Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis

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BACKGROUND: Polycystic ovary syndrome (PCOS) is a common condition in reproductive-aged women associated with impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM2) and the metabolic syndrome.

METHODS: A literature search was conducted (MEDLINE, CINAHL, EMBASE, clinical trial registries and hand-searching) identifying studies reporting prevalence or incidence of IGT, DM2 or metabolic syndrome in women with and without PCOS. Data were presented as odds ratio (OR) [95% confidence interval (CI)] with fixed- and random-effects meta-analysis by Mantel–Haenszel methods. Quality testing was based on Newcastle–Ottawa Scaling and The Cochrane Collaboration’s risk of bias assessment tool. Literature searching, data abstraction and quality appraisal were performed by two investigators.

¹ Developed as part of an Androgen Excess PCOS Society (AE-PCOS) consensus task force on cardiovascular impact of PCOS under the leadership of R.A.W. and R.J.N.
**RESULTS:** A total of 2192 studies were reviewed and 35 were selected for final analysis. Women with PCOS had increased prevalence of IGT (OR 2.48, 95% CI 1.63, 3.77; BMI-matched studies OR 2.54, 95% CI 1.44, 4.47), DM2 (OR 4.43, 95% CI 4.06, 4.82; BMI-matched studies OR 4.00, 95% CI 1.97, 8.10) and metabolic syndrome (OR 2.88, 95% CI 2.40, 3.45; BMI-matched studies OR 2.20, 95% CI 1.36, 3.56). One study assessed IGT/DM2 incidence and reported no significant differences in DM2 incidence (OR 2.07, 95% CI 0.68, 6.30). One study assessed conversion from normal glucose tolerance to IGT/DM2 (OR 2.4, 95% CI 0.7, 8.0). No studies reported metabolic syndrome incidence.

**Conclusions:** Women with PCOS had an elevated prevalence of IGT, DM2 and metabolic syndrome in both BMI and non-BMI-matched studies. Few studies have determined IGT/DM2 or metabolic syndrome incidence in women with and without PCOS and further research is required.

**Key words:** polycystic ovary syndrome / impaired glucose tolerance / type 2 diabetes mellitus / metabolic syndrome / systematic review

**Introduction**

Polycystic ovary syndrome (PCOS) is a common condition estimated to affect 4–18% of women of reproductive age (Diamanti-Kandarakis et al., 1999; March et al., 2009). PCOS is associated with reproductive (hyperandrogenism, menstrual irregularity, anovulation, infertility and increased pregnancy complications), psychological (impaired quality of life and increased anxiety and depression) and metabolic [increased risk factors for impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM2) and cardiovascular disease (CVD)] sequelae (Azziz et al., 2006; Boomsma et al., 2006; Himlelein and Thatcher 2006). Insulin resistance is proposed as a key pathophysiological feature of PCOS contributing to both reproductive and metabolic disturbances. Reproductively, insulin resistance increases hyperandrogenism through insulin increasing ovarian androgen production, both in isolation and synergistically with luteinizing hormone (Barbieri et al., 1986), and reducing hepatic sex hormone-binding globulin production (Plymate et al., 1988). Insulin resistance may also contribute to increased cardiometabolic risk for women with PCOS. Populations with prevalent insulin resistance are known to be at increased risk for IGT, DM2 and CVD (Haffner et al., 1990; Lundgren et al., 1990; Lilloja et al., 1993; Folsom et al., 1997; Ruige et al., 1998; Lehto et al., 2000; Rutter et al., 2005). Women with PCOS often have more severe insulin resistance than weight-matched non-PCOS populations (Dunaif et al., 1989). It is postulated that women with PCOS have intrinsic insulin resistance mechanistically distinct from obesity-associated insulin resistance (Teede et al., 2007). Some evidence suggests that women with PCOS have a greater predisposition to obesity (Glueck et al., 2005) which may aggravate PCOS-related intrinsic insulin resistance and associated reproductive (Kiddy et al., 1990; Balen et al., 1995) and metabolic disturbances (Legro et al., 1999; Legro et al., 2001; Boudreaux et al., 2006; Ehrmann et al., 2006).

There is increasing focus on the complications associated with metabolic disturbances among women with PCOS. An economic evaluation estimated that 40% of the economic costs of PCOS can be attributed to DM2 in the USA. This highlights the need for prevention of long-term complications through appropriate screening, diagnosis and intervention (Azziz et al., 2005). Risk factors for DM2 and CVD in PCOS include insulin resistance, obesity, abdominal obesity, dyslipidaemia, inflammation and elevations in circulating proteins thought to lead to vascular damage. Greater endothelial dysfunction, arterial stiffness, presence of carotid and aortic plaque, carotid intima media wall thickness and coronary artery calcification (Dunaif et al., 1989; Legro et al., 1999, 2001; Talbott et al., 2004; Tarkun et al., 2004; Apridonidze et al., 2005; Glueck et al., 2005; Meyer et al., 2005a, b) have all been reported in women with PCOS compared with controls. PCOS is also identified as a significant non-modifiable risk factor associated with DM2 by the International Diabetes Federation (Alberti et al., 2007) and women with PCOS are also proposed to have a more rapid conversion from IGT to DM2 (Norman et al., 2001). Epidemiological studies suggest that DM2-associated morbidity, estimated over 20- to 30-year follow-up, is higher (Pierpoint et al., 1998; Wild et al., 2000). Although epidemiological evidence is not yet complete and has its short-comings (Pierpoint et al., 1998; Wild et al., 2000), recent evidence indicates a more frequent CVD deaths in women with PCOS (Shaw et al., 2008). Furthermore, women with PCOS have an elevated prevalence of the metabolic syndrome (Apridonidze et al., 2005; Bhattacharya, 2008) and individuals with the metabolic syndrome are at increased risk for DM2 and CVD (Isomaa et al., 2001; Lorenzo et al., 2003; Cameron et al., 2007). Disturbingly, even adolescents with PCOS commonly have IGT, DM2 and the metabolic syndrome, suggesting an adverse contribution of PCOS to metabolic health across the female lifespan (Palmert et al., 2002; Coviello et al., 2006).

There is therefore an increasing body of literature indicating an elevated prevalence of IGT, DM2, the metabolic syndrome, risk factors for CVD and potentially CVD in PCOS. However, the definitions of IGT, DM2, the metabolic syndrome and PCOS in the literature are quite varied. The phenotypic variation in presentation of PCOS is also heterogeneous and dependent on factors such as age, weight and ethnicity and diagnosis of PCOS. The objective of this systematic review and meta-analysis therefore is to assess and weight the evidence to provide a realistic estimate of differences in prevalence and incidence of IGT, DM2 and metabolic syndrome in women with and without PCOS and to assess the effect of the confounding factor adiposity on IGT, DM2 and metabolic syndrome prevalence in women with and without PCOS.

