Original Article

Relationships among insulin resistance, obesity, diagnosis of the metabolic syndrome and cardio-metabolic risk

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Abstract

The aim of this study is to test the hypotheses that: 1) diagnosing the metabolic syndrome does not effectively identify insulin-resistant (IR) individuals; and 2) waist circumference (WC) is no better than body mass index (BMI) in predicting insulin resistance or the components of the metabolic syndrome (MetS). Measurements of BMI, WC, blood pressure, and fasting plasma glucose, insulin (FPI), triglycerides (TG), and HDL-cholesterol (HDL-C) concentrations were made in 1,300 adults, without known cardiovascular disease (CVD) or drug treatment of hypertension or diabetes. Receiver operating characteristic curves were used to determine the ability of the MetS, and its components, to identify IR individuals. In addition, comparisons were made of CVD risk factors following division of the population into quartiles of FPI concentrations, and univariate and multiple regression analysis used to compare the ability of WC, BMI, and FPI as predictors of MetS components. The MetS was no more effective in identifying IR individuals than several individual components (sensitivity~40%), and IR individuals not identified were at significantly increased CVD risk. FPI concentration was the best predictor of an abnormal glucose, TG, and HDL-C, whereas the adiposity indices were better predictors of abnormal blood pressure. The relationship between BMI and WC with the MetS and its components seemed comparable.

Keywords

Cardiovascular disease, insulin resistance, metabolic syndrome

Introduction

In 1988 it was suggested that insulin resistance/compensatory hyperinsulinaemia increased the likelihood that a non-diabetic individual would develop a cluster of abnormalities,[1] including some degree of glucose intolerance, elevated blood pressure (BP), and a high plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration. Although insulin resistance was known to be associated with type 2 diabetes,[2] it was suggested that this cluster of abnormalities related to insulin resistance, designated Syndrome X, increased risk of cardiovascular disease (CVD) in non-diabetic individuals. Although the intent of Syndrome X was to provide a mechanism explaining why its components clustered together, its four components have been joined by a fifth (excess adiposity) in order to create a new diagnostic category; the metabolic syndrome (MetS). Initial versions of the MetS varied as a function of which organisation proposed it.[3-5] More recently, the World Health Organisation[6] has concluded that the MetS has 'limited practical utility as a diagnostic or management tool', and the Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF) have agreed upon a single 'harmonised' version of the MetS.[7]

Although there is a substantive conceptual difference between the diagnostic category of the MetS and the putative role of insulin resistance in Syndrome X, this distinction is often blurred. For example, the ATP III acknowledge that the MetS is closely associated with insulin resistance, and in their Guidelines Slide Set they use 'metabolic syndrome', 'syndrome X' and 'insulin resistance syndrome' synonymously (http://hp2010.nhlbihin.net/ncep_slds/menu.htm#6).

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Thus, it is not surprising that efforts have been made to see how closely the MetS identifies insulin resistant (IR) individuals.[8-10] The fact that only one version of the MetS remains operative does not necessarily mean that questions as to the relationship between the MetS and insulin resistance lack interest. Thus, the first goal of this study was to assess the utility of the MetS in indentifying IR individuals, and the relative abilities of the MetS and insulin resistance in finding individuals at greatest risk of CVD. In addition, it seemed to be important to evaluate CVD risk of subjects, considered to be IR, but not meeting the diagnostic criteria of the MetS.

Secondly, in the process of 'harmonising' the ATP III and IDF diagnostic criteria, the presence of abdominal obesity was downgraded to represent only one of the three abnormalities required for a diagnosis. Despite this, the authors of the 'harmonised' definition state[11] that 'Evidence now indicates that the metabolic syndrome all begins with central obesity'. Since this is an important issue, the second goal of this study is to evaluate the presumptive unique association between abdominal obesity and the components of the MetS, as contrasted to overall obesity, as estimated by body mass index (BMI), and fasting plasma insulin concentration (FPI), a surrogate estimate of insulin resistance.

Materials and methods

The study population consisted of 547 individuals (168 men and 379 women, aged 20–80 years), who had participated in the Rauch project (Rauch, Buenos Aires) and 753 (221 men and 532 women, aged 15–80 years) in the PROCER project (San Andrés de Giles, Buenos Aires). Subjects with CVD or type 2 diabetes, or those taking pharmacological agents to treat hypertension, were excluded from this analysis, and data for each component of MetS were available for each included subject.

