Impact of the Metabolic Syndrome on Macrovascular and Microvascular Outcomes in Type 2 Diabetes Mellitus

United Kingdom Prospective Diabetes Study 78

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Background—The metabolic syndrome (MetS) and type 2 diabetes mellitus are both associated with increased cardiovascular disease risk. We examined retrospectively the degree to which the presence of MetS in individuals with type 2 diabetes mellitus increased their risk of diabetic complications using United Kingdom Prospective Diabetes Study data.

Methods and Results—Of 5102 United Kingdom Prospective Diabetes Study patients recruited with newly diagnosed type 2 diabetes mellitus and followed up for a median of 10.3 years, 4542 had the requisite data for these analyses. After a 3-month dietary run-in, MetS, diagnosed with National Cholesterol Education Program Adult Treatment Panel III, World Health Organization, International Diabetes Federation, or European Group for the Study of Insulin Resistance criteria, was present in 61%, 38%, 54%, and 24%, respectively. Those with MetS by these criteria had increased cardiovascular disease risks relative to those without MetS of 1.33 (95% confidence interval 1.14 to 1.54), 1.45 (95% confidence interval 1.26 to 1.66), 1.23 (95% confidence interval 1.07 to 1.42), and 1.31 (95% confidence interval 1.10 to 1.57), respectively, but similar risks for microvascular complications. The positive predictive value of MetS for cardiovascular disease events, however, was only 18%, 13%, 18%, and 39%, respectively.

Conclusions—MetS, diagnosed by Adult Treatment Panel III, World Health Organization, or International Diabetes Federation criteria, identifies diabetic patients at greater risk of macrovascular but not microvascular complications. Poor discrimination by MetS with respect to cardiovascular disease outcomes means that it is of limited clinical value for cardiovascular disease risk stratification in type 2 diabetes mellitus. **(*Circulation*. 2007;116:2119-2126.)**

Key Words: diabetes mellitus ■ cardiovascular diseases ■ risk factors ■ metabolic syndrome X

The metabolic syndrome (MetS) describes a clustering of cardiovascular risk factors in individuals that may greatly increase their risk of vascular and metabolic disease.[1–3] Although different diagnostic criteria have been proposed by the National Cholesterol Education Program's Adult Treatment Panel III (ATP-III),[4,5] the World Health Organization (WHO),[6] the International Diabetes Federation (IDF),[7] and the European Group for the Study of Insulin Resistance (EGIR),[8] all of these definitions include measures of glucose intolerance, hypertension, obesity, hypertriglyceridemia, and decreased high-density lipoprotein (HDL) cholesterol as part of the syndrome. The value of MetS is primarily its promise to identify asymptomatic individuals thought to be at increased risk of cardiovascular disease (CVD)[9] for whom increased clinical surveillance and earlier institution of risk-modifying therapies might be appropriate. Its utility, however, is being increasingly questioned.[10,11]

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Glucose intolerance is a component of all current MetS definitions, but it remains a matter for debate whether people with established type 2 diabetes mellitus (T2DM) should be included within this criterion. T2DM is a well-established CVD risk factor thought by some authors to be a coronary heart disease risk equivalent.[11–13] Because the diagnosis of T2DM should prompt detailed clinical evaluation and treatment of all CVD risk factors, including those that are MetS components, the degree to which identifying MetS in T2DM patients might be helpful in clinical practice remains uncertain. However, if the presence of MetS in T2DM patients does identify those at greatly increased risk of diabetic complications, even more stringent treatment goals for blood pressure and lipids may be indicated for these patients. We have used United Kingdom Prospective Diabetes Study (UKPDS) data to

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Table 1. Clinical Characteristics of UKPDS Patients After Their Dietary Run-In Period, Classified by the Presence or Absence of MetS, Defined According to ATP-III, WHO, IDF, or EGIR Criteria