**Methods**

**Search Strategy**

We searched the listed electronic databases for studies using the MeSH terms reported below: MEDLINE (1950 to March 2009), CINAHL (1937 to 2009) and EMBASE (1980 to 2009) were utilized. We also hand searched references of relevant reviews and systematic reviews,
and we referenced search lists of included studies to locate other poten-
tially eligible studies. The Cochrane Central Register of Controlled Trials
(The Cochrane Library until first quarter of 2009), National Institute of
Health Clinical Trials register (http://clinicaltrials.gov), the Australian
New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and
the National Institute for Health Research (https://portal.nihr.ac.uk/)
were each searched using the term polycystic ovary syndrome. These
searches were performed through April 2009 and we aimed to locate
all studies reported in all languages. Authors were contacted for additional
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Health Clinical Trials register (http://clinicaltrials.gov), the Australian
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the National Institute for Health Research (https://portal.nihr.ac.uk/)
were each searched using the term polycystic ovary syndrome. These
searches were performed through April 2009 and we aimed to locate
all studies reported in all languages. Authors were contacted for additional
details where required.

The search strategy in Table I was designed specifically for MEDLINE.
This search was modified for EMBASE and CINAHL using their subject
headings instead of the MeSH subject headings.

### Table I MeSH terms.

| 1 | exp Polycystic Ovary Syndrome/ |
| 2 | Polycystic Ovar¥\$,tw |
| 3 | pco.tw or pcoc.tw |
| 4 | (sclerocystic adj3 ovar\$).tw |
| 5 | stein leventhal.tw |
| 6 | or/1–5 |
| 7 | animals/not (animals/and humans/) |
| 8 | 6 not 7 |
| 9 | diabet\$tw |
| 10 | NIDDM.tw |
| 11 | exp Diabetes Mellitus, Type 2/ |
| 12 | exp glucose intolerance/ |
| 13 | glucose intoleran$\$.tw |
| 14 | impaired glucose toleran$\$.tw |
| 15 | (obes$ adj diabet$).tw |
| 16 | dm2.tw |
| 17 | (non insulin$ depend$ or noninsulin$ depend$ or noninsulin/depend$ or non insulin/depend$).tw |
| 18 | ((typ$ 2 or typ$II or typ$ ii) adj diabet$).tw |
| 19 | (keto$resist$ or non$keto$).tw |
| 20 | ((adult$ or matur$ or late or slow or stabl$) adj diabet$).tw |
| 21 | (insulin$ defic$ adj relativ$).tw |
| 22 | (exp obesity/or obes$ mp) and (exp diabetes mellitus/or Diabet$.mp) |
| 23 | or/9–22 |
| 24 | exp Diabetes Insipidus/ |
| 25 | diabet$ insipidus.tw |
| 26 | 24 or 25 |
| 27 | 23 not 26 |
| 28 | (insulin$ resistan$ adj3 syndrome$).tw |
| 29 | metabolicsyndrom$.tw or exp metabolic syndrome X/ |
| 30 | (pluri metabolic$.syndrom$ or plurimetabolic$.syndrom$).tw |
| 31 | (syndrome$ adj x).tw |
| 32 | or/28–31 |
| 33 | 8 and (27 or 32) |

Unless otherwise stated, search terms were free text terms. MeSH, Medical Subject
Heading for Medline; Exp, exploded MeSH; mp, title, original title, abstract, name of
substance word, subject heading word; tw, text word; adj, adjacency; $, any character;
*, substitute one or no characters.

### Selection criteria

We included studies where women with PCOS were compared with
women without PCOS for the end-points of prevalence or incidence of
IGT, DM2 or the metabolic syndrome. We included articles where
PCOS was defined by the National Institute of Health (Zawdaki and
Dunaif, 1992) or European Society for Human Reproduction and Embry-
ology/American Society for Reproductive Medicine (ESHRE/ASRM) diag-
nostic criteria as two of the three criteria of hyperandrogenism, polycystic
ovaries on ultrasonad (PCO) and irregular anovulatory periods (Rotter-
dam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group,
2004a, b). Metabolic syndrome was defined by physician diagnosis or any
of the existing criteria including Adult Treatment Panel III (ATP III)
or modifications (NCEP, 2002), American Heart Association/National
Heart Lung Blood Institute (AHA) criteria or modifications (Grundy
et al., 2005), World Health Organization (WHO) criteria (Alberti and
Zimmet, 1998), International Diabetes Federation (IDF) (Alberti et al.,
2005) and other criteria (adolescent modifications (Cook et al., 2003; de
Ferranti et al., 2004; Covello et al., 2006)). criteria suggested in the ESHRE/
ASRM consensus document (Caliskan et al., 2007; Rotterdam ESHRE/
ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, b). Each
study had to have at least three of the five factors as defined by each criterion.
IGT and DM2 were defined by physician diagnosis or by oral glucose tolerance
test (OGTT) measures according to the National Diabetes Group (NDG,
1979)/National Institute of Health (NIH) criteria 1979, WHO criteria
(1985, 1980) and ADA 1997 or 2006 (Expert Committee on the Diagnosis
and Classification of Diabetes Mellitus, 1997; ADA, 2006). We excluded
studies where abnormal glucose tolerance, DM2 or IGT were exclusion cri-
eria except for incidence studies where exclusion of existing IGT/DM2
was a requirement for determining incidence rate. To avoid selection bias,
two independent reviewers (L.J.M. and F.A., see below), who were not
blinded to the names of investigators or sources of publication, identified
and selected the articles that met the inclusion criteria. Disagreements
between them were discussed and resolved by consensus or arbitration

### Data extraction

Demographic characteristics of the study population (age, BMI, study
location and ethnicity), criteria used for PCOS, IGT, DM2 or metabolic
syndrome diagnosis and pre-existing medication use were extracted
from all included studies.

### Critical appraisal

Included studies were critically appraised by two independent review
authors using a priori criteria based on the Newcastle–Ottawa Scaling
for non-randomized studies (Wells et al., 2000) and The Cochrane Collab-
oration’s tool for assessing risk of bias (Higgins and Green, 2008) (Table II
and Supplementary Table SIII). Criteria assessed representativeness of par-
ticipants selected to PCOS and control groups; comparability of partici-
pants on the basis of BMI and/or age; validity of diagnostic criteria and
outcome measurement; withdrawals and losses to follow-up; and the
presence of selective reporting. Inter-rater agreement was evaluated by
means of k-test, and disagreement was resolved by consensus.

