Obesity Comorbidity

The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis

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Received 12 July 2012; revised 2 September 2012; accepted 13 September 2012

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Summary

While many women with polycystic ovary syndrome (PCOS) are overweight, obese or centrally obese, the effect of excess weight on the outcomes of PCOS is inconsistent. The review aimed to assess the effects of overweight, obesity and central obesity on the reproductive, metabolic and psychological features of PCOS. MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PSYCINFO were searched for studies reporting outcomes according to body mass index categories or body fat distribution. Data were presented as mean difference or risk ratio (95% confidence interval). This review included 30 eligible studies. Overweight or obese women with PCOS had decreased sex hormone-binding globulin (SHBG), increased total testosterone, free androgen index, hirsutism, fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance index and worsened lipid profile. Obesity significantly worsened all metabolic and reproductive outcomes measured except for hirsutism when compared to normal weight women with PCOS. Overweight women had no differences in total testosterone, hirsutism, total-cholesterol and low-density lipoprotein-cholesterol compared to normal weight women and no differences in SHBG and total testosterone compared to obese women. Central obesity was associated with higher fasting insulin levels. These results suggest that prevention and treatment of obesity is important for the management of PCOS.

Keywords: Central obesity, obesity, overweight, polycystic ovary syndrome.

obesity reviews (2013) 14, 95–109

Introduction

The prevalence of obesity has increased worldwide in the last few decades including Europe, United States and Australia (1–3). This had significant impact on the development of chronic diseases such as the metabolic syndrome, coronary heart disease and type 2 diabetes. In addition, obesity also has a significant impact on reproductive health, as excess body weight is the main cause for ovulatory infertility (4). This is closely associated with polycystic ovary syndrome (PCOS), a common endocrine disorder among reproductive-aged women associated with anovulation, infertility and hyperandrogenism. It is estimated that 4–7% of reproductive-aged women have PCOS according to the National Institutes of Health (NIH) criteria of hyperandrogenism and anovulation (5–9) or 15–18% according to the European Society of Human Reproductive and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria of two of the three features of (i) anovulation; (ii) hyperandrogenism; and (iii) polycystic ovaries on ultrasound (10,11). Women with PCOS have increased risk of metabolic syndrome (12), type 2 diabetes (13–15), and cardiovascular diseases including coronary heart disease and stroke (16,17). Many women with PCOS also suffer from psychological comorbidities including anxiety, depression,
low health-related quality of life, psychological distress and body dissatisfaction (18–21).

A large proportion of women with PCOS are overweight, obese or centrally obese. However, the exact prevalence is not known due to the lack of representative population data. A US study reported that the prevalence of obesity in women with PCOS has increased from 51% in 1987–1990 to 74% in 2000–2002 (22). Conversely, a study in Italy reported that only 14% of women with PCOS were obese (23). Excess body weight worsens certain features of PCOS including hyperandrogenism (24–27), menstrual disturbances (24,25,27), infertility (24,28), insulin resistance (29–31) and dyslipidaemia (29,30). Obesity also further increases the risk of metabolic syndrome, impaired glucose tolerance (IGT) and type 2 diabetes in women with PCOS (13,14,32). However, several studies suggest that obesity has little or no impact on the symptoms or the development of PCOS (6,22). Furthermore, even studies reporting a negative impact of obesity on the features of PCOS fail to report a consistent pattern in their findings. While one study reported that obesity is associated with biochemical hyperandrogenemia and not hirsutism (25), another study found that both biochemical hyperandrogenemia and hirsutism are affected (24). Similarly, studies have not been in consensus on whether excess body mass index (BMI) would have a significant impact on reproductive and metabolic features of PCOS such as sex hormone-binding globulin (SHBG) levels, total testosterone levels, ovarian volume, infertility and dyslipidaemia (24,25,27,29,30). Obesity may contribute to the psychiatric comorbidities of PCOS such as anxiety and depression, but this is not consistently reported (20,33–36). It is additionally unclear if being overweight would be as detrimental as being obese for women with PCOS. Studies in the general population have shown that for many health outcomes there is a critical threshold for BMI, beyond which the risk of disease would greatly increase (37–39). The distribution of body fat may also contribute significantly to some features of PCOS. While women with PCOS and upper body obesity appeared to have significantly higher fasting insulin levels (40–42), its impact on the other features of PCOS is unclear (40–44).

Having excess body weight or a central distribution of adiposity is likely to have an effect on at least some aspects of PCOS. However, the effect of being overweight, obese or centrally obese on the metabolic, reproductive and psychological features of PCOS is inconsistent from the existing literature. It is also unclear if being overweight but not obese would be deleterious to the health of women with PCOS.

Accordingly, the objective of this study was to determine the effects of overweight, obesity and central obesity on the metabolic, reproductive and psychological features of PCOS.

