

# Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis

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**BACKGROUND:** Our aim was to assess differences in anxiety and depression between women with and without (controls) polycystic ovary syndrome (PCOS).

**METHODS:** We conducted a systematic review and meta-analysis of published literature comparing women with PCOS to control groups on anxiety and depression. Electronic databases were searched up to 17 December 2010. The inverse variance method based, as appropriate, on a random- or fixed-effects model in Review Manager, Version 5 was used to analyse the data.

**RESULTS:** Twelve comparative studies were included; all studies assessed depression (910 women with PCOS and 1347 controls) and six also assessed anxiety (208 women with PCOS and 169 controls). Analysis revealed higher depression ( $Z = 17.92$ ,  $P < 0.00001$ ; Hedges'  $g = 0.82$ ; 95% CI 0.73–0.92) and anxiety ( $Z = 5.03$ ,  $P < 0.00001$ ; Hedges'  $g = 0.54$ ; 95% CI 0.33–0.75) scores in the participants with, than without, PCOS. Studies controlling for BMI showed a smaller difference between women with PCOS and controls on anxiety and depression scores than studies not controlling for BMI.

**CONCLUSIONS:** Women with PCOS on average tend to experience mildly elevated anxiety and depression, significantly more than women without PCOS. Women with PCOS with lower BMI tended to have slightly lower anxiety and depression scores, suggesting that having a lower BMI reduces anxiety and depression. Future studies might consider (i) controlling for BMI, (ii) stratifying by medication use in order to control for any anti-androgenic effects of medication and (iii) excluding women with polycystic ovaries from control groups.

**Key words:** polycystic ovary syndrome / anxiety / depression / medication / meta-analysis

## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormone disorders affecting women, with a prevalence of 5–10% in women of reproductive age (Franks, 1995). It is the most common cause of androgen excess in women and the most common cause of ovulatory failure. Clinically, the androgen excess presents as hirsutism and acne, whereas anovulation presents as sub-fertility and menstrual irregularity. In addition, PCOS is associated with obesity. It is therefore perhaps not surprising that women with PCOS experience mood dysfunction and psychiatric problems to a greater degree than women without PCOS (Farrell and Antoni, 2010). Many studies, for example, Hollinrake *et al.* (2007) have found that anxiety and depression are higher in PCOS than healthy women. Most studies have focused on depression but others, such as Månsson *et al.* (2008), have found that anxiety in PCOS is also an important issue.

It has been suggested that mood problems in PCOS are caused by the distress associated with the symptoms often seen in PCOS (obesity, hirsutism etc.; Eggers and Kirchengast, 2001). In general, studies find that obesity is related to depression, both in healthy women (Stunkard *et al.*, 2003) and in PCOS (Rasgon *et al.*, 2003). In their review of the quality of life (QoL) literature on PCOS Jones *et al.* (2008) found that weight problems had the greatest negative impact on QoL. However, not all studies of obesity in PCOS have found this (Hahn *et al.*, 2005) and some studies, such as Weiner *et al.* (2004), find that depression is higher in women with PCOS even after controlling for BMI.

Women vary in how much their mood is affected by the various PCOS symptoms. For example, Farrell and Antoni (2010) suggest that PCOS symptoms that affect appearance are more likely to cause distress in younger women than older women. Because PCOS involves so many potentially distressing symptoms, it is difficult to identify the main cause of distress or the relative contribution of

causal factors. The physical symptoms of PCOS are largely the result of elevated testosterone; for example, hirsutism is caused by elevated androgen levels (Young and Sinclair, 1998). Hirsutism is also associated with distress in women with PCOS (Kitzinger and Willmott, 2002). Thus, it is tempting to view distress in PCOS as mainly an indirect effect of testosterone and the cure for distress, therefore, to lower testosterone levels.