The two projects were community-based programmes aimed at surveying CVD risk factors, and consisted of random samples obtained from subjects living in the chosen blocks. Ethical Committee permission for these studies was provided by the relevant health authorities in the two communities. BP was measured sitting, after a minimum resting period of 5 min, using a mercury sphygmomanometer. Phase I and V Korotkoff sounds were used to identify systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively; SBP and DBP values were an average of the three measurements. Weight was determined with individuals wearing light clothes and no shoes. Height was also measured with no shoes on, using a metallic metric tape, and waist circumference (WC) measured with a relaxed abdomen using a metallic metric tape on a horizontal plane above the iliac crest. BMI was calculated using the weight/height^2 formula, and concentrations of plasma glucose, HDL-C, TG, and insulin (FPI) determined after an overnight fast.[12-14]

Plasma for the insulin measurements was extracted by centrifugation (15 min at 3,000 rpm), and frozen at -20°C until assayed. FPI concentrations from the Rauch population were determined using an immunoradiometric assay, with two monoclonal antibodies against two different epitopes of the insulin molecule. The inter- and intra-assay coefficients of variation (CV) were 8.0% and 3.8%, respectively, with the lowest detectable level of 1.4 pmol/L. FPI concentrations from the San Andrés de Giles population were determined using solid-phase chemiluminescent assay, using commercially available kits (Immunolite Diagnostic Products Co, Los Angeles, CA, USA) with an analytical sensitivity of 1.4 pmol/L, inter- and intra-assay CV of less than 8%, and proinsulin cross-reactivity of less than 8.5%. Since there were two different populations, and two different insulin assay methods, each population was divided into quartiles on the basis of their FPI concentrations, and the respective quartiles from each population combined for analysis. FPI quartiles were calculated separately for each sex and for each sample, and subjects were assigned to a given FPI quartile according to their relative positions in the FPI distribution curve (men and women, Rauch and San Andrés de Giles separately), and not according their absolute FPI values. Thus, subjects that belong to the top quartile of FPI concentration in each population are there independently of their absolute FPI values.

A diagnosis of the MetS was based on the 'harmonised' version of the ATP III and IDF, in which three of the following five criteria must be satisfied:[7]

- WC: ≥94 cm in men and ≥80 cm in women
- HDL-C: <1.0 mmol/L (40 mg/dl) in men and <1.3 mmol/L (50 mg/dl) in women
- TG: ≥1.7 mmol/L (150 mg/dl)
- SBP ≥130 mmHg or DBP ≥ 85 mmHg
- glucose: ≥5.6 mmol/L (100 mg/dl)

FPI, rather than the homeostatic model assessment–insulin resistance (HOMA-IR) model, was used as a surrogate estimate of insulin resistance. This decision was based on the fact that HOMA-IR uses glucose as part of the estimate, and glucose concentration is a diagnostic criterion of the MetS. FPI concentration is known to correlate significantly with specific measures of insulin action,[15,16] and the correlation between HOMA-IR and FPI concentrations in our population was 0.93, and 80–90% of individuals were in the same quartile when classified by FPI or HOMA-IR.

The 25% of the population with the highest FPI concentration was classified as IR, with the remaining 75% classified as non-IR, a stratification based on results of a population-based, prospective study, showing that 25% of the most hyperinsulinaemic participants developed glucose intolerance, hypertension, and CVD to a significantly greater degree.[17] Finally, since assays for plasma insulin are not standardised, the actual values that determined the cut-points in our study will not be the same as those used in the one referred to above, but it seems reasonable to assume

that the distribution of the population at risk to develop adverse clinical outcomes will be reasonably similar in two populations of predominantly European ancestry.

In addition, FPI distribution in both Rauch and San Andrés de Giles populations were compared and adjusted for age, BMI and WC using ANCOVA. Pearson and multiple linear regression analysis was used to identify relationships between three factors FPI, BMI, WC and SBP, DBP, glucose, TG and HDL-C. The variables were used as *z*-scores.

