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ARTICLE

# Cardiovascular and metabolic characteristics of infertile Chinese women with PCOS diagnosed according to the Rotterdam consensus criteria

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Meng Guo was born on 10 December 1982 in Jinan, Shandong, PR China. In 2000, she went to Medical School of Shandong University. After 5 years' fundamental medicine study and 2 years' internship in Shandong Provincial Hospital, which is affiliated to Shandong University, she got her master degree in clinical medicine in 2007. After that, she came to Holland starting her PhD study in Utrecht University.

**Abstract** Polycystic ovary syndrome (PCOS) is strongly associated with metabolic abnormalities in Western women. However, data from other populations and geographical regions are scarce. This study evaluated cardiovascular and metabolic risk factors in Chinese infertile women diagnosed with PCOS using the 2003 Rotterdam consensus criteria. A total of 615 women representing the four PCOS phenotypes (oligo- or anovulation (AO) + hyperandrogenism (HA) + polycystic ovaries (PCO), AO + HA, AO + PCO and HA + PCO) underwent standardized metabolic screening including a 75 g oral glucose tolerance test. All groups presented with similar reproductive characteristics, with the only difference being a significantly higher Ferriman–Gallwey score for hirsutism ($P = 0.01$) in the subgroup characterized by HA + PCO. Overall, the prevalence of metabolic syndrome was 6.4%, with no difference among the four groups (range of 2.3–12.2%). Metabolic syndrome was associated with body mass index ($P < 0.001$), waist/hip ratio ($P = 0.002$), index of insulin resistance ($P = 0.005$) and fasting insulin ($P = 0.009$) in multivariate analysis. Compared with Caucasians and Chinese women in Westernized societies, mainland Chinese women with PCOS have a low risk of metabolic syndrome and its presence does not vary across the specific PCOS phenotypes.



**KEYWORDS:** ethnicity, infertility, insulin resistance, metabolic syndrome, polycystic ovary syndrome

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## Introduction

Polycystic ovary syndrome (PCOS) is primarily known for the reproductive consequences of oligo- and amenorrhoea resulting from anovulation. However, PCOS is increasingly recognized as a disorder with increased risk of (cardio) vascular and metabolic abnormalities (Teede et al., 2006; Westerveld et al., 2008). The prevalence of obesity, insulin resistance and dyslipidaemia, either as individual features or clustered in the metabolic syndrome, is increased compared with the general population (Azziz, 2002). As insulin resistance, both intrinsic (Dunaif, 1997) and secondary to obesity (Barber et al., 2006; Welt et al., 2006) plays a central role in the development of PCOS, the concept of PCOS as a metabolic disorder has recently been proposed (Sam and Dunaif, 2003).

The prevalence of metabolic syndrome in PCOS women is reported to vary between 8—43% (Apridonidze et al., 2005; Carmina et al., 2006; Cussons et al., 2008; Goverde et al., 2009; Hahn et al., 2005; Kauffman et al., 2008; Shroff et al., 2007) depending on the age, body mass index (BMI) and geographical origin of the population studied. In addition, the specific criteria applied for diagnosing PCOS affects the metabolic profile. Women diagnosed with PCOS according to the Rotterdam consensus criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) have a lower prevalence of metabolic disturbances than those meeting the criteria proposed by the National Health Institutes (Broekmans et al., 2006; Zawadski and Dunaif, 1992). Under the Rotterdam consensus criteria, the phenotypical spectrum of PCOS has expanded by the inclusion of two subgroups characterized by oligo- or anovulation and polycystic ovaries without hyperandrogenism, and hyperandrogenism plus polycystic ovaries without oligo- or anovulation, respectively. In particular, the hyperandrogenic phenotypes of PCOS seem to carry an increased risk of metabolic abnormalities (Chang et al., 2005; Goverde et al., 2009; Shroff et al., 2007), while the PCOS phenotype of oligo- or anovulation with polycystic ovaries is associated with the mildest metabolic abnormalities at a level comparable with women who do not suffer from PCOS (Kauffman et al., 2008; Shroff et al., 2007).

Most of what is known about PCOS is derived from reports on Caucasian women from Western societies. Data on PCOS and its associated metabolic characteristics in (East) Asian women have only recently started to emerge. In comparison to controls, Asian PCOS women tend to have unfavourable weight and fat distribution and higher rates of glucose intolerance and insulin resistance (Chae et al., 2008; Chen et al., 2006a; Cheung et al., 2008; Wei et al., 2009). Overall, the prevalence of the insulin resistance and metabolic syndrome seems less in Asian PCOS women than in Western PCOS women, and it is speculated that this may be because of a lower bodyweight (Li et al., 2007). Similarly to Western women, the prevalence of metabolic syndrome in Asian PCOS women varies with the geographical region, as metabolic syndrome prevalence rates of 14.5% in South Korean (Park et al., 2007), 16% in Taiwanese (Chen et al., 2006b) and up to 24.9% in Hong Kong Chinese (Cheung et al., 2008) women are reported. Within the phenotypical spectrum of PCOS, hyperandrogenaemic Asian women tend to be at increased risk for metabolic abnormalities (Lam et al., 2009) as do women without polycystic ovaries (Shi et al., 2008).

