Cardiometabolic risk in polycystic ovary syndrome: a comparison of different approaches to defining the metabolic syndrome

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BACKGROUND: Polycystic ovary syndrome (PCOS) is associated with insulin resistance and features in common with the metabolic syndrome (MetS)—factors shown to predict cardiovascular risk and type 2 diabetes. We investigated the prevalence and characteristics of the MetS in PCOS by three definitions—World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) and International Diabetes Federation (IDF)—and compared that with the background population. METHODS: Cross-sectional study of 168 women with PCOS and 883 age-matched controls from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. RESULTS: Prevalence of the MetS in PCOS subjects was 33% by WHO, 37% by NCEP-ATP-III and 40% by IDF criteria, compared with 10% by NCEP-ATP-III and 13% by IDF in controls (\(P<0.001\)). MetS by WHO criteria was not calculated in the AusDiab population. Age was an independent predictor of MetS in PCOS and controls. The prevalence of MetS was significantly higher among those with PCOS (\(P=0.027\)) in obese women (BMI > 30 kg/m\(^2\)), and higher but not significantly so in overweight (BMI 25–30 kg/m\(^2\)) women (\(P=0.052\)). Dehydroepiandrosterone sulphate was associated with a lower risk of the MetS—Odds ratio 0.86 (95% confidence interval, 0.77–0.97, \(P=0.011\)). CONCLUSIONS: An approximate 4-fold increase in the prevalence of the MetS in women with PCOS compared with the general population, consistent with the proposed major role of insulin and obesity in the syndrome, implies greater risk of cardiometabolic disease in women with PCOS. However, this estimate is likely to vary according to PCOS definition, ethnicity and different aetiological pathways to PCOS.

Keywords: polycystic ovary syndrome; metabolic syndrome; insulin resistance; cardiovascular risk

Introduction

Polycystic ovary syndrome (PCOS) is a syndrome of hyperandrogenism and disordered ovulation and is the most common endocrinopathy in women of reproductive age (Knochenhauer et al., 1998). Although there are undoubtedly subtypes of PCOS, insulin resistance and hyperinsulinaemia are thought to be implicated in the pathogenesis of the syndrome in the majority. Moreover, PCOS is associated with many features of the metabolic syndrome (MetS) (Conway et al., 1992), a cluster of factors that have been shown to predict a greater risk of future cardiovascular events and type 2 diabetes (Reaven, 2002).

Although the only long-term study of PCOS has not shown an increase in coronary artery morbidity and mortality (Wild et al., 2000), increasingly, studies of vascular function and structure in PCOS have identified abnormalities in young women that imply early cardiovascular disease (Cussons et al., 2006).

Both PCOS and the MetS have undergone revision of the diagnostic criteria recently. Although other studies have examined the prevalence of MetS in PCOS (Glueck et al., 2003; Faloia et al., 2004; Talbott et al., 2004; Apridonidze et al., 2005; Dokras et al., 2005; Carmina et al., 2006; Ehrmann et al., 2006; Hahn et al., 2007; Park et al., 2007), variability of methodology makes translation of the results problematic in terms of prediction of the risk of cardiovascular disease and type 2 diabetes compared with the background population risk. This variability includes the definition of PCOS, the definition of MetS, which is inconsistent between studies, the method of recruitment of the PCOS group, the selection of controls and the age, race and weight of the participants.
The objectives of this study were to investigate the prevalence of the MetS in PCOS using three different criteria—the World Health Organization (WHO) (Alberti and Zimmet, 1998), National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) (Grundy et al., 2005) and the International Diabetes Federation (IDF) (Alberti et al., 2005) diagnostic criteria (Table I)—and to compare the prevalence of MetS in PCOS with that of a large Australian population study (Dunstan et al., 2002) which has been carefully age-matched to the age distribution of the PCOS group.

The hypotheses were that women with PCOS would exhibit an increased prevalence of the MetS compared with an age-matched background population; that the prevalence of MetS in PCOS would be greater by the WHO definition than by other definitions, given that insulin resistance is central to both PCOS and the WHO MetS definition; and that MetS in PCOS would be significantly associated with increased androgen production and increased androgen bioavailability by the suppression of sex hormone-binding globulin (SHBG), both driven by hyperinsulinaemia.