Methods

Identification of studies and eligibility criteria

Relevant studies were identified from the following electronic databases using the subject headings as shown in Supporting Information Table S1: MEDLINE, EMBASE, CINAHL, PSYCINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). All articles published before November 2010 were considered for eligibility. Only articles published in the English language were included. The search strategy shown in Supporting Information Table S1 was constructed for MEDLINE. Equivalent subject headings were used for the searches in other databases. All reviewers were also asked to provide any potentially relevant studies for consideration. All studies of women with PCOS were considered for eligibility. We selected studies where the metabolic, reproductive and psychological outcomes of PCOS were compared between overweight or obese and normal weight women and where participants were either consecutively recruited or randomly sampled. We excluded studies where body weight, BMI, waist circumference or waist–hip ratio was part of the selection criteria. For study inclusion, PCOS was defined according to the NIH (5) or ESHRE/ASRM (45) criteria. Overweight or obesity in adults was defined by World Health Organization (WHO) (46) (BMI ≥ 25 kg m⁻² for overweight, BMI ≥ 30 kg m⁻² for obesity). In studies on Asian subjects, overweight was considered at BMI ≥ 23 and obesity at BMI ≥ 25 (46). For adolescents, age–gender specific percentile distributions for BMI in the Centers for Disease Control and Prevention growth charts were used to identify those who were overweight (85th–95th percentile) or obese (>95th percentile) (47). Central obesity was defined as waist–hip ratio above 0.85 (48). Two reviewers (SL and LM) independently identified the articles that met the selection criteria of this review. Discrepancies were resolved by consultation and arbitration (SL, LM, RN and MD).

Data extraction

General characteristics of the study (author, year of publication, study location, study period, study design), characteristics of the study population (recruitment source, sampling method, age, ethnicity, number of women with and without PCOS, proportion of women who were lean, overweight, obese or centrally obese), definition of PCOS, pre-existing medication, physical activity and diet history, definition of obesity or central obesity, measurement of height, weight and waist circumference, and the outcomes of PCOS by BMI (total-cholesterol, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol, triglycerides, fasting insulin, fasting glucose, homeostatic model assessment-insulin resistance index.
[HOMA-IR], prevalence of impaired fasting glucose [IFG] or IGT, prevalence of type 2 diabetes, SHBG, total testosterone, free androgen index [FAI], hirsutism, acne, irregular menses, psychological disturbances) were extracted from all included studies. One reviewer extracted the data from all articles while another independently extracted the data from 10% of randomly selected studies. Inter-reviewer agreement of 0.99 was reached. Discrepancies were resolved by consensus.

Quality assessment
Quality of the included studies was assessed using criteria based on the Newcastle–Ottawa scale for non-randomized studies (49). Criteria assessed the selection of women with PCOS, comparability of the normal weight, overweight, obese or centrally obese groups, and the quality of outcome measurement. One reviewer assessed all the articles while another independently appraised 10% of randomly selected studies. Inter-reviewer agreement of 0.78 was reached, and discrepancies were resolved by consensus.

Outcomes of interest
The primary a priori end points were the metabolic, reproductive and psychological outcomes of overweight and obese women combined compared to normal weight women with PCOS. The secondary a priori end point was the comparison of metabolic, reproductive and psychological outcomes in normal weight, overweight and obese women with PCOS as separate subgroups (i.e. comparing normal weight with overweight, normal weight with obese, and overweight with obese women with PCOS), and in PCOS women with or without central obesity.

Data analysis
Mean differences (MDs) and 95% confidence intervals (CIs) were calculated for each continuous outcome for all included studies. Risk ratio (RR) and 95% CI were calculated for each dichotomous outcome for all included studies. Continuous data were combined using the inverse variance model while dichotomous data were combined using the Mantel–Haenszel model. Heterogeneity between the studies was examined by $\chi^2$ tests for significance ($P < 0.1$ was considered statistically significant). Inconsistency between studies was quantified using $I^2$ tests ($I^2 < 25\%$ was considered low heterogeneity, $I^2 > 50\%$ was considered substantial heterogeneity). The fixed fixed-effects model was used when there was no statistically significant heterogeneity and the random-effects model was used when significant statistical heterogeneity was present. Funnel plots were used to assess publication bias. The data analyses were performed using Review Manager (RevMan) 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark).

Results
Characteristics of included studies and quality assessment
The search yielded 9,874 citations as shown in Fig. 1. Based on our selection criteria, 1,485 studies were identified for further assessment in full text. Of these, 670 were excluded due to insufficient data to determine the proportion of women who were overweight, obese or centrally obese, 234 due to women with PCOS not being consecutively or randomly sampled, 188 due to PCOS diagnosis not consistent with NIH or ESHRE/ASRM criteria, 178 due to definition of the overweight and obesity not consistent with WHO criteria, 91 due to patients recruited based on BMI or body weight, 77 due to outcomes not presented according to BMI categories, 7 due to non-English reports, and 10 due to duplication of data. Finally, 30 studies were included in this systematic review and meta-analysis.