### Outcomes of interest

The primary a priori end-point was odds of prevalence or incidence of IGT,
DM2 or the metabolic syndrome in women with PCOS compared with
women without PCOS. The secondary a priori end-point was to explore
the effects of obesity per se; therefore, odds of prevalence or incidence
of IGT, DM2 or the metabolic syndrome in subgroups with either BMI
matching, waist circumference or waist–hip ratio (WHR) matching or
Table II  Summary of critical appraisal of included studies using the Newcastle–Ottawa Quality Assessment Scale for case–control studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Selection (max 4 stars)</th>
<th>Comparability (max 2 stars)</th>
<th>Exposure (max 3 stars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Blasco et al. (2006)</td>
<td>***</td>
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<tr>
<td>Apridonidze et al. (2005)</td>
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<td>Attaoua et al. (2008)</td>
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<tr>
<td>Bhattacharya (2009)</td>
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<tr>
<td>Boudreaux et al. (2006)</td>
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<td>Caliskan et al. (2007)</td>
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<td>Carmina et al. (2006)</td>
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<tr>
<td>Cheung et al. (2008)</td>
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<tr>
<td>Ciampelli et al. (1998)</td>
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<tr>
<td>Cibula et al. (2000)</td>
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<tr>
<td>Coviello et al. (2006)</td>
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<td>Cussons et al. (2008)</td>
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<tr>
<td>Diamanti-Kandarakis et al. (2005)</td>
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<td>Dokras et al. (2005)</td>
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<tr>
<td>dos Reis et al. (1995)</td>
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<td>Dunaff et al. (2001)</td>
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<tr>
<td>Echiburu et al. (2008)</td>
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<tr>
<td>Falioa et al. (2004)</td>
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<td>Glueck et al. (2003)</td>
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<td>Gulcelik et al. (2008)</td>
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<tr>
<td>Legro et al. (2005)</td>
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<tr>
<td>Leibel et al. (2006)</td>
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<td>Lo et al. (2006)</td>
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<tr>
<td>Marquez et al. (2008)</td>
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<td>Moini and Eslami (2009)</td>
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<td>Phy et al. (2004)</td>
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<tr>
<td>Rajkhowa et al. (1996)</td>
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<tr>
<td>Sawathiparnich et al. (2005)</td>
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<td>Shaw et al. (2008)</td>
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<tr>
<td>Shroff et al. (2007b)</td>
<td>***</td>
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<tr>
<td>Shroff et al. (2007a)</td>
<td>**</td>
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<tr>
<td>Sir-Petermann et al. (2004)</td>
<td>***</td>
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<tr>
<td>Vrbikova et al. (2005)</td>
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<tr>
<td>Welt et al. (2006)</td>
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<tr>
<td>Yarali et al. (2001)</td>
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</tbody>
</table>

**SELECTION**

1. Is the case definition adequate? (a) yes, with independent validation*, (b) yes, e.g. record linkage or based on self-reports, (c) no description.
2. Representativeness of the cases: (a) consecutive or obviously representative series of cases*, (b) potential for selection biases or not stated.
3. Selection of controls: (a) community controls*, (b) hospital controls, (c) no description.
4. Definition of controls: (a) no history of disease (end-point)*, (b) no description of source.

**COMPARABILITY**

1. Comparability of cases and controls on basis of design or analysis: (a) study controls for ___ (most important factor)*, (b) study controls for any additional factor* (could be modified to indicate specific control for a second factor).

**EXPOSURE**

1. Ascertainment of exposure: (a) secure record (e.g. surgical records)*, (b) structured interview where blind to case/control status*, (c) interview not blinded to case/control status, (d) written self-report or medical record only, (e) no description.
2. Same method of ascertainment for cases and controls: (a) yes*, (b) no.
3. Non-response rate: (a) same rate for both groups*, (b) non-respondents described, (c) rate different and no designation.
lean participants only were compared in women with PCOS compared with controls.

**Statistical analysis**

The dichotomous outcome measure was the proportion of patients with IGT, DM2 or the metabolic syndrome (prevalence) or the proportion of patients who developed IGT, DM2 or the metabolic syndrome over time (incidence). Data are presented as odds ratio [(OR, 95% confidence interval (CI)]. $I^2$ was used to assess heterogeneity with significance set at $P < 0.1$. Data with no statistical heterogeneity were combined for meta-analysis to calculate a pooled estimate of IGT, DM2 or the metabolic syndrome prevalence or incidence and both fixed- and random-effects modelling (Mantel–Haenszel methods) for analysis were used. Subgroup analyses were performed to examine the contribution of the confounding factors of adiposity (BMI matching) and adiposity distribution (waist circumference or WHR matching) and for studies assessing lean participants only. The statistical analyses were performed using RevMan5 (2008).

**Results**

**Characteristics of included studies**

The search yielded 2192 citations. On the basis of a priori selection criteria (see below), screening for title or abstract identified 126 studies for assessment of full text. Of these, 2 articles were excluded due to duplication of data, 47 due to exclusion criteria of IGT or DM2, 13 due to PCOS diagnosis not consistent with ESHRE/ASRM or NIH criteria and 29 due to lack of data or unable to determine IGT, DM2 or metabolic syndrome prevalence or incidence. We included 35 full-text studies for our final analysis. All included studies were observational employing a cross-sectional or cohort study design. All of the final 35 studies describing IGT, DM2 and the metabolic syndrome (Fig. 1, Tables III and IV) were included (Supplementary Tables SI and SII). Of these, 24 used diagnosis consistent with NIH criteria and 11 used diagnosis consistent with ESHRE/ASRM criteria (Rajkhowa et al., 1996; Vrbikova et al., 2005; Carmina et al., 2006; Leibel et al., 2006; Welt et al., 2006; Calissan et al., 2007; Shroff et al., 2007b; Attaoua et al., 2008; Cheung et al., 2008; Gulcelik et al., 2008; Moini and Eslami 2009). All studies assessed post-menarcheal and pre-menopausal women with the exception of three which assessed adolescents (Sawathiparnich et al., 2005; Coviello et al., 2006; Leibel et al., 2006), two which assessed post-menopausal women only (Cibula et al., 2000; Shaw et al., 2008) and one assessed both pre- and post-menopausal women (Lo et al., 2006). Four used population studies for controls (Cibula et al., 2000; Glueck et al., 2003; Apridonidze et al., 2005; Coviello et al., 2006). The majority of studies assessed overweight or obese women with PCOS with the exception of five studies where lean subgroups were assessed or the mean BMI of the population was $< 25$ kg/m² (dos Reis et al., 1995; Ciampelli et al., 1998; Faloia et al., 2004; Vrbikova et al., 2005; Attaoua et al., 2008).

![Flow chart for systematic review and meta-analysis.](https://academic.oup.com/humupd/article-abstract/16/4/347/802669)
Methodological quality

Only 5 of the 35 included studies were found to have a high risk of detection bias; however, all were found to be at high risk of selection bias, performance bias, attrition bias (incomplete outcome data) and reporting bias (selective outcome reporting). Thirty-one of the 35 studies provided adequate criteria for diagnosis of the outcomes of interest and all studies provided a description of how the outcomes were measured (Table II and Supplementary Table SIII). Five studies did not report whether the same method was used for both groups to measure the outcomes. Fifteen studies selected participants consecutively. Twenty-one studies reported that cases and controls were selected from the same community sample, whereas the remainder used different population samples for cases and controls. In most of the included studies (31), family history of the outcome of interest was unclear or not reported. Three studies excluded family history of the outcome of interest for all participants (Dunaif et al., 2001; Diamanti-Kandarakis et al., 2005; Legro et al., 2005), thus introducing a potentially healthier control population and biased estimates. Comparability of participants on the basis of BMI and/or age was addressed in all but six studies. Age- and BMI-matched populations were reported in 10 studies.