	ATP-III			WHO			IDF		
	No MetS	MetS	P‡	No MetS	MetS	P‡	No MetS	MetS	P‡
No. of patients	1784	2770		2923	1824		2086	2462	
Age at diagnosis, y	52 (9)	53 (9)	0.0066	52 (9)	52 (9)	0.36	52 (9)	53 (9)	0.014
Sex, % male	76	47	<0.0001	66	49	<0.0001	72	48	<0.0001
Ethnicity, %			<0.0001			<0.0001			<0.0001
White	78	84		80	85		80	84	
Afro-Caribbean	10	6		8	5		9	5	
Indian Asian	11	9		11	8		10	10	
Other	1	1		1	1		1	1	
Smoking status, %			0.64			0.79			0.014
Never	35	36		35	36		34	37	
Ex-smoker	35	34		34	34		34	35	
Current	30	30		31	30		32	29	
Weight, kg	72 (12)	81 (17)	<0.0001	73 (12)	85 (18)	<0.0001	70 (12)	83 (16)	<0.0001
Hemoglobin A_{1c}, %*	6.7 (5.8, 8.2)	7.0 (6.1, 8.3)	<0.0001	7.0 (6.0, 8.4)	7.2 (6.1, 8.8)	<0.0001	7.0 (6.0, 8.7)	7.1 (6.1, 8.5)	0.54
Plasma insulin, pmol/L†	70 (40, 121)	103 (61, 175)	<0.0001	75 (45, 133)	113 (67, 191)	<0.0001	71 (41, 123)	107 (64, 180)	<0.0001
HOMA %S*	67 (48, 94)	49 (36, 69)	<0.0001	60 (42, 85)	41 (30, 57)	<0.0001	64 (47, 92)	43 (32, 62)	<0.0001
HOMA %B*	54 (31, 85)	54 (34, 80)	0.71	53 (32, 79)	62 (39, 91)	<0.0001	49 (29, 72)	61 (40, 91)	<0.0001
Total cholesterol, mmol/L	5.2 (1.0)	5.5 (1.2)	<0.0001	5.3 (1.1)	5.7 (1.2)	<0.0001	5.3 (1.1)	5.6 (1.2)	<0.0001
LDL cholesterol, mmol/L	3.3 (0.94)	3.6 (1.1)	<0.0001	3.4 (1.0)	3.7 (1.1)	<0.0001	3.4 (1.0)	3.6 (1.1)	<0.0001

HOMA %S indicates insulin sensitivity by homeostasis model assessment; HOMA %B, β-cell function as estimated by homeostasis model assessment calculator. Values are mean (SD), proportion (%), *median (IQR), or †geometric mean (1-SD interval).

‡Wilcoxon signed rank test for continuous variables and χ^2 test for categorical variables.

assess the impact of MetS on future risk of developing both macrovascular and microvascular clinical outcomes in patients with newly diagnosed T2DM.

Methods

Study Participants

The UKPDS was a clinical trial designed to evaluate the effects of more intensive blood glucose and/or tighter blood pressure control on the incidence of complications in patients with T2DM.[14,15] It received ethics committee approval in all 23 participating clinical centers and conformed to the guidelines of the Declarations of Helsinki. Briefly, 5102 of 7616 patients referred with newly diagnosed T2DM entered the study between 1977 and 1991 and provided informed consent. They were 25 to 65 years of age and had fasting plasma glucose (FPG) levels >6.0 mmol/L on 2 occasions after T2DM was diagnosed. On self-reported ethnicity, 81% were white Caucasian, 10% Indian Asian, and 9% Afro-Caribbean. After a 3- to 4-month dietary run-in, therapies for glycemic control were allocated randomly according to the UKPDS protocol. A subset of hypertensive participants (n=1148) were subsequently also allocated randomly to therapies for blood pressure control.[16] All patients were followed up quarterly in UKPDS clinics for up to 20 years (median 10.3 years).

