended in the NCEP definition [2]. The presence of more than two of the five criteria defined the presence of the metabolic syndrome.

HbA_1c was measured using HPLC. Fasting serum total cholesterol and HDL cholesterol and triglycerides were measured at baseline using standard laboratory methods and LDL cholesterol was calculated using Friedwald's equation when triglycerides were <4.5 mmol/l. Blood pressure was measured twice in the semi-recumbent position in the non-dominant arm with a mercury sphygmomanometer and the average reading noted. An ECG was recorded and Minnesota-coded [14]. Height and weight were measured, and the BMI calculated. Smokers were defined as those who had smoked during the previous 12 months. Hospital and primary-care notes were reviewed to ascertain pre-existing cardiovascular illness. Pre-existing illness was defined as evidence of a cardiovascular illness during the note-review process and/or interview, or the presence of probable myocardial infarction on ECG based on the Minnesota code. The study closed on 31 July 2001 with a mean follow-up of 4.2 (SD±0.6) years. Coronary (ICD9 codes 410–414) and cardiovascular (ICD9 codes 390–459) mortality and morbidity during the study were determined in participants using death certificates, post-mortems, and hospital and primary-care records.

Incident cardiovascular and incident coronary events were recorded and analysed independently, and subsequent events were excluded from the data analysis. Pre-defined endpoints were used to identify cardiovascular events both at baseline and during the course of the study (Table 1). Treatment changes from diagnosis were collected from data held on the primary-care prescribing databases.

A cross-sectional analysis was performed at the time of diagnosis to investigate the prevalence of metabolic syndrome and its individual features. The prevalence of CVD and CHD in those with and without metabolic syndrome was calculated and the odds ratio (OR) for the presence of metabolic syndrome for each of these outcomes determined after adjustment

Table 1 Definition of cardiovascular endpoints used in the study protocol

Coronary heart disease	
Myocardial infarction	In-patient diagnosis *or* ICD9 code on death certificate *or* post-mortem evidence
Angina	Hospital admission with unstable angina *or* symptoms + positive treadmill test *or* symptoms + abnormal coronary angiography
Cerebrovascular disease	
Stroke	In-patient diagnosis + persistent neurological deficit *or* persistent neurological deficit + positive brain imaging
Transient ischaemic attack	In-patient diagnosis + motor weakness resolving within 24 h *or* episodic, altered level of consciousness + CT evidence of ischaemia
Heart failure	In-patient diagnosis *or* symptoms + decreased left ventricular function on echocardiography *or* symptoms + evidence of pulmonary congestion on chest X-ray
Peripheral vascular disease	Claudication pain or ulceration or absent foot pulses + *either* ankle/brachial pulse index ≤0.5 *or* monophasic waveform on pulse wave Doppler

for age, sex, smoking status and total cholesterol. Unadjusted ORs in those aged above 50 years were also determined to allow direct comparison with the results from the NHANES III dataset [10].

In the prospective analysis, the hazard ratio (HR) for the presence of metabolic syndrome after adjustment for age, sex, smoking status, total cholesterol, antiplatelet therapy, antihypertensive therapy and lipid-lowering therapy was determined both for incident CVD and for CHD. A further analysis based on the number of features of the metabolic syndrome and incident CVD and CHD outcomes was performed. Therapy-related data were treated as categorical variables and adjusted for in those individuals who remained event-free during the study, or when the therapeutic intervention was instituted prior to the CVD or CHD event but not consequent to it.

The East Dorset Local Research Ethics Committee approved the study protocol and informed consent was obtained from all the participants.

Statistical methods

All data were analysed using SPSS version 12.0. Summary statistics are presented as means (SE) for continuous measures or median (interquartile range) for measures with a skewed distribution and frequency (percentage) for discrete measures. Cross-sectional ORs were analysed using binary logistic regression and in the prospective analysis, a Cox regression model was employed. Fisher's exact test was used to compare discrete measures and proportions.

Results

Baseline characteristics The baseline characteristics of participants in the cross-sectional and prospective analyses are summarised in Table 2. The prevalence of the NCEP-defined metabolic syndrome in people with newly diagnosed diabetes was very high in both studies (82.9% in the cross-sectional analysis and 82.5% in the prospective). There was a greater prevalence of metabolic syndrome in women than in men at the time of diagnosis of type 2 diabetes (89.9 vs 78.2% [$p<0.001$] in the cross-sectional study and 90.3 vs 76.3% [$p<0.001$] in the prospective study). Participants with metabolic syndrome were comparatively younger than those without metabolic syndrome (at the time of diagnosis of type 2 diabetes) both in the cross-sectional and in the prospective analyses (58.9 vs 62.8 [$p=0.001$] and 57.8 vs 62.5 [$p=0.01$], respectively).