### Materials and Methods

Clinical and biochemical data were retrieved from a database of patients referred to an endocrinologist for diagnosis and management between 2000 and 2005. These patients had varying presentations—menstrual irregularity, amenorrhoea, hirsutism, alopecia, weight gain or infertility. The diagnosis of PCOS was made according to the National Institutes of Health (NIH) criteria of oligomenorrhoea together with either biochemical or clinical hyperandrogenism, with the exclusion of disorders that can mimic PCOS. Although diagnosis was by the NIH criteria these criteria conform to both the NIH criteria and the more recent European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria (Zawadski and Dunai, 1992; The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Ethics approval was obtained for this study from the Human Rights Committee of Sir Charles Gairdner Hospital.

Initially 477 PCOS case notes were reviewed, and subjects were excluded if there were insufficient data, measured together on one single occasion, to make the diagnosis of the MetS by all three definitions. To allow an age-matched comparison with the Australian population study, PCOS subjects younger than 25 years were necessarily excluded, since the Australian Diabetes, Obesity and Lifestyle study (AusDiab) did not recruit subjects younger than 25 years, leaving 168 women from the initial 477 PCOS subjects available for this analysis. The most common reasons for exclusion were age <25 years and missing data—waist circumference (WC), blood pressure and lipids. We did not impute WC from BMI.

A population group for comparison was selected from the AusDiab study. AusDiab is a national, population-based cross-sectional study of adults aged ≥25 years, which was undertaken in 1999–2000 (Dunstan et al., 2002). The age-matched control group was selected after dividing the female AusDiab study group (n = 4616) into 5-year age groups and undertaking a randomized selection [utilizing Statistical Package for the Social Sciences (SPSS) 11.5 statistical software] to achieve the same age distribution as the group of PCOS women. This proportional sampling process resulted in an available control group of 883 women for comparison with the PCOS women. This is substantially less than the total AusDiab female cohort because of the difference in the age distribution in the unselected AusDiab population compared with the PCOS women. The AusDiab and PCOS subjects were predominantly of Caucasian ethnicity (>98% of subjects).

### Definition of the MetS

Three definitions of the MetS were applied—the WHO diagnostic criteria (Alberti and Zimmet, 1998), the NCEP-ATP-III guidelines (Grundy et al., 2005) and the IDF definition (Alberti et al., 2005) (Table I). A homeostasis assessment model for insulin resistance (HOMA-IR) score was included in the WHO criteria as a measure of insulin resistance when assessing the PCOS subjects. The HOMA-IR score was calculated as: (fasting glucose (mmol/l) × fasting insulin (mU/l))/22.5, and the threshold value for the HOMA-IR score was derived from the upper quartile of HOMA-IR scores from local population data. Although the use of the HOMA-IR score to define insulin resistance is a modification of the methods, i.e. euglycaemic clamp, originally described in WHO criteria, it is in keeping with the methods applied by the AusDiab study and others utilizing the WHO criteria (Mertens et al., 2006).

### Clinical and laboratory assessment of the PCOS subjects

Weight was measured in light clothing without shoes and height was measured using a stadiometer. BMI was calculated by the formula: weight (kg)/height (m)². WC was measured with the patient standing, at a point midway between the lower costal margin and iliac crest.

### Table I. Criteria for MetS.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>IR essential, either: fasting glucose ≥ 6.1 mmol/l</td>
<td>Presence of 3 or more of: WC ≥ 88 cm</td>
<td>Essential: WC &gt; 79 cm</td>
</tr>
<tr>
<td>2 h glucose ≥ 11.1 (OGTT) or insulin resistance</td>
<td>2 h glucose ≥ 85 mmHg or on Rx for raised BP</td>
<td>plus 2 or more of: TG ≥ 1.7 mmol/l or Rx</td>
</tr>
<tr>
<td>plus 2 or more of: Obesity, either: WHR &gt; 0.85, BMI ≥ 30 kg/m² or WC ≥ 94 cm</td>
<td>TG ≥ 1.7 mmol/l or on Rx for raised TG</td>
<td>HDL &lt; 1.29 mmol/l or Rx</td>
</tr>
<tr>
<td>Dyslipidaemia, either: TG ≥ 1.7 mmol/l or HDL &lt; 1.0 mmol/l</td>
<td>HDL or on Rx for reduced HDL</td>
<td>BP ≥ 130/85 mmHg or Rx fasting glucose ≥ 5.6 mmol/l, or Diabetes or Rx</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>fasting glucose ≥ 5.6 mmol/l, or on Rx for raised glucose</td>
<td></td>
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</tbody>
</table>

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the mid-axillary line. Blood pressure was measured manually with a
sphygmomanometer.

