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# The atypical presentation of the metabolic syndrome components in black African women: the relationship with insulin resistance and the influence of regional adipose tissue distribution

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**Abstract**

The appropriateness of the metabolic syndrome criteria as an indicator of cardiovascular disease risk has been challenged in black Africans. Hence, the aims of this study were (1) to examine the level of agreement between the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel III (ATP III) metabolic syndrome criteria, which differ in their emphasis on central obesity; (2) to investigate the degree to which these criteria predict insulin resistance, as estimated by the homeostasis model assessment of insulin resistance (HOMA-IR); and (3) to investigate the extent to which a diagnosis of the metabolic syndrome and insulin resistance may be explained by body fat and its distribution. In 103 normal-weight (body mass index ≤25 kg/m$^2$, mean: 22.0 ± 1.8 kg/m$^2$) and 119 obese (body mass index ≥30 kg/m$^2$, mean: 33.9 ± 5.5 kg/m$^2$) urbanized black South African women (27 ± 7 years old), body composition (dual-energy x-ray absorptiometry), fat distribution (waist and computed tomography), blood pressure, fasting glucose, HOMA-IR, and lipid profiles were measured. *Insulin resistance* was defined as the upper tertile of HOMA-IR. The overall proportion of individuals who met the IDF and ATP III metabolic syndrome criteria were 13% and 10%, respectively. Agreement was high between the IDF and ATP III metabolic syndrome criteria ($\kappa$ = 0.87); however, neither criteria predicted HOMA-IR ($\kappa$ = 0.16, 95% confidence interval: 0.05-0.27 and 0.14, 95% confidence interval: 0.05-0.27, respectively). Visceral adipose tissue was the largest contributor to diagnosis of the metabolic syndrome, and waist alone (>80 cm or >88 cm) had an improved specificity (21% or 18% higher, respectively) and positive predictive value (64% or 57% higher, respectively) for identifying insulin resistance compared with the metabolic syndrome criteria. Waist circumference was a better predictor of HOMA-IR than the IDF or ATP III metabolic syndrome criteria in young black African women without known disease. The measurement of waist circumference, as an indicator of disease risk, should therefore be encouraged in the public health setting.


## 1. Introduction

In 1988, Gerald Reaven [1] noted that insulin-resistant individuals presented with a clustering of risk factors for cardiovascular disease (CVD), including glucose intolerance, high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C) levels, and elevated blood pressure (BP), compared with insulin-sensitive individuals. Consequently, the term *syndrome X* was proposed as a conceptual framework to illustrate the relationship between insulin resistance and CVD. More recently, the components of syndrome X, together with central obesity, have been used as criteria for the diagnosis of the *metabolic syndrome* [2,3], a clustering of risk factors associated with increased risk of type 2 diabetes mellitus and CVD [4,5].

Despite the plethora of research on the metabolic syndrome, there is still no uniform definition of the syndrome. Based on the hypothesis of Reaven [1], diagnosis of the metabolic syndrome using the World Health Organization [6] and European Group for Study of Insulin Resistance [7] criteria requires the presence of insulin resistance, measured using clamp methodology or fasting insulin levels, respectively, limiting their application in

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underresourced communities. In contrast, the International Diabetes Federation (IDF) [2] and the National Cholesterol Education Program Adult Treatment Panel III (ATP III) [3] do not require the diagnosis of insulin resistance. Both include identical cut points for fasting glucose, TG, HDL-C, and BP as diagnostic components, but differ in terms of waist circumference cut points (IDF, >80 cm; ATP III, >88 cm). Furthermore, the IDF criteria require the presence of central obesity, in addition to 2 or more components, whereas the ATP III criteria require any 3 components for a positive diagnosis of metabolic syndrome. Despite this difference in diagnostic criteria, both IDF and ATP III criteria have been shown to predict future risk of CVD and type 2 diabetes mellitus, though largely in white populations [8-12]. In contrast, the ATP III criteria have been shown to have low sensitivity for identifying insulin resistance in white populations [13,14], despite the presumption that insulin resistance is the underlying factor in the metabolic syndrome [1] and is associated with increased risk for CVD and type 2 diabetes mellitus [15].

There has been considerable debate regarding the clinical significance of the metabolic syndrome diagnostic criteria as well as the applicability of these clinical criteria across different ethnic groups [16]. For example, African Americans have a higher prevalence of obesity, insulin resistance, type 2 diabetes mellitus, and CVD than white Americans [17], but a lower prevalence of metabolic syndrome according to the ATP III definition [18]. Although no national prevalence data for type 2 diabetes mellitus, insulin resistance, or the metabolic syndrome exist in South Africa, epidemiologic studies conducted during the 1990s suggest a relatively high occurrence of insulin resistance and type 2 diabetes mellitus in black South African women [19-21]. On the other hand, both African Americans and urban black South African women are notable for their favorable lipid profiles [22,23], perhaps due in part to their relatively low levels of visceral adipose tissue (VAT) compared with whites [20,24]. These ethnic differences may render current metabolic syndrome cut points and the weighting of the components inappropriate for use in some groups [25].