Direct cardiovascular and metabolic comparisons among all four separate phenotypes described by the Rotterdam consensus criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) in Chinese PCOS women have not yet been reported. The aim of the present study was therefore to investigate whether markers of cardiovascular and metabolic risk differed among the four phenotypes in a large group of infertile Chinese women diagnosed with PCOS according to the Rotterdam consensus criteria.

## Materials and methods

### Patients

All women visiting the Reproductive Medical Centre at Shandong Provincial Hospital, Shandong Medical University, during the period from January 2002 to January 2007 for infertility (defined as failure to conceive after 2 years of regular intercourse without contraception) and suspected to have PCOS underwent standardized initial evaluation. This consisted of evaluation of cycle duration (oligomenorrhoea mean interval between bleedings 35—181 days) or amenorrhoea (mean interval between bleedings $\geq$182 days), basic serum hormone analysis (FSH, LH, total testosterone, oestradiol, prolactin and thyroid-stimulating hormone) and ultrasound examination on day 3 of the menstrual cycle or a progestin-induced bleed in women with oligomenorrhoea or at random in women with amenorrhoea. PCOS cases were identified according to the Rotterdam consensus criteria of 2003 (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), i.e. presence of at least two of the following characteristics: oligo- or anovulation (AO), biochemical and/or clinical hyperandrogenism (HA) and polycystic ovaries (PCO). The presence of non-classic 21-hydroxylase deficiency, Cushing syndrome and androgen secreting tumours was excluded on the basis of the serum concentrations of cortisol, 17-hydroxy progesterone and total testosterone. In case of doubt, an endocrinologist was consulted following additional investigation with dexamethasone suppression test or adrenocorticotrophic hormone stimulation test and, where indicated, computed tomography or magnetic resonance imaging scan. All women identified as having PCOS then underwent standardized screening consisting of personal and family history and clinical examination. In addition, venous blood was drawn after overnight fasting for endocrine and metabolic assessment, on a random day. None of the women reported having used any medication (including Chinese or Western medicine) in the 3 months before the assessment. This study is part of a large-scale standardized assessment of women presenting with PCOS at the Reproductive Medical Centre at Shandong Provincial Hospital, Shandong Medical University approved by the ethics committee of Shandong University, of which another subset of patients was included in a pilot study on clinical and metabolic characteristics comparing women with and without PCO (Shi et al., 2008). All individuals

who participated in this study had provided written informed consent.

## Clinical investigation

Anthropometric variables such as body height, weight and waist and hip circumferences were measured and the degree of hirsutism was assessed by one research physician (YS) according to the modified Ferriman–Gallwey score (Ferriman and Gallwey, 1961), with a cut-off score of ≥6. Waist circumference was measured as the minimum value between the iliac crest and the lateral costal margin and hip circumference was measured at the most prominent point of hip level. Blood pressure was measured in sitting position after a 10-min rest using an electronic blood pressure monitor with an inflatable cuff size appropriate for the upper arm circumference. In cases where the reading was abnormal, a second measurement was done, in which cases the average of both measurements was used. Prehypertension was diagnosed when systolic blood pressure was 120–139 mmHg or diastolic blood pressure was 80–89 mmHg according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Chobanian et al., 2003). Transvaginal ultrasound was performed with Log-IQ-200 Pro series ultrasonic machine (GE Company, New York, USA) with a 6.5 Hz vaginal probe. Polycystic ovaries were defined as the presence of at least one ovary with a volume >10 ml and/or containing at least 12 follicles 2–9 mm in diameter (Balen et al., 2003).

## Endocrine and lipid parameters

Serum sex hormone analysis included FSH, LH, prolactin, total testosterone and oestradiol; these were measured by chemiluminescent immunoassay (Beckman Access Health Company, Miami, FL, USA). In all hormonal assays, the intra-assay coefficient of variation (CV) was <6% and the inter-assay CV was <15%.

Assessment of a lipid panel consisting of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides was performed after overnight fasting between 08.00 and 10.00 a.m. on a random cycle day. Plasma lipids were determined by the precipitation and enzymatic method (Ft-7060, Beckman Coulter Inc, Galway, Ireland) and the intra- and inter-assay CV were <3%.

## Assessment of glucose tolerance and insulin sensitivity

All women underwent a 75 g oral glucose tolerance test (OGTT). They were checked for a normal diet in the days preceding the test by asking them on the day of the OGTT. Plasma glucose was measured by the glucose oxidase method (AU640 automatic biochemistry analyser; Olympus Company, Hamburg, Germany); intra- and inter-assay CV were 3.5% and 5.6%, respectively. Insulin was measured by chemiluminescent immunoassay (Beckman Access Health Company) with intra- and inter-assay CVs of 4.5% and 6.3%, respectively.

Glucose metabolism was considered as abnormal if the fasting glucose measurement was ≥5.6 but <7.0 mmol/l (impaired fasting glucose) or post load glucose concentration at 120 min was 7.8–11.1 mmol/l (impaired glucose tolerance). Diabetes was defined as fasting glucose concentration ≥7.0 mmol/l or post-load glucose concentration at 120 min ≥ 11.1 mmol/l (American Diabetes Association, 2009). Insulin sensitivity was evaluated by the insulin sensitivity index ($ISI_{0,120}$) (Gutt et al., 2000) and the homeostatic model assessment (HOMA-IR). $ISI_{0,120}$ and HOMA-IR are surrogate markers for insulin resistance and, in general, correlate well with the findings of the hyperinsulinaemic euglycaemic clamp which is considered the gold standard for the evaluation of insulin sensitivity (Gutt et al., 2000; Legro et al., 2004). HOMA-IR was calculated as (fasting insulin x fasting glucose)/22.5 (Legro et al., 2004). $ISI_{0,120}$ was determined using the $t_0$ and $t_{120}$ OGTT values of both insulin and glucose as described earlier (Gutt et al., 2000) and as used by other groups (Legro et al., 2005). Neither OGTT nor calculated indices were modified for the Asian population.