Characteristics of the included studies are shown in Table 1. Twenty studies compared the outcomes of overweight and obese women to normal weight women with obesity reviews Obesity and central obesity in PCOS S. S. Lim et al. 97 © 2012 The Authors obesity reviews © 2012 International Association for the Study of Obesity 14, 95–109, February 2013
<table>
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<th>Author (year)</th>
<th>Country</th>
<th>PCOS definition</th>
<th>Age (mean ± SD or otherwise stated)</th>
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<tbody>
<tr>
<td>Adali et al., 2010</td>
<td>Turkey</td>
<td>ESHRE/ASRM</td>
<td>26.88 ± 2.21 24.73 ± 2.91</td>
<td>50; 24 lean, 26 owt/ob</td>
<td>Testosterone, hirsutism, total-C, HDL-C, LDL-C, triglyceride, HOMA-IR</td>
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<td>Barcellos et al., 2007</td>
<td>Brazil</td>
<td>NIH</td>
<td>25.6 ± 5.6</td>
<td>69; 18 lean, 19 owt, 32 ob</td>
<td>Fasting insulin, testosterone, HOMA-IR, fasting glucose</td>
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<tr>
<td>Bemasoni et al., 1996</td>
<td>Italy</td>
<td>ESHRE/ASRM</td>
<td>22.5 ± 5.3</td>
<td>112; 60 lean, 52 owt/ob 20 non-centrally ob, 32 centrally ob</td>
<td>SHBG, free T</td>
</tr>
<tr>
<td>Buyalos et al., 1995</td>
<td>Finland</td>
<td>NIH</td>
<td>31.0 ± 2.0 29.0 ± 1.0</td>
<td>16; 7 lean, 9 owt/ob</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Castelo-Branco et al., 2010</td>
<td>Spain</td>
<td>ESHRE/ASRM</td>
<td>28.4 ± 8.4</td>
<td>225; 85 lean, 47 owt, 65 ob</td>
<td>Triglyceride, HDL-C, HOMA-IR, LDL-C, total-C</td>
</tr>
<tr>
<td>Cheung et al., 2007</td>
<td>Brazil</td>
<td>NIH</td>
<td>25.6 ± 5.6</td>
<td>295; 117 lean, 178 owt/ob</td>
<td>IFG/IGT</td>
</tr>
<tr>
<td>Ciampelli et al., 1996</td>
<td>Italy</td>
<td>ESHRE/ASRM</td>
<td>26.4 ± 1.1</td>
<td>20; 8 lean, 12 owt/ob</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Cupisti et al., 2007a</td>
<td>Germany</td>
<td>NIH</td>
<td>Range: 15–34</td>
<td>16; 9 lean, 1 owt, 6 ob</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Cupisti et al., 2007b</td>
<td>Germany</td>
<td>NIH</td>
<td>Range: 15–34</td>
<td>108; 59 lean, 49 owt/ob</td>
<td>Testosterone, SHBG, hirsutism, FA, free T</td>
</tr>
<tr>
<td>Cupisti et al., 2008</td>
<td>Germany</td>
<td>NIH</td>
<td>28.2 ± 7.0</td>
<td>184; 74 lean, 110 owt/ob</td>
<td>Fasting glucose, testosterone, total-C, HOMA-IR, triglyceride, 2-h glucose, LDL-C, LDL-C, SHBG, FA</td>
</tr>
<tr>
<td>Economou et al., 2009</td>
<td>Greece</td>
<td>NIH</td>
<td>25.0 ± 4.9</td>
<td>80; 44 lean, 39 owt/ob</td>
<td>Fasting glucose, testosterone, total-C, HOMA-IR, triglyceride, fasting insulin, SHBG, FA</td>
</tr>
<tr>
<td>Escobar-Morneale et al., 2006</td>
<td>Spain</td>
<td>ESHRE/ASRM</td>
<td>26.0 ± 6.0</td>
<td>76; 25 lean, 17 owt, 34 ob</td>
<td>Triglyceride, hirsutism, SHBG, HDL-C, total-C, testosterone, LDL-C, fasting glucose, free T</td>
</tr>
<tr>
<td>Essah et al., 2008</td>
<td>United States and Italy</td>
<td>NIH</td>
<td>Italy: 24.7 ± 5.2 United States: 28.9 ± 7.5</td>
<td>108; 34 lean, 10 owt, 33 ob; United States: 106; 11 lean, 17 owt, 78 ob</td>
<td>Triglyceride, HDL-C, total-C, LDL-C, fasting glucose, free T</td>
</tr>
<tr>
<td>Gennarelli et al., 1997</td>
<td>Sweden</td>
<td>ESHRE/ASRM</td>
<td>24.0 ± 1.0 27.4 ± 1.2</td>
<td>18; 10 lean, 8 owt/ob</td>
<td>Fasting glucose, testosterone, fasting insulin, SHBG, FA</td>
</tr>
<tr>
<td>Glintborg et al., 2004</td>
<td>Denmark</td>
<td>NIH</td>
<td>Median: 29 (23–34, 25th and 75th %ile)</td>
<td>125; 43 lean, 82 owt/ob</td>
<td>Diabetes, IFG/IGT</td>
</tr>
<tr>
<td>Hahn et al., 2007</td>
<td>Germany</td>
<td>NIH</td>
<td>28.0 ± 6.3</td>
<td>411; 140 lean, 75 owt, 196 ob</td>
<td>Hirsutism, SHBG, testosterone, HOMA-IR, FA</td>
</tr>
<tr>
<td>Kiddy et al., 1990</td>
<td>UK</td>
<td>ESHRE/ASRM</td>
<td>NA</td>
<td>263; 172 lean, 91 owt/ob</td>
<td>SHBG, testosterone, free T</td>
</tr>
<tr>
<td>Lee et al., 2003</td>
<td>Korea</td>
<td>ESHRE/ASRM</td>
<td>26.0 ± 5.0</td>
<td>194; 118 lean, 20 owt, 55 ob</td>
<td>IFG/IGT</td>
</tr>
<tr>
<td>Marcondes et al., 1995</td>
<td>United States</td>
<td>ESHRE/ASRM</td>
<td>22.0 ± 4.4</td>
<td>5; 4 lean, 1 owt</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Marsden et al., 2001</td>
<td>UK</td>
<td>NIH</td>
<td>27.5 ± 4.1</td>
<td>20; 2 lean, 8 owt, 10 ob</td>
<td>Testosterone, fasting insulin, SHBG, free T</td>
</tr>
<tr>
<td>Martinez-Guisasola et al., 2001</td>
<td>Spain</td>
<td>NIH</td>
<td>24.2 ± 5.1</td>
<td>167; 117 lean, 50 owt/ob</td>
<td>Fasting glucose, testosterone, fasting insulin, SHBG</td>
</tr>
<tr>
<td>Mozannega et al., 2004</td>
<td>Italy</td>
<td>ESHRE/ASRM</td>
<td>30.0 ± 1.4</td>
<td>18; 10 lean, 8 owt/ob</td>
<td>Fasting glucose, testosterone, fasting insulin, SHBG</td>
</tr>
<tr>
<td>Mukherjee et al., 2009</td>
<td>India</td>
<td>ESHRE/ASRM</td>
<td>24.8 ± 5.3</td>
<td>180; 75 lean, 105 owt/ob</td>
<td>Fasting glucose, testosterone, HDL-IR, fasting insulin, 2-h glucose, SHBG, FA, free T</td>
</tr>
<tr>
<td>Pasquali et al., 1993</td>
<td>Italy</td>
<td>ESHRE/ASRM</td>
<td>20.8 ± 5.9</td>
<td>100; 59 non-centrally ob, 41 centrally ob</td>
<td>Fasting insulin, fasting glucose, testosterone, SHBG</td>
</tr>
<tr>
<td>Sharifi et al., 2010</td>
<td>Iran</td>
<td>ESHRE/ASRM</td>
<td>24.8 ± 5.6</td>
<td>103; 34 lean, 69 owt/ob</td>
<td>Fasting glucose, total-C, HOMA-IR, triglyceride, fasting insulin, HDL-C</td>
</tr>
<tr>
<td>Siddiqui et al., 2010</td>
<td>Saudi Arabia</td>
<td>ESHRE/ASRM</td>
<td>35.9 ± 5.0</td>
<td>62; 22 lean, 40 owt/ob</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Springer et al., 2004</td>
<td>Germany</td>
<td>NIH</td>
<td>28.9 ± 0.6</td>
<td>63; 17 lean, 46 owt/ob</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Yildizhan et al., 2009</td>
<td>Turkey</td>
<td>ESHRE/ASRM</td>
<td>25.5 ± 9.9</td>
<td>100; 43 lean, 57 owt/ob</td>
<td>Testosterone, total-C, HOMA-IR, triglyceride, hirsutism</td>
</tr>
</tbody>
</table>

