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Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis

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BACKGROUND: Polycystic ovary syndrome (PCOS) is closely associated with obesity but the prevalence of obesity varies between published studies. The objective of this research was to describe the prevalence of overweight, obesity and central obesity in women with and without PCOS and to assess the confounding effect of ethnicity, geographic regions and the diagnostic criteria of PCOS on the prevalence.

METHODS: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PSYCINFO were searched for studies reporting the prevalence of overweight, obesity or central obesity in women with and without PCOS. Data were presented as prevalence (%) and risk ratio (RR) [95% confidence interval (CI)]. Random-effect models were used to calculate pooled RR.

RESULTS: This systematic review included 106 studies while the meta-analysis included 35 studies (15129 women). Women with PCOS had increased prevalence of overweight [RR (95% CI): 1.95 (1.52, 2.50)], obesity [2.77 (1.88, 4.10)] and central obesity [1.73 (1.31, 2.30)] compared with women without PCOS. The Caucasian women with PCOS had a greater increase in obesity prevalence than the Asian women with PCOS compared with women without PCOS [10.79 (5.36, 21.70) versus 2.31 (1.33, 4.00), $P < 0.001$ between subgroups).

CONCLUSIONS: Women with PCOS had a greater risk of overweight, obesity and central obesity. Although our findings support a positive association between obesity and PCOS, our conclusions are limited by the significant heterogeneity between studies and further studies are

now required to determine the source of this heterogeneity. Clinical management of PCOS should include the prevention and management of overweight and obesity.

Key words: polycystic ovary syndrome / obesity / central obesity / prevalence / meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. The National Institutes of Health (NIH) defined PCOS as the presence of hyperandrogenism and anovulation (Zawadski and Dunaif, 1992), while the more recent European Society for Human Reproductive and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria included those with polycystic ovaries on ultrasound (Broekmans *et al.*, 2006). The prevalence of PCOS varies according to the diagnostic criteria used, with estimates of 4–7% in women of reproductive age using the NIH criteria for PCOS (Knochenhauer *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999; Asuncion *et al.*, 2000; Azziz *et al.*, 2004b) and up to 15–18% for the ESHRE/ASRM criteria (March *et al.*, 2010; Mehrabian *et al.*, 2011).

PCOS is associated with reproductive, metabolic and psychological dysfunction including anovulatory infertility, increased risk of the metabolic syndrome (Hudecova *et al.*, 2011), impaired glucose tolerance (Ehrmann *et al.*, 1999; Legro *et al.*, 1999; Norman *et al.*, 2001; Moran *et al.*, 2010), type 2 diabetes (Ehrmann *et al.*, 1999; Legro *et al.*, 1999; Moran *et al.*, 2010), cardiovascular diseases (Meyer *et al.*, 2005; de Groot *et al.*, 2011) and anxiety and depression (Himelein and Thatcher, 2006; Upadhya and Trent, 2007; Deeks *et al.*, 2010; Li *et al.*, 2011). It was estimated that over $4 billion per year in the USA were spent on PCOS and its co-morbidities, identifying PCOS as a significant economic burden to health care (Azziz *et al.*, 2005).

PCOS is closely associated with obesity. Obesity worsens hyperandrogenism (Kiddy *et al.*, 1990; Holte *et al.*, 1994; Balen *et al.*, 1995; Liou *et al.*, 2009) and menstrual disturbances (Kiddy *et al.*, 1990; Balen *et al.*, 1995; Liou *et al.*, 2009) in PCOS. Given the association between obesity and these clinical diagnostic features, PCOS may also be more prevalent among overweight and obese women. In support of this, a study in Spain reported that 28% of overweight and obesity women were diagnosed with PCOS (Alvarez-Blasco *et al.*, 2006). Overweight and obese women with PCOS may present with a worse reproductive clinical presentation and are therefore more likely to be diagnosed, potentially contributing to an over-exaggeration of the association between obesity and PCOS.

In addition to potentially increased risk for obesity in PCOS, women with PCOS are also more likely to carry excess adiposity in the central body region compared with body mass index (BMI)-matched controls (Strowitzki *et al.*, 2002; Cosar *et al.*, 2008; Svendsen *et al.*, 2008; Carmina *et al.*, 2009a; Godoy-Matos *et al.*, 2009; Karabulut *et al.*, 2011). Central or visceral obesity is associated with greater insulin resistance (Lord *et al.*, 2006; Cosar *et al.*, 2008; Kalra *et al.*, 2009; Karabulut *et al.*, 2011). In keeping with the key role of insulin resistance in the pathophysiology of PCOS, central obesity worsens the insulin-related metabolic and reproductive features of PCOS including hyperandrogenemia (Cosar *et al.*, 2008; Svendsen *et al.*, 2008; Godoy-Matos *et al.*, 2009), anovulation (Carmina *et al.*, 2009a) and dyslipidemia (Pasquali *et al.*, 1994; Lord *et al.*, 2006).

Despite the close association between PCOS and obesity, the prevalence of obesity in women with PCOS is highly variable. Obesity prevalence is known to differ according to age, ethnicity and geographic regions in the general population (Reynolds *et al.*, 2007; Flegal *et al.*, 2010). Women with PCOS, as defined by the NIH criteria, may also have higher body weight compared with those identified using the ESHRE/ASRM criteria or non-NIH phenotypes (Moran and Teede, 2009). Current understanding on the overall prevalence of obesity in women with PCOS is limited by the lack of representative population-based data. Therefore, the objective of this systematic review and meta-analysis was to provide an evidence-based assessment of the prevalence of overweight and obesity, obesity and central obesity in women with PCOS and to assess the confounding effect of age, ethnicity, geographic region and the diagnostic criteria of PCOS on the prevalence.

Methods

Identification of studies and eligibility criteria

Search strategy

We searched the following electronic databases: MEDLINE, EMBASE, CINAHL, PSYCINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). All articles published before November 2010 was considered for eligibility. Only articles published in the English language were included. The search strategy as shown in Supplementary data, Table SI was constructed for MEDLINE. Equivalent subject headings were used for the searches in other databases. In addition to the database search, all reviewers (i.e. co-authors) were asked to provide any potentially relevant studies for consideration.

Selection criteria

Two separate research questions were considered in this review: (i) the assessment of the prevalence of overweight and obesity, obesity and central obesity in women with PCOS and (ii) a comparison of the prevalence of overweight and obesity, obesity and central obesity in women with and without PCOS. All studies of women with PCOS, with or without a control group, were considered for eligibility. We included studies in which the prevalence of overweight and obesity, obesity or central obesity was available or determinable. We included studies where women with PCOS were either consecutively recruited or randomly sampled. We excluded studies where participants were selected by body weight, BMI, waist circumference (WC) or waist–hip ratio (WHR). For study inclusion, PCOS was defined according to the NIH (Zawadski and Dunaif, 1992) or ESHRE/ASRM (Broekmans *et al.*, 2006) criteria. For studies comparing the prevalence of overweight and obesity in women with and without PCOS, the control subjects were not diagnosed with PCOS and were not weight- or BMI matched to the PCOS subjects. For studies comparing the prevalence of central obesity in women with and without PCOS, the control subjects were not diagnosed

with PCOS and were not matched to their cases by WC or WHR. Overweight and obesity in adults was defined by the World Health Organization (WHO) criteria (BMI $\geq$25 kg/m^2 for overweight and obesity, BMI $\geq$30 kg/m^2 for obesity; WHO, 2000). In studies on Asian subjects, overweight and obesity was defined as a BMI $\geq$23 kg/m^2 and obesity was defined as a BMI $\geq$25 kg/m^2 according to the International Obesity Task Force (IOTF; WHO, 2000). For adolescents, overweight was defined as 85th to 95th percentile and obesity as $\geq$95th percentile in the age–gender specific percentile distributions for BMI in the Centers for Disease Control and Prevention growth charts (Barlow, 2007). Central obesity was defined as a WC of $\geq$80 cm according to the International Diabetes Federation (IDF; Alberti *et al*., 2005), >88 cm according to the Adult Treatment Panel III (ATP III; National Cholesterol Education Program, 2001) or WHR of >0.85 according to WHO criteria (WHO, 1999). Adolescents were defined as aged $\leq$18 years. Geographic regions of the participants were determined according to the United Nations categories. Two reviewers (S.L. and L.M.) independently screened and selected the articles that met the selection criteria of this review. Discrepancies were resolved by consultation and arbitration (S.L., L.M., R.J.N. and M.D.).