The high prevalence of type 2 diabetes mellitus and insulin resistance in black women, despite low levels of VAT, is unexpected because VAT and insulin resistance are closely associated [26]. However, central obesity, measured by waist circumference, has been associated with elevated fasting insulin and TG levels as well as low HDL-C levels in urban black hypertensive South African women [27]. This suggests that abdominal subcutaneous adipose tissue (SAT) may play a metabolic role linking obesity and insulin resistance in black African women. Indeed, a recent study in African American women found that SAT was more closely associated with insulin resistance than VAT [28]. Therefore, quantification of SAT, specifically deep subcutaneous adipose tissue (DSAT) [29], may assist with the interpretation of anthropometric measures of risk in black African women.

The applicability of the current IDF and ATP III metabolic syndrome criteria and the association of the metabolic syndrome components with insulin resistance have not been explored in a black South African population. Thus, the aims of this study were (1) to examine the level of agreement between the IDF and ATP III metabolic syndrome criteria in a cohort of relatively young black South African women; (2) to investigate the degree to which the IDF and ATP III metabolic syndrome criteria predict insulin resistance, as estimated by the homeostasis model assessment of insulin resistance (HOMA-IR); and (3) to investigate the extent to which insulin resistance and a diagnosis of the metabolic syndrome may be explained by body fat and its distribution. Insulin resistance (HOMA-IR) was used as the main outcome variable because (*a*) it has been suggested to be the primary etiologic factor for the metabolic syndrome components and consequently the underlying cause of CVD [1,4], (*b*) it is an independent predictor of CVD and type 2 diabetes mellitus [9-12], (*c*) it has been used as a primary indicator of CVD risk in similar studies [22], and (*d*) lipid levels may not be good indicators of CVD risk in black African women [22,30].

## 2. Subjects and methods

### 2.1. Subjects

The study population consisted of 103 normal-weight (body mass index [BMI] $\leq$25 kg/m$^2$) and 122 obese (BMI $\geq$30 kg/m$^2$) premenopausal urban black South African women. Subjects were recruited from church groups, community centers, and universities and through the local press, and were included in the study if they (1) were 18 to 45 years old; (2) had no known diseases and were not taking medications for type 2 diabetes mellitus, hypertension, HIV/AIDS, or any other metabolic diseases; (3) were not pregnant, lactating, or postmenopausal (self reported); and (4) were of black South African ancestry. Three of the obese subjects were subsequently classified as having type 2 diabetes mellitus based on a fasting glucose level of at least 7.0 mmol/L. These subjects were excluded from the analysis. The Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town gave approval for the study, and written informed consent was obtained from all participants.

### 2.2. Testing procedures

Subjects completed one morning of testing after an overnight fast. A venous blood sample (10 mL) was drawn for the determination of plasma glucose, serum insulin, free fatty acids (FFA), and lipid profile (TG, total cholesterol [TC], HDL-C, and low-density lipoprotein cholesterol [LDL-C] concentrations). Blood pressure was measured 3 times at 1-minute intervals using an appropriately sized cuff and an automated BP monitor (Omron 711; Omron Health Care, Hamburg, Germany). Body composition measure-

ments were taken: weight, height, waist (level of umbilicus) and hip circumferences (largest level of the hips), and body fatness using dual-energy x-ray absorptiometry (DXA) (Hologic QDR 4500 Discovery-W, software version 4.40; Hologic, Bedford, MA). Regional body fat distribution was measured using DXA [31] and computerized tomography (CT) (Toshiba X-press Helical Scanner, Tokyo, Japan) at the level of L4-5. Visceral adipose tissue, DSAT, and superficial subcutaneous adipose tissue (SSAT) areas were quantified and converted to mass (in kilograms) using regression equations derived by Smith et al [29]. Total body superficial subcutaneous adipose tissue (tSSAT) (in kilograms) was determined by subtracting VAT and DSAT mass from total body fat mass. A cut point of VAT greater than 100 $cm^2$ was used as an indicator of CVD risk [32].