## Metabolic syndrome

Two classifications were used to define the metabolic syndrome. Firstly, under the National Cholesterol Education Program – Adult Treatment Panel (NCEP ATP) III criteria modified for the Asian population (Grundy et al., 2004), metabolic syndrome is present if at least three out of five criteria are present: waist circumference ≥80 cm, triglycerides ≥1.7 mmol/l, HDL cholesterol <1.3 mmol/l, blood pressure ≥130/85 mmHg and fasting plasma glucose ≥5.6 mmol/l. According to International Diabetes Federation (Alberti et al., 2005), the diagnosis of metabolic syndrome requires waist circumference ≥80 cm and additionally two of the following criteria: triglycerides ≥1.7 mmol/l, HDL cholesterol <1.3 mmol/l, blood pressure ≥130/85 mmHg and fasting plasma glucose ≥5.6 mmol/l.

## Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows version 11.2 (SPSS, Chicago, IL, USA). Descriptive characteristics were presented in mean ± standard deviation (SD) with 95% confidence interval of the mean among different subgroups. Homogeneity tests for variance, independent sample *t*-test, and contingency table chi-squared criterion were performed when necessary.

Differences among the PCOS subgroups were analysed using ANOVA and post-hoc with Fisher's least significance definition test. Proportions were compared using the chi-squared test. Statistical significance was considered at the two-tailed *P* level of 0.05. Univariate logistic regression analysis was applied to quantify the association between several clinical and laboratory variables and the presence of metabolic syndrome as defined by the modified NCEP ATP III criteria (Grundy et al., 2004). Variables that appeared to be associated were further analysed using multivariate logistic regression analysis with backward stepwise selection, using a *P* level for entry of 0.1. The predictive

performance of these factors was assessed with receiver operating characteristic curves and finally the area under the curve.

## Results

Initially, 1059 women were diagnosed with PCOS according to the Rotterdam consensus criteria, of which 615 had undergone full metabolic standardized screening and this latter group formed the study cohort. The remaining 444 patients had incomplete metabolic assessment because of missing lipid profiles. The distribution of the study cohort across the four PCOS subgroups is depicted in **Figure 1**. The largest PCOS subgroup of the study cohort was characterized by AO + HA + PCO ($n = 471$). Together with the subgroup characterized by AO + HA but lacking PCO, they represent the phenotypes that would have also been diagnosed with PCOS according to the 1990 National Health Institutes criteria (Zawadski and Dunaif, 1992), making up 86% of the study cohort. The remaining 14.0% (85/615) of the study cases had PCO in combination with either HA or AO, representing the new PCOS subtypes under the Rotterdam consensus criteria.

The findings of the clinical and laboratory evaluation of the study group as a whole and subdivided to the PCOS phenotype, as well as those of the excluded cases, are presented in **Table 1**. Overall, small but statistically significant differences between the excluded cases and the study cases were present for weight ($P = 0.001$), BMI ($P < 0.001$), fasting glucose ($P = 0.021$), as well as $ISI_{0,120}$ ($P < 0.001$) and HOMA-IR ($P < 0.001$).

The study cohort subjects had a mean age of 28.3 ± 3.4 years (range 20—41 years), mean BMI of 25.3 ± 4.2 kg/m$^2$ (range 16.5—41.3 kg/m$^2$) and mean Ferriman—Gallwey score of 3.9 ± 5.3. The four subgroups present mostly with similar physical, endocrine and biochemical characteristics (**Table 1**). However, the subgroup characterized by HA + PCO had a slightly higher Ferriman—Gallwey score compared with the AO + HA subgroup ($P = 0.008$) in the absence of differences in testosterone concentrations.

Impaired glucose tolerance and diabetes were found in 19.0% and 7% of the total study, respectively. There were no significant differences in the indices for glucose tolerance or insulin sensitivity among the four PCOS subgroups (**Table 1**).

Most of the women (68%) presented with one or more metabolic syndrome component (**Figure 2**). In this group, increased waist circumference and elevated blood pressure were the most prevalent features. These abnormalities were mostly isolated findings, as the full metabolic syndrome was only observed in 6.5% (modified NCEP ATP III criteria; Grundy et al., 2004) and 6.4% (IDF criteria; Alberti et al., 2005)) of the total study group (**Table 2**). The prevalence of the separate metabolic syndrome components was similar across the four PCOS subgroups as was the presence of a full metabolic syndrome.