Data extraction

General study characteristics (author, year of publication, study location, study period, study design, number of women with and without PCOS), characteristics of the study population (recruitment source, sampling method, age, ethnicity), definition of PCOS (NIH or ESHRE/ASRM), pre-existing medication use, physical activity and diet history, definition of obesity (WHO, IOTF) and central obesity (IDF, ATPIII, WHO), measurement of height, weight and WC, and the proportion of women who were overweight and obese, obese or centrally obese were extracted from all included studies. One reviewer extracted the data from all articles, while another independently extracted the data from 10% of the studies identified through random selection. Inter-reviewer agreement of 0.91 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 (Wells *et al*., 2010). These criteria assessed the selection of PCOS and control groups, comparability of PCOS and control groups, and the quality of outcome measurement. One reviewer assessed all the articles, while another independently appraised 10% of the studies identified through random selection. Inter-reviewer agreement of 0.86 was reached, and disagreement was resolved by consensus.

Outcomes of interest

The primary *a priori* end-points were the prevalence of overweight and obesity, obesity and central obesity in women with PCOS and a comparison of the prevalence in women with and without PCOS. The secondary *a priori* end-point was the prevalence of overweight and obesity, obesity or central obesity in women with and without PCOS according to the study quality score, PCOS diagnostic criteria, age, ethnicity and geographic region.

Data analysis

The proportion of women with PCOS with overweight and obesity, obesity or central obesity was expressed as a percentage. A contour-enhanced funnel plot was conducted to assess a risk of publication bias. Pooled estimates with 95% confidence interval (CI) of the prevalences for overweight and obesity, obesity and central obesity were calculated using random-effects meta-analysis in STATA 11.2. The risks of overweight and obesity, obesity or central obesity in women with PCOS compared with women without PCOS were expressed as risk ratio (RR) with 95% CI. Data were combined for meta-analysis with the use of the Mantel-Haenszel random effects model owing to the presence of clinical and/or statistical heterogeneity. Heterogeneity between the studies was examined by χ^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). *A priori* subgroup analyses were conducted to assess heterogeneity, including the study quality score, PCOS diagnostic criteria, age, ethnicity and geographic region. Differences between the subgroups were assessed using the method described by Borenstein *et al*. (2008). Data analyses were performed using RevMan 5.1 (2011).

Results

Characteristics of included studies and quality assessment

The search yielded 9874 citations as shown in Supplementary data, Fig. S1. Based on our selection criteria, 1485 studies were identified for further assessment in full text. Of these, 188 studies were excluded because PCOS diagnosis was not consistent with NIH or ESHRE/ASRM criteria, 178 because definition of overweight and obesity was not consistent with WHO criteria, 670 had insufficient data to determine the prevalence of obesity or central obesity, in 234 patients with PCOS were not consecutively or randomly sampled, in 91 patients were selected based on BMI or body weight, 1 had a definition of central obesity inconsistent with IDF, ATP III or WHO criteria, 7 were not in English and 10 had duplicated data. Finally, 106 studies were included for the systematic review for the first research question of assessing the prevalence of overweight and obesity, obesity and central obesity in women with PCOS. From these studies, 71 were excluded from the meta-analysis owing to lack of a control group that was not BMI- or body-weight matched to the PCOS group. Finally, 35 studies were included in the meta-analysis for the second research question of comparing the prevalence of overweight and obesity, obesity and central obesity in women with and without PCOS.

Characteristics of the included studies are shown in Tables I and III. The majority of studies (70%) used a cross-sectional design. Of the studies that reported their sampling frame, all except for two (Hashemipour *et al*., 2004; Yildiz *et al*., 2008) recruited their patients from a hospital or clinic. A hundred and one studies reported the prevalence of overweight and obesity, of which 32 studies included a control group (Table III). Eleven studies reported the prevalence of central obesity, of which six included a control group (Table III). Eighty-three studies reported the prevalence of overweight and obesity (BMI $\geq$25 kg/m^2 or BMI $\geq$23 kg/m^2 for Asians), while 57 reported the prevalence of obesity (BMI $\geq$30 kg/m^2 or BMI $\geq$25 kg/m^2 for Asians). Of the 11 studies reporting the prevalence of central obesity, five used the IDF definition (WC $\geq$80 cm), four used the ATP III definition (WC > 88 cm) and two used the WHO definition (WHR >0.85). The date of publication for included studies ranged from 1990 to 2010.

Most studies were conducted on adults only, with the exception of six studies that included both adults and adolescents (Sahin *et al*.,

Table I Characteristics of studies included in the meta-analysis.

Author (year)	Study design; period	Country, PCOS recruitment source	Control recruitment source	Control description
Adali *et al.* (2008)	Cross-sectional; September 2007–April 2008	Turkey, outpatients clinics of Department of Gynecology and Obstetrics at University	Same clinic as PCOS	Age-matched, similar SES
Al-Ojaimi (2006)	Cross-sectional; June 1996–June 2000	Bahrain, tertiary referral teaching hospital	Same department same time period	Normal menses, no hyperandrogenism
Altieri *et al.* (2010)	Retrospective; January–April 2006	Italy, academic hospital	Same group as PCOS	Eumenorrheic, no signs of hyperandrogenism and normal ovarian morphology
Amato *et al.* (2008)	Retrospective, study period not stated	Italy, outpatients clinic	Same group as PCOS	Suspected of PCOS
Azziz *et al.* (2004a)	Cross sectional, October 1987 and June 2002	USA, reproductive endocrinology clinic	Same group as PCOS	
Bernasconi *et al.* (1996)	Cross sectional; study period not stated	Italy, endocrinology clinic	Not stated	Nonhirsute, eumenorrheic, age matched
Beydoun *et al.* (2009)	Retrospective; 1 January 2000–31 December 2006	USA, fertility treatment center	Same time period and fertility treatment center as PCOS	Age- and period-matched non-PCOS women
Carmina *et al.* (2006)	Retrospective, 1980–2004	Italy, two endocrinology departments at university	Same group as PCOS referred for hyperandrogenism	Idiopathic hirsutism and idiopathic hyperandrogenism; normal ovulatory cycles and normal ovaries on ultrasound
Chae *et al.* (2008)	Retrospective; January 2004 to December 2007	South Korea, Department of Obstetrics and Gynecology at Seoul National University Hospital	Health-care center in our hospital as a part of group check-up for work or an association or an individual need for annual comprehensive medical check-up with no specific health problems	No hirsutism, acne or male-type alopecia, all had regular menstrual cycles, none had PCO, none had any of the Rotterdam criteria
Chen *et al.* (2010)	Cross-sectional, case–control; study period not stated	Taiwan, reproductive endocrinology clinic	Consecutive series (<35 years old) receiving voluntary annual medical check-up at the same hospital as PCOS	Matched by 3-year age strata
Cheung *et al.* (2008)	Cross-sectional; July 2003–April 2007	Hong Kong, endocrinology and infertility clinics at university hospital	61 from the community and the remaining were from same clinic as PCOS, mostly presented with tubal infertility	Regular menstrual cycles, no hirsutism/acne or ultrasound features of PCO
Chhabra and Venkatraman (2010)	Cross-sectional; study period not stated	India, gynecological outpatient unit	From the same group	Menstrual dysfunction
Ciampelli *et al.* (2000)	Cross sectional; study period not stated	Italy, referred to authors' hospital	Not stated	Normoovulatory
Dokras *et al.* (2005)	Retrospective; 2002	USA, endocrinology clinic	Randomly selected from women who were seen for an annual examination by two healthcare providers in the gynecology clinic over the same time period as the patients with PCOS.	Regular menses and an absence of hirsutism
Echiburu *et al.* (2008)	Cross sectional; 2002–2006	Chile, endocrinology unit of university	Community centers of the same geographical area as the patients had the same socioeconomic level.	Regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and absence of galactorrhea and/or thyroid dysfunction
Economou *et al.* (2009)	Cross sectional; study period not stated	Greece, PCOS-endocrine unit at hospital	Not stated	Normo-androgenemic and regularly ovulating women