Retrospective analyses were performed on 4542 individuals who had the requisite data for MetS components available after their dietary run-in. UKPDS biochemical and clinical measurement methods have been described previously.[14,17]

MetS Definitions

Four definitions of MetS were used in the present analysis: ATP-III, WHO, IDF, and EGIR. ATP-III[4] requires the presence of any 3 of 5 criteria: (1) FPG >6.0 mmol/L; (2) waist circumference >102 cm (men) or >88 cm (women); (3) triglycerides ≥1.7 mmol/L; (4) HDL cholesterol <1.0 mmol/L (men) or <1.3 mmol/L (women); and (5) blood pressure ≥130/85 mm Hg or current use of antihypertensive therapy (ie, known hypertension). WHO[6] requires either known diabetes mellitus, FPG >6.0 mmol/L, or insulin resistance in the highest quartile for the population, in addition to at least 2 of the following: (1) waist-hip-ratio >0.9 (men) or >0.85 (women) or body mass index >30 kg/m^2; (2) triglycerides ≥1.7 mmol/L; (3) HDL cholesterol <0.9 mmol/L (men) or <1.0 mmol/L (women), (4) blood pressure ≥160/90 mm Hg or known hypertension; or (5) urinary albumin >50 mg/L, albumin-to-creatinine ratio ≥20 mg/g, or urinary albumin excretion rate ≥20 μg/min. IDF[7] requires central obesity (defined by waist circumference >94 cm in white Caucasian or Afro-Caribbean men, >90 cm in Indian Asian men, or >80 cm in women), in addition to at least 2 of the following: (1) known diabetes mellitus or FPG >5.6 mmol/L; (2) triglycerides ≥1.7mmol/L; (3) HDL cholesterol <0.9 mmol/L (men) or <1.0 mmol/L (women); or (4) blood pressure ≥135/85 mm Hg or known hypertension. EGIR[8] requires patients to have insulin resistance (defined by lowest quartile for homeostasis model assessment of insulin sensitivity[18] in the general population), in addition to at least 2 of the following: (1) known diabetes mellitus or FPG >6.0 mmol/L; (2) waist circumference >94 cm (men) or >80 cm (women); (3) triglycerides >2.0 mmol/L; (4) HDL cholesterol <1.0 mmol/L; or (5) blood pressure ≥140/90 mm Hg or known hypertension. We derived the lowest homeostasis model assessment of insulin sensitivity quartile (77.8%) from the population of nondiabetic individuals recruited to determine UKPDS reference ranges.[17]

End Points

Four composite outcomes were examined: (1) CVD, defined as the first to occur of sudden death, fatal or nonfatal myocardial infarction (MI), or fatal or nonfatal stroke; (2) MI, defined as the first to occur of sudden death or fatal or nonfatal MI; (3) stroke, defined as the first

Table 1. Continued.

EGIR		
No MetS	MetS	P‡
2953	925	
53 (9)	52 (9)	<0.0001
62	49	<0.0001
		0.024
82	84	
8	5	
9	11	
1	1	
		0.10
35	37	
34	35	
31	28	
75 (14)	87 (18)	<0.0001
6.9 (5.9, 8.1)	7.2 (6.1, 9.6)	<0.0001
76 (46, 115)	175 (130, 235)	<0.0001
61 (47, 84)	29 (23, 32)	<0.0001
51 (31, 74)	75 (49, 106)	<0.0001
5.3 (1.1)	5.6 (1.2)	<0.0001
3.5 (1.0)	3.6 (1.1)	0.0027

to occur of fatal or nonfatal stroke; and (4) microvascular complications, defined as the first to occur of retinopathy requiring photocoagulation, vitreous hemorrhage, or fatal or nonfatal renal failure.