Sensitivity and specificity of the MetS criteria to detect insulin resistance were calculated. Receiver operating characteristic (ROC) curves were constructed to provide a graphical representation of the relationship between false-positive (i.e. 1-specificity) and true-positive (sensitivity) detection rates for the counting of categorical MetS components. In addition, ROC curves were constructed for each component (SBP, DBP, WC, glucose, TG, and HDL-C). To evaluate diagnostic accuracy, the area under the ROC curves was calculated and the 95% confidence limits determined. We also estimated the sensitivity and specificity of the cut-point of each MetS component.

FPI, SBP, DBP, BMI, WC, HDL-C, TG and glucose values were compared between the FPI quartiles of the two populations by ANOVA. The prevalence of MetS between FPI quartiles was compared using chi square. In addition, in individuals with or without the MetS, FPI, SBP, DBP, BMI, WC, HDL-C, TG, and glucose values were compared between IR and non-IR individuals, using *t*-test for independent samples. Data were summarised by calculating means ± SE for quantitative variables and percentages for categorical variables. The significance level accepted was $p<0.05$. The data were processed using SPSS.

Results

The prevalence of the MetS was somewhat lower in women (22% vs. 31%, $p=0.002$) than in men. The actual cut-points for FPI concentrations used to define the IR subset were relatively comparable for men (62.8 vs. 67.3 pmol/L) and women (63.0 vs. 70.7 pmol/L) in the Rauch and San Andreas de Giles populations, respectively. After adjustments for age, BMI and WC, there were no differences in FPI concentrations (men $p=0.40$; women $p=0.36$) among those from Rauch and San Andrés de Giles.

The areas under the ROC curves are presented in Table 1, in which BMI is also included. Areas were somewhat higher in the case of BMI, MetS, WC, and TG, with intermediate values for HDL-C and glucose, and the lowest values for SBP and DBP. Figure 1 contains ROC curves describing the ability of a diagnosis of the MetS, as well as individual components of the MetS, to predict the presence of insulin resistance.

Table 1 also displays the sensitivity and specificity with which the MetS and its individual components identified IR individuals, and demonstrates that the MetS was not uniquely effective in accomplishing this task. Indeed, the sensitivity and specificity of a TG concentration ≥1.7 mmol/L or a BMI ≥30.0 kg/m² are comparable with that achieved by a diagnosis of MetS. The most sensitive predictors of IR are an abnormal WC, a BMI ≥25 kg/m², or an abnormal HDL-C, but these all have low specificity.

Table 2 compares experimental variables as a function of quartiles of FPI concentration, with the results provided separately for the two different populations. These data show that the prevalence of the MetS increases progressively with increases in FPI concentration, reaching rates of

Table 1. Sensitivity, specificity and area (and 95% confidence limits) under the receiver-operating characteristic curves, for the metabolic syndrome and its individual components as markers of insulin resistance

	Women				Men			
	ROC curves	Sensitivity and Specificity			ROC curves	Sensitivity and Specificity		
	Area (IC 95%)	Cut-point	Sensitivity	Specificity	Area (IC 95%)	Cut-point	Sensitivity	Specificity
MetS	0.67 (0.63–0.71)	3 criteria	43	80	0.66 (0.60–0.72)	3 criteria	38	81
WC	0.68 (0.64–0.72)	≥80 cm	87	26	0.64 (0.57–0.71)	≥94 cm	63	59
BMI	0.72 (0.68–0.76)	≥30 kg/m²	45	85	0.68 (0.61–0.74)	≥30 kg/m²	41	84
BMI		≥25 kg/m²	76	55		≥25 kg/m²	80	44
TG	0.67 (0.63–0.71)	≥1.7 mmol/L	36	86	0.60 (0.54–0.67)	≥1.7 mmol/L	49	71
HDL-C	0.63 (0.59–0.68)	<1.3 mmol/L	73	14	0.63 (0.56–0.70)	<1.0 mmol/L	87	7
Glucose	0.63 (0.58–0.67)	≥5.6 mmol/L	28	84	0.60 (0.54–0.67)	≥5.6 mmol/L	48	68
SBP	0.57 (0.53–0.62)	≥130 mmHg	31	73	0.55 (0.47–0.62)	≥130 mmHg	32	76
DBP	0.56 (0.51–0.60)	≥85 mmHg	32	78	0.53 (0.46–0.60)	≥85 mmHg	54	55

MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides

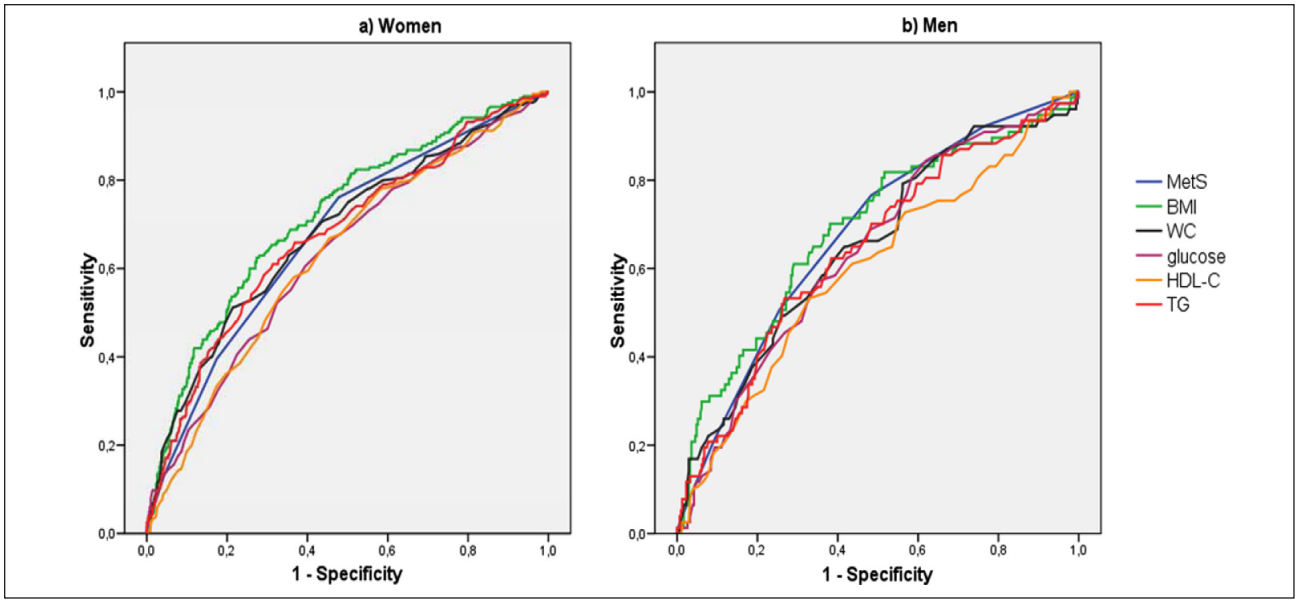

Figure 1. Receiver operating characteristic curves (ROC) constructed using the number of components of the metabolic syndrome and constructed using quantitative traits of the metabolic syndrome.
MetS, metabolic syndrome criteria; BMI, body mass index; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides

Table 2. Risk profile characteristics of individuals in each insulin concentration quartile