### 2.3. Blood analyses

Fasting plasma glucose concentrations were measured using the glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA), and the intraassay coefficient of variation was 0.67%. Serum insulin levels were measured by a Micro Particle Enzyme Immunoassay (AxSym Insulin Kit; Abbott, Abbott Park, IL); and the intra- and interassay coefficients of variation were 3.2% and 2.3%, respectively. Serum FFA concentrations were measured using a commercial kit (FFA Half-Micro Test; Roche, Mannheim, Germany), and the intraassay coefficient of variation was 2.1%. Serum TC, TG, and HDL-C concentrations were measured on the Roche Modular Auto Analyzer using enzymatic colorimetric assays. Low-density lipoprotein cholesterol was calculated using the Friedewald equation [33]. Insulin resistance was estimated using HOMA-IR [34] and HOMA2 [35]. Because the results obtained using the 2 methods did not differ, we used HOMA-IR to facilitate comparison with previous similar studies [22]. The HOMA-IR ranged from 0.25 to 10.90. Subjects were divided into tertiles by HOMA-IR values (tertile 1, ≤1.07; tertile 2, 1.08-2.59; and tertile 3, ≥2.60). *Insulin resistance* in this case was defined as the upper tertile for HOMA-IR and was comparable with that reported by Sumner and Cowie [22] (HOMA-IR = 2.73) in an African American population.

### 2.4. Metabolic syndrome criteria

The ATP III [3] and IDF [2] metabolic syndrome criteria for women were used to describe the sample. Metabolic syndrome, as defined by the IDF criteria, was diagnosed when central obesity (waist circumference) and an additional 2 or more of the following components were present: fasting glucose of at least 5.6 mmol/L, systolic BP of at least 130 mm Hg or diastolic BP of at least 85 mm Hg, TG of at least 1.7 mmol/L, and HDL-C not exceeding 1.29 mmol/L. Metabolic syndrome is diagnosed using the ATP III criteria when any 3 of the same components are present. The cut points for waist circumference are also different between the IDF and ATP III criteria (80 vs 88 cm, respectively). Because of the subject exclusion criteria for medication use, the lipid and BP medication criteria for both the ATP III and IDF definitions were not applicable to this study.

### 2.5. Statistical analysis

To explore the metabolic effects of extreme ranges in BMI, while maintaining a unimodal distribution for all other parameters (body fat percentage, waist circumference, VAT, SAT, BP, HOMA-IR, and lipid profile), we sampled women with a BMI not exceeding 25 $kg/m^2$ and those with a BMI of at least 30 $kg/m^2$. The data were analyzed using the STATISTICA Version 7 statistical program (StatsSoft, Tulsa, OK) and expressed as unadjusted means and standard deviations. Data were normalized by log transformation if required. Analysis of variance and the Bonferroni post hoc test were used to determine differences in basic subject characteristics and metabolic outcomes between the HOMA-IR tertiles. Linear trends were determined to describe the patterns found in the prevalence of the metabolic syndrome components by HOMA-IR tertiles. In addition, $\kappa$ statistics were used to determine the specificity and sensitivity of the ATP III and IDF metabolic syndrome criteria, using the highest tertile for HOMA-IR as the insulin-resistant group and the remainder as insulin sensitive. Values of $\kappa$ less than 0.20, 0.21 to 0.40, 0.41 to 0.60, and greater than 0.60 were considered as poor, fair, moderate, and good agreement, respectively. Visceral adipose tissue, DSAT, and tSSAT (all in kilograms) were used in logistic regression analysis to determine their contribution to a positive diagnosis of the metabolic syndrome as defined by the IDF and ATP III. Statistical significance was accepted as $P$ less than .05.

## 3. Results

### 3.1. Basic subject characteristics and metabolic outcomes

The normal-weight subjects were younger than the obese subjects, with mean ages of 24 ± 6 years and 29 ± 6 years, respectively ($P < .01$). By design, BMI (22.0 ± 1.8 $kg/m^2$ vs 33.9 ± 5.5 $kg/m^2$, $P < .01$), weight (57 ± 6 kg vs 92 ± 14 kg, $P < .01$), waist circumference (73 ± 6 cm vs 102 ± 12 cm, $P < .05$), and total adiposity (30% ± 5% vs 45% ± 4%, $P < .01$) were lower in the normal-weight women than in the obese women. There were no differences in height between the normal-weight and obese women. Despite the subjects being either of normal weight or obese, measures of body fatness and HOMA-IR were unimodally distributed. For subsequent analyses, subjects were subdivided into tertiles of HOMA-IR to explore factors associated with HOMA-IR between these groups.

The basic characteristics and metabolic outcomes of the normal-weight and obese subjects by HOMA-IR tertile are presented in Table 1. Age and height did not differ between