In order to identify factors predictive of the full metabolic syndrome, univariate analysis was carried out with metabolic syndrome as the dependent variable and age, weight, waist/hip ratio, BMI, serum LH, LH/FSH ratio, biochemical hyperandrogenism (yes/no), clinical hyperandrogenism (yes/no), PCO, fasting glucose, fasting insulin, insulin 120 min, glucose/insulin ratio (fasting and 120 min), HOMA-IR, $ISI_{0,120}$, testosterone and non-HDL cholesterol as independent variables. Table 3 lists the factors which were significantly associated with metabolic syndrome. Subsequent multivariate backward stepwise regression anal-

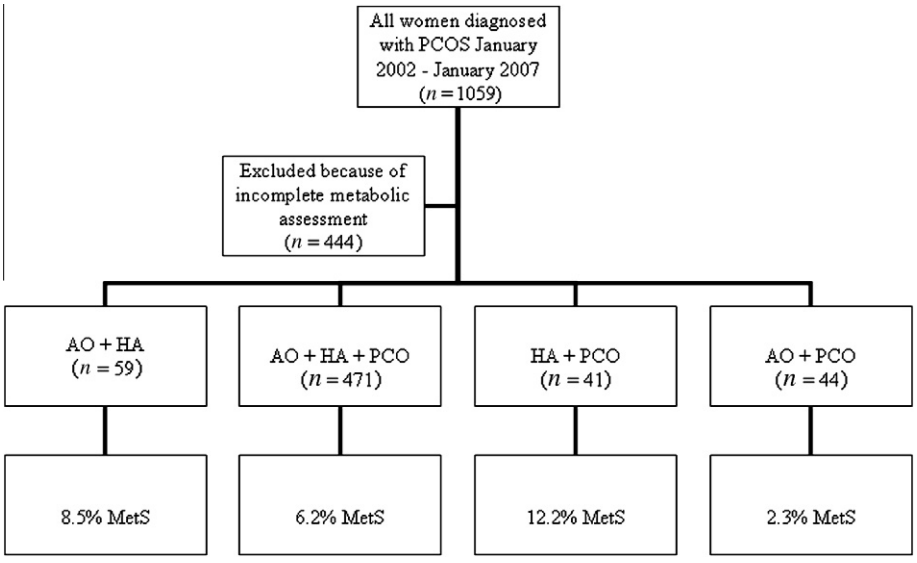


**Figure 1** Distribution of the PCOS phenotypes in the study cohort according to the Rotterdam consensus criteria (Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004) and the percentage of women with metabolic syndrome according to the modified National Cholesterol Education Program—Adult Treatment Panel III definition (Grundy et al., 2005). AO = oligo- or anovulation; HA = biochemical and/or clinical hyperandrogenism; MetS = metabolic syndrome; PCO = polycystic ovaries; PCOS = polycystic ovary syndrome.

