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Metabolic syndrome, or What you will: definitions and epidemiology

CAROLINE DAY

Abstract

The 'metabolic syndrome' is a clustering of risk factors which predispose an individual to cardiovascular morbidity and mortality. There is general consensus regarding the main components of the syndrome (glucose intolerance, obesity, raised blood pressure and dyslipidaemia [elevated triglycerides, low levels of high-density lipoprotein cholesterol]) but different definitions require different cut points and have different mandatory inclusion criteria. Although insulin resistance is considered a major pathological influence, only the World Health Organization (WHO) and European Group for the study of Insulin Resistance (EGIR) definitions include it amongst the diagnostic criteria and only the International Diabetes Federation (IDF) definition has waist circumference as a mandatory component.

The prevalence of metabolic syndrome within individual cohorts varies with the definition used. Within each definition, the prevalence of metabolic syndrome increases with age and varies with gender and ethnicity. There is a lack of diagnostic concordance between different definitions. Only about 30% of people could be given the diagnosis of metabolic syndrome using most definitions, and about 35–40% of people diagnosed with metabolic syndrome are only classified as such using one definition. There is currently debate regarding the validity of the term metabolic syndrome, but the presence of one cardiovascular risk factor should raise suspicion that additional risk factors may also be present and encourage investigation. Individual risk factors should be treated.

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Key words: metabolic syndrome, cardiovascular risk, diabetes, obesity.

Introduction

In 1600, when deciding upon the title of a play to be performed on the last day of Christmas, William Shakespeare opted for 'Twelfth Night, or What you will'. With regard to

Table 1. Components of Syndrome X originally identified by Gerald Reaven

Syndrome X	
●	Insulin resistance
●	Hyperinsulinaemia
●	Glucose intolerance
●	↑ Triglyceride
●	↓ High density lipoprotein
●	Hypertension

the ongoing debate concerning the existence of a syndrome of increased vascular risk and the range of diagnostic criteria for such a syndrome, this review is following the Bard's example and leaving the choice of terminology to the reader.^{1,2} However, for conformity and to reduce confusion, the term 'metabolic syndrome' will be used throughout.

Insulin resistance

Insulin insensitivity as a feature of what we now call type 2 diabetes was brought to attention in 1936, when the term insulin-resistant was used to describe patients who required very high insulin doses.³ It was almost a quarter of a century before this conceptual terminology could be validated, courtesy of the advent of insulin radioimmunoassay and improved methodologies for accurate glucose measurement,^{4,5} and intense research has ensued.

Insulin resistance was again brought to the fore by Gerald Reaven in 1988 during the American Diabetes Association Banting Lecture, when he described how it was a fundamental feature of several conditions associated with coronary artery disease.⁶ He used the term Syndrome X (table 1) but it is also known as Reaven's syndrome, insulin resistance syndrome and metabolic syndrome. Metabolic syndrome is the most widely used terminology. It is noteworthy that at this time abdominal adiposity was not recognised as a key component. There are, however, subtle distinctions between the insulin resistance syndrome and the metabolic syndrome: these have been expertly addressed by Gerald Reaven,⁷ with metabolic syndrome being considered the clinical manifestation of conditions which increase vascular risk. Interestingly, a description of the metabolic syndrome, a condition associating hyperglycaemia, hypertension and gout, was first published by Kylin, a Swedish physician, in 1923.⁸

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Table 2. Diagnostic criteria for the metabolic syndrome