Continued

Table I *Continued*

Author (year)	Study design; period	Country, PCOS recruitment source	Control recruitment source	Control description
Ferk *et al.* (2007)	Cross sectional; 2002–2005	Slovenia, department of obstetrics and gynecology at university	Authors' clinic	Age matched, healthy with proven fertility (seen in clinic for normal pregnancy), no menstrual cycle irregularities, with no clinical or biochemical hyperandrogenism and without polycystic ovaries. They also had no history of endocrinological or auto-immune disorders and no surgery to the pelvic region
Glueck *et al.* (2003a)	Cross sectional; study period not stated	USA, possibly outpatients of cholesterol center	Same group as PCOS, hospital personnel	Idiopathic intracranial hypertensive
Glueck *et al.* (2003b)	Cross sectional; study period not stated	USA, location not stated	NHANES III	NHANES III
Glueck *et al.* (2005b)	Cross sectional; study period not stated	USA, patients of cholesterol center	NHANES I and community obstetrics practice study	Same age group
Glueck *et al.* (2005a)	Cross sectional; study period not stated	USA, possibly outpatients of cholesterol center	Same group as PCOS	Idiopathic intracranial hypertensive
Glueck *et al.* (2006b)	Case–control; 1997–2003	USA, adolescents from Ohio, Kentucky, West Virginia, Indiana, Michigan and included all at cholesterol center	NHLBI growth and health study	Normal, regularly cycling
Glueck *et al.* (2008a)	Cross sectional; study period not stated	USA, outpatients of cholesterol center	Same group as PCOS	
Glueck *et al.* (2009)	Case–control; July 1995–May 2008	USA, patients of cholesterol center	Princeton follow-up study	Healthy free-living population, regular menses
Hahn *et al.* (2005)	Cross sectional; study period not stated	Germany, outpatient clinics	Health-screening program for employees instituted at the University of Duisburg-Essen Medical Center and by public advertisement	No NIH PCOS or other medical conditions
Hahn *et al.* (2007)	Cross sectional; study period not stated	Germany, outpatient clinics	Screening program for employees of the University of Duisburg-Essen	Matched in sociodemographic variables, including family status, education and employment. No PCOS (NIH) or any known medical condition
Liou *et al.* (2009)	Retrospective; 1 April 2004 to 31 December 2007	Taiwan, reproductive endocrinology clinic at Taipei Medical University	Same group as PCOS	No more than one of the following three PCOS components: (a) polycystic ovaries, (b) oligomenorrhea and (c) hyperandrogenism
Mukherjee *et al.* (2009)	Case–control; study period not stated	India, infertility clinic and endocrinology clinic	General population	Age-matched, regular menstrual cycles and no clinical and/or biochemical signs of hyperandrogenemia or polycystic ovaries
Nacul *et al.* (2007)	Case–control; study period not stated	Brazil, consulting patients (from where?)	Same group as PCOS	Age-matched women with regular, ovulatory cycles, normal androgen levels and idiopathic hirsutism
Pasquali *et al.* (1993)	Retrospective; study period not stated	Italy, location not stated	Those who attended the institute for evaluation and treatment of obesity or for general health check-up, and hospital staff	Normal menses, no hirsutism or other signs of androgenization
Patel *et al.* (2008)	Retrospective; September 2001–June 2006	USA, endocrinology clinic	Randomly selected from among female patient with regular menses by the same endocrinologist in the same time period	Regular menses recruited at same time period by the same endocrinologist
Shroff *et al.* (2007)	Retrospective chart review; 2002–2005	USA, reproductive endocrinology clinic	Seen for annual examination at gynecology clinic during the same time period	Regular menses, no hirsutism

Continued

Table I *Continued*

Author (year)	Study design; period	Country, PCOS recruitment source	Control recruitment source	Control description
Spranger *et al.* (2004)	Cross sectional; study period not stated	Germany, location not stated	Not stated	No menstrual disorders or signs of hyperandrogenism
Vrbikova *et al.* (2007)	Cross sectional; 1997–2006	Czech Republic, outpatient tertiary endocrine department	Via advertisement	All lacked symptoms of hyperandrogenism, had a regular menstrual cycle (21–35 days) and had androgen levels within the reference range
Wang *et al.* (2009)	Cross sectional; 1 January 2004–30 August 2006	China, reproductive center clinic	Same geographic area, recruited in the same period and evaluated consecutively	Age-matched, normal ovulatory menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and absence of sonographic signs of PCOS. None of them had sign of galactorrhea and thyroid dysfunction or personal or family history of diabetes

NHANES, National Health and Nutrition Examination Survey; NHLBI, National Heart, Lung and Blood Institute.

1993; Ciampelli *et al.*, 1999; Cupisti *et al.*, 2007a; Chhabra and Venkatraman, 2010; Dewailly *et al.*, 2010; Farid ur *et al.*, 2010) and four studies that included adolescents only (Glueck *et al.*, 2001, 2006a, 2008a; Hashemipour *et al.*, 2004). Forty-three studies used a diagnosis consistent with the NIH criteria, while 63 used a diagnosis consistent with the ESHRE/ASRM criteria (Table III). In terms of the geographic region, 31 studies were conducted in the Americas, 45 in Europe, 28 in Asia and 2 in Oceania. Thirty-seven studies reported ethnicity for women with PCOS. The WHO-IOTF definition of overweight and obesity were used for the seven studies conducted in Asian women (Table III). Seven studies described the measurement of body height and weight, 14 studies reported the diet and physical activity of the subjects and 69 studies reported on the use of medication that could affect the study outcome (Supplementary data, Table SII). Further description of the studies is reported in Supplementary data, Table SII.

Supplementary data, Table SIII reports the quality assessment of the studies using criteria based on the Newcastle–Ottawa scale. As determined by our inclusion criteria, all women with PCOS were recruited either consecutively or randomly. All controls were recruited from hospitals or clinics except in nine studies (Glueck *et al.*, 2005b, 2006b, 2009; Hahn *et al.*, 2005; Hahn *et al.*, 2007; Vrbikova *et al.*, 2007; Mukherjee *et al.*, 2009; Wang *et al.*, 2009). Most studies (98%) provided adequate criteria for the diagnosis of PCOS, except in two studies (Shroff *et al.*, 2007; Altieri *et al.*, 2010) which relied on record linkage data or self-reported data. Outcome (i.e. body weight, height, WC and/or hip circumference) was independently measured in 56 studies (Supplementary data, Table SIII). Twenty-two of the 35 studies with control groups reported that the same method was used to ascertain the outcomes in both groups. Six studies (Ferk *et al.*, 2007; Chae *et al.*, 2008; Cheung *et al.*, 2008; Mukherjee *et al.*, 2009; Wang *et al.*, 2009; Altieri *et al.*, 2010) included controls with no feature of PCOS. Comparability between the groups in terms of age or other factors (e.g. socioeconomic status) was met in 21 studies. No study reported on the non-response rate for the women with or without PCOS. Seventeen studies were categorized as being higher quality ($\geq$5/9) and 89 studies were categorized as being lower ($\leq$4/9) quality (Supplementary data, Table SIII).

A contour-enhanced funnel plot was conducted to assess the risk of publication bias. For studies on overweight and obesity (Supplementary data, Fig. S2), the plot was asymmetric (*P*-value of the test for symmetric funnel plot, arcsine test = 0.015). The arcsine test proposed by Rucker *et al.* (2008) was conducted since neither the Egger's (Egger *et al.*, 1997) nor Harbord's (Harbord *et al.*, 2006) test was appropriate. The Egger's test is used for continuous endpoints and the Harbord's (or modified Egger's test) is not recommended for a review with large imbalance in the group sizes and/or with substantial heterogeneity. A publication bias could not be excluded for studies on overweight and obesity, although true heterogeneity in effect sizes would be another source of asymmetry in the funnel plot (Egger *et al.*, 1997). For studies on obesity, the contour-enhanced funnel plot was relatively symmetric (Supplementary data, Fig. S3, *P* value = 0.39). Given true heterogeneity in effect sizes, a publication bias is unlikely. The impact of potential future studies on the meta-analysis was assessed using the method proposed by Langan *et al.* (2012). The significant contours indicated very little chance that any additional studies would change the pooled finding to statistical non-significance. The finding of the current meta-analysis would be altered if, and only if, an additional study of enormous sample size which is far more than the largest study ever conducted [(Glueck *et al.*, 2005b) with SE of 0.06] provides significant negative effect. It is thus concluded that the meta-analysis finding is robust.

Prevalence of overweight and obesity (BMI $\geq$25 kg/m^2), obesity (BMI $\geq$30 kg/m^2 and central obesity

The proportion of women with PCOS who were overweight and obese ranged from 6% (Ansarin *et al.*, 2007) to 100% (Peppard *et al.*, 2001; Glueck *et al.*, 2003b; Villaseca *et al.*, 2004) with a pooled estimated prevalence of 61% (95% CI: 54–68%). In the 21 studies that provided data on the prevalence of overweight and

Table II Summary of subgroup analyses according to study quality score, PCOS definition, age, ethnicity and geographic region in women with and without PCOS.