**Table 1** Descriptive characteristics of the four PCOS subgroups of the study cohort and the excluded patients.

| *Characteristic* | *All included patients (n = 615)* | *AO + HA + PCO (n = 471)* | *AO + HA (n = 59)* | *HA + PCO (n = 41)* | *AO + PCO (n = 44)* | *All excluded patients (n = 444)* |
|---|---|---|---|---|---|---|
| General characteristics | | | | | | |
| Age (years) | 28.3 ± 3.4 (28.0–28.6) | 28.3 ± 3.4 (28.0–28.6) | 28.5 ± 3.5 (27.6–29.4) | 28.0 ± 3.2 (27.0–29.1) | 27.9 ± 3.5 (27.2–29.0) | 28.4 ± 3.5 |
| Ferriman–Gallwey score[a] | 3.9 ± 5.3 (3.9–4.3) | 3.9 ± 5.2 (3.4–4.3) | 2.6 ± 3.8 (1.6–3.6) | 5.5 ± 7.1 (3.3–7.7) | 4.2 ± 6.6 (2.1–6.1) | 3.5 ± 4.7 |
| Height (cm)[b] | 161.0 ± 4.9 (160.6–161.4) | 161.0 ± 5.0 (160.5–161.4) | 160.8 ± 4.5 (159.6–162.0) | 159.8 ± 4.8 (158.3–161.3) | 162.5 ± 4.6 (161.1–163.9) | 160.6 ± 4.6 |
| Weight (kg)[c] | 65.8 ± 12.1 (64.9–66.8) | 65.7 ± 12.2 (64.6–66.8) | 67.5 ± 12.6 (64.2–70.8) | 63.0 ± 11.2 (59.5–66.5) | 68.0 ± 11.9 (64.1–71.2) | 63.3 ± 1.12 |
| Body mass index (kg/m$^2$)[d] | 25.3 ± 4.2 (25.0–25.7) | 25.3 ± 4.2 (24.9–25.7) | 26.1 ± 4.5 (24.9–27.2) | 24.6 ± 3.9 (23.4–25.9) | 25.5 ± 4.1 (24.3–26.7) | 24.1 ± 5.1 |
| Waist circumference (cm) | 82.8 ± 10.8 (81.9–83.6) | 82.6 ± 10.8 (81.6–83.5) | 84.9 ± 11.0 (82.0–87.8) | 81.6 ± 9.8 (78.5–84.7) | 83.1 ± 10.5 (80.2–86.6) | 81.8 ± 10.6 |
| Waist/hip ratio | 0.85 ± 0.06 (0.84–0.85) | 0.84 ± 0.06 (0.84–0.85) | 0.86 ± 0.05 (0.85–0.87) | 0.85 ± 0.06 (0.83–0.87) | 0.86 ± 0.06 (0.84–0.87) | 0.85 ± 0.07 |
| Systolic BP (mmHg) | 119.1 ± 11.1 (118.2–119.9) | 119.2 ± 11.3 (118.1–120.2) | 119.5 ± 10.5 (116.8–122.2) | 118.3 ± 11.5 (114.7–121.9) | 118.0 ± 9.3 (115.6–121.2) | 117.9 ± 11.8 |
| Diastolic BP (mmHg) | 75.4 ± 10.1 (74.6–76.2) | 75.5 ± 10.3 (74.5–76.4) | 75.5 ± 9.2 (73.1–77.9) | 75.7 ± 9.4 (72.7–78.6) | 74.5 ± 9.9 (71.8–77.8) | 75.1 ± 11.6 |
| Pulse pressure (mmHg) | 43.6 ± 9.2 (42.9–44.4) | 43.7 ± 9.1 (42.9–44.5) | 44.1 ± 10.4 (41.3–46.8) | 42.6 ± 10.6 (39.3–46.0) | 43.4 ± 7.5 (41.3–45.8) | 42.4 ± 10.3 |
| Sex hormones | | | | | | |
| FSH (IU/l) | 6.9 ± 3.3 (6.6–7.2) | 6.9 ± 3.6 (6.5–7.2) | 7.2 ± 1.5 (6.8–7.6) | 7.0 ± 1.9 (6.3–7.6) | 6.9 ± 3.0 (5.9–8.0) | 6.7 ± 1.8 |
| LH (IU/l) | 10.2 ± 5.8 (9.7–10.7) | 10.0 ± 5.9 (9.4–10.5) | 10.4 ± 5.2 (9.0–11.8) | 10.9 ± 6.1 (8.8–13.0) | 11.5 ± 5.9 (9.5–13.6) | 10.1 ± 6.7 |
| LH/FSH ratio | 1.6 ± 2.3 (1.4–1.8) | 1.6 ± 2.6 (1.4–1.9) | 1.5 ± 0.8 (1.2–1.7) | 1.6 ± 1.0 (1.3–2.0) | 1.8 ± 1.1 (1.4–2.2) | 1.5 ± 0.9 |
| Total testosterone (ng/dl) | 64.9 ± 36.2 (61.9–67.9) | 64.5 ± 39.3 (60.8–68.3) | 63.6 ± 20.4 (58.1–69.2) | 67.8 ± 26.3 (58.8–76.8) | 68.6 ± 24.1 (60.6–76.6) | 65.3 ± 23.6 |
| Prolactin (ng/ml) | 59.9 ± 43.0 (56.1–63.6) | 59.9 ± 39.9 (55.9–63.8) | 70.2 ± 73.8 (48.8–91.6) | 53.3 ± 24.1 (44.7–61.8) | 52.7 ± 33.1 (42.1–63.3) | 59.3 ± 52.8 |
| Oestradiol (pg/ml) | 19.3 ± 17.1 (17.8–20.8) | 19.1 ± 18.8 (17.2–20.9) | 19.3 ± 12.3 (15.8–22.9) | 20.7 ± 6.4 (18.5–22.9) | 20.2 ± 10.6 (16.7–23.7) | 18.5 ± 15.6 |
| Lipids | | | | | | |
| Total cholesterol (mmol/l) | 4.7 ± 0.9 (4.6–4.7) | 4.7 ± 0.9 (4.6–4.8) | 4.6 ± 0.8 (4.4–4.9) | 4.7 ± 1.1 (4.3–5.0) | 4.6 ± 0.8 (4.3–4.8) | NA |
| Triglycerides (mmol/l) | 1.1 ± 1.0 (1.0–1.1) | 1.1 ± 1.0 (1.0–1.1) | 1.1 ± 0.7 (0.9–1.3) | 1.1 ± 0.7 (0.8–1.3) | 1.1 ± 0.8 (0.9–1.4) | NA |
| HDL cholesterol (mmol/l) | 1.7 ± 0.4 (1.7–1.7) | 1.7 ± 0.4 (1.7–1.7) | 1.7 ± 0.4 (1.6–1.8) | 1.7 ± 0.4 (1.5–1.8) | 1.7 ± 0.4 (1.6–1.8) | NA |
| LDL cholesterol (mmol/l) | 3.0 ± 1.1 (2.9–3.1) | 3.0 ± 1.1 (2.9–3.1) | 3.1 ± 1.0 (2.8–3.4) | 3.1 ± 1.4 (2.7–3.6) | 2.7 ± 1.0 (2.4–3.0) | NA |
| Non-HDL cholesterol (mmol/l) | 3.0 ± 1.0 (2.9–3.0) | 3.0 ± 1 1.0 (2.9–3.1) | 3.0 ± 1.0 (2.7–3.2) | 3.0 ± 1.1 (2.7–3.4) | 2.8 ± 0.9 (2.5–3.1) | NA |
| Glucose metabolism | | | | | | |
| Fasting glucose (mmol/l)[e] | 4.8 ± 0.7 (4.8–4.9) | 4.8 ± 0.7 (4.8–4.9) | 4.7 ± 0.7 (4.5–4.9) | 4.9 ± 0.9 (4.6–5.2) | 5.0 ± 0.7 (4.7–5.2) | 5.0 ± 1.0 |
| Glucose 120 min (mmol/L) | 7.1 ± 3.5 (6.8–7.40) | 7.2 ± 3.9 (6.9–7.6) | 6.8 ± 2.0 (6.3–7.3) | 6.9 ± 2.4 (6.1–7.6) | 7.3 ± 2.0 (6.3–7.3) | 7.6 ± 6.1 |
| Fasting insulin (mU/l) | 10.3 ± 8.0 (9.7–11.0) | 10.5 ± 7.9 (9.8–11.3) | 10.7 ± 10.2 (8.1–13.4) | 8.8 ± 4.9 (7.2–10.3) | 9.6 ± 5.5 (7.1–11.8) | 9.6 ± 6.3 |
| Insulin 120 min (mU/l) | 66.8 ± 54.5 (62.5–71.2) | 66.4 ± 56.7 (61.2–71.6) | 69.1 ± 53.3 (55.1–83.1) | 61.2 ± 35.4 (49.7–72.7) | 76.3 ± 60.3 (59.6–88.4) | 68.8 ± 58.2 |
| Fasting G/I ratio | 0.7 ± 0.4 (0.6–0.7) | 0.7 ± 0.4 (0.6–0.7) | 0.7 ± 0.6 (0.6–0.9) | 0.7 ± 0.4 (0.6–0.8) | 0.7 ± 0.3 (0.6–0.8) | 0.7 ± 0.4 |
| G/I ratio 120 min | 0.2 ± 0.1 (0.2–0.2) | 0.2 ± 0.1 (0.2–0.2) | 0.1 ± 0.1 (0.1–0.2) | 0.2 ± 0.2 (0.1–0.2) | 0.1 ± 0.1 (0.1–0.1) | 0.2 ± 0.6 |
| HOMA-IR[f] | 2.2 ± 2.0 (2.1–2.4) | 2.3 ± 2.0 (2.1–2.5) | 2.3 ± 2.1 (1.7–2.8) | 1.9 ± 1.1 (1.6–2.2) | 2.1 ± 1.4 (1.5–2.8) | 1.6 ± 1.6 |
| $ISI_{0.120}$[g] | 79.1 ± 32.2 (76.5–81.7) | 78.3 ± 30.1 (75.5–81.1) | 80.3 ± 32.4 (71.7–88.8) | 85.5 ± 45.4 (71.2–99.9) | 80.0 ± 20.8 (67.9–91.1) | 74.8 ± 35.7 |