Components	WHO (modified) ^{13,14}	EGIR ¹⁵	NCEP (ATP III) ¹⁶	AACE (modified) ¹⁷	IDF ^{18,19}	AHA/NHLBI ²⁰
IR*	Presence	Presence				
IFG (FPG) or IGT (2h PG) mmol/L	≥ 6.1 ≥ 7.8 or T2DM	≥ 6.1	≥ 6.1	≥ 6.1 > 7.8 (not T2DM)	≥ 5.6 or Rx	≥ 5.6 or Rx
Waist (cm)** or WHR	WHR > 0.9 (> 0.85)	≥ 94 (≥ 80)	> 102 (> 88)		≥ 94 (≥ 80)***	> 120 (> 88)***
BMI (kg/m ²)	> 30			≥ 25		
BP (mmHg)	≥ 140/90	≥ 140/90	≥ 130/85	≥ 130/85	≥ 130/85 or Rx	≥ 130/85 or Rx
TG (mmol/L)	≥ 1.7	> 2.0	≥ 1.7	≥ 1.7	≥ 1.7 or Rx	≥ 1.7 or Rx
HDL-C (mmol/L)	< 0.9 (1.0)	< 1.0	< 1.04 (<1.29)	< 1.04 (< 1.29)	≤ 1.03(≤ 1.29) or Rx	≤ 0.9 (≤ 1.1) or Rx
Number of components for diagnosis	<i>IR or IFG or IGT plus ≥ 2 others from: central obesity (using WHR +/- or BMI), ↑ BP, dyslipidaemia (↑ TG +/- ↓ HDL-C) or Micoalbuminuria</i>	<i>IR plus ≥ 2 others from: central obesity (waist circumference), IFG, ↑ BP, dyslipidaemia (↑ TG +/- ↓ HDL-C)</i>	≥ 3 of the components above	Diagnosis depends on clinical judgement based on risk factors/features of insulin resistance	<i>Central obesity (waist circumference) plus 2 other components. Waist circumference defined for different ethnic groups</i>	≥ 3 of the components above

Key: WHO = World Health Organization; EGIR = European Group for the Study of Insulin Resistance; NCEP (ATP III) = National Cholesterol Education Program (Adult Treatment Panel III); AACE = Association of American Clinical Endocrinologists; IDF = International Diabetes Federation; AHA/NHLBI = American Heart Association/National Heart, Lung and Blood Institute; BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; IAAT = intra-abdominal adipose tissue; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; IR = insulin resistance; PG = plasma glucose; TG = triglycerides; WHR = waist:hip ratio; Rx = receiving treatment

*IR: defined by sex- and cohort-specific top 25% distribution of fasting insulin conc. in non-diabetic population.

** 80 cm = 30.5 ins, 88 cm = 35 ins, 94 cm = 37 ins, 102 cm = 40 ins. *** in Europids. (*italics*) values in females

Type 2 diabetes and cardiovascular risk

Atherosclerotic macrovascular disease – primarily coronary artery disease, cerebrovascular and peripheral vascular disease – accounts for much of the increased morbidity and premature mortality associated with type 2 diabetes. In 1984, Jarrett suggested that atherosclerosis and type 2 diabetes develop as a result of a shared antecedent⁹ and this was developed by Stern in 1995 as the ‘common soil’ hypothesis.¹⁰

Biological systems are multifaceted and whilst insulin resistance may be a key element of type 2 diabetes and features associated with atherogenesis, its role as a direct promoter of atherogenesis has been difficult to establish.¹¹ The conundrum has been succinctly reviewed by Andrew Krentz.¹² The inter-relationship of co-morbidities with associated vascular risk can be appreciated via the metabolic syndrome, particularly if allowances are made for the interplay of genes and environmental factors throughout life – starting *in utero*.^{10,11}

Metabolic syndrome, or What you will

The clustering of cardiovascular risk within individuals has prompted several learned bodies to publish criteria considered diagnostic of the metabolic syndrome.¹³⁻²⁰ These definitions have much commonality but they also offer distinct

differences (table 2) which can confuse interpretation of epidemiological studies. These differences may appear superficial, for example central adiposity in men using the World Health Organization (WHO) definition requires body mass index (BMI) > 30 kg/m² or waist:hip ratio > 9.0, whereas waist circumference is required by the National Cholesterol Education Program (NCEP) (> 102 cm), European Group for the study of Insulin Resistance (EGIR) and International Diabetes Federation (IDF) (> 94 cm).

Amongst 4,715 non-diabetic men, central obesity (diagnostic for the metabolic syndrome) was present in 61.1% (WHO) or 19.5% (NCEP) or 50.4% (IDF), depending on the criteria employed²¹ and their associated relative risks of cardiovascular death (crude data with 95% confidence intervals) were 2.03 (1.48–2.80) WHO, 1.79 (1.32–2.42) NCEP and 1.79 (1.34–2.38) IDF.