C, cholesterol; ESHRE/ASRM, European Society for Human Reproductive and Embryology/American Society for Reproductive Medicine; FAI, free androgen index; free T, free testosterone; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NA, not applicable; NIH, National Institutes of Health; ob, obese; owt, overweight; PCOS, polycystic ovary syndrome; SD, standard deviation; SHBG, sex hormone-binding globulin.
PCOS, eight studies compared the outcomes of obese, overweight and normal weight women with PCOS, and two studies compared women with PCOS with or without central obesity (Table 1). All studies were conducted in adults, with the exception of one study (50) that included both adolescents and adults. Eleven studies used a diagnosis consistent with the NIH criteria while 19 used a diagnosis consistent with the ESHRE/ASRM criteria (Table 1). Three studies were conducted in the Americas, 20 in Europe, and 7 in Asia and Middle East. Of the studies that reported reproductive and metabolic outcomes, all of them reported the laboratory methods for hormonal, lipid or glucose assessments. All studies used the Ferriman–Gallwey method to assess hirsutism. Nine studies measured insulin resistance using HOMA-IR while one study (51) used HOMA-B and insulin sensitivity index instead. Only studies reporting HOMA-IR were included in the meta-analyses. Twenty-five studies reported the use of medication that could affect the study outcomes (Supporting Information Table S2). No studies reported acne, irregular menses or psychological disturbances as outcomes (Table 1). The date of publication for included studies ranged from 1990 to 2010.

A summary of the methodological quality of the studies is shown in Table 2. The assessment criteria were based on the Newcastle–Ottawa scale for observational studies (49). As determined by our inclusion criteria, all participants were recruited either consecutively or randomly. Independent measurements of height and weight were reported in 15 studies. All cases and controls were recruited from the same source. As consistent with our inclusion criteria, all studies defined overweight or obesity according to the WHO criteria. None of the studies specifically controlled for age or any other factors as part of the study design when comparing outcomes between the lean and obese groups. All studies determined their reproductive and metabolic outcomes through independent assessments. The same method of assessment was used between the comparative groups in all studies. Eighteen studies reported that the non-response rate for lean and overweight or obese groups was the same. The funnel plot for studies on SHBG was largely symmetrical (Supporting Information Fig. S1). Funnel plot for studies on total testosterone showed some asymmetry for smaller studies (Supporting Information Fig. S2). The number of studies for the other outcomes was too small for the assessment of publication bias through funnel plots.

**Overweight or obese women (BMI ≥ 25 or BMI ≥ 23 for Asian population) compared to normal weight women with polycystic ovary syndrome**

Being overweight or obese was associated with significantly lower SHBG and HDL-cholesterol and significantly increased total testosterone, FAI, hirsutism scores, fasting insulin, HOMA-IR, fasting glucose, glucose at 2 h during the oral glucose tolerance test (OGTT), insulin at 2 h during OGTT, total-cholesterol, LDL-cholesterol and triglycerides in women with PCOS (Table 3). There was no significant heterogeneity in studies reporting SHBG, hirsutism, 2-h insulin and LDL-cholesterol. Significant statistical heterogeneity was observed in studies reporting total testosterone, FAI, fasting insulin, HOMA-IR, fasting glucose, 2-h glucose, total-cholesterol, HDL-cholesterol and triglycerides.