Subgroup	Risk ratio (95% CI), *P*-value	χ^2 (*P*-value)	I^2 (%)	*P*-value for subgroup differences
Overweight and obesity				
High-quality score	2.31 (1.67, 3.19), $P < 0.001$	302.63 ($P < 0.001$)	96	0.06
Low-quality score	1.49 (1.08, 2.05), $P = 0.02$	37.38 ($P < 0.001$)	81	
Obesity				
High-quality score	4.68 (2.52, 8.70), $P < 0.001$	191.13 ($P < 0.001$)	96	0.006
Low-quality score	1.84 (1.41, 2.39), $P < 0.001$	56.84 ($P < 0.001$)	84	
Central obesity				
High-quality score	2.27 (1.48, 3.48), $P < 0.001$	6.88 ($P = 0.03$)	71	0.14
Low-quality score	1.38 (0.83, 2.27), $P = 0.21$	26.40 ($P < 0.001$)	92	
Overweight and obesity				
NIH PCOS	1.76 (1.27, 2.42), $P < 0.001$	28.40 ($P < 0.001$)	79	0.49
ESHRE/ASRM PCOS	2.06 (1.49, 2.85), $P < 0.001$	338.45 ($P < 0.001$)	96	
Obesity				
NIH PCOS	2.95 (1.69, 5.14), $P < 0.001$	87.36 ($P < 0.001$)	92	0.78
ESHRE/ASRM PCOS	2.63 (1.53, 4.54), $P < 0.001$	360.60 ($P < 0.001$)	98	
Central obesity				
NIH PCOS	1.98 (1.82, 2.15), $P < 0.001$	0.33 ($P = 0.56$)	0	0.47
ESHRE/ASRM PCOS	1.61 (0.93, 2.79), $P = 0.09$	24.55 ($P < 0.001$)	88	
Overweight and obesity				
Adults	1.92 (1.48, 2.48), $P < 0.001$	348.40 ($P < 0.001$)	95	0.85
Adolescents	2.25 (0.42, 11.98), $P = 0.34$	36.82 ($P < 0.001$)	97	
Obesity				
Adults	2.57 (1.68, 3.93), $P < 0.001$	465.13 ($P < 0.001$)	97	0.37
Adolescents	5.91 (1.00, 35.02), $P = 0.05$	11.49 ($P < 0.001$)	91	
Overweight and obesity				
Caucasian	2.90 (1.93, 4.35), $P < 0.001$	99.86 ($P < 0.001$)	95	0.41
Asian	2.00 (0.92, 4.34), $P = 0.08$	11.27 ($P < 0.001$)	91	
Obesity				
Caucasian	10.79 (5.36, 21.70), $P < 0.001$	6.80 ($P = 0.03$)	71	<0.001
Asian	2.31 (1.33, 4.00), $P = 0.003$	6.67 ($P = 0.01$)	85	
Central obesity				
Caucasian	1.98 (1.81, 2.15), $P < 0.001$	0.33 ($P = 0.56$)	0	0.65
Asian	2.41 (1.02, 5.67), $P = 0.04$	6.90 ($P = 0.009$)	86	
Overweight and obesity				
Americas	1.98 (1.35, 2.90), $P < 0.001$	158.15 ($P < 0.001$)	96	0.85
Europe	1.84 (1.22, 2.76), $P = 0.003$	84.93 ($P < 0.001$)	89	
Asia	2.20 (1.39, 3.47), $P < 0.001$	21.45 ($P < 0.001$)	86	
Obesity				
Americas	2.94 (1.65, 5.23), $P < 0.001$	435.67 ($P < 0.001$)	98	0.44
Europe	3.78 (1.03, 13.95), $P = 0.05$	16.25 ($P < 0.001$)	88	
Asia	2.07 (1.50, 2.86), $P < 0.001$	13.21 ($P = 0.004$)	97	
Central obesity				
Americas	1.97 (1.80, 2.14), $P < 0.001$	NA	NA	0.31
Europe	1.39 (0.88, 2.20), $P = 0.16$	12.79 ($P = 0.002$)	84	
Asia	2.41 (1.02, 5.67), $P = 0.04$	6.90 ($P = 0.009$)	86	

Table III Summary of studies assessing overweight, obesity or central obesity in women with PCOS and the prevalence of overweight, obesity and central obesity.

Study (year)	PCOS (*n*)	Age, mean ± SD or otherwise stated	PCOS definition	Country	PCOS ethnicity	Prevalence of overweight and obesity, % (definition)	Prevalence of obesity, % (definition)	Prevalence of central obesity, % (definition)
Adali *et al.* (2008)	42	23.5 ± 3.1	ESHRE/ASRM	Turkey		66.7 (WHO)		
Adali *et al.* (2010)	50	26.9 ± 2.2, 24.7 ± 2.9	ESHRE/ASRM	Turkey		52.0 (WHO)		
Al-Ojaimi (2006)	134	29.4 ± 5.5	ESHRE/ASRM	Bahrain			59.7 (WHO)	
Al-Ruhaily *et al.* (2008)	148	24.5 ± 6.6	ESHRE/ASRM	Saudi Arabia	Arab Saudi	39.9 (WHO)	27.0 (WHO)	
Altieri *et al.*, 2010)	15	34.7 ± 4.2	ESHRE/ASRM	Italy	Italian	40.0 (WHO)		
Amato *et al.* (2008)	170	24.5 ± 5.8	ESHRE/ASRM	Italy				66.5 (IDF)
Ansarin *et al.* (2007)	494	NA	ESHRE/ASRM	Iran	Iranian	5.9 (WHO)		
Azziz *et al.* (2004a)	716	27.7 ± 7.3	NIH	USA			60.1 (WHO)	
Barcellos *et al.* (2007)	69	25.6 ± 5.6	NIH	Brazil		73.9 (WHO)	46.4 (WHO)	
Bernasconi *et al.* (1996)	112	22.5 ± 5.3; 23.2 ± 6.9	ESHRE/ASRM	Italy		46.4 (WHO)		61.5 (WHO)
Beydoun *et al.* (2009)	69	32.3 ± 4.1	NIH	USA		53.6 (WHO)	49.3 (WHO)	
Buyalos *et al.* (1993)	25	28.0 ± 1.0	NIH	USA		56.0 (WHO)		
Buyalos *et al.* (1995)	16	31.0 ± 2.0; 29.0 ± 1.0	NIH	Finland		56.3 (WHO)		
Carmina *et al.* (2005)	204	24.8 ± 5.6	NIH	Italy			28.9 (WHO)	
Carmina *et al.* (2006)	685	24.5 ± 4.7; 24.3 ± 4.5	ESHRE/ASRM	Italy			15.8 (WHO)	
Carmina *et al.* (2007)	110	25.1 ± 4.9	NIH	Italy		63.6 (WHO)	31.8 (WHO)	
Carmina *et al.* (2009b)	95	24.2 ± 3	ESHRE/ASRM	Italy		67.4 (WHO)	34.7 (WHO)	
Castelo-Branco *et al.* (2010)	223	28.4 ± 8.4	ESHRE/ASRM	Spain		50.2	29.1 (WHO)	
Cerda *et al.* (2007)	41	24.7 ± 7.2	ESHRE/ASRM	Chile			58.5 (WHO)	
Chae *et al.* (2008)	166	25.5 ± 5.8	ESHRE/ASRM	South Korea	Korean			23.1 (IDF)
Charnvises *et al.* (2005)	121	29.1 ± 6.1	ESHRE/ASRM	Thailand			49.6 (WHO)	34.2 (WHO)
Chen *et al.* (2010)	273	24.5 ± 5.1	ESHRE/ASRM	Taiwan		41.4 (WHO)		
Cheung *et al.* (2008)	295	30.2 ± 6.4	ESHRE/ASRM	Hong Kong	Chinese	60.3 (IOTF)		53.1 (ATP III)
Chhabra *et al.* (2010)	100	15–34	NIH	India			30 (IOTF)	
Ciampelli *et al.* (1999)	110	17–33	ESHRE/ASRM	Italy	Native Italians	56.4 (WHO)		
Ciampelli *et al.* (2000)	20	26.4 ± 1.1; 27.3 ± 1.0	ESHRE/ASRM	Italy		60.0 (WHO)		
Ciampelli *et al.* (2001)	27	19–33	ESHRE/ASRM	Italy		59.3 (WHO)		
Ciampelli *et al.* (2002)	20	19–33	ESHRE/ASRM	Italy	Caucasian	60.0 (WHO)		