AO = oligo- or anovulation; G/I = glucose/insulin; HA = clinical and/or biochemical hyperandrogenism; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCO = polycystic ovaries on ultrasound; BP = blood pressure; HOMA-IR = homeostatic model assessment for insulin resistance; $ISI_{0,120}$ = insulin sensitivity index; NA = not assessed.
Values are as mean ± SD (95% CI).

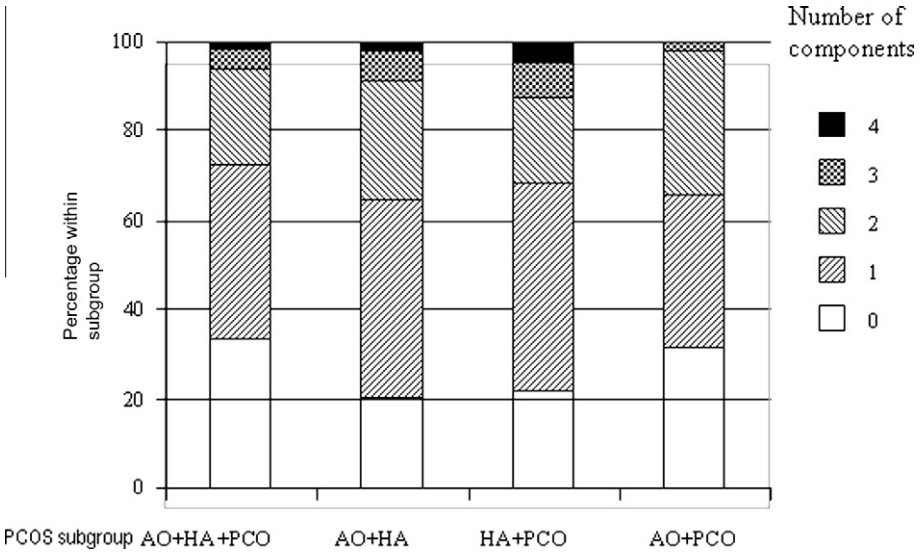


**Figure 2** Frequency of the components of metabolic syndrome according to the modified National Cholesterol Education Program—Adult Treatment Panel III criteria (Grundy et al., 2004) in the study cohort. Components: 0 = none; 1,2,3,4 = number of metabolic abnormalities; AO = oligo- or anovulation; HA = biochemical and/or clinical hyperandrogenism; PCO = polycystic ovaries; PCOS = polycystic ovary syndrome.