		Insulin quartile[c]				
		1	2	3	4	
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*
San Andrés de Giles	FPI (pmol/L)	18 (0.6)	37 (0.5)	57 (0.5)	116 (5.1)	<0.001[a]
n=753	Age (years)	36 (1.1)	38 (1.2)	38 (1.1)	38 (1.2)	0.41[b]
	% Women	70.7	70.7	70.4	70.7	1[b]
	% MetS	8.0	14.9	28.0	42.0	<0.001[a]
	BMI (kg/m^2)	24.7 (0.3)	26.1 (0.4)	27.8 (0.4)	30.4 (0.5)	<0.001[a]
	WC (cm)	84.7 (0.8)	88.5 (0.9)	93.5 (1.0)	98.3 (1.2)	<0.001[a]
	SBP (mmHg)	117 (1.1)	120 (1.1)	120 (1.2)	123 (1.4)	0.003[a]
	DBP (mmHg)	69 (0.8)	71 (0.9)	72 (0.8)	73 (0.9)	0.014[a]
	Glucose (mmol/L)	5.1 (0.07)	5.3 (0.06)	5.5 (0.08)	5.7 (0.08)	<0.001[a]
	HDL-C (mmol/L)	1.8 (0.03)	1.7 (0.03)	1.6 (0.03)	1.5 (0.03)	<0.001[a]
	TG (mmol/L)	1.1 (0.03)	1.2 (0.04)	1.4 (0.05)	1.8 (0.10)	<0.001[a]
Rauch	FPI (pmol/L)	24 (0.6)	39 (0.3)	54 (0.5)	92 (2.91)	<0.001[a]
n=547	Age (years)	49 (1.4)	51 (1.4)	49 (1.2)	48 (1.3)	0.42[b]
	% Women	70.1	69.0	68.1	69.9	0.99[b]
	% MetS	16.4	17.6	36.3	38.2	<0.001[a]
	BMI (kg/m^2)	23.7 (0.3)	24.5 (0.4)	25.9 (0.4)	27.7 (0.4)	<0.001[a]
	WC (cm)	88.1 (0.7)	90.7 (1.0)	93.6 (1.2)	96.9 (1.3)	<0.001[a]
	SBP (mmHg)	126 (1.4)	128 (1.4)	129 (1.4)	132 (1.4)	0.027[a]
	DBP (mmHg)	79 (0.9)	79 (0.8)	80 (0.9)	82 (1.0)	0.009[a]
	Glucose (mmol/L)	4.8 (0.05)	5.0 (0.06)	5.1 (0.09)	5.2 (0.11)	0.015[a]
	HDL-C (mmol/L)	1.6 (0.03)	1.6 (0.03)	1.5 (0.03)	1.5 (0.03)	0.003[a]
	TG (mmol/L)	1.3 (0.07)	1.2 (0.05)	1.6 (0.07)	1.8 (0.10)	<0.001[a]

MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides; FPI, fasting plasma insulin; SE, standard error
[a] ANOVA among insulin quartiles; [b] Chi square among insulin quartiles; [c] San Andrés de Giles and Rauch FPI quartiles

42% and 38% in the two populations. All other variables associated with the MetS also underwent statistically significant change as FPI concentrations increased across the quartiles, and this was true of both experimental groups. Furthermore, the actual values of the plasma glucose, TG and HDL-C concentrations were resonantly comparable in each FPI quartile in the two populations.

To further pursue the relationship between insulin resistance, MetS and cardio-metabolic risk, the population was divided on the basis of both gender and the diagnosis of the MetS. These groups were then subdivided into IR (the 25% of the population with the highest FPI concentrations) and non-IR (the remaining 75% of the population) groups. Table 3 compares cardio-metabolic risk factors in these four groups. Approximately 60% of IR men and 50% of IR women did not meet MetS diagnostic criteria. Individuals not diagnosed with the MetS were 10–15 years younger than those with the MetS, whether or not they were IR, or women or men. Measures of adiposity, both WC and BMI, were consistently higher in the IR group, men or women, and whether or not they had the MetS. The adverse effect of IR on cardio-metabolic risk appeared to be greatest in women, with IR women having significantly higher glucose and TG and lower HDL-C concentrations than non-IR women, with or without the MetS. In contrast, the only significant difference was lower HDL-C concentrations in IR men, whether or not they had the MetS. The clinical impact of being IR is most obvious in IR women who do not have the MetS. They are, on average, 12 years younger than IR women with the MetS, with lower values for WC and BMI, but a significant number already have abnormal values for glucose (15%), TG (19%) and HDL-C (14%), and 46% have at least one abnormality – twice as common as in the non-IR women without the MetS (23%, $p<0.01$).

Since the results in Table 2 showed that both BMI and WC increased from the lowest to the highest quartile of FPI concentration, in Table 4 we defined the univariate relationship between these three predictors and the individual features of the MetS. The magnitude of the relationship between either BMI or WC and the individual components of the MetS seems comparable in both genders; with the lowest values between BMI and WC and HDL-C in women.