Blood tests including an oral glucose tolerance test were performed
after an overnight fast with water allowed. Plasma insulin levels were
measured by Tosoh AIA 600 two-site immunoenzymometric assay
(Tosoh Corporation, Tokyo, Japan). Plasma glucose levels were per-
formed by glucose oxidase spectrophotometry with Beckman elec-
trode and LX20 chemistry analyser (Beckman-Coulter, Fullerton,
CA, USA). Total cholesterol, triglycerides (TG) and high density lipo-
protein (HDL) were measured by LX20 timed-endpoint method
(Beckman-Coulter, Fullerton, CA, USA). Low density lipoprotein
cholesterol (LDL-C) was calculated by the Friedewald formula:
LDL-C = Total Chol – (0.46 × TG) + HDL-C. Dehydroepiandroster-
one sulphate (DHEAS) and SHBG were analysed with chemilumi-
nescent immunometric assays on an Immulite® 2000 analyser
(Diagnostic Products Corporation, Los Angeles, CA, USA). Testoster-
one was assessed using solid phase radio-immunossay (Diagnostic
Products Corporation). The HOMA-IR threshold value for defining
insulin resistance was 1.8. The free androgen index (FAI) was calcu-
lated as: (total testosterone (nmol/l)/SHBG (nmol/l)) × 100.

Clinical and laboratory assessment of the AusDiab subjects
Fasting and 2 h post-load plasma glucose, fasting serum HDL, TGs
and urinary albumin and creatinine were determined enzymatically
using the Olympus AU600 analyser (Olympus Optical Co Ltd,
Tokyo, Japan), and insulin was assayed by radioimmunossay
(Linco Research Inc, St Charles, MO, USA). In the AusDiab study,
insulin assays were performed only in subjects aged ≥ 35 years.
Similarly to the PCOS population, the threshold value for the HOMA-IR
score was derived from the upper quartile of the reference population.
Additional details of the AusDiab study methods have been published
elsewhere (Dunstan et al., 2002).

Statistical analysis
For comparison of continuous variables a Student’s t-test was per-
formed, while a chi-square analysis was utilized for comparison of cat-
ergorical variables. McNemar’s test was applied when comparing the
prevalence of the three MetS definitions in the PCOS group. When
assessing the effects of variables such as BMI and age on the prev-
alence of the MetS, binary logistic regression analysis was employed,
with more than 10 cases per variable in all models used. The
models contained age, BMI and MetS status, and the interaction
between age and the presence of the MetS by each of the three defi-
nitions was tested. The model examining androgen status and MetS
used only data from the PCOS group. DHEAS and FAI were the
independent variables used and the model was adjusted for age. All
models were adjusted for age. All statistical analysis was performed
using SPSS version 15.0, (SPSS Inc., Chicago, IL, USA), with statisti-
cal significance defined as $P < 0.05$.

Results
Clinical and biochemical characteristics of the PCOS
and AusDiab groups
Of the 168 PCOS subjects, 28 (17%) were taking the oral con-
traceptive pill, 6 were taking treatment for hypertension, 9
subjects were taking metformin, 6 subjects had type 2 diabetes as
defined by standard criteria, fasting blood glucose ≥ 7 mmol/1
or 2 h blood glucose ≥ 11.1 mmol/1 after 75 g glucose load,
and 3 subjects had impaired glucose tolerance (2 h blood glucose
≥ 7.8 mmol/l). There was no significant difference in
BMI, blood pressure, glucose and lipids, except for TG,
between included and excluded age-matched PCOS patients.
Geometric mean for TG (95% confidence interval) in excluded
patients was 1.38 (1.02, 1.55) mmol/l compared with 1.03
(0.91, 1.55) in the included group ($P = 0.001$).

Clinical and biochemical characteristics of the PCOS and the
AusDiab subjects are shown in Table II. Women with PCOS
had a significantly higher BMI, systolic and diastolic blood
pressure and LDL, and a significantly lower HDL than the
AusDiab population group. However, fasting blood glucose was
not significantly different between the groups.