Results of the cross-sectional study

The overall prevalence of CVD at diagnosis of type 2 diabetes was 20.1% and of CHD was 14.2%. After adjusting for age, sex, total cholesterol and smoking status, the presence of metabolic syndrome was an independent predictor of CVD (OR 2.54 [95% CI 1.31–4.93; $p=0.006$]) and CHD (OR 4.06 [95% CI 1.66–9.92; $p=0.002$]). In those aged above 50 years and prior to adjustment for age, sex, total cholesterol and smoking status, the presence of metabolic syndrome was still strongly associated with both CVD (OR 2.07 [95% CI 1.04–4.2; $p=0.026$]) and CHD (OR 3.02 [95% CI 1.21–8.04; $p=0.01$]).

Results of the prospective study

Forty (9.3%) participants died during the course of the study (CVD was the underlying cause in 18 [45%]). Ninety-eight incident cardiovascular events occurred during the course of the study (angina 37; fatal/non-fatal myocardial infarction 11; cerebrovascular disease 21 [strokes nine; transient ischaemic attacks 12]; peripheral vascular disease 17; and heart failure 12). Sixty incident CHD events occurred (angina 47; and myocardial infarction 13). Participants suffering a non-CHD (as defined in the study protocol) cardiovascular event followed by an incident CHD event explain the difference in the number of angina and myocardial infarction events in CVD and CHD as these two study endpoints were analysed independently.

In relation to therapeutic interventions in study participants initiated prior to an incident CVD event or who remained event-free, lipid-lowering therapy was 2.5 times

Table 2 Characteristics of the participants in the cross-sectional and prospective studies both with and without metabolic syndrome (MetS)