Table 1
Basic characteristics and metabolic outcomes of subjects according to tertiles of insulin resistance (HOMA-IR)

| | Tertile 1 | Tertile 2 | Tertile 3 | *P* value |
|---|---|---|---|---|
| | HOMA-IR ≤1.07 | HOMA-IR = 1.08-2.59 | HOMA-IR ≥2.60 | |
| | (n = 75) | (n = 74) | (n = 73) | |
| Age (y) | 28 ± 1 | 27 ± 1 | 26 ± 1 | .425 |
| Height (cm) | 161 ± 0 | 160 ± 0 | 161 ± 0 | .631 |
| Weight (kg) | 67.3 ± 2.2‡ | 73.3 ± 2.2† | 88.2 ± 2.1†, ‡ | ≤.001 |
| BMI (kg/m$^2$) | 25.1 ± 0.8‡ | 26.8 ± 0.9† | 32.4 ± 0.8†, ‡ | ≤.001 |
| Body fat (%) | 34.3 ± 1.0‡ | 36.3 ± 0.9† | 42.1 ± 1.0†, ‡ | ≤.001 |
| Waist (cm) | 79.8 ± 1.8*,‡ | 87.5 ± 1.8*,† | 100.7 ± 1.8†, ‡ | ≤.001 |
| Fasting glucose (mmol/L) | 4.1 ± 0.1‡ | 4.4 ± 0.1† | 4.7 ± 0.1†, ‡ | ≤.001 |
| Fasting Insulin (mU/L) | 4.5 ± 0.5*,‡ | 8.7 ± 0.5*,† | 19.1 ± 0.5†, ‡ | ≤.001 |
| HOMA-IR | 0.79 ± 0.16*,‡ | 1.68 ± 0.16*,† | 4.46 ± 0.16†, ‡ | ≤.001 |
| TG (mmol/L) | 0.65 ± 0.04‡ | 0.69 ± 0.04† | 0.84 ± 0.04†, ‡ | ≤.001 |
| TC (mmol/L) | 3.9 ± 0.1 | 3.9 ± 0.1 | 3.8 ± 0.1 | .499 |
| HDL-C (mmol/L) | 1.4 ± 0.1‡ | 1.4 ± 0.1† | 1.2 ± 0.5†, ‡ | .030 |
| LDL-C (mmol/L) | 2.4 ± 0.1 | 2.2 ± 0.1 | 2.3 ± 0.1 | .359 |
| TC/HDL-C | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.5 ± 0.5 | .989 |
| TG/HDL-C | 0.66 ± 0.09 | 0.62 ± 0.09 | 0.79 ± 0.10 | .276 |
| Systolic BP (mm Hg) | 105 ± 2*,‡ | 111 ± 2* | 112 ± 2‡ | ≤.001 |
| Diastolic BP (mm Hg) | 69 ± 1*,‡ | 75 ± 1* | 76 ± 1‡ | ≤.001 |

Values are expressed as means ± SE. Data and *P* values are unadjusted.
* $P < .05$ between tertiles 1 and 2.
† $P < .05$ between tertiles 2 and 3.
‡ $P < .05$ between tertiles 1 and 3.

tertiles, but all measures of body fatness increased with increasing tertile. By design, HOMA-IR was highest in tertile 3. The increase in HOMA-IR across tertiles could not be attributed to changes in fasting glucose concentrations, but was rather due to increases in fasting insulin levels (2- and 4-fold increase from tertile 1 to tertiles 2 and 3, respectively). Triglyceride levels were relatively low in all tertiles, but were significantly higher in tertile 3 compared with tertiles 1 and 2. Conversely, HDL-C concentrations were higher in tertiles 1 and 2 compared with tertile 3. High-density lipoprotein cholesterol in tertile 3 was the only metabolic outcome that met ATP III or IDF metabolic syndrome cut points. Notably, TC, LDL-C, TC/HDL-C, and TG/HDL-C were not different between the tertiles, whereas systolic and diastolic BP rose with increasing tertile.

### 3.2. Frequency of metabolic syndrome risk components

In the total subject population, the frequency of the metabolic syndrome was 13.1% and 9.9% for the IDF and

Table 2
Percentage of individuals presenting with components of the metabolic syndrome according to the ATP III and IDF criteria

| | All subjects | Tertile 1 | Tertile 2 | Tertile 3 | Linear trend | $\chi^2$ |
|---|---|---|---|---|---|---|
| | | HOMA-IR≤1.07 | HOMA-IR = 1.08-2.59 | HOMA-IR ≥ 2.60 | | |
| | (N = 223) | (n = 75) | (n = 74) | (n = 73) | *P* value | *P* value |
| *Waist circumference* | | | | | | |
| ATP III: ≥88 cm | 48.2 | 25.3 | 43.4 | 75.4 | <.001 | <.001 |
| IDF: ≥80 cm | 61.3 | 37.3 | 61.8 | 84.9 | <.001 | <.001 |
| *Fasting plasma glucose* | | | | | | |
| IDF and ATP III: ≥5.6 mmol/L | 2.2 | 1.3 | 1.3 | 6.8 | .021 | .026 |
| *Lipids* | | | | | | |
| IDF and ATP III: TG ≥1.7 mmol/L | 3.9 | 2.7 | 1.3 | 6.7 | .193 | .181 |
| IDF and ATP III: HDL-C ≤1.29 mmol/L | 46.0 | 38.9 | 37.8 | 64.9 | <.001 | .006 |
| *BP* | | | | | | |
| IDF and ATP III: ≥130/85 mm Hg | 19.9 | 12.0 | 23.7 | 25.0 | .024 | .139 |
| *Metabolic syndrome* | | | | | | |
| ATP III: ≥3 components | 10.4 | 5.3 | 6.7 | 18.7 | <.001 | .017 |
| IDF: central obesity, ≥2 components | 12.9 | 6.8 | 10.7 | 21.9 | .009 | .012 |