The most common individual component of the MetS
present in the PCOS group was an elevated WC, followed by
reduced HDL, then insulin resistance indicated by HOMA-
IR. The least prevalent individual component was an elevated
fasting glucose. The majority of PCOS subjects had one or
more components of the MetS when using any of the defi-
nitions. The percentage of PCOS subjects that did not have
any component of the MetS by WHO, NCEP-ATP-III and
IDF definitions was 19, 15 and 13%, respectively.

Prevalence of the MetS in PCOS and AusDiab population
The prevalence of the MetS in the 168 PCOS subjects was 33%
by WHO, 37% by NCEP-ATP-III and 40% by IDF criteria.

Table II. Characteristics of the PCOS and the AusDiab study subjects.

<table>
<thead>
<tr>
<th></th>
<th>PCOS, $n=168$, Mean (SD)</th>
<th>AusDiab, $n=883$, Mean (SD)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.3 (6.3)</td>
<td>33.7 (6.5)</td>
<td>0.246</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>25–54</td>
<td>25–53</td>
<td>NA</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.3 (8.1)</td>
<td>25.8 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI &lt; 25 (%)</td>
<td>27 (16.2%)</td>
<td>494 (55.9%)</td>
<td></td>
</tr>
<tr>
<td>BMI 25–30 (%)</td>
<td>33 (19.8%)</td>
<td>215 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 30 (%)</td>
<td>107 (64.1%)</td>
<td>174 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>WC (cm)</td>
<td>97.1 (15.2)</td>
<td>81.6 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>118 (16)</td>
<td>115 (11)</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 (11)</td>
<td>64 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.1 (1.0)</td>
<td>5.1 (0.9)</td>
<td>0.775</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.2 (0.4)</td>
<td>1.5 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>3.3 (1.0)</td>
<td>3.1 (0.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>TG (mmol/l) (mean, 95% CI)</td>
<td>1.03 (0.91, 1.13)</td>
<td>0.96 (0.93, 0.99)</td>
<td>0.098</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>3.9 (1.1)</td>
<td>3.6 (0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>5.1 (0.6)</td>
<td>5.1 (0.7)</td>
<td>0.397</td>
</tr>
</tbody>
</table>
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There was no statistically significant difference in the prevalence by the three definitions.

The 168 PCOS subjects and 883 AusDiab subjects were included in the age-matched analysis of the prevalence of the MetS using NCEP-ATP-III and IDF criteria (Fig. 1). In the AusDiab study, insulin assays were performed only in subjects aged ≥35 years, therefore the WHO criteria for MetS, using HOMA-IR, could not be compared between the groups. The prevalence of the MetS in the age-matched AusDiab study group was 10% for NCEP-ATP-III definition and 13% for the IDF definition. The prevalence of the MetS was higher in the PCOS group by both definitions (both P < 0.001). The prevalence of MetS in all women in the AusDiab group (n = 4616) has been reported elsewhere as 18% by both NCEP-ATP-III definition and IDF definitions (Cameron et al., 2007). The odds ratios (OR) (95% CI) for the prevalence of each of the MetS definitions in PCOS subjects compared with controls were similar for NCEP-ATP-III 4.76 (3.20, 7.09) and IDF 4.36 (3.02, 6.30).

Figure 1: Prevalence of the MetS in 168 women with PCOS, using the WHO, 33.3% (95% CI 26.6, 40.8), NCEP-ATP-III, 36.9% (CI 30.0, 44.0) and IDF, 39.9% (CI 33.0, 47.0), criteria. Prevalence of the MetS in 883 age-matched female controls from the AusDiab study by NCEP-ATP-III 10.3% (CI 8.0, 12.0), and IDF 13.0% (CI 11.0, 15.0) criteria is shown for comparison (open columns). Error bars represent 95% CIs. Difference in prevalence between PCOS and AusDiab was significant (P < 0.001). Comparison by the WHO definition was not available because AusDiab subjects younger than 35 years did not have fasting insulin measured. CI, confidence interval; NCEP-ATP, National Cholesterol Education Program Adult Treatment Panel; IDF, International Diabetes Federation; AusDiab, Australian Diabetes, Obesity and Lifestyle.