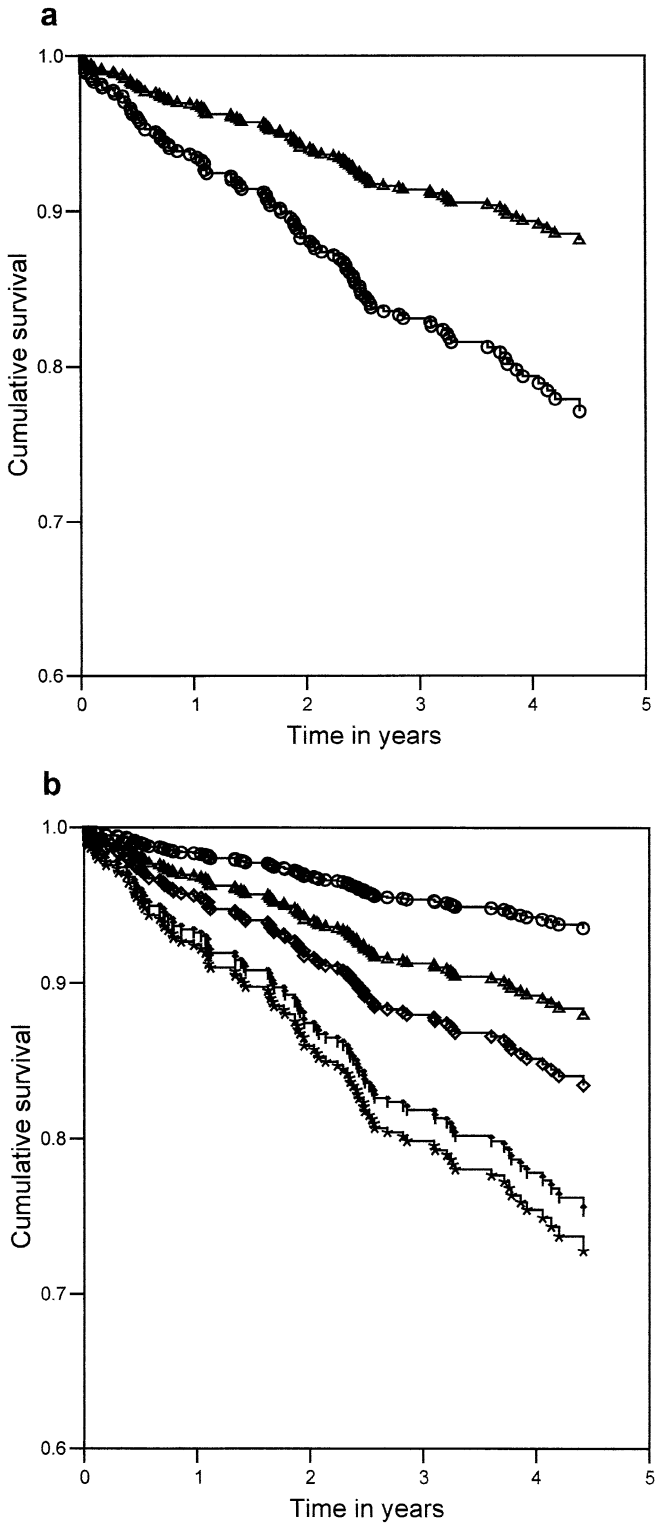
	Cross-sectional analysis		Prospective analysis	
	MetS, *n*=462 (82.9%)	No MetS, *n*=95 (17.1%)	MetS, *n*=353 (82.5%)	No MetS, *n*=75 (17.5%)
Age (years)	58.9 (0.5)	62.8 (1.0)	57.8 (0.6)	62.5 (1.2)
Males (%)	258 (55.8)	72 (75.8)	184 (52.1)	57 (76.0)
Females (%)	204 (44.2)	23 (24.2)	169 (47.8)	18 (24.0)
Systolic blood pressure (mmHg)	142.5 (1.0)	134.0 (2.0)	143.0 (1.1)	134.7 (2.5)
Diastolic blood pressure (mmHg)	81.5 (0.6)	77.4 (1.2)	82.2 (0.6)	77.6 (1.5)
Total cholesterol (mmol/l)	5.9 (0.1)	5.5 (0.1)	5.9 (0.1)	5.5 (0.1)
Triglycerides (mmol/l)	2.3 (1.3)†	1.3 (0.5)†	2.2 (1.3)†	1.3 (0.5)†
HDL cholesterol (mmol/l)	1.11 (0.02)	1.31 (0.03)	1.13 (0.01)	1.34 (0.04)
LDL cholesterol (mmol/l)*	3.7 (0.1)	3.4 (0.1)	3.7 (0.1)	3.4 (0.1)
Total cholesterol : HDL ratio	5.7 (0.1)	4.3 (0.1)	5.7 (0.1)	4.2 (0.1)
HbA_1c (%) at diagnosis	10.6 (0.1)	10.3 (0.3)	10.6 (0.1)	10.1 (0.3)
BMI at diagnosis (kg/m^2)	32.2 (0.3)	26.3 (0.4)	32.6 (0.4)	25.9 (0.4)
Active smokers (%)	78 (16.9)	23 (24.2)	77 (21.8)	23 (24.2)
Antihypertensives at diagnosis (%)	211 (45.7)	27 (28.4)	122 (34.5)	14 (14.7)

Values are means (±SE) or *n* (%) unless otherwise stated
†Median (interquartile range)
*Not calculated in those individuals with a triglyceride level >4.5 mmol/l

Table 3 Results of the cross-sectional and prospective studies

	Metabolic syndrome	No metabolic syndrome
Cross-sectional study		
Prevalence of CVD	99/465 (21.3%)	13/97 (13.4%)
Prevalence of CHD	70/369 (19.0%)	6/83 (7.2%)
OR for CVD	1.75 (95% CI 0.94–3.27; *p*=0.080)	
OR for CHD	2.82 (95% CI 1.19 6.70; *p*=0.018)	
OR for CVD*	2.54 (95% CI 1.31–4.93; *p*=0.006)	
OR for CHD*	4.06 (95% CI 1.66–9.92; *p*=0.002)	
Prospective study		
CVD events/1,000 patient-year follow-up	69.3	54.6
CHD events/1,000 patient-year follow-up	38.9	34.2
HR for CVD	1.27 (95% CI 0.72–2.23; *p*=0.410)	
HR for CHD	1.14 (95% CI 0.56–2.31; *p*=0.720)	
HR for CVD*	2.00 (95% CI 1.10–3.62; *p*=0.022)	
HR for CHD*	1.86 (95% CI 0.88–3.91; *p*=0.103)	
HR for CVD†	2.05 (95% CI 1.13–3.74; *p*=0.019)	
HR for CHD†	1.94 (95% CI 0.92–4.09; *p*=0.070)	