Interpretation of data may be further complicated by studies modifying inclusion criteria and by updates from expert groups. Using NCEP 2001²² and 2004 (revised)¹⁶ criteria, the prevalence of metabolic syndrome in the DECODE cohort was 25.9% and 32.2% for men, and 23.4% and 28.5% for women, respectively.²¹ Meigs *et al.* 2003 showed how the prevalence of metabolic syndrome can vary with definition and criteria modification (table 3).²³

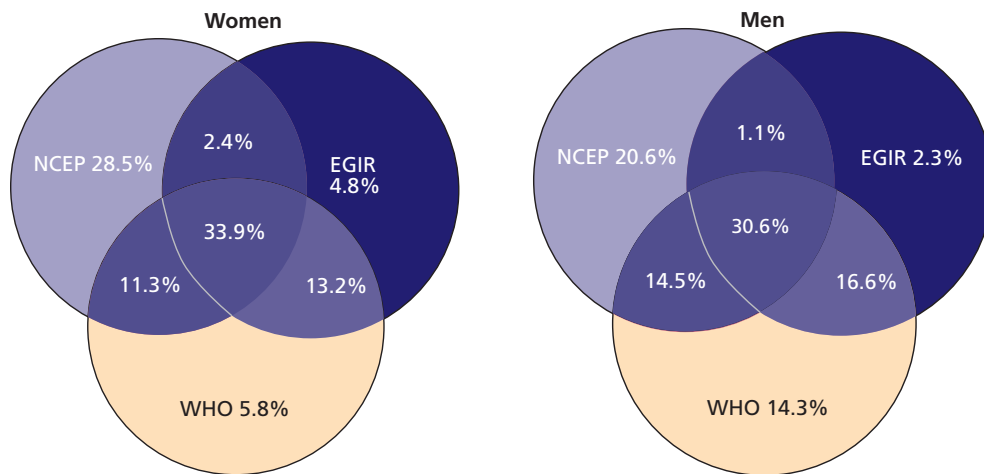
The lack of diagnostic concordance between different

Table 3. Prevalence of metabolic syndrome using NCEP and WHO criteria among non-diabetic adults (30–79 years) in the Framingham Offspring Study (1991–95) and San Antonio Heart Studies (1992–96). Meigs et al.²³

	White (n=3,224)		Non-Hispanic white (n=1,081)		Mexican-American (n=1,656)	
	Men	Women	Men	Women	Men	Women
NCEP waist \geq 102 cm, \geq 88 cm	26.9	21.4	24.7	21.3	29	32.8
NCEP; BMI instead of waist	25.2	17.8	22.1	15	28.4	26.8
WHO BMI \geq 30 kg/m ²	30.3	18.1	24.7	17.2	32	28.3

Key: NCEP = National Cholesterol Education Program; WHO = World Health Organization; BMI = body mass index

Figure 1. Venn diagrams showing the agreement and disparity in the diagnosis of the metabolic syndrome using the modified WHO definition, the EGIR definition and the NCEP definition among those 1,484 men and 1,503 women who qualified for the diagnosis of the metabolic syndrome by at least one of these definitions²⁴



Key: WHO = World Health Organization; EGIR = European Group for the Study of Insulin Resistance; NCEP = National Cholesterol Education Program

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definitions poses a dilemma.¹ Only about 30% of people appear to be diagnosable by most definitions, and about 35–40% of people diagnosed with metabolic syndrome are only eligible for such classification using one definition. The concordance and disparity between diagnoses using the WHO, EGIR and NCEP definitions amongst non-diabetic Europeans are shown in figure 1.²⁴

Metabolic syndrome prevalence

Regardless of the definition of metabolic syndrome employed, the prevalence of the condition increases with age,²³⁻²⁵ but there are ethnic and national differences. In a USA cohort (National Health and Nutrition Examination Survey, NHANES) of 8,814 people, the prevalence amongst those aged 20–29 years was almost 7% whilst a prevalence in excess of 40% was noted in people aged 60–69 years.²⁵ Interestingly, African-American women had a 57% higher prevalence than men and Mexican-American women had a

26% higher prevalence than men.²⁵ Although prevalence increased with age in a European population (n=9,140), the highest prevalence of 32% was recorded in men aged 60–69 years using the WHO definition.²⁴ Differences in prevalence between the USA and Europe cannot be due to population genetics alone and the differential prevalences of single components may be more readily indicative of environmental influences.