Logistic regression analysis, adjusted for covariates, showed age to be an independent predictor of the prevalence of MetS in both PCOS and controls. Using the IDF classification, an increase in age of 1 year increased the odds of MetS by a ratio of 1.071 (1.043, 1.101) (OR, 95% CI). Logistic regression analysis, adjusted for BMI did not show an independent effect of PCOS on the MetS. This is not surprising since there was a correlation of 0.92 between BMI and WC, a criterion for MetS in NCEP and IDF. However, using BMI < 25 as the reference group, a BMI 25–30 (overweight) had an OR (95% CI) of MetS of 7.341 (3.915, 13.764) and a BMI > 30 (obese) an OR (95% CI) of 20.660 (11.325, 37.691). As shown in Fig. 2, there was a significant upward trend (P < 0.001) in the prevalence of MetS as BMI increased. In women who were not overweight or obese there was no significant difference in the prevalence of MetS between those with or without PCOS. Among overweight women, prevalence of MetS was greater in the presence of PCOS but did not reach statistical significance (P = 0.522). In obese women the rate of MetS was significantly higher among those with PCOS (P = 0.027).

Figure 2: Prevalence of the MetS by IDF criteria according to BMI in women in the AusDiab or PCOS groups. There was a significant trend (P < 0.001) in the prevalence of MetS as BMI increased, with a statistically significant difference between PCOS and controls only in women with BMI > 30 kg/m².

Comparison of PCOS subjects with and without the MetS
As seen in Table III women with PCOS with MetS were older and more insulin resistant, indicated by a higher HOMA-IR score, had higher FAI scores consistent with lower SHBG, with no significant difference in plasma testosterone between the groups. FAI was a significant predictor of the presence of the MetS independent of age and DHEAS, with an OR of 1.13 (95% CI 1.07–1.19, P < 0.001) for 1 unit increase in FAI. An increase in DHEAS was associated with a lower risk of the MetS—OR 0.86 (95% CI, 0.77–0.97, P = 0.011), adjusted for age.

Discussion
This study has found a high prevalence of MetS in PCOS by three definitions—WHO, NCEP-ATP-III and IDF, and has found an approximate 4-fold increase in the prevalence of the MetS in women with PCOS compared with the age-matched female population. It has also shown a relationship between MetS and hyperandrogenism in PCOS, as assessed by FAI, but not with DHEAS.

Previous studies of the prevalence of the MetS in PCOS have documented an increased prevalence of MetS in women with PCOS, with some variations depending upon age, the diagnostic criteria and the comparison group studied (Fig. 3). The comparison group used for our study is a population comparison rather than disease-free ‘control’ comparison. Other studies have used normal, disease-free controls for comparison, a
method that is likely to over-estimate the burden of the MetS and therefore the imputed cardiovascular risk of PCOS in comparison with the population (Falòia et al., 2004; Dokras et al., 2005; Carmina et al., 2006; Hahn et al., 2007). There is no doubt that some of the AusDiab participants do have PCOS since it is a common endocrinopathy. We agree with Bloom et al. that population comparisons are the most informative for assessment of relative cardiovascular risk (Bloom et al., 2006). Moreover, we have been careful to select the AusDiab group to match the age distribution, rather than simply the age range, of the PCOS subjects. The prevalence of MetS in age-selected females in AusDiab was 10% by NCEP-ATP-III and 13% by IDF definition compared with 18% for all females in the AusDiab population (Cameron et al., 2007).

The revision of the diagnostic criteria, by including the ultrasound findings as a diagnostic criterion (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), has introduced new phenotypes that are less likely to have insulin resistance (Azziz, 2006). The one study that has used these criteria noted a lower prevalence of MetS in women with PCOS than has been found in other studies (Carmina et al., 2006). However, there was a similar MetS prevalence (NCEP) in ESHRE/ASRM-classified (8.2%) and NIH-classified (8.9%) PCOS. Those patients whose clinical characteristics satisfied only ESHRE/ASRM criteria had a significantly lower MetS prevalence (5%).

Our study found a very similar prevalence of MetS to a recent German study using IDF criteria (Hahn et al., 2007). Studies conducted in the USA report a somewhat higher prevalence of MetS, 46–47% (Glueck et al., 2003; Dokras et al., 2005), except for one that was conducted in the process of clinical trial recruitment and excluded women with diabetes or cardiovascular disease (Ehrmann et al., 2006). Conversely, a relatively low prevalence, 14.5%, was reported in a Korean study (Park et al., 2007) as well as in the Italian study by Carmina et al. (2006), 8–16%, suggesting a modifying effect of racial and/or cultural differences. Of interest, although our study and those of others have shown an increase in the prevalence of MetS with age, one smaller study that studied women of average age 38.7 ± 4.8 years, reported a prevalence of 15.3% (Talbott et al., 2004).