### Table III Summary of studies assessing IGT and DM2 in women with and without PCOS.

<table>
<thead>
<tr>
<th>Author</th>
<th>PCOS</th>
<th>Control</th>
<th>IGT/DM2 definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajkhowa et al. (1996)</td>
<td>N = 72 ESHRE/ASRM, age: 26 years, BMI: 31.6 kg/m²</td>
<td>N = 39, age: 30 years, BMI: 25.9 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Cibula et al. (2000)</td>
<td>N = 28 NIH, age: 51.9 years, BMI: 28.0 kg/m²</td>
<td>N = 752, age: 51 years, BMI: 28.2 kg/m²</td>
<td>Fasting glucose ≥ 7.0 mmol/l, current medical tx</td>
</tr>
<tr>
<td>Dunaif et al. (2001)</td>
<td>N = 14 NIH, age: 29 years, BMI: 40.5 kg/m²</td>
<td>N = 12, age: 30 years, BMI: 40.5 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Yarali et al. (2001)</td>
<td>N = 30 NIH, age: 27.9 years, BMI: 27.3 kg/m²</td>
<td>N = 30, age: 31.4 years, BMI: 25.0 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Falioa et al. (2004)</td>
<td>N = 50 NIH, age: 22 years, BMI: n = 23 lean 22 kg/m², n = 27 overweight 32 kg/m²</td>
<td>N = 20, age: 26 years, BMI: n = 12 lean 20 kg/m², n = 8 overweight 37 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Phy et al. (2004)</td>
<td>N = 7 NIH, age: 30.9 years, BMI: 30.9 kg/m²</td>
<td>N = 18, age: 31.1 years, BMI: 25.0 kg/m²</td>
<td>ADA</td>
</tr>
<tr>
<td>Sir-Petermann et al. (2004)</td>
<td>N = 146 NIH, age: 22 years, BMI: 29.0 kg/m²</td>
<td>N = 97, age: 24 years, BMI: 24.8 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Diamanti-Kandarakis et al. (2005)</td>
<td>N = 29 NIH, age: 25.8 years, BMI: 27.2 kg/m²</td>
<td>N = 22, age: 28.1 years, BMI: 23.3 kg/m²</td>
<td>OGTT, not stated</td>
</tr>
<tr>
<td>Legro et al. (2005)</td>
<td>N = 71 NIH, age: 27–29.6 years, BMI: 35.7–38.7 kg/m²</td>
<td>N = 23, age: 36.2 years, BMI: 29.3 kg/m²</td>
<td>ADA/WHO</td>
</tr>
<tr>
<td>Sawthiparnich et al. (2005)</td>
<td>N = 6 NIH, age: 14.1 years, BMI: 37.4 kg/m²</td>
<td>N = 6, age: 14.5 years, BMI: 34.2 kg/m²</td>
<td>ADA</td>
</tr>
<tr>
<td>Alvarez-Blasco et al. (2006)</td>
<td>N = 32 NIH, age: 26 years, BMI: 34.8 kg/m²</td>
<td>N = 72, age: 32 years, BMI: 35.2 kg/m²</td>
<td>Not stated</td>
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<tr>
<td>Boudreaux et al. (2006)</td>
<td>N = 97 NIH, age: 38.0 years, BMI: 31.6 kg/m²</td>
<td>N = 95, age: 40.0 years, BMI: 26.2 kg/m²</td>
<td>Fasting glucose ≥ 7.0 mmol/l or doctor diagnosis</td>
</tr>
<tr>
<td>Leibel et al. (2006)</td>
<td>N = 36 ESHRE/ASRM, age: 16 years, BMI: 30.3–37.9 kg/m²</td>
<td>N = 21, age: 15.2 years, BMI: 24.9 kg/m²</td>
<td>ADA</td>
</tr>
<tr>
<td>Lo et al. (2006)</td>
<td>N = 11 035, age: 30.7 years, BMI: 67% obese</td>
<td>N = 55 175, age: 30.8 years, BMI: 31.4% obese</td>
<td>Hospital discharge or ≥ 2 outpatient diagnosis</td>
</tr>
<tr>
<td>Attoua et al. (2008)</td>
<td>N = 207 (107 lean, 100 obese) ESHRE/ASRM, age: 23.1–26.3 years, BMI: 23.0–34.9 kg/m²</td>
<td>N = 100, age: 34.1 years, BMI: 22.2 kg/m²</td>
<td>ADA (2006)</td>
</tr>
<tr>
<td>Echiburu et al. (2008)</td>
<td>N = 159 NIH, age: 24.3 years, BMI: 28.7 kg/m²</td>
<td>N = 93, age: 24.6 years, BMI: 25.5 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Marquez et al. (2008)</td>
<td>N = 50 NIH, age: 28.8 years, BMI: 33.3 kg/m²</td>
<td>N = 70, age: 28.6 years, BMI: 23.4 kg/m²</td>
<td>Fasting glucose ≥ 7.0 mmol/l or history of DM2</td>
</tr>
<tr>
<td>Shaw et al. (2008)</td>
<td>N = 104 NIH, age: 62.5 years, BMI: 31.1 kg/m²</td>
<td>N = 286, age: 65.8 years, BMI: 28.4 kg/m²</td>
<td>Fasting glucose ≥ 7.8 mmol/l or medication</td>
</tr>
<tr>
<td>Bhattacharya (2009)</td>
<td>N = 264 NIH, age: 23.1 years, BMI: 26.8 kg/m²</td>
<td>N = 116, age: 25.7 years, BMI: 24.56 kg/m²</td>
<td>WHO</td>
</tr>
<tr>
<td>Moini and Eslami (2009)</td>
<td>N = 273 ESHRE/ASRM, age: 27.95 years, BMI: 27.91 kg/m²</td>
<td>N = 276, age: 31.1 years, BMI: 25.56 kg/m²</td>
<td>Self-report</td>
</tr>
</tbody>
</table>

ADA, American Diabetes Association; DM2, type 2 diabetes mellitus; ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; IGT, impaired glucose tolerance; NDG, National Diabetes Group; NIH, National Institute of Health; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; WHO, World Health Organization.
of BMI-matched studies, nine reported on waist circumference (Yarali et al., 2001; Faloia et al., 2004; Alvarez-Blasco et al., 2006) and two assessed DM2 prevalence (Cibula et al., 2000; Alvarez-Blasco et al., 2006). Four of the studies assessing metabolic syndrome prevalence (Faloia et al., 2004; Alvarez-Blasco et al., 2006; Shroff et al., 2007a; Gulcelik et al., 2008) were waist or WHR matched (Supplementary Table SIII). The included studies were conducted in a range of countries with varying ethnicities (Supplementary Tables SI and II). Given the design of the included studies, it was difficult to assess withdrawals and losses to follow-up.