**Table 2** The prevalence of cardiovascular and metabolic abnormalities and the metabolic syndrome according to the different definitions in the study cohort.

| *Abnormality* | *Total (n = 615)* | *AO + HA + PCO (n = 471)* | *AO + HA (n = 59)* | *HA + PCO (n = 41)* | *AO + PCO (n = 44)* |
|---|---|---|---|---|---|
| Waist circumference ≥80 cm | 55.8 | 54.1 | 69.5 | 56.1 | 54.5 |
| Triglycerides ≥1.7 mmol/l | 11.7 | 11.5 | 11.9 | 12.2 | 13.6 |
| HDL cholesterol <1.3 mmol/l | 6.3 | 5.5 | 8.5 | 14.6 | 4.5 |
| Fasting glucose ≥5.6 mmol/l | 10.2 | 9.6 | 8.5 | 17.1 | 13.6 |
| Blood pressure ≥130/85 mmHg | 21.5 | 20.6 | 27.1 | 26.8 | 18.2 |
| Prehypertension[a] | 51.1 | 48.8 | 54.2 | 61.0 | 59.1 |
| Metabolic syndrome | | | | | |
| Modified NCEP ATP III[b] | 6.5 | 6.2 | 8.5 | 12.2 | 2.3 |
| IDF[c] | 6.4 | 6.0 | 8.6 | 12.2 | 2.3 |

AO = oligo- or anovulation; HA = clinical and/or biochemical hyperandrogenism; IDF = International Diabetes Federation; NCEP ATP = National Cholesterol Education Program — Adult Treatment Panel; PCO = polycystic ovaries. Values are percentages. There were no statistically significant differences between the groups.

ysis showed that waist/hip ratio ($P = 0.002$), BMI ($P < 0.001$), HOMA-IR ($P = 0.005$), and fasting insulin ($P = 0.009$) were significantly associated with the presence of metabolic syndrome (**Table 3**).

## Discussion

In this large, well-phenotyped cohort of Chinese women diagnosed with PCOS, in which the four phenotypic subgroups of PCOS according to the Rotterdam consensus criteria are represented, no striking differences in metabolic risk factors or glucose tolerance among the four PCOS subgroups were found. Approximately two-thirds of the study cases presented with at least one of the criteria of metabolic syndrome, in particular increased waist circumference and increased blood pressure. However, the overall prevalence of metabolic syndrome in this cohort was only 6.4%.

Determination of metabolic syndrome by the NCEP ATP III definition modified for the Asian population (Grundy

**Table 3** Logistic regression analysis of predictive clinical and biochemical variables for the metabolic syndrome according to the modified NCEP ATP III criteria (Grundy et al., 2004).

| *Variable* | *P-value* | *Odds ratio (95% CI)* | *Area under the curve* |
|---|---|---|---|
| Univariate analysis | | | |
| Weight (kg) | <0.001 | 1.07 (1.04–1.10) | 0.76 |
| BMI (kg/m$^2$) | <0.001 | 1.25 (1.15–1.35) | 0.79 |
| WHR (per 0.1 points) | <0.001 | 3.86 (2.24–6.65) | 0.72 |
| LH | 0.026 | 0.92 (0.86–0.99) | 0.61 |
| LH/FSH ratio | 0.042 | 0.61 (0.38–0.98) | 0.59 |
| Non-HDL cholesterol | 0.005 | 1.59 (1.15–2.19) | 0.65 |
| Fasting insulin | <0.001 | 1.03 (1.001–1.06) | 0.61 |
| Insulin 180 | 0.033 | 1.007 (1.001–1.013) | 0.60 |
| HOMA-IR | 0.015 | 1.16 (1.03–1.30) | 0.64 |
| Fasting G/I ratio | NS | 0.89 (0.39–1.99) | 0.54 |
| $ISI_{0,120}$ | NS | 0.99 (0.98–1.004) | 0.59 |
| Multivariate analysis[a] | | | |
| BMI | <0.001 | 1.22 (1.12–1.35) | |
| WHR (per 0.1 points) | 0.002 | 2.72 (1.45–5.08) | |
| Non-HDL cholesterol | 0.097 | 1.33 (0.95–1.87) | |
| Fasting insulin | 0.009 | 0.74 (0.59–0.93) | |
| HOMA-IR | 0.005 | 3.32 (1.44–7.66) | 0.85 |

BMI = body mass index; G/I = glucose/insulin; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment for insulin resistance; WHR = waist/hip ratio.
[a]Result of backward stepwise selection, $P < 0.10$ for inclusion in the model.

et al., 2004) and by the IDF 2005 definition (Alberti et al., 2005) showed very similar results with metabolic syndrome prevalence rates of 6.5% and 6.4%, respectively. This implies that both definitions are comparable in establishing metabolic syndrome in this population as has also been shown in a Western PCOS cohort (Cussons et al., 2008). Unfortunately, figures of background population prevalence of metabolic syndrome in the same age group in China are lacking. Strikingly, the prevalence of metabolic syndrome in this large Chinese PCOS cohort is much lower than reported from other Asian areas. Metabolic syndrome was found in 14.5% South Korean PCOS women (Park et al., 2007), in 16% Taiwanese PCOS women with PCOS (Chen et al., 2006a) and in up to 24.9% Hong Kong Chinese PCOS women (Cheung et al., 2008). It has been suggested that, with the adoption of a Western lifestyle and the introduction of fast food diets, Asian populations tend to increase the risk of metabolic abnormalities and metabolic syndrome (Cheung et al., 2008). It is very likely that this has already happened in Hong Kong, South Korea and Taiwan as these areas have been oriented towards a Western lifestyle for some time while mainland China has only recently started to change in this regard. Indeed, the prevalence of metabolic syndrome in this Chinese cohort is also much lower than in most Western PCOS cohorts, which rates ranging from 16% (Goverde et al., 2009) up to 43% (Apridonidze et al., 2005).