Statistical Analysis

Statistical analyses were performed with SAS versions 8.2 and 9.1.3 (SAS Institute Inc, Cary, NC). Data are reported as mean (SD), geometric mean (1-SD interval), median (interquartile range), or percentages. The homeostasis model assessment calculator (available at http://www.dtu.ox.ac.uk/homa) was used to estimate β-cell function and insulin sensitivity.[18] The UKPDS risk engine[19,20] was used to estimate 10-year CVD risks. Comparisons between groups used 2-sample t tests or the Wilcoxon signed rank test for nonnormally distributed data. Categorical comparisons used the χ^2 test or Fisher's exact test. The Cochran-Armitage test for trend, the κ-test for agreement, and the Breslow-Day test for homogeneity of odds ratios were used as appropriate. Kaplan-Meier survival analysis of time to event with the log-rank test was used for comparison of groups with and without MetS. Proportional hazards models were used to derive hazard ratios as estimates of relative risk, which are quoted with 95% confidence intervals. Absolute risks are quoted as events per 1000 person-years. To allow for multiple testing, only probability values <0.01 were considered significant. Discrimination with respect to CVD for the 4 different definitions of MetS was compared by calculating CVD specificity, sensitivity, positive predictive value, and likelihood ratios.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Table 1 shows the clinical characteristics of the 4542 UKPDS patients studied here, classified by the presence or absence of MetS according to ATP-III, WHO, IDF, and EGIR criteria. The prevalence of MetS was 60.8%, 38.4%, 54.1%, and 23.8%, respectively. Patients with MetS were more likely to be female; to have higher hemoglobin A_{1c}, total cholesterol, and LDL cholesterol; and to have lower homeostasis model assessment of insulin sensitivity. Among 3367 patients with baseline data available to evaluate all 4 MetS definitions, there were 480 (14%) with MetS in all cases and 901 individuals (27%) free of the syndrome by all definitions, and there were 556 individuals (17%) with MetS by ATP-III, WHO, and IDF criteria. ATP-III and IDF definitions were concordant in 3366 cases (74%; 2041 with/with, 1325 without/without, 431 without/with, and 760 with/without, respectively; $\kappa=0.47$, $P<0.0001$).

Table 2 shows the values observed for individual MetS components according to the different definitions. Probability values for the comparison between those with and without MetS are given only for variables not included in a particular definition.

Over a median 10.3 years of follow-up, there were 773 CVD cases, 620 MI cases, 194 stroke cases, and 418 cases of microvascular complications. Individuals with MetS diagnosed by ATP-III, WHO, IDF, or EGIR exhibited a significantly increased risk compared with those without MetS for CVD, MI, and stroke, but MetS, however defined, was not associated with an increased risk for microvascular complications (Table 3). The ATP-III and WHO MetS criteria had less specificity but greater sensitivity than those for IDF and EGIR MetS (Table 4), but the positive predictive value was low and similar for all 4 definitions of MetS (18.2%, 20.4%, 17.7%, and 18.1%, respectively).

UKPDS risk engine calculations showed that patients with ATP-III MetS had higher median (interquartile range) 10-year CVD risk estimates than those without MetS (24.9% [16.5% to 35.0%] versus 18.8% [11.9% to 28.1%], $P<0.0001$) but with a very substantial overlap in 10-year CVD risk distributions for the 2 groups (Figure). Of those without ATP-III MetS, 47% had 10-year estimated CVD risks $\geq$20%, whereas 37% of those with ATP-III MetS had 10-year estimated CVD risks $<$20%.

Discussion

We have shown in the present study that individuals with newly diagnosed T2DM exhibit a high prevalence of MetS, whether defined by ATP-III, WHO, IDF, or, to a lesser degree, EGIR criteria. MetS, diagnosed by any of these definitions, identifies diabetic patients at higher risk of future macrovascular but not microvascular complications. MetS, however, is a poor discriminator of CVD outcomes in individual patients and as such is of limited clinical value for CVD risk stratification in T2DM.

Previous studies have demonstrated a high prevalence of MetS consistently in diabetic populations.[2,21–23] The present report extends these observations by evaluating 4 definitions of MetS simultaneously in the UKPDS cohort. In this population with newly diagnosed T2DM, we confirm the high prevalence of MetS, although this varies markedly according to the criteria used (ATP-III 60.8%, IDF 54.1%, WHO 38.4%, and EGIR 23.4%). The much smaller proportion detected by the EGIR criteria suggests that this definition may differ substantially from the other 3.