Overweight or obese women with PCOS had higher RR of IFG/IGT and type 2 diabetes compared to those with normal weight but this did not reach statistical significance (Table 3). Significant heterogeneity was seen in the analysis for IFG/IGT while only one study reported the prevalence of type 2 diabetes (52).

**Subgroup analyses**

**Overweight women (BMI 25–29.9 or BMI 23–24.9 for Asian population) compared to normal weight women with polycystic ovary syndrome**

Overweight women with PCOS had lower SHBG and HDL-cholesterol, and higher FAI, fasting insulin, HOMA-IR, fasting glucose and triglyceride (Table 4). Being overweight had no significant effect of total testosterone, hirsutism, total-cholesterol and LDL-cholesterol in women with PCOS. No studies comparing overweight women to normal weight women reported 2-h OGTT insulin or glucose. Significant heterogeneity was seen in studies reporting hirsutism, HOMA-IR, but not in studies reporting SHBG, total testosterone, fasting insulin, fasting glucose and all lipid parameters.

According to the only study reporting the prevalence of IFG/IGT of overweight and normal weight women with PCOS (53), those who were overweight had higher RR for IFG/IGT compared to those with normal weight (Table 4). No study comparing overweight to normal weight women with PCOS reported the prevalence of type 2 diabetes.

**Obese women (BMI ≥ 30 or BMI ≥ 25 for Asian) compared to normal weight women with polycystic ovary syndrome**

Obese women with PCOS had lower SHBG and HDL-cholesterol, and higher total testosterone, FAI, fasting insulin, HOMA-IR, fasting glucose, total-cholesterol, LDL-cholesterol and triglyceride compared to normal weight women (Table 4). Obesity had no significant effect on hirsutism. No studies comparing obese to normal weight women with PCOS reported 2-h OGTT insulin or glucose. There was significant heterogeneity in the studies reporting SHBG, hirsutism, fasting insulin, HOMA-IR, HDL-cholesterol and triglyceride, but no heterogeneity was seen...
in studies reporting total testosterone, fasting glucose levels, total-cholesterol and LDL-cholesterol.

Obesity was associated with significantly higher RR for IFG/IGT (53) (Table 4). No study comparing obese and normal weight women with PCOS reported the prevalence of type 2 diabetes.

Obese women (BMI $\geq 30$ or BMI $\geq 25$ for Asian) compared to overweight (BMI 25–29.9 or BMI 23–24.9 for Asian) women with polycystic ovary syndrome

Obese women had higher FAI, hirsutism, fasting insulin, HOMA-IR and fasting glucose compared to overweight women with PCOS (Table 4). The SHBG and total testoster-
one and fasting lipids did not differ significantly between obese and overweight women with PCOS. There was significant heterogeneity among studies reporting SHBG, HOMA-IR, HDL-cholesterol and triglyceride, but not among those reporting total testosterone, hirsutism, fasting insulin, fasting glucose, total-cholesterol and LDL-cholesterol.

The RR for IFG/IGT was not significantly higher among the obese women compared to the overweight women with PCOS (Table 4). No study comparing obese and overweight women with PCOS reported the prevalence of type 2 diabetes.

Central obesity compared to non-central obesity women with polycystic ovary syndrome

Two studies (n = 121) reported the effect of central obesity on SHBG (41,44). Central obesity had no significant effect on SHBG in women with PCOS (MD 2.04 [−3.01, 7.09], P = 0.43). There was no significant heterogeneity in this analysis (I² = 0%, χ² = 0.01, P = 0.94).

One study (41) reported the effect of central obesity on total testosterone (n = 75), fasting insulin (n = 92) and fasting glucose (n = 94). In this study, total testosterone (MD 0.19 [−0.26, 0.65], P = 0.40) and fasting glucose (MD −0.01 [−0.20, 0.18], P = 0.92) did not differ significantly between those with and without central obesity. Central obesity was associated with increased fasting insulin (MD 95.00 [54.81, 135.19], P < 0.001).

No study comparing women with and without central obesity reported outcomes on FAI, hirsutism scores, acne, irregular menses, HOMA-IR, OGTT glucose or insulin, IGT/IGF, type 2 diabetes, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride or psychological morbidities.

Discussion

Principal findings

We report here that being overweight or obese was associated with significantly worse reproductive and metabolic features of PCOS. We additionally report that being obese was significantly associated with worse metabolic and reproductive outcomes measured, except for hirsutism, when compared to normal weight women with PCOS. In contrast, women who were overweight but not obese only had no differences in total testosterone, hirsutism, total-cholesterol and LDL-cholesterol compared to normal weight women, and no differences in SHBG, total testosterone and fasting lipids compared to obese women. Central obesity was associated with higher fasting insulin. There were no data on psychological parameters and limited data on prevalence of IFG, IGT and type 2 diabetes mellitus.

Interpretation of findings

Overweight and obesity on sex hormone-binding globulin

BMI has previously been shown to be negatively associated with SHBG in women with and without PCOS (27,54,55) with this relationship likely to be mediated by insulin. SHBG and insulin were inversely related in women with and without PCOS, as insulin inhibits hepatic SHBG production (56). Decreased SHBG contributes to hyperandrogenism by increasing bioavailable androgens delivered to target organs (57,58) and is therefore a negative reproductive consequence of being overweight or obese. From the current analysis, it is possible that the effect of adiposity on SHBG predominantly occurs in overweight women with...
the effect plateauing in obesity. Alternatively, the regulation of SHBG may occur independent of insulin (59) with dietary influences such as monosaccharide-induced lipogenesis also attenuating SHBG levels (60). It is unclear if the apparent uncoupling between BMI and SHBG with increasing adiposity reflects the influence of these other factors, or that a saturation effect accounts for the attenuation of SHBG by obesity.