Table 3. Comparison of the risk profile in insulin-resistant (IR) and non-insulin resistant (non- IR) individuals who meet or do not meet the criteria of the metabolic syndrome

	Subjects without metabolic syndrome			Subjects with metabolic syndrome		
	mean (SE)	mean (SE)	p^a	mean (SE)	Mean (SE)	p^b
women	IR n=140	non-IR n=567		IR n=88	non-IR n=116	
FPI (pmol/L)	105 (4.3)	38 (0.6)	<0.001	108 (5.3)	45 (1.4)	<0.001
Age (years)	36 (1.4)	40 (0.7)	0.004	48 (1.6)	54 (1.3)	0.005
BMI (kg/m^2)	28.2 (0.5)	24.7 (0.2)	<0.001	32.1 (0.6)	27.8 (0.4)	<0.001
WC (cm)	94.1 (1.5)	87.0 (0.5)	<0.001	103.6 (1.4)	95.8 (0.9)	<0.001
SBP (mmHg)	120 (1.2)	118 (0.7)	0.38	134 (1.9)	134 (1.5)	0.99
DBP (mmHg)	73 (1.0)	72 (0.47)	0.51	81 (1.3)	82 (0.9)	0.62
Glucose (mmol/L)	5.1 (0.05)	4.9 (0.02)	0.001	5.9 (0.15)	5.5 (0.07)	0.018
HDL-C (mmol/L)	1.6 (0.03)	1.7 (0.02)	0.001	1.4 (0.04)	1.6 (0.05)	0.001
TG (mmol/L)	1.4 (0.08)	1.1 (0.02)	<0.001	2.2 (0.16)	1.8 (0.07)	0.035
men	IR n=52	non-IR n=218		IR n=45	non-IR n=74	
FPI (pmol/L)	108 (13.8)	32 (1.1)	<0.001	104 (5.5)	42 (1.8)	<0.001
Age (years)	36 (2.3)	40 (1.1)	0.089	51 (1.7)	54 (1.5)	0.13
BMI (kg/m^2)	27.0 (0.7)	24.9 (0.3)	0.009	31.2 (0.6)	29.3 (0.5)	0.020
WC (cm)	92.5 (2.1)	89.3 (0.7)	0.14	104.7 (1.3)	101.4 (1.3)	0.07
SBP (mmHg)	123 (2.3)	122 (0.9)	0.91	138 (3.2)	139 (2.0)	0.83
DBP (mmHg)	74 (1.7)	74 (0.8)	0.87	85 (2.1)	85 (1.2)	0.89
Glucose (mmol/L)	5.3 (0.09)	5.1 (0.04)	0.28	6.2 (0.27)	6.3 (0.26)	0.69
HDL-C (mmol/L)	1.4 (0.05)	1.6 (0.03)	0.026	1.3 (0.05)	1.4 (0.04)	0.029
TG (mmol/L)	1.4 (0.10)	1.3 (0.04)	0.45	2.7 (0.26)	2.3 (0.13)	0.15

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides; FPI, fasting plasma insulin; SE, standard error

[a] *t*-test for independent samples between insulin-resistant and non insulin-resistant in subjects without MetSyn; [b] *t*-test for independent samples between insulin-resistant and non insulin-resistant in subjects with MetSyn.

Table 4. Univariate relationship (*r*-values) between fasting plasma insulin, body mass index, and waist circumference and the individual metabolic syndrome variables

	Women				
	SBP	DBP	Glucose	HDL-C	TG
FPI	0.08[a]	0.06	0.28[b]	–0.18[b]	0.33[b]
BMI	0.30[b]	0.25[b]	0.26[b]	–0.06	0.31[b]
WC	0.38[b]	0.33[b]	0.23[b]	–0.06	0.30[b]
	Men				
	SBP	DBP	Glucose	HDL-C	TG
FPI	0.03	0.06	0.10[a]	–0.16[b]	0.20[b]
BMI	0.35[b]	0.26[b]	0.25[b]	–0.17[b]	0.25[b]
WC	0.43[b]	0.36[b]	0.19[b]	–0.16[b]	0.26[b]

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides; FPI, fasting plasma insulin
[a] $p<0.05$; [b] $p<0.01$.

The relationship between BP and either index of adiposity is greater than that between FPI and BP in women and men. In general, TG concentration was the variable most consistently related to all three indices in both genders. In addition, in women, the relationship between glucose and FPI (0.28) BMI (0.26) and WC (0.23) was also comparable, whereas in men the three indices were also comparably correlated to HDL-C, with values of -016, -0.17, and -0.16 for FPI, BMI, and WC, respectively.