Continued

Table III *Continued*

Study (year)	PCOS (*n*)	Age, mean ± SD or otherwise stated	PCOS definition	Country	PCOS ethnicity	Prevalence of overweight and obesity, % (definition)	Prevalence of obesity, % (definition)	Prevalence of central obesity, % (definition)
Cupisti *et al.* (2007a)	16	15–34	NIH	Germany		43.8 (WHO)	37.5 (WHO)	
Cupisti *et al.* (2007b)	108	31.4 ± 5.8; 32.6 ± 6.7	ESHRE/ASRM	Germany		45.4 (WHO)		
Cupisti *et al.* (2008)	184	28.2 ± 7.0; 28.0 ± 6.9	NIH	Germany		59.8 (WHO)		
de Vries *et al.* (2007)	8	16–20	ESHRE/ASRM	Israel			12.5 (CDC)	
Dewailly *et al.* (2010)	841	16–40	ESHRE/ASRM	France				60.8 (IDF)
Dokras *et al.* (2005)	129	median: 28	NIH	USA	96% white		62.8 (WHO)	
Echiburu *et al.* (2008)	159	24.3 ± 5.8	NIH	Chile			39.0 (WHO)	
Economou *et al.* (2009)	83	25.0 ± 4.9	NIH	Greece		47.0 (WHO)		
Eden and Warren (1999)	1019	NA	ESHRE/ASRM	Australia		31.1 (WHO)	13.5 (WHO)	
Elsenbruch *et al.* (2006)	143	31.3 ± 1.3; 28.6 ± 0.5	NIH	Germany	Caucasian	71.3 (WHO)	52.4 (WHO)	
Escobar-Morreale *et al.* (2006)	76	26.0 ± 6.0	ESHRE/ASRM	Spain	Caucasian	67.1 (WHO)	44.7 (WHO)	
Espinos-Gomez *et al.* (2009)	103	26.7 ± 6	NIH	Spain		57.3 (WHO)		
Essah *et al.* (2008)	Italy: 108, US: 106	Italian: 24.7 ± 5.2, US 29.9 ± 7.5	NIH	USA and Italy	Italy: Italian; USA: 92% Caucasian, 8% African-American	68.5 (WHO)	30.6 (WHO)	
Farid ur *et al.* (2010)	41	13–48	ESHRE/ASRM	Pakistan		51.2 (WHO)	24.4 (WHO)	
Ferk *et al.* (2007)	123	24.4 ± 4.4	ESHRE/ASRM	Slovenia	European (Slovenian) origin	13.0 (WHO)		
Fox (1999)	64	Median: 30 (range: 19–37)	ESHRE/ASRM	UK		48.4 (WHO)		
Fulghesu *et al.* (1999)	100	Range: 19–36	ESHRE/ASRM	Italy		56.0 (WHO)		
Gambarin-Gelwan *et al.* (2007)	88	31.4	NIH	USA		56.8 (WHO)	42.0 (WHO)	
Gambineri *et al.* (2004)	121	28.1 ± 5.7; 23.5 ± 5.8; 23.6 ± 5.2	ESHRE/ASRM	Italy		84.3 (WHO)		
Gennarelli *et al.* (1998)	49	25.0 ± 5.3	ESHRE/ASRM	Sweden		49.0 (WHO)		
Gennarelli *et al.* (1997)	18	24 ± 1.0; 27.4 ± 1.2	ESHRE/ASRM	Sweden		44.4 (WHO)		
Glintborg *et al.* (2004)	125	Median: 29 (23–34; 25th and 75th %ile)	NIH	Denmark	Caucasian	65.6 (WHO)		
Glueck *et al.* (2001)	11	16.2 ± 1.7	NIH	USA	White American teenage girls	81.8 (WHO)	81.8 (WHO)	
Glueck *et al.* (2003c)	33	37.2 ± 8.1	NIH	USA	Caucasian	93.9 (WHO)	75.8 (WHO)	
Glueck *et al.* (2003a)	15	30.7 ± 6.3	NIH	USA	1 black, 14 whites	100.0 (WHO)	93.3 (WHO)	

Glueck *et al.* (2003b)	138	31.0 ± 9.0	NIH	USA	White			85.5 (ATP III)
Glueck *et al.* (2004)	39	30.0 ± 4.0	NIH	USA	Caucasian	84.6 (WHO)	64.1 (WHO)	
Glueck *et al.* (2005b)	401	30.0 ± 6.0	ESHRE/ASRM	USA	Caucasian	91.0 (WHO)	76.1 (WHO)	
Glueck *et al.* (2005a)	37	PCOS and control: 34 median; IQR: 28–39	ESHRE/ASRM	USA	PCOS and control: 64 white 1 black		94.6 (WHO)	
Glueck *et al.* (2006a)	35	17.0 ± 2.0	ESHRE/ASRM	USA		77.1 (CDC)	54.3 (CDC)	
Glueck *et al.* (2006b)	37	Median: 16.1	ESHRE/ASRM	USA	Whites	83.8 (CDC)	73.0 (CDC)	
Glueck *et al.* (2008b)	138	30.0 ± 5.0	ESHRE/ASRM	USA	131 Caucasian, 1 African-American, 10 other	83.3 (WHO)	68.1 (WHO)	
Glueck *et al.* (2008a)	10	12.6 ± 1.5	ESHRE/ASRM	USA	2 Blacks 8 Whites	80.0 (WHO)	80.0 (WHO)	
Glueck *et al.* (2009)	488	Median: 35.2 (IQR 33–39)	ESHRE/ASRM	USA	White	92.6 (WHO)		
Gul *et al.* (2008)	30	25.1 ± 6.9	ESHRE/ASRM	Turkey			43.3 (WHO)	20.0 (ATP III)
Hahn *et al.* (2005)	120	29.0 ± 5.4	NIH	Germany		72.5 (WHO)	52.5 (WHO)	
Hahn *et al.* (2006)	278	27.9 ± 6.5; 27.6 ± 5.9; 27.8 ± 5.8	NIH	Germany	Caucasian	68.7 (WHO)	48.9 (WHO)	
Hahn *et al.* (2007)	411	28 ± 6.3	NIH	Germany	Caucasian	65.9 (WHO)	47.7 (WHO)	74.5 (IDF)
Haq *et al.* (2007)	508	27.1 ± 4.5	ESHRE/ASRM	Pakistan		93.7 (WHO)		
Hashemipour *et al.* (2004)	30	16.0 ± 1.9	NIH	Iran		20.0 (WHO)		
Homburg *et al.* (1996)	20	29.4 ± 4.8	ESHRE/ASRM	Israel		40.0 (WHO)		
Jahanfar and Eden (1993)	77	27.0 ± 5.3; 26.5 ± 6.4	ESHRE/ASRM	Australia		59.7 (WHO)		
Kiddy *et al.* (1990)	263	NA	ESHRE/ASRM	UK		34.6 (WHO)		
Lee *et al.* (2009)	194	26.0 ± 5.0; 29.0 ± 5.0	ESHRE/ASRM	Korea	Korean	38.7 (IOTF)	28.4 (IOTF)	
Liou *et al.* (2009)	295	26.7 ± 5.4	ESHRE/ASRM	Taiwan	Taiwan Chinese		39.0 (IOTF)	
Luque-Ramirez *et al.* (2008)	40	24.5 ± 5.8	NIH	Spain		72.5 (WHO)	40.0 (WHO)	
Marcondes *et al.* (1995)	5	22.0 ± 4.4	ESHRE/ASRM	USA		20.0 (WHO)		
Marcondes *et al.* (2007)	73	25.0 ± 6.0	NIH	Brazil	Brazilian and Caucasian			49.3 (ATP III)
Marsden *et al.* (2001)	20	27.5 ± 4.1	NIH	UK		90.0 (WHO)	50.0 (WHO)	
Martinez-Guisasola *et al.* (2001)	167	24.2 ± 5.1	NIH	Spain		29.9 (WHO)		
Mohlig *et al.* (2006)	118	28.7 ± 0.5	NIH	Germany		76.3 (WHO)		
Mozzanega *et al.* (2004)	18	30.0 ± 1.4; 29.4 ± 2.3	ESHRE/ASRM	Italy		44.4 (WHO)		
Mubarak *et al.* (2006)	100	28.0 ± 3.9	ESHRE/ASRM	UK			41.0 (WHO)	
Mukherjee *et al.* (2009)	180	24.8 ± 5.3	ESHRE/ASRM	India	Indian	58.3 (IOTF)		
Nacul *et al.* (2007)	31	22.4 ± 7.1	NIH	Brazil		61.3 (WHO)		