Another striking finding relates to the frequency distribution of the separate metabolic syndrome components. About two-thirds of the study cohort presented with at least one of the metabolic syndrome criteria. After increased waist circumference, elevated blood pressure was the second most prevalent metabolic syndrome component, while dyslipidaemia and impaired fasting glucose were observed less frequently. This is in sharp contrast with data from PCOS cohorts from the USA as well as from Asia, and with what is known of the Chinese background population. In US PCOS cohorts, dyslipidaemia is the second most prevalent metabolic abnormality behind increased waist circumference (Apridonidze et al., 2005; Ehrmann et al., 2006; Lo et al., 2006). In South Korean and Taiwanese PCOS cohorts, dyslipidaemia was found most often, and increased waist circumference and increased blood pressure were the second and third most frequent abnormality (Chen et al., 2006b; Park et al., 2007). In the general female Chinese population aged 35–44 years, dyslipidaemia and increased BMI $\geq$ 25 kg/m$^2$ were also the most frequently observed metabolic abnormalities (Gu et al., 2005). It is possible that true blood pressure values have been overestimated in part of the study subjects with the single blood pressure measurement, as this single blood pressure reading was done only in subjects with a normal blood pressure and those with an abnormal first blood pressure reading had their blood pressure measured twice. The low frequency of reduced HDL cholesterol concentrations is intriguing and warrants further study. In this cohort, frank diabetes was found in 7% and, using HOMA-IR and $ISI_{0,120}$, impaired glucose tolerance in 19.0%. These figures are in concordance with reports from other Asian PCOS cohorts. In a Thai PCOS cohort, impaired glucose tolerance was found in 20.3% and type 2 diabetes mellitus in 9.5% (Weerakiet et al., 2001), and in a smaller cohort from China, impaired glucose tolerance was present in 20.5%, and type 2 diabetes mellitus in 1.9% (Chen et al., 2006a). Although in general the HOMA-IR and

$ISI_{0,120}$ are considered to correlate well with the findings of the hyperinsulinaemic euglycaemic clamp (Gutt et al., 2000; Legro et al., 2004), the outcomes of these indices in the present study group should be interpreted with care. HOMA-IR may not always correctly represent the degree of insulin resistance, especially in women with PCOS (Ciampelli et al., 2005; Diamanti-Kandarakis et al., 2004). In addition, ethnicity is known to affect fat mass and, thus, insulin resistance (Lear et al., 2009), although the precise effects on indices of insulin sensitivity and resistance still need to be determined.

The second main finding of the current study is the absence of differences among the four phenotype groups in lipids, glucose metabolism or metabolic syndrome prevalence. Previous research involving part of the current dataset has shown that the PCOS phenotype group without PCO had higher clinical and biochemical hyperandrogenism parameters and higher total and LDL cholesterol than the PCOS phenotypes with PCO grouped together (Shi et al., 2008). In contrast in the present study, where all four phenotypes were analysed separately, no differences in cardiovascular and metabolic risk factors among the subgroup of AO + HA (without PCO) compared with the other PCOS subgroups with PCO were observed. It is possible that these differences among groups are small, in which case analysing the four PCOS phenotypic subgroups separately, with one subgroup being distinctively larger than the remaining three, did not allow for demonstrating these subtle differences. This study could not confirm the differences in hyperandrogenism parameters as described previously (Shi et al., 2008), in fact it found a significantly lower Ferriman—Gallway score in the AO + HA group compared with HA + PCO. Of note, this study shows that also in Chinese women, who present with a normal BMI and accompanying low insulin concentrations, higher ovarian sensitivity to insulin could be the mechanism of disease in PCOS, as has been pointed out previously in Western women (Baillargeon and Nestler, 2006; Ben-Shlomo et al., 1998).The strength of this study emanates from the standardized screening of a large cohort of Chinese PCOS with complete metabolic data collected in a systematic way. Moreover, all four PCOS phenotypes are represented in this population. Of note, the study subjects were recruited from a clinical infertility cohort. However, a limitation of this study is that some bias in collecting the study subjects, and thus assessing the true prevalence of metabolic abnormalities, cannot be ruled out since more than one-third of the original PCOS cohort was excluded because of incomplete metabolic assessment. Indeed, statistically significant differences were found between the study cohort and the excluded cases cohort for weight, BMI, waist circumference and systolic blood pressure, as well as for fasting insulin concentrations and HOMA-IR. However, since the clinical differences are very small it is unlikely that the results of the evaluation of metabolic syndrome in Chinese women with PCOS would have been different if the now-excluded cases had been part of that analysis. Another weakness of this study is that blood pressure measurement was done twice only in subjects with an abnormal first reading, which may have led to slight overestimation of the blood pressure in women with a normal reading.

In conclusion, although Chinese women with PCOS often demonstrate one or more components of metabolic syndrome, the prevalence of full metabolic syndrome is significantly lower than reported in other cohorts, both from Western and other Asian populations. In contrast to Caucasian women, the metabolic risk profile of Chinese women appears not to differ across the four phenotypes of PCOS definable under the Rotterdam criteria.

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