For diagnosis of PCOS, 7 studies did not assess for exclusion of related reproductive disorders (dos Reis et al., 1993; Rajkhowa et al., 1996; Ciampelli et al., 1998; Boudreaux et al., 2006; Lo et al., 2006; Caliskan et al., 2007; Shaw et al., 2008) and 16 did not assess for medication use that could affect study outcomes (Rajkhowa et al., 1996; Cibula et al., 2000; Phy et al., 2004; Sir-Petermann et al., 2004; Cussons et al., 2008). Of the BMI-matched studies, nine reported on waist circumference or WHR measurements (Cibula et al., 2000; Yarali et al., 2001; Faloia et al., 2004; Diamanti-Kandarakis et al., 2005; Alvarez-Blasco et al., 2006; Shroff et al., 2007a; Attaoua et al., 2008; Gulcelik et al., 2008; Moini and Esfami, 2009), three studies assessed IGT prevalence (Yarali et al., 2001; Faloia et al., 2004; Alvarez-Blasco et al., 2006) and

<table>
<thead>
<tr>
<th>Author, date</th>
<th>PCOS</th>
<th>Control</th>
<th>MetSyn definition</th>
</tr>
</thead>
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<tr>
<td>Glueck et al. (2003)</td>
<td>N = 138 NIH, age: 31 years, BMI: not stated</td>
<td>N = 1887 NHANES III, age/BMI: not stated</td>
<td>ATP III</td>
</tr>
<tr>
<td>Faloia et al. (2004)</td>
<td>N = 50 NIH, age: 22 years, BMI: n = 23 lean 22 kg/m², n = 27 overweight 32 kg/m²</td>
<td>N = 20, age: 26 years, BMI: n = 12 lean 20 kg/m², n = 8 overweight 37 kg/m²</td>
<td>ATP III</td>
</tr>
<tr>
<td>Apridonidze et al. (2005)</td>
<td>N = 106 NIH, age: 29.1 – 31 years, BMI: 33.7–39.2 kg/m²</td>
<td>NHANES III, age/BMI: details not given</td>
<td>ATP III; BMI 32 kg/m² as a surrogate for WC 88 cm</td>
</tr>
<tr>
<td>Dokras et al. (2005)</td>
<td>N = 129 NIH, age: 28 years, BMI: details not given</td>
<td>N = 1887 NHANES Age/BMI: details not given</td>
<td>WHO</td>
</tr>
<tr>
<td>Vrbikova et al. (2005)</td>
<td>N = 69 ESHRE/ASRM, age: 24 years, BMI: 23 kg/m²</td>
<td>N = 73, age: 23.8 years, BMI: 21.9 kg/m²</td>
<td>ATP III</td>
</tr>
<tr>
<td>Alvarez-Blasco et al. (2006)</td>
<td>N = 32 NIH, age: 26 years, BMI: 34.8 kg/m²</td>
<td>N = 72, age: 32 years, BMI: 35.2 kg/m²</td>
<td>ATP III</td>
</tr>
<tr>
<td>Carmina et al. (2006)</td>
<td>N = 282 ESHRE/ASRM, age: 24.9 years, BMI: 27.2 kg/m²</td>
<td>N = 85, age: 25.2 years, BMI: 23.3 kg/m²</td>
<td>ATP III, WHO</td>
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<tr>
<td>Coviello et al. (2006)</td>
<td>N = 49 NIH, age: 17 years, BMI: 32 kg/m²</td>
<td>N = 165, age: 15 years, BMI: 23 kg/m²</td>
<td>Modified ATP III</td>
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<tr>
<td>Lebel et al. (2006)</td>
<td>N = 36 ESHRE/ASRM, age: 16 years, BMI: 30.3–37.9 kg/m²</td>
<td>N = 21, age: 15.2 years, BMI: 24.9 kg/m²</td>
<td>Modified ATP III, modified AHA</td>
</tr>
<tr>
<td>Welt et al. (2006)</td>
<td>N = 418 ESHRE/ASRM, age: 28.7–30.2 years, BMI: 24.7–32.0 kg/m²</td>
<td>N = 64, age: 30.8 years, BMI: 27.3 kg/m²</td>
<td>Not stated</td>
</tr>
<tr>
<td>Caliskan et al. (2007)</td>
<td>N = 182 ESHRE/ASRM, age: 23.21 years, BMI: 25.0 kg/m²</td>
<td>N = 182, age: 23.6 years, BMI: 23.52 kg/m²</td>
<td>ATP III, WHO, AHA, IDF, Rotterdam</td>
</tr>
<tr>
<td>Shroff et al. (2007b)</td>
<td>N = 258 ESHRE/ASRM, age: 27–30 years, BMI: 29.4–36.6 kg/m²</td>
<td>N = 110, age: 37.9 years, BMI: 29 kg/m²</td>
<td>3 of 5: BMI &gt; 30, TG ≥ 1.7 mmol/l, HDL-C &lt; 1.3 mmol/l, BP ≥ 130/85, FPG &gt; 6.1 mmol/l or DM2 presence</td>
</tr>
<tr>
<td>Shroff et al. (2007a)</td>
<td>N = 24 NIH, age: 32 years, BMI: 36 kg/m²</td>
<td>N = 24, age: 35 years, BMI: 35 kg/m²</td>
<td>AHA</td>
</tr>
<tr>
<td>Attaoua et al. (2008)</td>
<td>N = 207 (107 lean, 100 obese), ESHRE/ASRM, age: 23.1–26.3 years, BMI: 23.0–34.9 kg/m²</td>
<td>N = 100, age: 34.1 years, BMI: 22.2 kg/m²</td>
<td>ATP III</td>
</tr>
<tr>
<td>Cheung et al. (2008)</td>
<td>N = 295 ESHRE/ASRM, age: 30.2 years, BMI: 25.8 kg/m²</td>
<td>N = 98, age: 33.4 years, BMI: 21.3 kg/m²</td>
<td>ATP III, AHA</td>
</tr>
<tr>
<td>Cussons et al. (2008)</td>
<td>N = 168 NIH, age: 34 years, BMI: 32.3 kg/m²</td>
<td>N = 883, age: 33.7 years, BMI: 25.8 kg/m²</td>
<td>ATP III, IDF</td>
</tr>
<tr>
<td>Gulcelik et al. (2008)</td>
<td>N = 60 ESHRE/ASRM, age: 24.6 years, BMI: 28 kg/m²</td>
<td>N = 60, age: 26.1 years, BMI: 26.7 kg/m²</td>
<td>ATP III</td>
</tr>
<tr>
<td>Shaw et al. (2008)</td>
<td>N = 104 NIH, age: 62.5 years, BMI: 31.1 kg/m²</td>
<td>N = 286, age: 65.8 years, BMI: 28.4 kg/m²</td>
<td>ATP III</td>
</tr>
</tbody>
</table>