Continued

Table III *Continued*

Study (year)	PCOS (*n*)	Age, mean ± SD or otherwise stated	PCOS definition	Country	PCOS ethnicity	Prevalence of overweight and obesity, % (definition)	Prevalence of obesity, % (definition)	Prevalence of central obesity, % (definition)
Ni *et al.* (2009)	578	20–41	ESHRE/ASRM	China		38.4 (IOTF)	23.0 (IOTF)	
Pasquali *et al.* (1993)	100	20.8 ± 5.9	ESHRE/ASRM	Italy		75.0 (WHO)		
Patel *et al.* (2008)	189	28.9 ± 7.7	NIH	USA			39.7 (WHO)	
Peppard *et al.* (2001)	5	29.4 ± 8.4	NIH	USA		100.0 (WHO)	100.0 (WHO)	
Sahin *et al.* (1993)	31	17–33	ESHRE/ASRM	Turkey		61.3 (WHO)		
San Millan *et al.* (2006)	139	25.0 ± 6.0	NIH	Spain	Caucasian	64.7 (WHO)	41.7 (WHO)	
Schwimmer *et al.* (2005)	70	Median: 28 (range 21–39); median 28 (range: 22–42)	NIH	USA	Hispanic, 63%; white, non-Hispanic, 17%; black, non-Hispanic, 10%; and Asian, non-Hispanic, 10%.	90.0 (WHO)	74.0 (WHO)	
Sharifi *et al.* (2010)	103	24.8 ± 5.6	ESHRE/ASRM	Iran		67.0 (WHO)		
Shroff *et al.* (2007)	258	27.0 ± 5.3; 30.0 ± 6.3; 28.9 ± 5; 28.2 ± 5.8	ESHRE/ASRM	USA			64.0 (WHO)	
Siddiqui *et al.* (2010)	62	35.9 ± 5.0	ESHRE/ASRM	Saudi Arabia	Saudi females	64.5 (WHO)		
Spranger *et al.* (2004)	63	28.9 ± 0.6	NIH	Germany		73.0 (WHO)		
Targher *et al.* (2009)	14	23.0	NIH	Italy		57.1 (WHO)	14.3 (WHO)	
Tasali *et al.* (2008)	52	29.7 ± 0.7	NIH	USA	62% African-American or Hispanics	96.2 (WHO)	92.3 (WHO)	
Telli *et al.* (2002)	50	21.4 ± 2.74	ESHRE/ASRM	Turkey		34.0 (WHO)		
Tropeano *et al.* (1997)	10	23.0 ± 2.3	ESHRE/ASRM	Italy		70.0 (WHO)		
Villaseca *et al.* (2004)	31	23.9 ± 5.1; 22.4 ± 6.1	NIH	Chile		100.0 (WHO)	71.0 (WHO)	
Villuendas *et al.* (2005)	103	25.0 ± 6.0	NIH	Spain	Caucasian	61.2 (WHO)	40.8 (WHO)	
Vrbikova *et al.* (2007)	244	27.4 ± 7.5	ESHRE/ASRM	Czech Republic		50.8 (WHO)	27.9 (WHO)	
Wang *et al.* (2009)	271	28.9 ± 3.4	ESHRE/ASRM	China	Chinese		48.3 (IOTF)	
Weerakiet *et al.* (2001)	79	28.2 ± 6.2	ESHRE/ASRM	Thailand		62.0 (WHO)	26.6 (WHO)	
Weerakiet *et al.* (2007)	170	28.8 ± 5.9	ESHRE/ASRM	Thailand		52.9 (WHO)	35.9 (WHO)	55.9 (IDF)
Yildiz *et al.* (2008)	746	27.8 ± 6.5, 27.7 ± 8.0; 26.9 ± 7.5; 27.8 ± 7.6; 27.3 ± 6.9	NIH	USA			61.4 (WHO)	
Yildizhan *et al.* (2009)	100	25.5 ± 3.9; 26.7 ± 3.6	ESHRE/ASRM	Turkey		57.0 (WHO)		

NIH, National Institute of Health; ESHRE/ASRM, European Society for Human Reproductive and Embryology/American Society for Reproductive Medicine; IDF, International Diabetes Federation; WHO, World Health Organization; ATP III, Adult Treatment Panel III; IOTF, International Obesity Taskforce; CDC, Centers for Disease Control and Prevention.

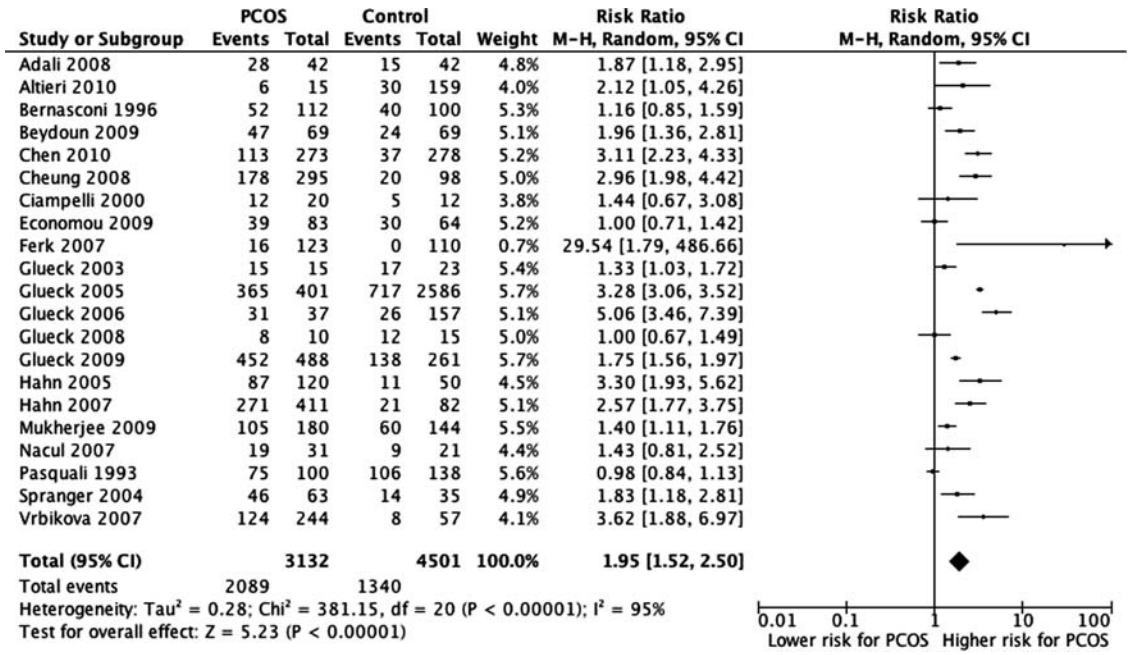

Figure 1 Meta-analysis of the prevalence of overweight and obesity (BMI $\geq$25 kg/m^2) in women with and without PCOS. CI, confidence interval; M-H, Mantel-Haenszel; PCOS, polycystic ovary syndrome.

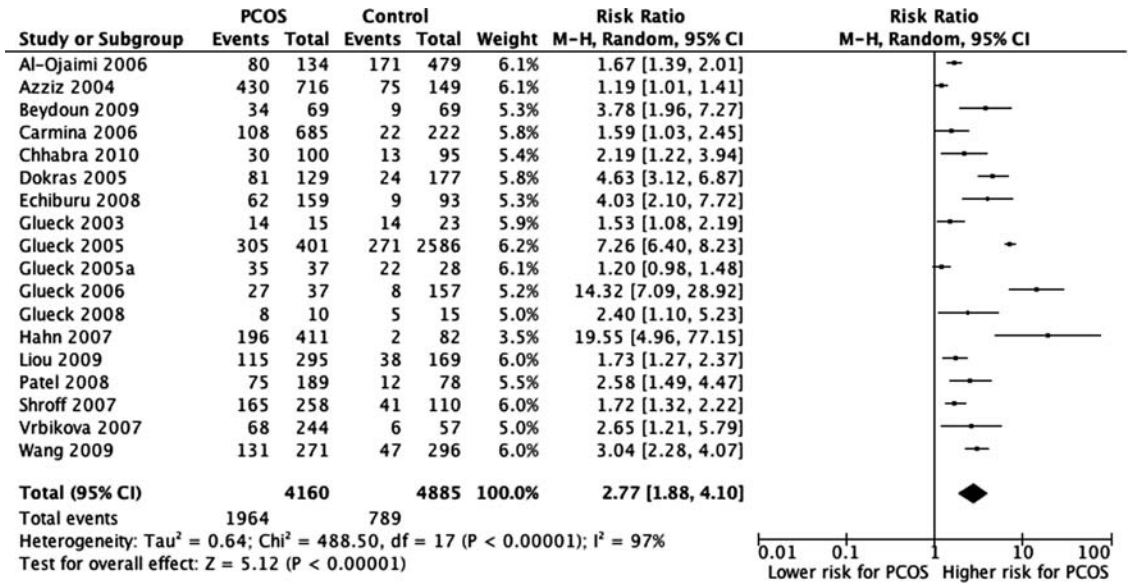

Figure 2 Meta-analysis of the prevalence of obesity (BMI $\geq$30 kg/m^2) in women with and without PCOS.

obesity in women with and without PCOS, the prevalence of overweight and obesity was significantly higher in women with PCOS (Fig. 1). Significant statistical heterogeneity was present.

The prevalence of obesity in women with PCOS ranged from 12.5% (de Vries *et al.*, 2007) to 100% (Peppard *et al.*, 2001) with a pooled estimated prevalence of 49% (95% CI: 42–55%). In the 18 studies that provided data on the prevalence of obesity in women with and without PCOS, the prevalence of obesity was significantly higher in women with PCOS (Fig. 2). Significant statistical heterogeneity was present.