Table 2. Values Observed for MetS Components in UKPDS Patients After Their Dietary Run-In Period, Classified by the Presence or Absence of MetS, Defined According to ATP-III, WHO, IDF, or EGIR Criteria

	ATP-III			WHO		
	No MetS	MetS	*P*‡	No MetS	MetS	*P*‡
FPG, mmol/L*	7.6 (5.9, 10.3)	8.4 (7.2, 10.5)		8.0 (6.6, 10.4)	8.5 (7.2, 11.4)	
Blood pressure, mm Hg						
Systolic	128 (19)	140 (19)		129 (17)	144 (21)	
Diastolic	79 (10)	85 (10)		79 (9)	88 (11)	
Body mass index, kg/m^2	24.9 (3.3)	29.5 (5.6)	<0.0001	25.5 (3.6)	30.9 (5.9)	
Waist circumference, cm						
Male	92 (9)	101 (13)		93 (10)	105 (13)	<0.0001
Female	81 (10)	97 (14)		86 (12)	101 (13)	<0.0001
Waist/hip ratio						
Male	0.92 (0.056)	0.96 (0.060)	<0.0001	0.93 (0.054)	0.98 (0.061)	
Female	0.83 (0.067)	0.88 (0.073)	<0.0001	0.84 (0.067)	0.89 (0.071)	
HDL cholesterol, mmol/L	1.17 (0.25)	1.01 (0.22)		1.11 (0.24)	1.01 (0.24)	
Plasma triglycerides, mmol/L†	1.14 (0.78, 1.66)	1.84 (1.14, 2.98)		1.29 (0.83, 2.01)	1.99 (1.24, 3.20)	
Percentage of patients with each criterion						
Glycemia		83			100	
Obesity		40			36	
Dyslipidemia		65			53	
Hypertension		63			23	
Albuminuria		N/A			12	

Probability values are given only for those variables not included in any particular MetS definition.
Values are mean (SD), proportion (%), *median (IQR), or †geometric mean (1-SD interval).
‡Wilcoxon signed rank test for continuous variables and χ^2 test for categorical variables.

The prospective impact of MetS on incident vascular disease in patients with T2DM has been unclear to date because of conflicting results in previous studies addressing this question. In a study of 946 diabetic patients followed up for a mean of 4.5 years, Bonora et al[22] reported that WHO-defined MetS at baseline was associated independently with incident CVD. In another study of 750 patients (164 with diabetes) followed up over 2.3 years, ATP-III–defined MetS remained a significant determinant of future vascular events in both the diabetic and normoglycemic cohorts.[24] In contrast, the Casale Monferrato Study reported that WHO-defined MetS was not associated with 11-year all-cause or CVD mortality in a population-based cohort of 1565 patients with T2DM.[21] Furthermore, in an 8-year study of 1424 Japanese patients with T2DM in which both WHO and ATP-III definitions were evaluated, only WHO-defined MetS in female patients was related to incident CVD, which led the authors to suggest that the clinical utility of these definitions is limited in Asian diabetic patients.[23]

The present analysis provides an opportunity to address these conflicting observations by evaluating multiple definitions simultaneously in a large, well-characterized cohort with >50 000 person-years of follow-up. By ATP-III, WHO, IDF, and EGIR criteria, MetS at baseline emerged as a consistent independent risk factor for CVD, MI, and stroke but not for microvascular complications. Thus, these data suggest that MetS, whether defined by ATP-III, WHO, IDF, or EGIR criteria, can help identify diabetic patients at risk of future macrovascular but not microvascular disease.