Our second hypothesis was that the prevalence of the MetS by WHO criteria would be significantly greater given the inclusion of insulin resistance in the WHO definition. This hypothesis was not upheld by the data. The prevalence of MetS was lower, but not significantly so, by WHO compared with the other criteria, despite the proposed central role of insulin resistance in the pathophysiology of PCOS. The one other study that compared MetS criteria, WHO and NCEP-ATP-III, did find a higher prevalence by WHO criteria (Carmina et al., 2006). The weight of subjects in that study was less than in our study and those of others and it is likely that that has influenced the findings. It seems that BMI outweighs the criterion of insulin resistance in overweight PCOS populations.

We, and others, have examined the prevalence of individual components contributing to the classification of MetS (Glueck et al., 2003; Apridonidze et al., 2005; Dokras et al., 2005; Carmina et al., 2006; Hahn et al., 2007; Park et al., 2007). The most common components of the MetS in the PCOS

### Table III. Comparison of PCOS subjects with and without MetS by any definition.

<table>
<thead>
<tr>
<th></th>
<th>PCOS – MetS (n = 101) (Mean and SD)</th>
<th>PCOS+MetS (n = 67) (Mean and SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.0 (5.8)</td>
<td>36.3 (6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.6 (7.5)</td>
<td>37.4 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>91.2 (15.8)</td>
<td>105.9 (14.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>111 (11)</td>
<td>127 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>66 (9)</td>
<td>76 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.8 (0.9)</td>
<td>5.5 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.3 (0.4)</td>
<td>1.1 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.78 (0.71, 0.87)</td>
<td>1.56 (1.37, 1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>4.9 (0.4)</td>
<td>5.4 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma insulin (mU/l)</td>
<td>8.77 (7.68, 10.01)</td>
<td>17.33 (14.35, 19.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR score</td>
<td>1.91 (1.66, 2.29)</td>
<td>4.16 (3.64, 4.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testosterone (mmol/l)</td>
<td>1.47 (1.52, 1.63)</td>
<td>1.79 (1.57, 2.05)</td>
<td>0.019</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>40.48 (35.15, 46.60)</td>
<td>24.27 (21.50, 27.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>3.78 (3.14, 4.56)</td>
<td>7.40 (6.18, 8.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>4.51 (4.03, 5.04)</td>
<td>4.30 (3.79, 4.89)</td>
<td>0.596</td>
</tr>
</tbody>
</table>

**Figure 3:** Prevalence of MetS found in studies of PCOS.

Studies are listed with first author and with definition of the MetS used. All studies have used only the NIH criteria for the diagnosis of PCOS, except for the studies of Carmina which examined both NIH and ESHRE/ASRM criteria. Prevalence of MetS in those studies using ESHRE/ASRM is designated Carmina (ESHRE), NIH, National Institutes of Health; ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine.

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subjects were elevated WC, elevated BMI and reduced HDL. Elevated fasting glucose is the least prevalent abnormality in all the studies including our own. In our study, fasting glucose was not significantly different between the PCOS and the AusDiab group. This is surprising given the supposed predictive value of MetS for the development of type 2 diabetes and the known association of PCOS with gestational diabetes and with a high rate of progression to type 2 diabetes (Norman et al., 1995; Lo et al., 2006). Legro et al. (1999) have highlighted the problems of the relative insensitivity of a fasting glucose in identifying impaired glucose metabolism in women.

There is debate as to whether the increased prevalence of the MetS in PCOS is independent of obesity. Studies by Apridonidze et al. (2005) and Talbott et al. (2004), both using NCEP-ATP-III criteria, found that the elevated prevalence of the MetS in women with PCOS was independent of BMI, although this finding has not been demonstrated in other studies (Falci et al., 2004; Dokras et al., 2005; Hahn et al., 2007). Using BMI < 25 as the referent group where there is no difference in MetS prevalence between the groups, our study showed an independent effect of PCOS on the diagnosis of the MetS significant only in the obese subjects with a BMI > 30 (Fig. 2).

Despite the findings of our study and those of others, there are no long-term studies showing clearly increased cardiovascular morbidity and mortality. In fact, the study by Wild et al. found that women with PCOS did not differ from age-matched controls in coronary artery mortality and morbidity, despite having significantly higher prevalence of both diabetes and family history of cardiovascular disease (Wild et al., 2000). These findings may be confounded by use of a non-standard definition of PCOS, by <50% of the original cohort being available for study and by the relatively short follow-up for the development of cardiovascular disease. An alternative hypothesis is that some unknown protective feature of PCOS, possibly DHEAS, is operating.