Table 5 presents multiple regression analysis of the association between FPI, BMI and WC and the components of the MetS. No simple generalisation can be derived from these data, but they seem to complement the findings in Table 4. For example, the strength of the relationship between adiposity (particularly WC) and BP is clearly seen in both women and men. In contrast, FPI concentrations are more closely related to glucose, HDL-C and TG concentrations in both genders than either index of adiposity. However, there are some exceptions, with BMI being significantly associated with glucose in women and men, and WC significantly related to TG concentrations in women.

Discussion

Although HOMA-IR is frequently used as a surrogate estimate of insulin resistance, we have used FPI concentration

Table 5. Multiple linear regression between systolic blood pressure, diastolic blood pressure, HDL-cholesterol, triglycerides and glucose (as dependent variables) and three factors: insulin levels, waist circumference and body mass index

Dependent variable		Women				Men			
		Standardised β	*t*	*p*	*r*	Standardised β	*t*	*p*	*r*
SBP					0.384				0.429
	BMI	0.009	0.176	0.861		–0.018	–0.219	0.827	
	WC	0.385	7.793	<0.001		0.449	5.404	<0.001	
	FPI	–0.036	–1.079	0.281		–0.040	–0.839	0.402	
DBP					0.327				0.368
	BMI	0.004	0.077	0.938		–0.123	–1.419	0.157	
	WC	0.334	6.603	<0.001		0.461	5.397	<0.001	
	FPI	–0.048	–1.399	0.162		0.012	0.240	0.811	
HDL-C					0.177				0.214
	BMI	0.017	0.318	0.751		–0.086	–0.948	0.344	
	WC	–0.016	–0.302	0.763		–0.065	–0.728	0.467	
	FPI	–0.178	–5.033	<0.001		–0.130	–2.541	0.011	
TG					0.399				0.306
	BMI	0.106	2.085	0.037		0.094	1.066	0.287	
	WC	0.146	2.963	0.003		0.149	1.706	0.089	
	FPI	0.250	7.584	<0.001		0.158	3.160	0.002	
Glucose					0.332				0.251
	BMI	0.131	2.515	0.012		0.270	3.001	0.003	
	WC	0.065	1.281	0.200		–0.043	–0.484	0.629	
	FPI	0.216	6.365	<0.001		0.049	0.974	0.331	

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HDL-C, HDL cholesterol; TG, triglycerides; FPI, fasting plasma insulin; *r*, multiple *r*.

for this purpose to avoid the fact that glucose concentration is both part of the formula to calculate HOMA-IR, as well as one of the MetS criteria. FPI and HOMA-IR were highly correlated (r=0.93) in this study, and there was an 80–90% overlap when participants were divided into quartiles based on their values for FPI or HOMA-IR. Thus, our findings would be essentially identical if HOMA-IR had been used to assess insulin action, and our decision to use FPI as the surrogate estimate of insulin resistance for the theoretical reasons alluded to above should not detract from our findings. There is no 'gold standard' definition of insulin resistance, and the operational definition we have used is based on results from a prospective study in which 25% of an apparently healthy population with highest insulin concentration developed glucose intolerance, hypertension and CVD to a significantly greater degree than did the remaining 75% of the population.[17]

Turning attention to the relationship between our experimental goals and the results, the data in Figure1 and Table1 demonstrate that a diagnosis of the MetS does not provide an effective way to identify IR individuals; this diagnosis is no better at predicting the presence of insulin resistance than several of its individual components. Our finding that the MetS is not an effective way to identify IR individuals is consistent with earlier publications that have arrived at the same conclusion.[8-10] Thus, it seems reasonable to conclude that the MetS criteria do not provide an effective way to identify individuals who are IR. As a corollary, these data also suggest that care be taken in the implication of a diagnosis of the 'harmonised' version of the MetS, differentiating between its use to describe a proposed specific diagnostic classification, or as a way to refer to a state of insulin resistance and associated metabolic abnormalities. Based upon our data, and previous publications,[8-10] only the former usage is justified.