In clinical diabetes care, the practical value of a concept such as MetS rests on its ability to characterize risk for individual patients. Currently, such risk estimation in patients with T2DM can be accomplished with the UKPDS risk engine, a diabetes-specific model that estimates CVD risk on the basis of continuous measures of conventional risk factors.[19] In the present analyses, there was considerable overlap in estimated 10-year CVD risks between patients with and without MetS. Indeed, 47% of those without ATP-III MetS had estimated 10-year CVD risks ≥20%, a threshold at which risk-modifying intervention is often recommended, and identification of MetS carried a low positive predictive value for CVD outcomes.

Several factors are likely to contribute to the poor discriminative capacity of MetS in this context. Because risk factors such as blood pressure, lipid levels, and blood glucose levels show continuous relationships with vascular disease, it is not surprising that dichotomized thresholds such as those used for MetS criteria should fail to capture fully the risk associated with these parameters.[11] Furthermore, although the various definitions of MetS give weight to each of their components equally, it is clear that some risk factors carry greater CVD prognostic capacity than others. This issue is particularly relevant in patients with diabetes mellitus, because glucose intolerance exhibits a disproportionate impact on CVD risk compared with some other MetS components. Indeed, the presence of impaired FPG (FPG >6.1 mmol/L) alone has emerged as a stronger predictor of CVD and all-cause

Table 2. Continued.

IDF			EGIR		
No MetS	MetS	*P*‡	No MetS	MetS	*P*‡
8.2 (6.7, 11.1)	8.3 (6.9, 10.8)	0.52	7.8 (6.4, 9.9)	8.8 (7.5, 11.5)	
128 (17)	141 (20)		134 (20)	138 (19)	
79 (9)	86 (10)		82 (10)	85 (10)	
24.7 (3.5)	30.1 (5.4)		26.6 (4.6)	31.5 (6.0)	<0.0001
89 (9)	106 (10)		95 (11)	105 (13)	
82 (12)	99 (12)		90 (13)	102 (14)	
0.91 (0.052)	0.98 (0.052)	<0.0001	0.94 (0.059)	0.97 (0.058)	<0.0001
0.82 (0.067)	0.89 (0.070)	<0.0001	0.86 (0.073)	0.89 (0.073)	<0.0001
1.12 (0.25)	1.03 (0.24)		1.09 (0.24)	1.02 (0.23)	
1.30 (0.82, 3.05)	1.81 (1.09, 3.00)		1.41 (0.88, 2.28)	2.20 (1.20, 3.37)	
	100			100	
	65			65	
	54			53	
	55			48	
	N/A			N/A	

mortality in the general population than either MetS or any of its other components.[3,25] Moreover, in data from the National Health and Nutrition Examination Survey II, Malik et al[26] noted that diabetes alone conveyed greater risk of coronary heart disease (hazard rate 5.0) and CVD (hazard rate 3.6) than the presence of MetS (hazard rate 3.5 and 2.7, respectively). Finally, in a study of patients with prevalent CVD, Stern and colleagues[27] demonstrated that the excess risk for fatal CVD

Table 3. Absolute Risk Rates and Unadjusted Estimated Relative Risks for CVD, MI, Stroke and Microvascular Disease in UKPDS Patients Classified by the Presence or Absence of MetS, Defined According to ATP-III, WHO, IDF, or EGIR Criteria