**Overweight and obesity on hyperandrogenemia**

In agreement with previous findings (27,29), we report here that overweight and obese women had higher total testosterone compared to normal weight women. This is likely to be due to the effects of obesity-induced hyperinsulinemia stimulating ovarian (58) and adrenal (61,62) androgen production, increasing the sensitivity of the pituitary to the effect of gonadotrophin-releasing hormone (63), and enhancing the ovarian response to gonadotrophins (64). Adipose tissue is also an important storage and metabolic site for steroid hormones including androgens (65). A positive relationship between BMI and biochemical hyperandrogenism was confirmed here with FAI increasing from normal to overweight and obesity on hyperandrogenemia.

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<th>Analysis</th>
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<tbody>
<tr>
<td>SHBG (nmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>2</td>
<td>252</td>
<td>-13.09 (-19.88, -6.30), fixed, $P &lt; 0.001$</td>
<td>1.19 ($P = 0.28$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>2</td>
<td>395</td>
<td>-21.83 (-40.84, -2.82), random, $P = 0.02$</td>
<td>12.78 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>2</td>
<td>317</td>
<td>-7.51 (-18.95, 3.94), random, $P = 0.20$</td>
<td>3.75 ($P = 0.05$)</td>
</tr>
<tr>
<td>Testosterone (nmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>4</td>
<td>299</td>
<td>0.05 (-0.17, 0.26), fixed, $P = 0.66$</td>
<td>0.59 ($P = 0.90$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>4</td>
<td>457</td>
<td>0.18 (0.00, 0.35), fixed, $P = 0.04$</td>
<td>5.27 ($P = 0.15$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>4</td>
<td>386</td>
<td>0.12 (-0.09, 0.33), fixed, $P = 0.26$</td>
<td>2.17 ($P = 0.57$)</td>
</tr>
<tr>
<td>FAI</td>
<td>Owt vs. normal</td>
<td>1</td>
<td>210</td>
<td>2.30 (0.90, 3.70), fixed, $P &lt; 0.001$</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>1</td>
<td>336</td>
<td>5.90 (4.63, 7.17), fixed, $P &lt; 0.001$</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>1</td>
<td>266</td>
<td>3.60 (1.95, 5.25), fixed, $P &lt; 0.001$</td>
<td>NA NA</td>
</tr>
<tr>
<td>Hirsutism (FG score)</td>
<td>Owt vs. normal</td>
<td>3</td>
<td>262</td>
<td>-1.78 (-6.22, 2.66), random, $P = 0.43$</td>
<td>9.93 ($P = 0.007$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>3</td>
<td>407</td>
<td>0.54 (-4.02, 5.11), random, $P = 0.82$</td>
<td>11.14 ($P = 0.004$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>3</td>
<td>335</td>
<td>2.17 (0.55, 3.78), fixed, $P = 0.009$</td>
<td>0.24 ($P = 0.89$)</td>
</tr>
<tr>
<td>Fasting insulin (pmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>2</td>
<td>79</td>
<td>36.37 (12.74, 59.99), fixed, $P = 0.003$</td>
<td>2.43 ($P = 0.12$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>2</td>
<td>109</td>
<td>123.13 (60.28, 185.97), random, $P &lt; 0.001$</td>
<td>4.51 ($P = 0.03$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>2</td>
<td>102</td>
<td>72.17 (41.30, 103.04), fixed, $P &lt; 0.001$</td>
<td>0.25 ($P = 0.62$)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Owt vs. normal</td>
<td>3</td>
<td>379</td>
<td>1.00 (0.40, 1.60), random, $P = 0.001$</td>
<td>7.69 ($P = 0.02$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>3</td>
<td>536</td>
<td>3.75 (1.69, 5.81), random, $P &lt; 0.001$</td>
<td>66.34 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>3</td>
<td>429</td>
<td>2.41 (0.89, 3.93), random, $P = 0.002$</td>
<td>23.95 ($P = 0.001$)</td>
</tr>
<tr>
<td>Fasting glucose (mmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>2</td>
<td>79</td>
<td>0.33 (0.15, 0.52), fixed, $P &lt; 0.001$</td>
<td>0.26 ($P = 0.61$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>2</td>
<td>109</td>
<td>0.59 (0.42, 0.77), fixed, $P &lt; 0.001$</td>
<td>0.01 ($P = 0.91$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>2</td>
<td>102</td>
<td>0.26 (0.05, 0.46), fixed, $P = 0.01$</td>
<td>0.32 ($P = 0.57$)</td>
</tr>
<tr>
<td>IFG/IGT (r)</td>
<td>Owt vs. normal</td>
<td>1</td>
<td>139</td>
<td>RR: 5.10 (1.91, 13.62), fixed, $P = 0.001$</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>1</td>
<td>174</td>
<td>RR: 6.18 (2.78, 13.75), fixed, $P &lt; 0.001$</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>1</td>
<td>75</td>
<td>RR: 1.21 (0.57, 2.58), fixed, $P = 0.62$</td>
<td>NA NA</td>
</tr>
<tr>
<td>Total-C (mmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>3</td>
<td>145</td>
<td>0.06 (-0.29, 0.40), fixed, $P = 0.74$</td>
<td>2.70 ($P = 0.26$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>4</td>
<td>365</td>
<td>0.62 (0.44, 0.80), fixed, $P &lt; 0.001$</td>
<td>5.46 ($P = 0.14$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>3</td>
<td>220</td>
<td>0.31 (-0.04, 0.65), fixed, $P = 0.08$</td>
<td>1.13 ($P = 0.57$)</td>
</tr>
<tr>
<td>LDL-C (mmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>3</td>
<td>145</td>
<td>0.10 (-0.17, 0.38), fixed, $P = 0.47$</td>
<td>2.77 ($P = 0.25$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>4</td>
<td>365</td>
<td>0.53 (0.36, 0.70), fixed, $P &lt; 0.001$</td>
<td>3.40 ($P = 0.33$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>3</td>
<td>220</td>
<td>0.24 (-0.04, 0.52), fixed, $P = 0.09$</td>
<td>2.76 ($P = 0.25$)</td>
</tr>
<tr>
<td>HDL-C (mmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>4</td>
<td>277</td>
<td>-0.08 (-0.14, -0.01), fixed, $P = 0.03$</td>
<td>5.72 ($P = 0.13$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>4</td>
<td>365</td>
<td>-0.29 (-0.49, -0.08), random, $P = 0.005$</td>
<td>23.45 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>4</td>
<td>332</td>
<td>-0.21 (-0.44, 0.01), random, $P = 0.06$</td>
<td>34.68 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>Triglyceride (mmol L$^{-1}$)</td>
<td>Owt vs. normal</td>
<td>4</td>
<td>277</td>
<td>0.13 (0.01, 0.25), fixed, $P = 0.03$</td>
<td>5.70 ($P = 0.13$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. normal</td>
<td>4</td>
<td>365</td>
<td>0.57 (0.25, 0.89), random, $P &lt; 0.001$</td>
<td>19.29 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Ob vs. owt</td>
<td>4</td>
<td>332</td>
<td>0.44 (-0.12, 0.99), random, $P = 0.12$</td>
<td>37.31 ($P &lt; 0.001$)</td>
</tr>
</tbody>
</table>