OR Odds ratio (metabolic syndrome vs no metabolic syndrome)
HR Hazard ratio (metabolic syndrome vs no metabolic syndrome)
*After adjustment for age, sex, total cholesterol, smoking status
†After adjustment for age, sex, total cholesterol, smoking status, lipid-lowering, antiplatelet and antihypertensive therapy



◀ **Fig. 1** Effect of metabolic syndrome on cardiovascular disease-free survival in patients with newly diagnosed type 2 diabetes. **a** Survival curves after adjustment for age, sex, smoking status, total cholesterol, antiplatelet therapy, antihypertensive therapy, and lipid-lowering therapy (metabolic syndrome, *circles*; no metabolic syndrome, *triangles*). Hazard ratio 2.05; p=0.019. **b** Survival curves for number of metabolic syndrome features present after adjustment for other factors (one feature, *circles*; two, *triangles*; three, *diamonds*; four, *arrows*; five, *stars*). p for trend=0.044. Since all study participants have type 2 diabetes, the minimum number of features present is one. Incremental hazard ratios (p value) for two, three, four and five features of the metabolic syndrome vs one feature (diabetes) alone: 1.93 (0.39), 2.71 (0.18), 4.23 (0.56), 4.76 (0.042)

more common in individuals with metabolic syndrome as compared with those without (29 vs 11.5%; p=0.004), antihypertensive use 1.5 times as common (51.7 vs 32.8%; p=0.01) and antiplatelet therapy did not differ between the two groups (11.5 vs 14.8%; p=0.515).

Unadjusted incident CVD rates were 69.3/1,000 patient-year follow-up in those with metabolic syndrome and 54.6/1,000 in those without metabolic syndrome. For men, the crude figures were 81.6/1,000 and 63.2/1,000, respectively (HR 1.29; p=0.43), and for women, 56.1/1,000 and 30.1/1,000, respectively (HR 1.87; p=0.39).

Prior to adjustment for other factors in the Cox regression model, the presence of metabolic syndrome did not predict incident CVD events (HR 1.27 [95% CI 0.72–2.23; p=0.41]) or incident CHD events (HR 1.14 [95% CI 0.56–2.31; p=0.72]). However, after adjustment for age, sex, smoking status, total cholesterol, antiplatelet therapy, antihypertensive therapy and lipid-lowering therapy, metabolic syndrome was an independent predictor of incident CVD (HR 2.05 [95% CI 1.13–3.74; p=0.019]). Increasing age (HR 1.07; p<0.001), female sex (HR 0.62; p=0.032), total cholesterol (HR 1.43; p=0.01) and lipid-lowering therapy (HR 0.32; p<0.001) were the other significant independent predictors of risk. After adjustment for the same factors, the HR for CHD (1.94 [95% CI 0.92–4.09; p=0.07]) showed the same trend but failed to reach conventional statistical significance. An increase in the number of features of metabolic syndrome was associated with a linear increase in the risk of an incident CVD event (p for trend=0.044). There was nearly a fivefold increase in the level of risk for those possessing all five features of the metabolic syndrome when compared with individuals with just diabetes (HR 4.76 [95% CI 1.10–21.03; p=0.042]).

Table 3 details the results of the cross-sectional and prospective studies and Fig. 1 shows the adjusted survival curve over time for incremental increases in numbers of features of metabolic syndrome identified at baseline.

Discussion

The novel results of our study demonstrate that on the basis of modified NCEP criteria, metabolic syndrome is associated with an increased risk of CVD events in the first 5 years following diagnosis of type 2 diabetes. Survival was incrementally and progressively worse in patients with increasing numbers of features of the syndrome (Fig. 1). This finding clearly demonstrates the continuum of risk represented by increasing features of the metabolic syndrome.