	Without		With		Absolute Risk			
	n	No. of Events	n	No. of Events	Without	With	Log Rank *P*	Relative Risk (95% CI)
CVD								
ATP-III	1784	269	2770	504	14.8	19.1	0.00018	1.33 (1.14–1.54)
WHO	2923	459	1824	372	15.6	21.7	0.00000012	1.45 (1.26–1.66)
IDF	2086	334	2462	436	15.7	18.7	0.0038	1.23 (1.07–1.42)
EGIR	1147	168	2731	493	14.5	18.7	0.0022	1.31 (1.10–1.57)
Fatal or nonfatal MI								
ATP-III	1784	221	2770	399	12.1	14.9	0.005	1.27 (1.07–1.49)
WHO	2923	373	1824	299	12.6	17.2	0.0000081	1.41 (1.21–1.65)
IDF	2086	274	2462	344	12.8	14.6	0.043	1.18 (1.01–1.38)
EGIR	1147	136	2731	395	11.6	14.8	0.0080	1.3 (1.07–1.58)
Fatal or nonfatal stroke								
ATP-III	1784	57	2770	137	3.1	5	0.00058	1.71 (1.26–2.33)
WHO	2923	109	1824	95	3.6	5.4	0.0011	1.58 (1.20–2.08)
IDF	2086	74	2462	119	3.4	4.9	0.0037	1.53 (1.15–2.05)
EGIR	1147	38	2731	125	3.2	4.6	0.042	1.46 (1.01–2.09)
Microvascular complications								
ATP-III	1784	169	2770	249	9.4	9.3	0.82	1.02 (0.84–1.24)
WHO	2923	258	1824	173	8.8	10	0.063	1.2 (0.99–1.46)
IDF	2086	194	2462	222	9.2	9.4	0.49	1.07 (0.88–1.30)
EGIR	1147	101	2731	232	8.8	8.7	0.90	1.02 (0.80–1.28)

Table 4. Discrimination by MetS, Defined According to ATP-III, WHO, IDF, or EGIR Criteria, With Respect to CVD Outcomes

	ATP-III	WHO	IDF	EGIR
Definition	Any 3 of following 5 criteria:	Known DM, FPG >6.0 mmol/L, or highest quartile of IR plus 2 or more of:	Central obesity (WC >94 cm in whites or Afro-Caribbean men, >90 cm in Indian Asian men, or >80 cm in women, plus 2 or more of:	IR (lowest quartile HOMA %S) plus 2 or more of:
	1. FPG >6.0 mmol/L	1. WHR >0.9 male or >0.85 female or BMI >30 kg/m^2	1. DM or FPG >5.6 mmol/L	1. DM, FPG >6.0 mmol/L
	2. WC >102 cm male, >88 cm female	2. TG ≥1.7 mmol/L	2. TG ≥1.7 mmol/L	2. WC >94 cm male, >80 cm female
	3. TG ≥1.7 mmol/L	3. HDL <0.9 mmol/L male, <1 mmol/L female	3. HDL <0.9 mmol/L male, <1 mmol/L female	3. TG >2.0 mmol/L
	4. HDL <1.0 mmol/L male, <1.3 mmol/L female	4. BP ≥160/90 mm Hg or Rx	4. BP ≥135/85 mm Hg or Rx	4. HDL <1.0 mmol/L
	5. BP ≥130/85 mm Hg or Rx	5. Urinary albumin >50 mg/L, albumin-to-creatinine ratio ≥20 mg/g, or UAE ≥20 μg/min		5. BP ≥140/90 mm Hg or Rx
Likelihood ratio	1.09	1.21	1.06	1.07
Specificity, %	40.0	44.8	56.6	74.6
Sensitivity, %	65.2	62.9	46.4	30.4
Positive predictive value, %	18.2	20.4	17.7	18.1

DM indicates diabetes mellitus; IR, insulin resistance; WC, waist circumference; HOMA %S, insulin sensitivity by homeostasis model assessment; WHR, waist-hip ratio; BMI, body mass index; TG, triglycerides; BP, blood pressure; Rx, treatment; and UAE, urinary albumin excretion.

associated with MetS was entirely driven by diabetes mellitus and that this excess risk could be eliminated on controlling for diabetes. Thus, the present findings are consistent with earlier reports and serve to emphasize the limited additional information regarding CVD risk stratification conveyed by MetS in the setting of T2DM.

Because the majority of patients in these analyses were randomized to different policies of glucose control in the UKPDS, and a subset of individuals were also randomized subsequently to different blood pressure control policies, an interaction between the presence of MetS and allocated therapies cannot be ruled out. However, the distribution of patients with and without MetS was found to be similar in both trial allocations (data not shown), which suggests that any interaction would not alter the conclusions reported here.