The prevalence of central obesity in women with PCOS ranged from 20% (Gul *et al.*, 2008) to 85.5% (Glueck *et al.*, 2003b) with a pooled estimated prevalence of 54% (95% CI: 43–62%). In the six studies that provided data on the prevalence of central obesity in

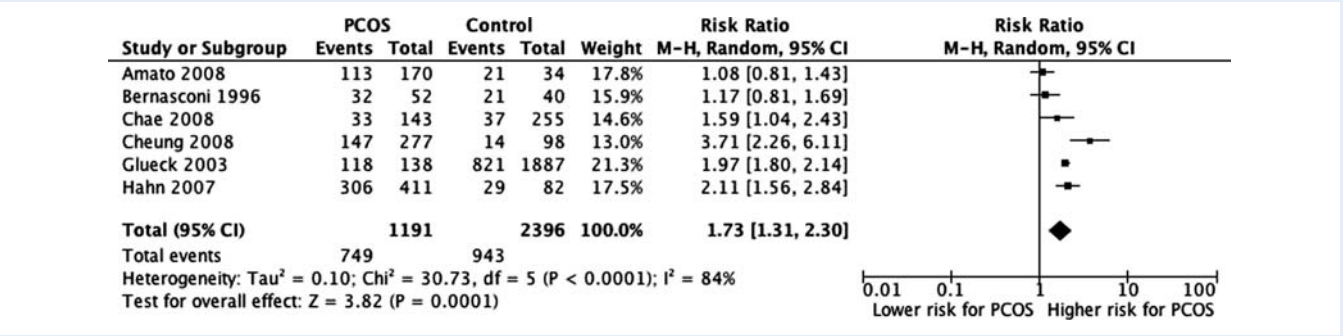

Figure 3 Meta-analysis of the prevalence of central obesity in women with and without PCOS.

women with and without PCOS, the prevalence of central obesity was significantly higher in women with PCOS (Fig. 3). There was significant statistical heterogeneity.

Subgroup analyses to assess potential sources of heterogeneity

Quality score

Subgroup analyses were performed for studies with a higher (≥5/9) or lower (≤4/9) study quality score (Table II). Significant statistical heterogeneity was found in all comparative subgroups for quality score. There was a trend for the association between PCOS and overweight and obesity being stronger in studies with a higher score compared with those with a lower score. The association between PCOS and obesity was stronger in studies with a higher score compared with those with a lower score. The association between PCOS and central obesity was similar in studies with higher and lower scores.

PCOS diagnosis

Subgroup analyses were performed for studies with PCOS diagnosis consistent with the NIH or ESHRE/ASRM criteria (Table II). Significant statistical heterogeneity was found in all comparative subgroups for PCOS diagnosis, except in the NIH subgroup for the prevalence of central obesity. The association between PCOS status and overweight and obesity was similar in both NIH and ESHRE/ASRM subgroups. The association between PCOS status and obesity was not different between the NIH and ESHRE/ASRM subgroups. The prevalence of central obesity was similar in the NIH and ESHRE/ASRM subgroups.

Age

Subgroup analyses were performed on studies with adolescents or adults (Table II). Significant statistical heterogeneity was present in all comparative subgroups for age. The association between PCOS status and overweight and obesity was similar in adults and adolescents. Adolescent girls with PCOS appeared to have a greater prevalence of obesity than adult women with PCOS but the difference did not reach statistical significance. Subgroup analyses were not performed for studies conducted in adolescents as all studies comparing the prevalence of central obesity in women with and without PCOS were conducted in adults.

Ethnicity

Subgroup analyses were performed on studies involving the Caucasian women or Asian women (Table II). Significant statistical heterogeneity was observed in all comparative subgroups for ethnicity, except in the Caucasian subgroup for the prevalence of central obesity. The association between PCOS and overweight and obesity was similar in both subgroups. The RR for obesity was higher in the Caucasian women than that of the Asian women. The prevalence of central obesity was similar in both Caucasian and Asian subgroups.

Geographic region

Subgroup analyses were performed across geographic regions, including Americas, Europe and Asia (Table II). Significant statistical heterogeneity was seen in all comparative subgroups for the geographic region. The association between PCOS status and overweight and obesity was not significantly different between Americas, Europe and Asia subgroups. The association between PCOS status and obesity was similar in all three regions. The association between PCOS status and central obesity was similar in all three regions.

Discussion

Principal findings

We report a comprehensive systematic review and meta-analysis of the prevalence of overweight and obesity, obesity and central obesity in women with and without PCOS. We found that women with PCOS had significantly elevated prevalence for overweight and obesity, obesity and central obesity, compared with controls. When only studies with high quality scores were considered, the RRs for being overweight and obese were even higher. The increased risk of being overweight and obese for women with PCOS was independent of PCOS diagnostic criteria, age and geographic region. The Caucasian women with PCOS had a greater prevalence of obesity than that of Asian women with PCOS.

Interpretation of findings

The primary aim of this review was to report on the prevalence of obesity in women with and without PCOS. It has been proposed that obesity plays an important role in the pathogenesis of PCOS. Obesity exacerbates the metabolic, reproductive and psychological features of PCOS (Kiddy *et al.*, 1990; Holte *et al.*, 1994; Balen *et al.*,

1995; Liou *et al*., 2009). In the long term, overweight or obese women with PCOS had increased risk of developing metabolic syndrome, impaired glucose tolerance and type 2 diabetes (Legro *et al*., 1999; Ehrmann *et al*., 2006). Obesity may also contribute to the psychological co-morbidities in women with PCOS, such as anxiety and depression (Himelein and Thatcher, 2006; Barry *et al*., 2011). One study has shown that weight gain precedes the onset of PCOS (Laitinen *et al*., 2003), lending further support to the causal role of obesity in the development of PCOS but this remains to be confirmed in further longitudinal studies.

The effect of obesity on the metabolic and reproductive symptoms in PCOS is likely to be mediated by insulin resistance (Diamanti-Kandarakis, 2007). Obesity, particularly central obesity, is known to increase insulin resistance (Carey *et al*., 1996; Tousignant *et al*., 2008). Hyperinsulinemia resulting from insulin resistance stimulates ovarian steroidogenesis and inhibits sex hormone-binding globulin (SHBG) production in the liver, thereby increasing the availability of free androgens (Plymate *et al*., 1988). The adipose tissue also provides storage and a metabolic site for various lipid-soluble steroids, such as androgens, which contributes further to hyperandrogenism (Pasquali *et al*., 2006). Women with PCOS who are more overweight and obese are therefore more likely to have a worse clinical reproductive presentation, with the resulting potential for an earlier diagnosis.

There is also evidence suggesting that PCOS contributes to obesity. Women with high androgen levels independent of PCOS status were found to have greater cravings for high-fat foods and carbohydrate-rich foods (Lim *et al*., 2009) and possibly a greater intake of these foods (Douglas *et al*., 2006). However, this was not found in all studies (Alvarez Blasco *et al*., 2011). Metabolic factors, such as hyperinsulinemia (Aas *et al*., 2009), reduced postprandial thermogenesis (Robinson *et al*., 1992) and basal metabolic rate (Georgopoulos *et al*., 2009) and alterations in (Baranowska *et al*., 1999; Hirschberg *et al*., 2004; Moran *et al*., 2004, 2007), could also contribute to weight gain in women with PCOS. The greater prevalence of overweight and obesity in PCOS may therefore additionally reflect an inherent predisposition to weight gain. It is not clear from this current study whether PCOS primarily contributes to obesity or obesity primarily contributes to PCOS.

Women with PCOS have greater tendency to accumulate fat in the upper body when compared with controls matched for weight or BMI (Kirchengast and Huber, 1999; Yucel *et al*., 2006; Svendsen *et al*., 2008). This effect could be present even in lean women with PCOS (Carmina *et al*., 2007; Svendsen *et al*., 2008). Central adiposity was associated with more severe metabolic and reproductive features of PCOS including hyperandrogenism (Pasquali *et al*., 1994; Cosar *et al*., 2008; Svendsen *et al*., 2008; Godoy-Matos *et al*., 2009), higher insulin levels (Pasquali *et al*., 1994), lower SHBG levels (Lord *et al*., 2006) and dyslipidemia (Pasquali *et al*., 1994; Lord *et al*., 2006; Wehr *et al*., 2009; Penaforte *et al*., 2010). On the other hand, high levels of insulin and androgens may potentially encourage a central body fat distribution (Sinha *et al*., 1996; Janssen *et al*., 2010), which could explain the greater risk of central obesity in women with PCOS. This could form a vicious cycle perpetuating the centrally obese state of women with PCOS. It is again not possible to determine from the current review whether the elevated prevalence of central obesity in PCOS primarily reflects an effect of PCOS on worsening central obesity or an effect of central obesity on worsening PCOS.