Table 4 lists recent metabolic syndrome prevalence studies which have simultaneously utilised the more popular metabolic syndrome definitions.^{21,26-42} The more recent American Heart Association/National Heart, Lungs and Blood Institutes (AHA/NHLBI) definition, in which inclusion of waist circumference is not mandatory for a diagnosis of metabolic syndrome, is considered similarly predictive to that of the NCEP. Amongst Greek adults (n=9,669), the age-adjusted cardiovascular disease prevalence was 23.3%, 22.6% and 18.3% using NCEP, AHA/NHLBI and IDF criteria, respectively.⁴³

Table 4. Prevalence of metabolic syndrome defined by NCEP, WHO and IDF criteria

	NCEP			WHO			IDF			Location and cohort information
	Men	Women	Total	Men	Women	Total	Men	Women	Total	
Jorgensen <i>et al.</i> 2004 ²⁶			17.9			20.7				Greenland, Inuit, n=917, adult
Rosenbaum <i>et al.</i> 2005 ²⁷			47.4			55.4				Brazil, Japanese-Brazilians n=1,166, 57.4±12.4 years
Guerrero-Romero and Rodriguez-Moran 2005 ²⁸			22.6			15.4			22.3	Mexico, Durango City, n=700, 30–64 years
Ford 2005 ²⁹	33.7	35.4	34.5				39.9	38.1	39.0	USA, NHANES (1992-2002) n=3,601 ≥ 20 years
Adams <i>et al.</i> 2005 ³⁰	19.4	14.4	15.0				26.4	15.7	22.8	Australia, Adelaide n=4,060 ≥ 18 years
Zimmet <i>et al.</i> 2005 ³¹			19.3						29.1	Australia, AusDiab n=11,247 ≥ 25 years
Athyros <i>et al.</i> 2005 ³²			24.5						43.4	Greece, n=9,669, adult
Lu <i>et al.</i> 2006 ³³			55.7			70.0			50.0	China, Downtown Shanghai n=1,008, T2DM, > 30 years
Ko <i>et al.</i> 2006 ³⁴			9.6			13.4			7.4	Hong Kong, Hong Kong Chinese n=1,513, 18–66 years
He <i>et al.</i> 2006 ³⁵	17.6	39.2	30.5				34.8	54.1	46.3	China, Urban Beijing n=2,334, 60–95 years
Lao <i>et al.</i> 2006 ³⁶			15.5						25.8	China, Guangzhou Biobank Cohort Study n=10,326, 50–85 years
DECODE & Qiao 2006 ³¹	32.2	28.5		27.0	19.7		35.0	34.1		European, DECODE n=10,269, no DM, 30–89 years
Rathmann <i>et al.</i> 2006 ³⁷	28	24		50	38		57	46		Germany, Augsburg KORA Survey 2000 n=1,373, 55–74 years
Lorenzo <i>et al.</i> 2006 ³⁸	0.0	1.2					14.4	3.7		Peru, Peruvian Insulin Resistance Study n=346, no DM, 35–64 years
	3.5	0.4					26.1	5.1		Mexico, Mexico City Diabetes Study n=1,990, no DM, 35–64 years
	2.3	1.5					16.2	5.7		Mexican-Americans, SAHS, n=1,150, no DM, 35–64 years
	2.5	1.2					11.5	4.1		Non-Hispanic whites, SAHS n=1,323, no DM, 35–64 years
	4.1	0.2					9.5	3.1		Spain, Spanish Insulin Resistance Study n=2,540, no DM, 35–64 years
Park <i>et al.</i> 2006 ³⁹	14.2	17.7					13.5	15.0		Korea, Korean NHANES 1998 n=6,824, 20–80 years
Lawlor <i>et al.</i> 2006 ⁴⁰		21.0			29.0			48.0		UK, British Women's Heart and Health Study n=3,589, 60–79 years
Lorenzo <i>et al.</i> 2007 ⁴¹	29.6	30.9		28.3	27.3		40.4	38.5		Mexican Americans, SAHS n=2,013, 25–64 years
	24.0	16.8		18.8	12.1		28.4	24.7		Non-Hispanic whites, SAHS n=928, 25–64 years
Assman <i>et al.</i> 2007 ⁴²	30.0	37.0					25.0	18.0		Dallas Heart Study (n=3,006) & USA NHANES 1999 (n=750) n=3,756, 19–67 years
	25.3	17.6					31.5	22.8		Germany, PROCAM n=7,131, 16–65 years