Table 3
The specificity and sensitivity of measures of central obesity and the ATP III and IDF metabolic syndrome criteria for predicting HOMA-IR and each other

| Criteria | Sensitivity (%) | Specificity (%) | Positive predictive (%) | Negative predictive (%) | κ |
|---|---|---|---|---|---|
| *IDF compared with ATP III metabolic syndrome criteria* | | | | | |
| IDF vs ATP III | 100.0 | 97.0 | 81.3 | 100.0 | 0.87 |
| *IDF and ATP III metabolic syndrome criteria as predictors of tertile 3* | | | | | |
| ATP III | 60.9 | 68.8 | 20.7 | 91.2 | 0.16 |
| IDF | 56.9 | 68.8 | 21.8 | 89.7 | 0.14 |
| *Waist circumference and VAT cut points as predictors of tertile 3* | | | | | |
| ATP III waist (>88 cm) | 55.4 | 85.2 | 78.4 | 66.2 | 0.40 |
| IDF waist (>80 cm) | 48.6 | 87.4 | 86.1 | 51.6 | 0.31 |
| VAT (>100 $cm^2$) | 64.3 | 69.8 | 40.9 | 85.7 | 0.45 |
| *IDF and ATP III metabolic syndrome criteria adjusted to include TC/HDL-C ratio (>4.4 mmol/L) rather than HDL-C* | | | | | |
| ATP III | 85.7 | 68.5 | 15.2 | 98.7 | 0.16 |
| IDF | 85.7 | 68.5 | 15.2 | 98.7 | 0.16 |

ATP III criteria, respectively. In the normal-weight women, the frequency of the metabolic syndrome by either criteria (IDF = 3.8%, ATP III = 0%) was lower compared with that in the obese women (IDF = 18.5%, ATP III = 18.1%). When examining the occurrence of the metabolic syndrome risk components in subjects by HOMA-IR tertiles, 2 major patterns emerged (Table 2). Firstly, there was a gradient of increasing waist circumference and BP across the tertiles. Secondly, the occurrences of impaired fasting glucose and low HDL-C concentrations were similar in tertiles 1 and 2, and increased markedly in tertile 3. This pattern was duplicated for TG levels, albeit not significantly because of the rarity of hypertriglyceridemia. The overall prevalence of impaired fasting glucose and elevated TG levels was remarkably low, even in tertile 3 (9.1% and 6.7%, respectively). The overall occurrence of the metabolic syndrome followed a similar pattern and increased 3-fold in tertile 3 compared with tertiles 1 and 2.

### 3.3. Sensitivity and specificity of the metabolic syndrome criteria and measures of central obesity

We subsequently investigated the agreement between IDF and ATP III criteria and the sensitivity and specificity of the ATP III and IDF metabolic syndrome criteria for predicting the highest level of HOMA-IR (tertile 3) (Table 3). Agreement between the IDF and ATP III metabolic syndrome criteria was very high. The sensitivity for predicting HOMA-IR was slightly higher for the ATP III than the IDF criteria, although the specificity did not differ. The positive predictive value of the IDF criteria was slightly higher than that of the ATP III criteria. The ability of both the ATP III and IDF metabolic syndrome to predict HOMA-IR was very poor. Because the low HDL-C levels may be an artifact of low TC levels in this population, we replaced the ATP III and IDF HDL-C cut points with the TC/HDL-C cut point (>4.4 mmol/L) [36]. Using this cut point, the sensitivity of both metabolic syndrome criteria to predict HOMA-IR improved by almost 30%, but remained low. The agreement between a TG/HDL-C ratio of greater than 3.0 mmol/L, which has been associated with insulin resistance [37], and the upper tertile of HOMA-IR was also very poor ($\kappa = 0.03$). However, the ability of VAT and waist circumference cut points to predict HOMA-IR was much greater. Furthermore, both waist circumference and VAT cut points had higher positive predictive values.