AHA, American Heart Association/National Heart Lung Blood Institute; ATP III, Adult Treatment Panel III; AusDiab, Australian Diabetes Obesity and Lifestyle survey; BMI, body mass index; BP, blood pressure; DM2, type 2 diabetes mellitus; ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; MetSyn, metabolic syndrome; NIH, National Institute of Health; PCOS, polycystic ovary syndrome; TG, triglycerides; WC, waist circumference; WHO, World Health Organization.
Impaired glucose tolerance and type 2 diabetes mellitus

For assessment of IGT and DM2, 21 prevalence and 2 incidence papers were identified (Table III and Supplementary Table SI). For prevalence studies, these used varying definitions of IGT and DM2. Eight (dos Reis et al., 1995; Rajkhowa et al., 1996; Dunaif et al., 2001; Yarali et al., 2001; Faloia et al., 2004; Sir-Petermann et al., 2004; Echiburu et al., 2008; Shaw et al., 2008; Moini and Eslami 2009) used WHO (1980) definitions. Five studies (Apridonidze et al., 2005; Attaoua et al., 2008; Legro et al., 2004; Leibel et al., 2006; Sawathiparnich et al., 2005; Alvarez-Blasco et al., 2005) defined IGT and DM2 according to ADA criteria, one used NDG criteria (1979), six used other criteria [fasting plasma glucose ≥7.0 or ≥7.8 mmol/L or doctor diagnosis/current treatment/history of DM2 or self-report (Cibula et al., 2000; Boudreaux et al., 2006; Lo et al., 2006; Marquez et al., 2008; Shaw et al., 2008; Moini and Eslami, 2009)] and two did not state which criteria were used (Diamanti-Kandarakis et al., 2005; Alvarez-Blasco et al., 2006).

Prevalence of IGT

For IGT, 13 studies provided data on number of women with and without PCOS diagnosed with IGT. No significant statistical heterogeneity was present ($I^2 = 26\%$, $\chi^2 = 16.26, P = 0.18$). Women with PCOS presented with greater prevalence of IGT than women without PCOS on both fixed-effects analysis [OR 2.48 (1.63, 3.77)] (Fig. 2a) or random-effects analysis [OR 2.62 (1.43, 4.80)].

(i) Subgroup analysis was performed for studies with BMI-matched populations (Rajkhowa et al., 1996; Dunaif et al., 2001; Yarali et al., 2001; Faloia et al., 2004; Py et al., 2004; Diamanti-Kandarakis et al., 2005; Sawathiparnich et al., 2005; Alvarez-Blasco et al., 2006; Attaoua et al., 2008). No significant statistical heterogeneity was present ($I^2 = 20\%$, $\chi^2 = 9.97, P = 0.27$). Women with PCOS had a greater prevalence of IGT than women without PCOS which was significant on fixed-effects analysis [OR 2.54 (1.44, 4.47)] (Fig. 2b) and random-effects analysis [OR 2.57 (1.21, 5.47)].

(ii) Subgroup analysis was performed for studies with BMI and waist or WHR matching (Yarali et al., 2001; Faloia et al., 2004; Alvarez-Blasco et al., 2006). No significant statistical heterogeneity was present ($I^2 = 2\%$, $\chi^2 = 0.32, P = 0.85$). Women with PCOS had a greater prevalence of IGT on fixed-effects analysis [OR 1.31 (0.46, 3.72)] or random-effects analysis [OR 1.29 (0.45, 3.71)]; however, neither was significant.

(iii) Subgroup analysis was performed for studies with lean women only (BMI < 25 kg/m²) (Faloia et al., 2004; Attaoua et al., 2008). No significant statistical heterogeneity was present ($I^2 = 0\%$, $\chi^2 = 0.79, P = 0.37$). Women with PCOS had a greater prevalence of IGT on fixed-effects analysis [OR 3.22 (1.26, 8.24)] and random-effects analysis [OR 3.18 (1.24, 8.16)].

Incidence of IGT and DM2

For IGT, 21 studies provided data on number of women with and without PCOS diagnosed with IGT. There were no PCOS or controls with DM2 in 5 of the 18 studies (Dunaif et al., 2001; Diamanti-Kandarakis et al., 2005; Faloia et al., 2004; Py et al., 2004; Echiburu et al., 2008). On meta-analysis, women with PCOS presented with a greater prevalence of DM2 than women without PCOS on fixed-effects analysis [OR 4.43 (4.06, 4.82)] (Fig. 3a) and random-effects analysis [OR 3.16 (1.87, 5.32)]; however, significant statistical heterogeneity was evident ($I^2 = 55\%$, $\chi^2 = 26.82, P = 0.008$).

(i) Subgroup analysis was performed for studies with BMI-matched populations (Rajkhowa et al., 1996; Cibula et al., 2000; Yarali et al., 2001; Sawathiparnich et al., 2005; Alvarez-Blasco et al., 2006; Moini and Eslami, 2009). These data were not heterogeneous ($I^2 = 0\%$, $\chi^2 = 4.27, P = 0.51$). Women with PCOS had a greater prevalence of DM2 than women without PCOS on fixed-effects analysis [OR 4.00 (1.97, 8.10)] (Fig. 3b) and random-effects analysis [OR 4.68 (2.29, 9.56)].

(ii) Subgroup analysis was performed for studies with BMI and waist or WHR matching (Cibula et al., 2000; Yarali et al., 2001; Alvarez-Blasco et al., 2006) and women with PCOS had a higher prevalence of DM2 on fixed-effects analysis [OR 3.26 (1.50, 7.09)] but not random-effects analysis [OR 2.51 (0.42, 15.00)], and statistical heterogeneity was not present ($I^2 = 48\%$, $\chi^2 = 3.87, P = 0.14$).