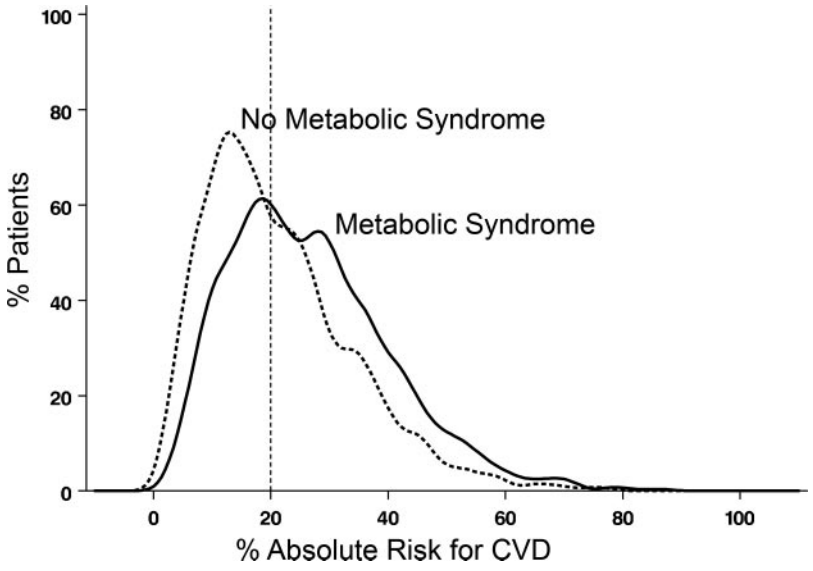

Figure. Kernel density plots of the distribution of estimated 10-year absolute CVD risk for UKPDS patients with newly diagnosed T2DM classified by the presence or absence of MetS, defined according to ATP-III criteria. Vertical dotted line denotes 20% 10-year risk.

The clinical message that arises from the present analysis is that use of MetS as a tool to identify diabetic patients at greatly increased risk of CVD can be misleading, insofar as some patients at high risk may not be detected, and others at lower risk may be identified incorrectly. Consistent with this notion, the American Diabetes Association and the European Association for the Study of Diabetes recently published a joint statement[11] that suggested that diabetes mellitus should be excluded from the definition of MetS, because diagnosis of the syndrome offers no extra information or treatment recommendations in diabetic patients. Instead, because a high proportion of diabetic patients with and without MetS can be at the same overall CVD risk, clinical management should be directed by an assessing an individual's global risk for complications, as can be accomplished with the UKPDS risk engine.

Conclusions

Individuals with newly diagnosed T2DM exhibit a high prevalence of MetS, whether defined by ATP-III, WHO, IDF, or, to a lesser degree, EGIR criteria. The presence of this syndrome by ATP-III, WHO, or IDF criteria identifies diabetic patients at increased risk of future macrovascular but not microvascular complications. However, because there is significant overlap in estimated 10-year CVD risks between patients with and without MetS, diagnosis of MetS holds limited clinical value for CVD risk stratification in T2DM.

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Disclosures

Dr Cull served as an expert witness for the UK Government Office of Fair Trading.

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CLINICAL PERSPECTIVE

The metabolic syndrome (MetS) and type 2 diabetes mellitus are both associated with increased cardiovascular disease risk, but the degree to which the presence of MetS in individuals with type 2 diabetes mellitus increases their cardiovascular disease risk is uncertain. We present data from the United Kingdom Prospective Diabetes Study showing that MetS (by National Cholesterol Education Program Adult Treatment Panel III criteria) increases cardiovascular disease risk by 33% but has no impact on microvascular complications. MetS in type 2 diabetes mellitus is, however, a poor discriminator of cardiovascular risk, with only 18% positive predictive value for cardiovascular disease events by use of the Adult Treatment Panel III criteria. MetS is of limited clinical value for cardiovascular disease risk stratification in type 2 diabetes mellitus.