### 3.4. Fat distribution and the metabolic syndrome

Because body fat and its distribution may impact the risk for HOMA-IR, we investigated the fat distribution of the

Table 4
Fat distribution of the subjects according to tertiles of insulin resistance (HOMA-IR)

| | Tertile 1 | Tertile 2 | Tertile 3 | *P* value |
|---|---|---|---|---|
| | HOMA-IR ≤1.07 | HOMA-IR = 1.08-2.59 | HOMA-IR ≥2.60 | |
| | (n = 75) | (n = 74) | (n = 73) | |
| VAT ($cm^2$) | 62.1 ± 5.1$^{\ddagger}$ | 68.9 ± 4.7$^{\dagger}$ | 85.6 ± 4.7$^{\dagger,\ddagger}$ | .009 |
| SSAT ($cm^2$) | 201.8 ± 8.5$^{*,\ddagger}$ | 208.8.5 ± 8.5$^{*,\ddagger}$ | 222.7 ± 8.3$^{\dagger,\ddagger}$ | .043 |
| DSAT ($cm^2$) | 124.4 ± 9.3$^{*,\ddagger}$ | 147.5 ± 8.5$^{*,\dagger}$ | 177.6 ± 8.4$^{\dagger,\ddagger}$ | ≤.001 |
| Peripheral fat mass (kg) | 14.7 ± 0.4 | 14.1 ± 0.4 | 15.0 ± 0.4 | .684 |

Data and *P* values are adjusted for body fat percentage. Corresponding superscripts indicate a significant difference between the HOMA-IR tertiles ($P < .05$).
* $P < .05$ between tertiles 1 and 2.
† $P < .05$ between tertiles 2 and 3.
‡ $P < .05$ between tertiles 1 and 3.

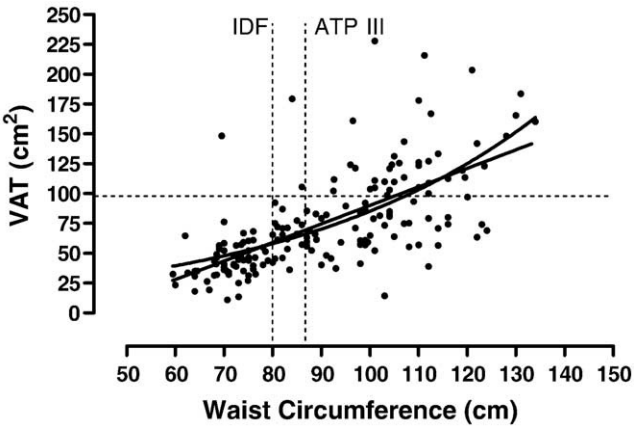


Fig. 1. Correlation of waist circumference and VAT area (linear regression, $r^2 = 0.46$, $P \leq .001$ vs nonlinear curve, $r^2 = 0.45$, $P \leq .001$). Suggested ATP III and IDF metabolic syndrome criteria waist circumference cut points are indicated by the dotted lines (88 cm and 80 cm, respectively). A VAT cut point of 100 $cm^2$ [32] is also indicated by a dotted line.

subjects by HOMA-IR tertiles (Table 4). After adjustment for total body fat percentage, VAT, SSAT, and DSAT areas increased with increasing tertile, whereas DXA-derived peripheral fat mass did not differ between tertiles.

We explored the contributions of the different adipose tissue depots to a positive diagnosis of the metabolic syndrome by entering the mass of the VAT, DSAT, and total tSSAT (in kilograms) depots into a regression model to avoid collinearity. Visceral adipose tissue (in kilograms) and tSSAT (in kilograms) were significant independent contributors to a diagnosis of the metabolic syndrome by both IDF and ATP III criteria. Within the model, VAT (in kilograms) was the largest contributor to both ATP III and IDF criteria, followed by tSSAT (in kilograms), while DSAT (in kilograms) did not contribute significantly.

### *3.5. The association between VAT and waist circumference*

Because VAT was the most significant determinant of the metabolic syndrome, we regressed VAT area against waist circumference as a means of illustrating the relationship between the physiologic marker of risk (VAT) and its clinical proxy (waist circumference) (Fig. 1). Although waist and VAT were significantly correlated, the association was extremely variable. For example, VAT ranged from 30 to 90 $cm^2$ for individuals with a waist circumference of 80 cm. Similarly, for individuals with a VAT of 100 $cm^2$, waist circumference ranged from 92 to 119 cm. Agreement between waist circumference and VAT cut points was stronger using the ATP III compared with the IDF waist cut point. Approximately 24% of the subjects met both waist circumference (IDF and ATP III) and VAT cut points, of whom 65% were in HOMA-IR tertile 3. Despite this, waist circumference by either IDF or ATP III criteria was a good predictor of HOMA-IR. A VAT cut point of greater than 100 $cm^2$ was a more sensitive predictor of HOMA-IR, although it had a low positive predictive value.

## 4. Discussion

The main findings of the study were that, although there was a high level of agreement between the IDF and ATP III criteria ($\kappa$ = 0.87), neither set of criteria was able to adequately detect insulin resistance as estimated by HOMA-IR ($\kappa$ = 0.16 and 0.14, respectively) in this cohort of relatively young black women. This may be explained by the atypical clustering of risk factors in the black African women compared with that suggested by the ATP III and the IDF expert panels [2,3]. In fact, cut points for waist circumference (ATP III, $\kappa$ = 0.40 and IDF, $\kappa$ = 0.31) and VAT ($\kappa$ = 0.45) were better indicators of HOMA-IR than the metabolic syndrome criteria.