Key: SAHS = San Antonio Heart Study; NHANES = National Health and Nutrition Examination Survey; PROCAM = Prospective Cardiovascular Munster Study; no DM = people with diagnosed diabetes excluded from study; NCEP = National Cholesterol Education Program; WHO = World Health Organization; IDF = International Diabetes Federation

The prevalence of metabolic syndrome in the Singapore Cardiovascular Cohort Study (n=4,334) was 17.7% by IDF criteria and 26.2% by AHA/NHLBI criteria, with Asian Indians having higher rates than Chinese or Malaysians. Compared to individuals without the condition, metabolic

syndrome with or without central obesity significantly increased the risk of ischaemic heart disease.⁴⁴ Amongst a similar cohort (n=4,723) in Singapore, the prevalence of metabolic syndrome by IDF criteria was 20.2% and 26.9% by AHA/NHLBI criteria. Within this population, 6.7% of sub-

jects had three or more features of metabolic syndrome, but did not have central obesity.⁴⁵ The authors suggest that the AHA/NHLBI definition may be a better predictor of increased cardiovascular disease risk whilst the IDF definition may be better at identifying insulin resistance and those at risk of type 2 diabetes.

Obesity, diabetes and cardiovascular disease

Obesity and intra-abdominal adipose tissue (IAAT) accumulation are associated with increased vascular risk.^{46,47} Different fat depots exhibit varying metabolic activity, with IAAT being associated with insulin resistance.^{48,49} The roles of insulin resistance and hyperinsulinaemia as promoters of vascular risk in the metabolic syndrome have been the subject of several excellent reviews.^{6,7,50-52} There is growing acceptance that for a given waist circumference – regardless of overall body weight – people have similar health risks;⁴⁸ waist circumference is a useful surrogate marker of IAAT. Surprisingly, according to IDF-defined waist circumference, about 20% of Korean adults would be considered obese, but by BMI this prevalence falls to 2.3%.³⁹

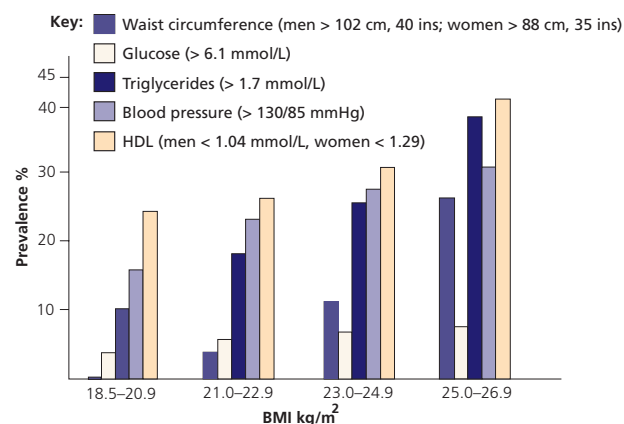
The prevalence of the metabolic syndrome increases with obesity, whether assessed by BMI or waist circumference.^{53,54} For example, in NHANES (1988–1994) the metabolic syndrome was present in 4.6% of normal-weight, 22.4% of overweight and 59.6% of obese men.⁵³ A similar distribution was observed in women, and the Insulin Resistance Atherosclerosis Study suggests that a large waist circumference, as a measure of obesity, is the best predictor of the incident development of the metabolic syndrome.⁵⁵

Whilst a wide waist would generally be considered indicative of increased vascular risk, people with normal waist circumference may also be at risk – especially if they are on the verge of being overweight (figure 2).⁵⁶ There is growing evidence that obesity is not a pre-requisite for IAAT deposition. In a study of non-obese subjects with coronary artery disease, 40% had increased IAAT which correlated with metabolic risk factors.⁵⁷

The obesity epidemic appears to be underpinning the rising tide of type 2 diabetes and other conditions of glucose intolerance (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]). Indeed, IGT is an independent risk predictor for cardiovascular morbidity and mortality, with postprandial hyperglycaemia doubling cardiovascular disease mortality.⁵⁸ In the USA, data from NHANES show that amongst adults (20–74 years) the prevalence of obesity has more than doubled from 15% (1976–80 survey) to 32.9% (2003–4 survey)⁵⁹ whilst the prevalence of overweight in children has risen from 5% to 13.9% in 2–5-year-olds, 6.5% to 18.8% in 6–11-year-olds and 5% to 17.4% in 12–19-year-olds.⁶⁰ The prevalence of diabetes in adults has risen from 8% in 2000⁶¹ to 9.4% in 2007, with a projected prevalence of 10.3% in 2025.¹⁹ In the USA, depending on the study, 8–45% of recently diagnosed diabetes in the young is due to type 2 diabetes.⁶²