**BMI**, body mass index; C, cholesterol; CI, confidence interval; FAI, free androgen index; FG, Ferriman–Gallwey; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NA, not applicable; ob, obese; owt, overweight; PCOS, polycystic ovary syndrome; RR, risk ratio; SHBG, sex hormone-binding globulin.
to be linear. Two (51,66) out of the three studies in this review (67) reported a J-shape relationship in which overweight women had the lowest hirsutism scores compared to the lean or obese women. Obesity increases both oestrogen and androgen production (58) and, in overweight women, the effect of hyperoestrogenism may counteract the effect of hyperandrogenism such that at a clinical level less hirsutism is observed.

**Overweight and obese and insulin and insulin resistance**

Insulin resistance is a common condition in PCOS and present in 14–24% according to ESHRE/ASRM criteria or 20–43% with NIH criteria (11,45,68). We report here a dose-dependent relationship between adiposity and surrogate measures of insulin resistance consistent with previous findings (69,70). Insulin resistance may be prevalent in PCOS due to intrinsic defects in insulin signalling or receptor activity (71,72), decreased insulin clearance due to the inhibitory effect of high testosterone levels (73), excess adiposity (29,74–77), and elevated adipose tissue free fatty acid or cytokine production such as tumour necrosis factor-alpha and interleukin-6 (78–81). Thus, in addition to defects intrinsic to PCOS, those with excess adiposity experience further impairment to the secretion, metabolism and action of insulin. This is consistent with women with PCOS being more insulin resistant than weight-matched women without PCOS and obesity worsening insulin resistance in PCOS (82–84).

**Overweight and obese on impaired fasting glucose/impaired glucose tolerance, type 2 diabetes**

We have previously reported an increased prevalence of IGT and type 2 diabetes in women with PCOS compared to women without PCOS (13–15), which is further increased in the presence of overweight or obesity (14,85). This is likely related to the association between obesity and insulin resistance with insulin resistance being an important predictor of IGT and type 2 diabetes in the general population (86,87) and specifically in populations at high risk of type 2 diabetes (88,89). It is unclear if being obese as compared to being overweight would further increase the risk for IFG/IGT and type 2 diabetes for women with PCOS. We report here an increased risk for IFG/IGT in overweight women compared to normal weight women but no differences between overweight and obese women. This result, from a single study (53) in a specific population (young Korean women), requires confirmation in future research.

**Overweight and obese and dyslipidaemia**

A previous meta-analysis reported a more atherogenic lipid profile in women with PCOS compared to women without PCOS (90). We extend this literature to report that being overweight or obese further worsens the fasting lipid profile, as an important risk marker for cardiovascular disease (91), in women with PCOS. This is consistent with previous cross-sectional studies demonstrating that PCOS and obesity exert synergistic effect on exacerbating fasting lipids (29,30,92–94) and epidemiological studies reporting dyslipidaemia worsens steadily from a BMI of 20 onwards (95). In contrast, total-cholesterol and LDL-cholesterol were not increased in overweight women compared to normal weight women with PCOS. The lipid pattern in overweight women with PCOS in this review likely reflects the influence of insulin resistance, which has previously been shown to be associated with increased triglyceride and decreased HDL-cholesterol (29,30,96–98). In contrast to previous studies (95), being obese did not consistently result in significantly worse fasting lipid levels compared to being overweight. Most of the studies included in the current analysis on lipid levels were from the Mediterranean region (51,99,100), thus diet and ethnicity may have influenced our results.