The metabolic syndrome stems from the premise that a cluster of related risk factors (glucose intolerance, high TG levels, low HDL-C levels, and elevated BP) occurs more commonly in insulin-resistant/hyperinsulinemic individuals, which increases CVD risk [1]. Although we found that insulin resistance (HOMA-IR tertile 3) was associated with increased waist circumference, high fasting glucose and TG levels, low HDL-C levels, and elevated BP in this sample of young black South African women (Tables 1 and 2), the ATP III and IDF metabolic syndrome diagnostic criteria had a low sensitivity (62%) and specificity (69%) for identifying insulin resistance. Only 22.4% and 24.2% of insulin-resistant women in this study were diagnosed with the metabolic syndrome using the ATP III and IDF criteria, respectively. Although the sensitivity and specificity for measuring insulin resistance were low in our study population, they were higher than those reported in apparently healthy whites. For example, Cheal et al [13] reported a 46% sensitivity of the ATP III metabolic syndrome criteria to identify insulin resistance (as measured by steady-state plasma glucose from an insulin suppression test); whereas Liao et al [14] found that the sensitivity of ATP III metabolic syndrome criteria to identify insulin resistance (as measured by euglycemic-hyperinsulinemic clamp) was 20%.

Similarly, 2 separate studies in African Americans reported lower sensitivity (30%-36%) but much higher specificity (90%-96%) for diagnosing insulin resistance using the ATP III criteria [38,39]. Furthermore, the positive predictive value for insulin resistance using the ATP III criteria was dramatically lower (20%) in our study compared with that in the African American studies (85%). These differences may relate to the relative youth of our subjects, the method of quantifying insulin resistance (insulin sensitivity index vs HOMA-IR), or the inclusion of both sexes in the African American studies. Conversely, in this study, waist circumference cut points had a 21% higher specificity and a 64% greater positive predictive value for determining HOMA-IR compared with the metabolic syndrome. Most (77.2% and 85.4% for ATP II and IDF, respectively) insulin-resistant subjects were identified using the metabolic syndrome waist cut point alone, suggesting that waist circumference may be a better indicator of insulin resistance

in young black South African women than the metabolic syndrome criteria. Therefore, in keeping with reports in African Americans [38,39], we demonstrated that the clinical criteria used to diagnose the metabolic syndrome may not be a dependable measure of insulin resistance and hence CVD risk in black Africans. Moreover, these findings suggest that insulin resistance is not the primary pathogenic feature of the syndrome in this population.

The low sensitivity and specificity of the metabolic syndrome in predicting insulin resistance in this study may relate to ethnic differences in the prevalence of the different components of the metabolic syndrome. Indeed, it has been consistently shown that black South African women have low lipid levels compared with their white counterparts [23]. In the present study, more than 45% of the subjects (65% insulin-resistant subjects in tertile 3 and 38% in tertiles 1 and 2) had HDL-C levels less than the ATP III and IDF cut point; but HDL-C levels were low, possibly as an artifact of low total cholesterol [23] rather than being indicative of increased disease risk. In the 1970s, a similar phenomenon was reported in Tarahumara Indians, who had very low HDL-C and low TC levels, but presented with no CVD [40]. Consequently, we used the TG/HDL and TC/HDL-C ratios as measures of risk and found that only 0% and 20% of the insulin-resistant women exceeded the suggested cut points of greater than 3 and less than 4.4, respectively [36,37]. Furthermore, when TC/HDL-C ratio was substituted for HDL-C in the metabolic syndrome criteria, the sensitivity of both the ATP III and IDF definitions improved by almost 30% (86%), although agreement with HOMA-IR remained poor ($\kappa = 0.16$).

Furthermore, Sumner and Cowie [22] have consistently shown that TG levels in African Americans are not reliable markers of insulin resistance. Although we demonstrated a marked difference in TG levels in the insulin-resistant subjects (tertile 3) compared with the subjects in tertiles 1 and 2, the relationship between HOMA-IR and TG levels was weak ($r = 0.22$, $P = .001$). Only 7% of the insulin-resistant subjects met the IDF and ATP III metabolic syndrome cut point for TG levels, which could result in underdiagnosis of insulin resistance using the metabolic syndrome criteria in black South African women. Sumner and Cowie [22] also found a positive association between TG levels and HOMA-IR in African Americans, white Americans, and Hispanics; but higher HOMA-IR values were observed for lower TG levels in the African Americans compared with other ethnicities. They further found that, although elevated TG levels were indicative of insulin resistance, the converse was not true in African Americans, resulting in an underdiagnosis of the metabolic syndrome [22]. Genetic studies in white and black African men suggest that racial differences in lipid levels, such as TG and HDL-C, are at least partially related to genetic differences. For example, in a small study by Vega et al [41], the protective allele of the −514T/C polymorphism in the hepatic lipase gene (*LIPC*), which was associated with lower levels of hepatic lipase activity and increased HDL-C levels, was 3 times more common in black African (n = 43) compared with white men (n = 45) between the ages of 20 and 40 years.