Burgeoning obesity, insulin resistance, diabetes and cardiovascular disease in children and adolescents is a major cause for concern and whilst lifestyle management – eat less, move more – is paramount, early recognition and intensive

Figure 2. Presence of metabolic syndrome risk factors in normal weight and borderline overweight (BMI 25–26.9) individuals⁵⁶



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treatment of the component conditions of the metabolic syndrome are recommended.⁶³ The prevalence of metabolic syndrome amongst 12–19-year-olds has almost doubled in the last 10 years and age- and gender-specific cut points for each criterion have recently been compiled to help in the identification of at-risk adolescents. These teen tables, based on the NCEP and IDF definitions, suggest a metabolic syndrome prevalence of 7.6% and 9.6%, respectively.⁶⁴

Risky relationships

Population-based surveys have shown that prevalence rates of type 2 diabetes, IGT, obesity, hypertension and dyslipidaemia are significantly higher when several of these conditions occur in conjunction, as opposed to occurring in isolation.⁵¹ This has been confirmed by a recent meta-analysis which showed that metabolic syndrome almost doubles the risk of developing cardiovascular disease (RR 1.78; 95% CI 1.58–2.00) and that an excess risk for cardiovascular events and death remains even after adjusting for traditional cardiovascular risk factors (RR 1.54, 95% CI 1.32–1.79) in people with metabolic syndrome or a clustering of three or more cardiac risk factors.⁶⁵

Practicalities

Insulin resistance and hyperinsulinaemia, although having aetiological importance, are not readily measured in routine clinical practice, but blood biochemistry for lipids and biomarkers of endothelial dysfunction is usually routinely available. Other parameters of metabolic syndrome can be easily assessed in the community due to the advent of simple-to-use blood glucose meters and blood pressure monitors, and obesity (BMI, waist:hip ratio, waist circumference) can be determined using a tape measure and bathroom scales.

Questionnaires may be helpful in identifying people with undiagnosed conditions of cardiovascular risk such as type 2 diabetes,^{66,67} and with a small amount of data on-line calculators such as the Framingham risk calculator⁶⁸ and the UKPDS risk engine⁶⁹ indicate individual cardiovascular risk.

The ADA's PHD (Personal Health Decisions) is a simple, patient-friendly risk engine which graphically displays risk of developing diabetes and its complications.⁷⁰

The prevalence of metabolic syndrome varies according to the diagnostic criteria employed, but if used as an umbrella term to describe a clustering of cardiovascular risk factors it serves a practical purpose. The presence of one cardiovascular risk factor should raise suspicion that additional risk factors may also be present and encourage investigation.¹ For example, investigation of primary care patients with hypertension revealed 2% with undiagnosed type 2 diabetes and 18.5% with IFG or IGT, and amongst patients with ischaemic heart disease nearly 2.5% had undiagnosed type 2 diabetes and 12.4% had IFG or IGT.⁷¹ All cardiovascular risk factors should be treated individually and intensively to reduce morbidity and mortality.^{1,63,72}

Conclusion

"The FDA does not necessarily consider the metabolic syndrome to represent a distinct disease entity"² and according to the ADA and EASD "the metabolic syndrome requires much more study before its designation as a syndrome is truly warranted", warning doctors against labelling patients with the term.¹ Nevertheless, in the USA a version of metabolic syndrome has an ICD-9 code (277.7) which permits healthcare reimbursement.

From a pragmatic perspective, providing a label to embrace possible components of cardiovascular risk clusters acts as an *aide memoire* to prompt a search for, or monitoring of, other risk factor variables, with appropriate treatment of each emergent factor. As Shakespeare's Juliet asked "What's in a name?" Metabolic syndrome, or What you will, is a cardiovascular risk factor alert tag.

Conflict of interest

CD declares no conflict of interest for this review, but records honoraria, advisory and educational activities associated with several pharmaceutical firms with an interest in anti-diabetic and antiobesity treatments.

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