Estimation of cardiovascular risk in young women with PCOS by the Framingham equation is unlikely to identify a high short-term, i.e. 10-year cardiovascular risk. The recent publication from the AusDiab study, examining the relationship between MetS and the Framingham risk equation identified that the presence of the MetS was associated with an increased OR (OR 5.6, 95% CI 4.8, 6.6, using the IDF definition) of a 10-year cardiovascular risk > 15% (Cameron et al., 2007). The odds for high cardiovascular risk were higher in women and in younger subjects. Given these data it seems reasonable to suggest that identification and modification of elements of the MetS in young women with PCOS may reduce their long-term cardiovascular risk.

We have also confirmed an association between hyperandrogenaemia or androgen bioavailability, specifically FAI, and the MetS in women with PCOS, as has been found by others (Apridonidze et al., 2005). There was, however, in our study a negative correlation between DHEAS and MetS. This finding is intriguing and not clearly explained. In subjects with PCOS, DHEAS has been negatively correlated with carotid intima-media thickness (Bernini et al., 1999; Meyer et al., 2005), which is in keeping with the negative association between DHEAS and the MetS demonstrated in our study. Several factors may influence this. First, unlike testosterone, DHEAS is not preferentially bound to SHBG and therefore not influenced in the same way by insulin (Longcope, 1996). Secondly, MetS increases with age and DHEAS declines with age and adrenal ageing (Davison et al., 2005). Finally, PCOS is probably a mixture of varied aetiologies under one syndromic definition and we speculate that those women with a higher DHEAS represent a different subgroup, with greater adrenal contribution to the syndrome, less insulin-driven androgen production and therefore less risk of MetS.

Our study’s strengths are the availability of a large age-matched group of women from the AusDiab study for comparison with PCOS women and the meticulous matching of the age distribution between both groups. Limitations with the AusDiab group were that insulin levels were not available for subjects aged <35 years, eliminating our ability to compare prevalence of MetS by the WHO definition in the 25–35-year-old age group, and the non-inclusion of women younger than 25 years so that younger age group was not available for comparison. Limitations of the PCOS group were that it was derived from an endocrinology practice database so may not be representative of women with PCOS who are not referred to a specialist. Patients were defined by NIH criteria and do not include the phenotypes diagnosed purely by ultrasound criteria with menstrual irregularity, or by ultrasound criteria with hyperandro-genism. As such the group may possibly have a greater prevalence of MetS than if all ESHRE/ASRM criteria phenotypes were included. However, the group does include both lean and overweight women. Some women over the age of 25 years were not included in the study because not all criteria for the diagnosis of MetS were available on one single visit. However, comparison of included versus non-included showed them to be well matched. The excluded group did have higher TGs which would, if anything, underestimate the prevalence of MetS in PCOS.

Conclusions and future perspectives

This study confirms that the prevalence of the MetS is increased in women with PCOS, with obesity playing a pivotal role in the relationship between the two conditions. We speculate that it is the factors of PCOS diagnostic criteria, ethnicity of study subjects and obesity, and not the definition of MetS, which creates the variability between our research findings and others.

These results imply greater future risk of cardiovascular disease in women with PCOS. Paradoxically, although an increased risk of type 2 diabetes has been found in PCOS, fasting glucose was the least prevalent qualifying criterion for MetS and was not different from the population control. This study also demonstrates a positive association between the MetS and hyperandrogenaemia, largely due to the reduction in SHBG associated with insulin resistance. The finding of a negative correlation between DHEAS and MetS requires further investigation of adrenal pathways contributing to the PCOS phenotype.

The limitation of this study and of others are the limitations of all cross-sectional studies. There is a need for prospective
long-term well-controlled cohort studies, preferably starting in the teens, investigating cardiovascular outcomes in PCOS, with particular reference to the influences of obesity and insulin resistance and with careful documentation of the diagnostic criteria used to diagnose PCOS (Guzick, 2008). The effects of the currently used interventions, such as exogenous estrogens and metformin in relation to cardiovascular risk should also be investigated further. Presently, however, current recommendations regarding the management of the MetS and its individual components, with particular focus on lifestyle intervention, should be applied to all women with the MetS, with or without accompanying PCOS.

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