The atypical presentation of risk in black South African women could also be related to the relatively low levels of VAT reported in African compared with white women [24]. In agreement with previous research, the black South African women in this study had lower levels of VAT relative to values reported in studies consisting of white women. For example, the insulin-resistant black South African women had a VAT of 86 $cm^2$ at a BMI of 32.7 $kg/m^2$, whereas Lovejoy et al [24] reported a VAT of 117 $cm^2$ at a BMI of 29.6 $kg/m^2$ in premenopausal white women. Lower VAT levels at similar levels of adiposity in black African women [24] may limit the usefulness of metabolic syndrome criteria in this population in 2 ways: (1) altering the lipid profile, complicating the use of TG and HDL-C cut points as described above; and (2) confounding the association between VAT and waist circumference, reducing the applicability of waist circumference cut points.

Despite lower levels of VAT, elevated waist circumference was the most prevalent and important component of the metabolic syndrome in the black South African women. In our regression analysis, VAT was a much larger contributor to a positive diagnosis of the metabolic syndrome than DSAT or tSSAT; but the relationship between VAT and waist circumference was highly variable. For a particular waist circumference, VAT ranged almost 200 $cm^2$; and for a particular VAT area, waist ranged up to 65 cm. This variability could make determination of ethnic-specific waist circumference cut points problematic in this population.

When we compared the subjects who were centrally obese according to waist circumference (>80 cm) and VAT (>100 $cm^2$) [32] cut points with those who had large waist circumferences (>80 cm) but low levels of VAT (<100 $cm^2$), we found that the subjects with both a large VAT area and waist circumference were older and had higher TG levels, BP, and HOMA-IR. After adjustment for age, these differences in metabolic outcomes remained, highlighting the additional negative impact of increased VAT level on health in centrally obese black South African women. Although centrally obese women with lower levels of VAT were at reduced risk compared with those with high VAT, centralization of fat still conferred risk, in that serum TG, BP, and HOMA-IR were elevated compared with those in the women who were not centrally obese. Therefore, in terms of health risk appraisal, waist circumference is a good indicator of insulin resistance in this population, regardless of the variability in VAT level. In fact, when we compared waist (>80 cm) and VAT (>100 $cm^2$) cut points as indicators of insulin resistance (>75th percentile of HOMA-IR), waist circumference had a 40% greater positive predictive value, although the sensitivity and specificity were higher for the VAT cut point (15 and 7%, respectively).

The strength of this study was the thorough characterization of body composition and fat distribution using DXA

and CT scans in a previously under-researched group; however, this study has some limitations. Firstly, the subjects were not randomly sampled, but were a convenience sample. The use of HOMA-IR as a measure of insulin resistance is a clear limitation of the study. However, HOMA-IR is an established risk factor for CVD as well as type 2 diabetes mellitus in black African women [42] and has been used in similar studies [22,38]. Finally, the IDF and ATP III metabolic syndrome criteria were developed to identify individuals at risk for CVD and type 2 diabetes mellitus, and not insulin-resistant individuals. However, these criteria were developed without inclusion of the African diaspora, in whom insulin resistance may be of greater clinical relevance given their peripheral fat deposition and favorable lipid profile.

In summary, despite the high level of agreement between the IDF and ATP III metabolic syndrome criteria, both were poor predictors of HOMA-IR in young black South African women. This is likely related to ethnic differences in lipids, as well as relatively low levels of VAT. Although VAT was a stronger predictor of a positive diagnosis of the metabolic syndrome than DSAT or tSSAT, there was large variability in the relationship between VAT and waist circumference. Nonetheless, waist circumference was still a good indicator of CVD risk in young black South African women. In fact, because of the atypical presentation of the metabolic syndrome criteria in this population, waist circumference was a better indicator of insulin resistance compared with the IDF or ATP III metabolic syndrome criteria.

This raises questions regarding the clinical significance of the metabolic syndrome criteria and suggests that, in black African women, the current metabolic syndrome criteria may not be greater than the sum of its parts. Furthermore, waist circumference was a sensitive marker of insulin resistance in young black African women without known disease. Although our data are cross-sectional, increased waist circumference has previously been reported to be a predictor of CVD risk in longitudinal studies in diverse ethnic groups [43]. This finding has important implications for public health in black African women, particularly in countries with limited resources, as waist circumference is an easily measurable risk factor for disease that does not involve blood sampling. To better identify individuals at risk of CVD, further research using prospective studies is required to determine ethnic-specific cut points for waist and lipid levels indicative of risk in black African women.

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