**Polycystic ovary syndrome and psychological health**

Women with PCOS experience high levels of psychological morbidities including anxiety, depression and body dissatisfaction (20,34). Obesity appears to be a contributing factor but not the sole cause for these conditions (34,35). The association between depression and obesity may be related to body image with this being strongly associated with depression in women with PCOS (33). Despite the significance of psychological impact resulting from PCOS and the potential role of obesity in mediating these effects, relatively few studies have been conducted in this area. No studies included in this review reported psychological outcomes, which is an important clinical and research gap.

**Central obesity and polycystic ovary syndrome**

Women with PCOS have a greater tendency to accumulate fat in the upper body when compared to controls matched for weight or BMI (101–106), although this is not consistently reported (107,108). Consistent with our current findings, central or visceral obesity is associated with elevated fasting and glucose-stimulated insulin levels (40,41) and greater insulin resistance in PCOS (43,102,106,109) likely mediated by free fatty acids and the paracrine actions of the visceral depot (78–81). No studies used more precise methods of measuring central obesity, such as dual X-ray absorptiometry, computed tomography or magnetic resonance imaging. We did not confirm previous findings of relationships between central obesity and SHBG (109), as measured by computed tomography scan, which may reflect the use of the less-sensitive measure of waist–hip ratio in the current analysis (41,44). We confirm previous findings of no relationship between central obesity and fasting glucose or total testosterone (40,109). While central adiposity has been previously, although not consistently
but not obese is also associated with adverse metabolic and psychological morbidities of PCOS. Significant statistical heterogeneity was found in half of the analyses, which may reflect clinical heterogeneity related to variability in PCOS diagnostic criteria, country setting, ethnicity, or diet and physical activity. This indicates that caution should be applied in extrapolating these results for wider applications. While we aimed to minimize selection bias by including only studies that recruited their participants in a consecutive or random manner, all trials in this review recruited participants from hospitals or clinics instead of general community which may represent a population with more a severe manifestation of PCOS. None of the studies controlled for potential confounders such as age, ethnicity or the use of medications when comparing the various BMI groups. We also note that as this is a cross-sectional investigation, the directionality of event could not be determined.

Clinical implications, research implications and future directions

Excess adiposity is associated with significantly worse reproductive, metabolic and psychological features of PCOS. However, the exact BMI cut-off that corresponds to the increased risk for each outcome is unclear. For the general population, the risk for coronary heart disease increased at BMI > 22 kg m\(^{-2}\) (95). It is unclear if the cut-off would be similar or lower in PCOS. Being overweight but not obese is also associated with adverse metabolic and reproductive outcomes in women with PCOS, although being obese appears to further worsen most of these outcomes. This highlights the importance of screening, detection, and management of both overweight and obesity in the treatment of PCOS. Lifestyle modification is recommended as a key initial treatment strategy in overweight and obese women with PCOS (113,114) and improves SHBG, hyperandrogenism, weight, waist circumference, insulin resistance and psychological function (114–121). Lifestyle interventions are also effective in preventing the development of chronic diseases such as type 2 diabetes in the general population (122). Given the contribution of obesity to the presentation of PCOS, future work should also focus on the comparative efficacy of pharmacological, surgical and lifestyle management of overweight and obesity. Prevention of weight gain is also an important aspect of obesity management, as weight gain is an important risk factor for various metabolic diseases (37) and young women of reproductive age are a high-risk group for weight gain (123). While the specific risk for longitudinal weight gain and the effect of weight gain on features of PCOS are not clear, this highlights the importance of prevention in addition to the treatment of overweight and obesity for women with PCOS.

This review highlights the need for studies examining the effect of overweight, obesity and central obesity on the psychological health of women with PCOS, and the effect of central obesity on the comorbidities in PCOS. We found that the relationship between BMI and certain health outcomes including SHBG and hirsutism may be non-linear. This warrants further examination for a range of outcomes and BMIs. The identification of a BMI threshold for each health outcome could aid the identification of target groups for the appropriate interventions. It may be that even those within the normal weight range may be at risk of some diseases and should be targeted for disease prevention. The effect of overweight, obesity and central obesity should also be explored longitudinally to determine the causal role of obesity in the development of these reproductive, metabolic and psychological outcomes.

Conclusion

This systematic review reports an evaluation of the metabolic and reproductive effects of overweight, obesity and central obesity in women with PCOS. We reported that being overweight adversely affects many aspects of PCOS, while being obese further worsens these outcomes. Further studies are required to describe the effect of central obesity on various outcomes of PCOS, and the effect of excess weight on the psychological health of women with PCOS. Research on the risks of metabolic, reproductive and psychological morbidities of PCOS across a wide range of BMIs in women with PCOS is needed to identify the highest
risk groups to target strategies for the prevention and treatment of adiposity-associated morbidities.

Conflict of Interest Statement

None.

References

68. Goverde AJ, van Koert AJB, Eijkemans MJ et al. Indicators for metabolic disturbances in anovulatory women with polycystic
ovary syndrome diagnosed according to the Rotterdam consensus criteria. Hum Reprod 2009; 24: 710–717.
84. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2001; 24: 89–94.


139. Siddiqui IA, Tamimi W, Tamim H, Aleisa N, Adham M. A study on clinical and sonographic features in obese and nonobese patients with polycystic ovary syndrome. *Arch Gynecol Obstet* 2010; **281**: 467–471.

140. Spranger J, Mohlig M, Wegewitz U et al. Adiponectin is independently associated with insulin sensitivity in women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **61**:738–746.


**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- Figure S1. Funnel plot for studies on SHBG.
- Figure S2. Funnel plot for studies on testosterone.
- Table S1. MeSH terms.
- Table S2. Description of included studies.