In addition to the potential confounders of obesity mentioned above, methodological factors, such as study design, definition of PCOS, sampling frame and measurement of obesity, could also influence the estimate of obesity prevalence. To account for these effects, we performed a subgroup analysis according to study quality scores. We found that studies with higher quality scores had higher obesity prevalence, which lends further support to our conclusion that women with PCOS had a greater prevalence of obesity. This also suggests that the pooled prevalence that included all studies is likely to be an underestimation of obesity risk for women with PCOS.

The secondary aim of this review was to examine the effect of PCOS diagnostic criteria, age, ethnicity and geographic region on obesity prevalence in women with and without PCOS. NIH PCOS phenotypes were reported to have more severe metabolic and reproductive symptoms compared with the ESHRE/ASRM PCOS phenotypes (Carmina *et al*., 2005; Broekmans *et al*., 2006; Welt *et al*., 2006; Hsu *et al*., 2007; Lam *et al*., 2009; Cho *et al*., 2011) but this was not reported by all studies (Moran *et al*., 2011a, c). Greater central obesity in NIH PCOS has also been previously reported in some studies (Welt *et al*., 2006; Barber *et al*., 2007; Hsu *et al*., 2007; Lam *et al*., 2009; Anaforoglu *et al*., 2011) but not in others (Hickey *et al*., 2011; Mehrabian *et al*., 2011; Tehrani *et al*., 2011). Our meta-analysis suggests that the risk for obesity and central obesity was similar in patients diagnosed with PCOS using the NIH and the ESHRE/ASRM criteria.

The prevalence of obesity in girls aged 12–19 years in the USA in 2007–2008 was 17% (Ogden and Carroll, 2010), compared with 50–80% among adolescent girls with PCOS over the similar time period (Glueck *et al*., 2006a, b, 2008a). Obesity and obesity-related co-morbidities are therefore of increasing relevance in adolescents. As seen in adults, greater adiposity (especially around the waist) was associated with lower insulin sensitivity, greater hyperandrogenemia, worse lipid profile and higher blood pressure in adolescents with PCOS (Silfen *et al*., 2003; Glueck *et al*., 2006b). This may have serious long-term implications as elevated BMI during adolescence, even within the normal range, predicted the incidence of diabetes and coronary heart disease in adulthood (Tirosh *et al*., 2011). Considering the risk of obesity (up to 6 times) among adolescents with PCOS compared with those without PCOS reported here, obesity interventions targeted at adolescents with PCOS are urgently needed.

While a difference in the prevalence of obesity according to geographic region or ethnicity is likely to be a result of the interaction between individual factors (e.g. genetic) and environmental factors (e.g. food supply; Swinburn *et al*., 2011), an increased risk of obesity in the Caucasian women with PCOS compared with the Asian women with PCOS in this meta-analysis suggests a difference in the nature of PCOS between these groups, considering that their comparative groups were controls of the same ethnicity and geographic region. In this meta-analysis, the Caucasian women were from the USA and Europe while the Asian women were from China and Taiwan. Another study comparing Eastern Asian populations with American and European patients reported a similar trend (Carmina *et al*., 1992). The same study also reported that the Japanese women with PCOS had lower body weight and fasting insulin levels compared with their American and Italian counterparts (Carmina

et al., 1992). Despite the lower obesity cut-off for Asians (WHO, 2000) used in this meta-analysis, the prevalence of obesity among the Asian women with PCOS was still significantly lower than that of the Caucasian women with PCOS. It is possible that the risk for PCOS escalates at an even lower BMI than the suggested cut-off point for the Asian women.

Strength and weaknesses

This is a comprehensive systematic review and meta-analysis on the subject of overweight, obesity and central obesity in women with PCOS. An extensive search was conducted to avoid missing any relevant information. Contour-enhanced funnel plots indicated that the results of this meta-analysis are robust and it is highly unlikely that additional studies would shift the results to non-significance. Significant clinical and statistical heterogeneity was present between the studies, indicating considerable variability in the data. This limits the applicability of our conclusions to all women with PCOS. Subgroup analyses were conducted to address the contribution of potential sources of clinical heterogeneity, such as age, ethnicity, PCOS diagnostic criteria and geographic region. However, the heterogeneity remained unexplained in most subgroups. Factors such as definition and recruitment of controls, sampling frame of PCOS women, physical activity, diet history, socio-economic status and family history of obesity may be sources of residual confounding. The omission of papers published in other languages may have also limited our ability to determine the association between PCOS and obesity in different ethnic groups. Despite this limitation, this meta-analysis reported a significant difference between the Caucasian and Asian women in the prevalence of obesity.

The optimal study design for the determination of obesity prevalence in women with and without PCOS would be a population study in which members of the general community were consecutively selected or randomly sampled in a way that would not bias the prevalence of obesity. Unfortunately, no study met these criteria. Most population studies in women with PCOS did not report the prevalence of obesity (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004b; March et al., 2010). Moreover, these studies tended to recruit their participants from public health campaigns, the university employment database, or blood donors lists (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004b; March et al., 2010). These sources may be overrepresented by disease-free, healthy-weight participants. Most participants included in studies in this review were recruited through convenience sampling, mostly from clinics or hospitals. Thus, the PCOS groups in this review may be over-represented by those with more severe symptoms and potentially with a higher BMI. However, controls recruited from these setting could also be less healthy, which would result in an underestimation of obesity risks for the PCOS group instead. To minimize the effects of further selection bias, we included only studies that recruited participants in a consecutive or random manner. There are potential biases inherent to the process of data extraction and quality assessment in this review, as most of the process was conducted by one reviewer, although good inter-rater agreements were achieved in the subset of papers extracted and assessed by the second reviewer. As this is a cross-sectional investigation, the directionality of event could not be determined. The question of whether obesity precedes PCOS is better addressed in longitudinal studies.

Clinical implications, research implications and future directions

Considering the high risk of overweight, obesity and central obesity in women with PCOS reported in this current study and the adverse effects of obesity on the disease, obesity management should play a central role in the treatment of PCOS. Lifestyle modification is recommended as a key initial treatment strategy in overweight and obese women with PCOS (Moran et al., 2009; Jean Hailes Foundation for Women's Health on behalf of the PCOS Australian Alliance, 2011) and has been shown to improve hyperandrogenism, hirsutism, body weight, WC and insulin resistance in women with PCOS (Moran et al., 2011b). There is a need for greater awareness on the increased risk of central obesity among PCOS patients, as this form of obesity could affect even those with a normal BMI. Overweight and obese adolescents with PCOS should also be advised to lose weight. This will not only assist with their immediate symptoms but also will help to prevent the development of diabetes and cardiovascular disease in adulthood. Lean women with PCOS should be cautioned of the high risk of overweight, obesity and central obesity associated with PCOS, and be encouraged to engage in health behaviors that prevent weight gain. This is important considering the trend for weight gain among women of reproductive age (Brown et al., 2006).

This review highlights the need for a representative population study reporting the prevalence of overweight, obesity and central obesity in women with and without PCOS. Future population studies should consider probability sampling, instead of convenience sampling, to minimize bias in their results (Kraschnewski et al., 2010). This is particularly important in the estimation of obesity prevalence, which is confounded by numerous factors. Our findings support the positive association between obesity and PCOS but our conclusions are limited by the significant heterogeneity between studies. Further studies are required to determine the source of heterogeneity in this association. This is essential in identifying the target groups among women with PCOS for obesity intervention, such as the Caucasian women identified in this review. Studies comparing the features of PCOS in different ethnic groups may also be of interest and may reveal clinically significant findings for the management of PCOS. While we report an overall increased prevalence of overweight, obesity and central obesity among women with PCOS, it is still unclear if obesity is the cause or effect of the disease. Longitudinal studies are needed to elucidate the role of obesity in the pathogenesis of PCOS.

Conclusion

This systematic review showed that women with PCOS had a greater prevalence of overweight and obesity, obesity and central obesity compared with women without PCOS. The Caucasian women with PCOS had a greater risk for obesity than that of the Asian women with PCOS. Further research on interventions assessing the most effective means of preventing and treating obesity for women with PCOS of all ages is urgently needed.

Authors' roles

S.S.L. contributed to the study design, literature search, analysis and interpretation of data and drafting the paper. L.J.M. contributed to the study design, literature search, analysis of data and revising the paper critically for important intellectual content. R.J.N. initiated the study, contributed to the study design, funded the salaries and revised the paper critically for important intellectual content. M.J.D contributed to the study design and revised the paper critically for important intellectual content. All authors were involved in the final approval of the version to be published.

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Conflict of interest

None declared.

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