The results in Table 2 also indicate that there is substantial risk in using the diagnosis of the MetS to identify individuals at high cardio-metabolic risk. Although less than half of the women and men in the most insulin-resistant quartile (Quartile 4) have the MetS, their BP is higher, as is their glucose and TG concentrations, and their HDL-C concentrations lower, as compared with the remainder of the study population. Consequently, more than half of the most insulin-resistant quartile, at increased cardio-metabolic risk, would not be identified if the diagnosis of the MetS is required. A similar finding, and concern, was expressed by Liao *et al*.[9] in their study in which the clamp technique was used define insulin resistance.

As seen in Table 3, individuals who do not have the MetS are around 10–15 years younger, less overweight, and approximately one out of five men and women who do not meet the criteria for MetS appear to be IR. These individuals are heavier, with higher glucose and TG and lower HDL-C concentrations than similarly aged persons without the MetS who do not meet the criteria for insulin resistance. The clinical impact of these findings is most clearly seen in the IR women who do not have the MetS, but already have abnormal values for glucose (15%), TG (19%) and HDL-C (14%), with twice as many having at least one abnormality as compared with the non-IR group without the MetS. Comparable findings were described by Liao and associates,[9] who also pointed out that IR individuals who did not have the MetS had increases in very low-density lipoprotein and smaller low-density lipoprotein particles, and decreases in large HDL particle concentration. It seems likely that as the IR individuals who do not currently meet the criteria for the MetS grow older and heavier, their cardio-metabolic risk will increase substantially. In other words, the time to intervene is now, not delaying until a diagnosis of the MetS can be made.

Finally, our results question the view that abdominal obesity is the index of excess adiposity most closely associated with the MetS. Since the correlation coefficients between BMI and WC were significant (p<0.001) in both women (0.78) and men (0.83), it was not surprising that the two variables had comparable univariate relationships with the individuals components of the MetS. The results of the multiple regression analysis in Table 5 are in general supportive of the univariate relationships, in that WC is independently associated with BP, whereas FPI concentrations are more closely related to TG, glucose and HDL-C concentrations, with significant independent associations to HDL-C (women and men), TG (women and men) and glucose (women). In contrast, WC is significantly associated with TG in women, whereas BMI is significantly associated with TG and glucose in women and glucose in men. We interpret the combined thrust of these data to mean that: 1) excess adiposity makes its greatest independent contribution to the BP components of the MetS; whereas 2) the major independent contributor to the metabolic components of the MetS is insulin resistance, as estimated by FPI concentration.

Certain limitations should be stated. In the first place, we used a surrogate estimate of insulin action and an arbitrary definition of insulin resistance. However, there is a significant correlation between FPI and a direct measurement of insulin action,[15,16] and the FPI concentration is as good an estimate of insulin action as is HOMA IR. In addition, we used the results of a prospective outcome study[17] to define the 25% of the population with the highest FPI concentrations as being IR.

A second major limitation of our study is that data were combined from two populations. This problem is particularly relevant given the lack of standardisation of insulin assays. However, the sampling was random, participants came from the same geographical area, and the distribution of insulin concentrations was essentially identical. Furthermore, the results in Table 2 indicate that the actual values of the metabolic components of the MetS within any FPI concentration quartile were comparable in the two populations.

Finally, since our population was primarily of European origin, our findings are not necessarily relevant to other racial groups. However, our study population of 1,300 is much larger than the 443,[8] 74[9] and 256[10] participants in previous studies.

Consequently, in view of the caveats expressed above, it was reassuring that our findings are consistent with those of previous studies in showing that a diagnosis of the MetS is not an effective way identify IR individuals. Indeed a diagnosis of the MetS is no better at accomplishing this task than some of its individual components. Of greater clinical relevance is that reliance on a diagnosis of the MetS to identify individuals at high cardio-metabolic risk will result in overlooking many IR individuals who will benefit greatly from therapeutic intervention. An issue not addressed in earlier, smaller studies was the relationship between an index of abdominal obesity (WC), as distinct from overall obesity (BMI), with the components of the MetS. Our results provide evidence there is not any major difference between BMI and WC in the relationship to the MetS, or to its individual components, and the statement that 'the metabolic syndrome all begins with central obesity'[11] is not consistent with our findings.

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Conflict of interest

None to declare.

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