The metabolic syndrome

For assessment of the metabolic syndrome, 18 prevalence and no incidence papers were identified (Table IV and Supplementary Table SI). These used varying definitions of the metabolic syndrome with 15 (Gluceck et al., 2003; Faloia et al., 2004; Apridonidze et al., 2005; Vrbikova et al., 2005; Alvarez-Blasco et al., 2006; Carmina et al., 2006; Coviello et al., 2006; Leibel et al., 2006; Caliskan et al., 2007; Shroff et al., 2007b; Attaoua et al., 2008; Cheung et al., 2008; Cussons et al., 2008; Gulcelik et al., 2008; Shaw et al., 2008) using the ATP III or modifications (NCEP, 2002), 4 (Leibel et al., 2006; Caliskan et al., 2007; Shroff et al., 2007a; Cheung et al., 2008) using the AHA criteria or modifications (Grundy et al., 2005), 3 (Dokras et al., 2005; Carmina et al., 2006; Caliskan et al., 2007) using the WHO criteria
Prevalence of the metabolic syndrome

Data on the number of women with and without PCOS diagnosed with the metabolic syndrome were provided in 16 studies. A number of different criteria were used for assessing metabolic syndrome and ATP III criteria were chosen for comparisons as the bulk of studies used this criteria. For Dokras et al. (2005), where two control populations were provided (either \(n = 177\) defined non-PCOS or \(n = 1887\) from population data NHANES III), for combined estimates, the NHANES III data were used. For Attaoua et al. (2008), where data on metabolic syndrome prevalence were provided for a BMI-matched lean PCOS population and a non-BMI-matched obese PCOS population, the lean PCOS population data were used for OR calculation. The frequency of the different components of the metabolic syndrome in women with PCOS (Supplementary Table SII) was elevated waist circumference or BMI (11–98%), decreased HDL-C (28.6–95%), increased triglycerides (5.5–56%), elevated blood pressure (BP; 7.3–70%) and elevated fasting glucose (0–43.5%). On meta-analysis, women with PCOS had a greater prevalence of the metabolic syndrome than women without PCOS on fixed-effects analysis [OR 2.88 (2.40, 3.45)] (Fig. 4a) and random-effects analysis [OR 3.01 (2.06, 4.41)]; however, significant statistical heterogeneity was evident (\(I^2 = 67\%), \chi^2 = 45.40, P < 0.0001\)).

(i) Subgroup analysis was performed for studies with BMI-matched populations (Falio et al., 2004; Alvarez-Blasco et al., 2006; Shroff et al., 2007a; Attaoua et al., 2008; Gulcelik et al., 2008). These data were not statistically heterogeneous (\(I^2 = 38\%), \chi^2 = 6.47, P = 0.17\)). Women with PCOS had a greater
prevalence of the metabolic syndrome than women without PCOS on fixed-effects analysis [OR 2.20 (1.36, 3.56)] (Fig. 4b) and random-effects analysis [OR 2.12 (1.11, 4.05)].

(ii) Subgroup analysis was performed for studies limited to those with BMI and waist or WHR matching (Faloia et al., 2004; Alvarez-Blasco et al., 2006; Shroff et al., 2007a; Gulcelik et al., 2008); these data were not statistically heterogeneous ($I^2 = 30\%, \chi^2 = 4.29, P = 0.23$). Women with PCOS had an elevated prevalence of the metabolic syndrome on fixed-effects analysis [OR 1.80 (1.05, 3.08)] but not random-effects analysis [OR 1.75 (0.88, 3.46)].

(iii) Subgroup analysis was performed for studies with studies assessing lean women only (BMI < 25 kg/m²) (Faloia et al., 2004; Vrbikova et al., 2005; Attaoua et al., 2008). These data were not statistically heterogeneous ($I^2 = 0\%, \chi^2 = 1.61, P = 0.45$). Women with PCOS had an elevated prevalence of the metabolic syndrome on fixed-effects analysis [OR 3.00 (1.30, 6.93)] and random-effects analysis [OR 2.90 (1.24, 6.78)].

Incidence of the metabolic syndrome
Our search did not identify any studies addressing the incidence of metabolic syndrome contrasting women with and without PCOS. The potential unique risk of having the metabolic syndrome for a woman with PCOS is best determined by comparing the incidence of CVD to an age- and sex-matched general population.

Discussion
This meta-analysis supports a greater prevalence of IGT, DM2 and the metabolic syndrome in women with PCOS compared with women without PCOS. The odds of metabolic disturbance reflected here were more than two to four times as high for women with PCOS compared with controls. Subgroup matching based on differences related to obesity also supports the inference that metabolic disturbance in PCOS may be present, although independent and additive to obesity. However, it is important to note that there are limited studies of high methodological quality assessing the magnitude of this metabolic disturbance and associated CVD risk in BMI- or abdominal obesity-matched groups and in lean women with and without PCOS.

The primary aim of this review was to report on prevalence and incidence of IGT, DM2 and the metabolic syndrome in women with and without PCOS. Increased IGT and DM2 in PCOS (Ehrmann et al., 1999; Legro et al., 1999) is proposed to be due to factors including peripheral insulin resistance (Dunaif et al., 1989), insulin...
hypersecretion and elevated β-cell function (O’Meara et al., 1993; Holte et al., 1995; Ciampelli et al., 1997; Vrbikova et al., 2002; Vrbikova et al., 2004). Defective glucose-stimulated insulin secretion as assessed through the minimal model and disposition index (Ehrmann et al., 1995; Dunaif and Finegood, 1996) and reduced secretion in response to dietary stimuli (O’Meara et al., 1993) have also been reported as early signs of β-cell exhaustion. Other factors associated with abnormal glucose tolerance in PCOS include elevated age, adiposity and abdominal adiposity (Legro et al., 1999), testosterone (Ehrmann et al., 1999; Gambineri et al., 2004; Espinos-Gomez et al., 2009), history of gestational diabetes (Koivunen et al., 2001) and family history of DM2 (Ehrmann et al., 1999; Legro et al., 1999; Gambineri et al., 2004). It is well documented that diagnosis of IGT or DM2 by fasting glucose alone and not OGTT measures may underestimate IGT and DM2 prevalence in PCOS (Legro et al., 1999; Mohlig et al., 2006). We attempted to minimize bias towards under diagnosis of abnormal glucose tolerance in PCOS through accepting OGTT measures. We also accepted clinician diagnosis in our selection criteria which may contribute to under-reporting.

Frequent diagnosis of the metabolic syndrome is reported in PCOS (Apridonidze et al., 2005) and is strongly associated with insulin resistance (Ehrmann et al., 2006), supporting the common aetiological role of insulin resistance in both PCOS and the metabolic syndrome (Haffner et al., 2003; Diamanti-Kandarakis and Papavassiliou, 2006). In this systematic review, the metabolic syndrome components of elevated adiposity or central adiposity and decreased HDL-C appeared relatively frequent, although they varied from study to study depending on factors including ethnicity and adiposity. Low frequencies of the relatively common components of elevated BMI, waist circumference, decreased HDL-C or elevated triglycerides were reported in the fewer number of studies with lower mean BMI’s.
Our review suggests that further longitudinal studies are warranted to support this suggestion.