Our cross-sectional data confirm the findings of Alexander et al. [10] from the NHANES dataset, despite differences in study design with respect to age cut-offs and diagnostic criteria for CHD. The prevalence of metabolic syndrome in

our cohort with newly diagnosed type 2 diabetes was 82.9% as compared with 86% in the diabetic subset from the NHANES III dataset. In the NHANES subgroup, it is likely that diabetes would have been present for markedly varying lengths of time, prior to identification of metabolic syndrome features. In our study, the ORs for metabolic syndrome and CHD in the diabetic population aged over 50 were increased by a factor of three, which is similar to the level of risk seen in the diabetic subset in NHANES III. Adjusting for age and sex, the presence of metabolic syndrome conferred a 2.5-fold increase in the risk of CVD at diagnosis of type 2 diabetes, and a fourfold increase in the risk of CHD. The results of the cross-sectional study demonstrate that people with newly diagnosed type 2 diabetes who additionally have metabolic syndrome tend to be younger, and that at diagnosis, a greater proportion of women than men have metabolic syndrome. The increased prevalence of metabolic syndrome in women with newly diagnosed type 2 diabetes related mainly to the greater proportion exceeding the BMI and HDL cholesterol thresholds of the metabolic syndrome criteria. This could reflect sex differences relating to the impact of obesity on glucose homeostasis, lipid sub-fractions and atherosclerosis [15, 16] and requires further study in a larger cohort.

As mentioned by Alexander et al. [10], a cross-sectional analysis is subject to survival bias and causality cannot be inferred. The prospective study was designed to address this issue in relation to people with newly diagnosed diabetes. The results of this study lend further weight to evidence from the UK Prospective Diabetes Study (UKPDS) [17] that hyperglycaemia per se may have only a relatively small contribution to CVD in type 2 diabetes when compared with other features of metabolic syndrome. Clearly, metabolic syndrome remained a strong predictor of CVD after adjustment for age, sex, cigarette smoking, total cholesterol and therapy. However, there was an attenuation of the HRs when results from the prospective analyses were compared with the cross-sectional study. This effect was more marked for risk of CHD than for risk of CVD in the prospective study, where the prediction of CHD events by metabolic syndrome failed to achieve conventional levels of statistical significance. The relatively small number of events is one possible explanation for this finding. Alternative explanations for this finding may be a 'survivor' effect and a differential absolute benefit of lipid-lowering therapy on risk of CHD in people with and without metabolic syndrome as seen in a subgroup analysis of the Scandinavian Simvastatin Survival Study [18].

Unlike results from the cross-sectional study, in the prospective follow-up, the unadjusted risk of CHD was not significantly increased. This finding is probably attributable to the considerably greater usage of lipid-lowering therapy in the metabolic syndrome group after diagnosis of type 2 diabetes (as occurred in our study) and may be particularly relevant and important data from the public health standpoint as it strengthens the case for achieving recommended treatment goals in this high-risk population.

Importantly, we also showed a clear incremental increase in CVD risk with increasing features of the metabolic syndrome in people with newly diagnosed type 2 diabetes. As each feature of the metabolic syndrome criteria is a proven cardiovascular risk factor [19, 20], these results show clearly that increasing numbers of metabolic syndrome features equate to increasing risk. This finding could offer a simple and pragmatic clinical addition to the multi-factorial risk assessment methods as used in the UK and elsewhere in Europe [21–24]. We have previously published the sensitivity and specificity of the UKPDS-derived, 15% 10-year CHD risk threshold for incident CVD in this study population [11]. Interestingly, the use of a combination of the presence of both metabolic syndrome and a 15% 10-year CHD risk threshold results in a small, statistically non-significant reduction in sensitivity (0.80 [0.72–0.86) vs 0.90 (0.82–0.95]) and a significant increase in specificity (0.45 [0.43–0.47] vs 0.30 [0.25–0.36]) for new-onset CVD.

Our study of patients with newly diagnosed diabetes took place in a defined community and the results reflect usual clinical practice in both hospital and primary care. A limitation of the study is use of a BMI equivalent instead of waist circumference. However, we believe that the presence of glucose dysregulation would mean that participant body weight is likely to correlate closely with central adiposity and not reflect increased muscle mass. Furthermore, patients with diabetes may find a weight and height measurement less intrusive than waist circumference measurement and waist circumference is more likely to be subject to measurement error than BMI. Conversely, accurate waist circumference measurement may well be a useful measure for patient self-care and is, in itself, an area of physician–patient interaction that needs to be explored.

In conclusion, we have shown that using modified NCEP criteria, metabolic syndrome is associated with an increased risk of incident CVD in the first 5 years following diagnosis of type 2 diabetes. Survival incrementally and progressively worsens with the number of features of metabolic syndrome that are present. In such individuals, a therapy geared to reversing the number of features of metabolic syndrome present could prove useful.

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