The secondary aim of this review was to examine the effect of adiposity and adiposity distribution on IGT, DM2 and metabolic syndrome prevalence in women with and without PCOS through performing subgroup analysis with either BMI matching, waist circumference or WHR matching or assessing lean participants only. Obesity is a well-documented risk factor for abnormal glucose tolerance with increased rates of IGT and DM2 reported for obese (31.3% and 7.5%, respectively) compared with lean (10.3% and 1.5%, respectively) women with PCOS (Legro et al., 1999). Likewise, obesity is a risk factor for CVD risk factors including metabolic syndrome and dyslipidaemia in women with PCOS (Legro et al., 2001; Ehrmann et al., 2006). Although greater prevalence of IGT, DM2 and metabolic syndrome was noted for PCOS women in this meta-analysis, it is difficult to determine whether this is an effect of PCOS status per se or confounding due to differences in age, adiposity and other factors. We attempted to stratify for adiposity (our a priori secondary aim) through subgroup analysis and we still found a greater prevalence in PCOS for IGT, DM2 and the metabolic syndrome. Given the potential for increased adiposity in PCOS proposed by some researchers (Gluck et al., 2005), although controversial (Yildiz et al., 2008), this further highlights to the clinician that the PCOS population is one of high prevalence of metabolic disturbance and of known CVD risk factors.

The issue also remains as to whether lean women with PCOS are at increased cardiometabolic risk compared with lean women without PCOS with this issue only being assessed by a small number of the identified studies. Even lean women with PCOS demonstrate intrinsic abnormalities in insulin resistance (Dunaif et al., 1989) that could potentially contribute to elevated risk for IGT, DM2, metabolic syndrome and CVD. Lean women with PCOS also have increased risk factors for IGT, DM2, metabolic syndrome and CVD including elevated BP, abnormal lipid profile (Vrbikova et al., 2003), platelet dysfunction (Dereli et al., 2003), endothelial function (Cussons et al., 2009, Orio et al., 2004) and inflammatory markers such as highly sensitive C-reactive protein (Tosi et al., 2009). Conversely, no differences have been reported between lean women with and without PCOS for CVD risk factors including insulin resistance, lipid profiles, plasminogen activator inhibitor-1, BP, arterial stiffness or endothelium-dependent and -independent flow-mediated dilatation in other studies (Bailargeon and Carpentier, 2007; Ketel et al., 2008; Cussons et al., 2009). In our systematic review, on subgroup analysis, increased prevalence of IGT and metabolic syndrome was maintained, whereas prevalence of DM2 was not calculated for lean women with and without PCOS (Falolia et al., 2004; Vrbikova et al., 2005; Attaoua et al., 2008). It is also possible that even where matched for adiposity, the proposed presence of increased abdominal obesity, reported by some (Godoy-Matos et al., 2009) but not all authors (Barber et al., 2008), in PCOS contributes to elevated cardiometabolic risk in PCOS (Escobar-Morreale and San Millan, 2007; Moran and Teede, 2009). Where women with and without PCOS have similar abdominal adiposity, this may therefore lead to similar cardiometabolic risk (Moran and Teede, 2009). This is supported by the association of waist circumference with subsets of PCOS with insulin resistance and highest metabolic risk (Goverde et al., 2009). Our meta-analysis provides insufficient evidence to support this. When subgroup analysis on waist- or
WHR-matched populations was performed, the increased IGT prevalence for PCOS was not statistically significant and the increased metabolic syndrome prevalence for PCOS was no longer significant when subgroup analysis for random-effects analysis was performed. Although the limited number of studies available for subgroup analysis and significant heterogeneity between studies limits the strength of our conclusions, a modifying presence of obesity and abdominal obesity on cardiometabolic risk in PCOS is possible.

The literature in this field varies greatly with a variety of potential confounding factors including ethnicity (Norman et al., 1995; Carmina et al., 2006; Essah et al., 2008), PCOS diagnostic criteria (Moran and Teede, 2009), medication use, age, adiposity, abdominal adiposity, recruitment source of participants, family history of DM2, geography and definition of controls as having either none or partial features of PCOS. Precise controlling for these factors will reduce clinical heterogeneity in future studies. With regards to PCOS diagnostic criteria, it is suggested that differences in risk factors for DM2 and CVD may be partially due to differences in adiposity and adiposity distribution between subsets (Moran and Teede, 2009), again supporting the usefulness of the BMI-matched analysis in assessment of IGT, DM2 and metabolic syndrome prevalence. We also observed a range of study sizes ranging from n = 12 (Sawathiparnich et al., 2005) to n = 66 210 (Lo et al., 2006). However, on removal of the largest study due to non-BMI matching (Lo et al., 2006), the significantly higher DM2 prevalence for PCOS women was largely unchanged, although the increased 95% CI indicates a less precise estimate. We also note that the only two studies with a significantly greater DM2 prevalence for PCOS were weighted considerably higher with Lo et al. (2006) at 90% in the total meta-analysis (Fig. 3a) and Cibula et al. (2000) at 45% in the BMI-matched analysis (Fig. 3b). This reflects the influence that a single large study can have on weighted results and highlights the need for caution on interpretation of results. We also noted methodological weaknesses in a number of studies through imprecise methods for determining IGT, DM2 or metabolic syndrome diagnosis (self-report, physician diagnosis, method of diagnosis not stated or fasting methods only for DM2) (Supplementary Tables SI and SII). Methodological quality was assessed for all studies (Table II and Supplementary Table SIII) and was addressed in subgroup analysis on case and control comparability for BMI, thus also assessing a potential source of methodological bias. The best study design to determine risk for an outcome is a prospective (or retrospective) cohort study because it allows the investigator to establish timing and directionality of events (incidence). In our review, only three cohort studies were identified. Although appropriate for quantifying the prevalence of a disease or risk factor and examining relationships between diseases as they exist in a defined population at one particular time, a cross-sectional study, at most, establishes associations, not causality (Centre for Evidence-Based Medicine, 2009). This suggests the need for a registry for women with PCOS and the need for a collaborative longitudinal cohort investigation to provide reliable incidence data.

In spite of the challenges described above, our review demonstrates that women with PCOS have an elevated prevalence of IGT, DM2 and the metabolic syndrome. This is an important burden which left unchecked is likely to lead to CVD. Future research in PCOS should identify optimal risk prediction tools for DM2 and CVD and optimal definition and utility of the metabolic syndrome for disease prediction. This will help clarify the optimal timing and determine best screening practices for minimizing cardiometabolic morbidity and mortality.

Authors’ roles
L.J.M. contributed to study conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. M.M. contributed to analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. R.A.W. contributed to study conception and design, revising it critically for important intellectual content and final approval of the version to be published. R.J.N. contributed to study conception and design, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

Supplementary data
Supplementary data are available at http://molehr.oxfordjournals.org/.

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References
Type 2 diabetes and metabolic syndrome in PCOS


Essah PA, Nestler JE, Carmina E. Differences in dyslipidemia between American and Italian women with polycystic ovary syndrome. J Endocrinol Invest 2008;31:35–41.


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Sawatipamich P, Weeraulkawattana L, Santiprabhob J, Likitmaskul S. Obese adolescent girls with polycystic ovary syndrome (PCOS) have more severe insulin resistance measured by HOMA-IR score than obese girls without PCOS. J Med Assoc Thai 2005; 88(Suppl 8):S33–S37.