Two drugs widely used to treat the symptoms of PCOS, metformin and the oral contraceptive co-cyprindiol (commonly marketed under the brand name 'Dianette'), differ in their action; metformin acts primarily to increase insulin sensitivity, whereas co-cyprindiol is composed of estrogen and anti-androgen. Some authors use the umbrella term 'anti-androgens' to describe these and other medications of this kind used to treat PCOS (Barnard *et al.*, 2007). In 52 women with PCOS, Harborne *et al.* (2003) found that co-cyprindiol was more effective than metformin in treating acne, whereas hirsutism responded better to metformin than co-cyprindiol.

Some authors suggest that the drugs commonly used to reduce symptoms of PCOS may also reduce the distress associated with these symptoms (Bruce-Jones *et al.*, 1993; Farrell and Antoni, 2010). In support of this suggestion, Rasgon *et al.* (2003) found that women with PCOS taking oral contraceptives were significantly less depressed than those with PCOS not taking oral contraceptives. In contrast, Barnard *et al.* (2007) found that rates of depression were slightly higher in women with PCOS taking anti-androgens (71%) than women with PCOS not taking anti-androgens (67%). Depression rates were lower in controls and showed the opposite pattern; 30% taking anti-androgens and 37% not taking anti-androgens showed some sign of depression. Thus there is, at present, uncertainty regarding the benefits of medications on mood in PCOS.

The primary objective of the present paper is to assess the degree to which women with PCOS score differently to women without PCOS on measures of anxiety and depression. The secondary objective is to determine whether there is an impact of BMI and PCOS medication use on anxiety and depression scores. All between-groups designs were considered.

## Materials and Methods

### Literature search

All studies that measured anxiety and depression in women with PCOS listed in Pubmed and Medline published up to 17 December 2010, and EMBASE from 1980 to 17 December 2010, were identified. The Cochrane Reviews database was also searched up to 17 December 2010. The keyword search terms 'polycystic ovary syndrome' and 'anxiety' or 'polycystic ovary syndrome' and 'depression', were entered simultaneously. From a search of Pubmed from 1968 to 2010, 98 articles emerged related to depression and 32 related to anxiety. A Medline search from 1950 produced 95 depression and 31 anxiety papers but none in addition to those cited in Pubmed. An EMBASE search from 1980 produced 79 depression and 36 anxiety papers, two of which were not found in other searches and met the inclusion criteria (see below) for the present meta-analysis. The 'related article' function was used to widen the results. Additionally two Medical Subject Heading (MeSH) searches were performed using firstly the terms 'polycystic ovary syndrome' AND 'depression' and 'polycystic ovary syndrome' AND 'anxiety'. This retrieved 27 and 15 publications, respectively, all of which were previously

found using the Pubmed keyword search. The Cochrane Reviews database did not produce any published reviews of PCOS and anxiety or depression. A hand search of relevant articles referenced in these publications was performed, which produced two publications not previously found, neither of which met the inclusion criteria. Also included was a paper by the present authors (Barry *et al.*, 2011). Each article was assessed by the first author and articles that fitted the main criteria (measuring anxiety and/or depression in PCOS) were accessed. Methodological quality was assessed by the first author based on the criteria of the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies (Wells *et al.*, 2000) adapted for cross-sectional studies. This adaptation meant changing the 'ascertainment of exposure' criterion to 'ascertainment of diagnosis'. The Cochrane Non-Randomized Studies Methods Working Group consider the NOS one of the best tools available for assessment of non-randomized studies (Reeves *et al.*, 2008).

### Inclusion and exclusion criteria

Studies that compared women with PCOS to controls were eligible for inclusion provided that:

- (i) The studies reported a quantitative outcome on a standardized measure of depression or anxiety.
- (ii) Comparison groups did not have a severe illness (for example, cancer) which would undermine the equivalence of the groups.
- (iii) The studies reported outcomes as mean and SD.
- (iv) The studies reported other relevant data, e.g. *n* values in each group.

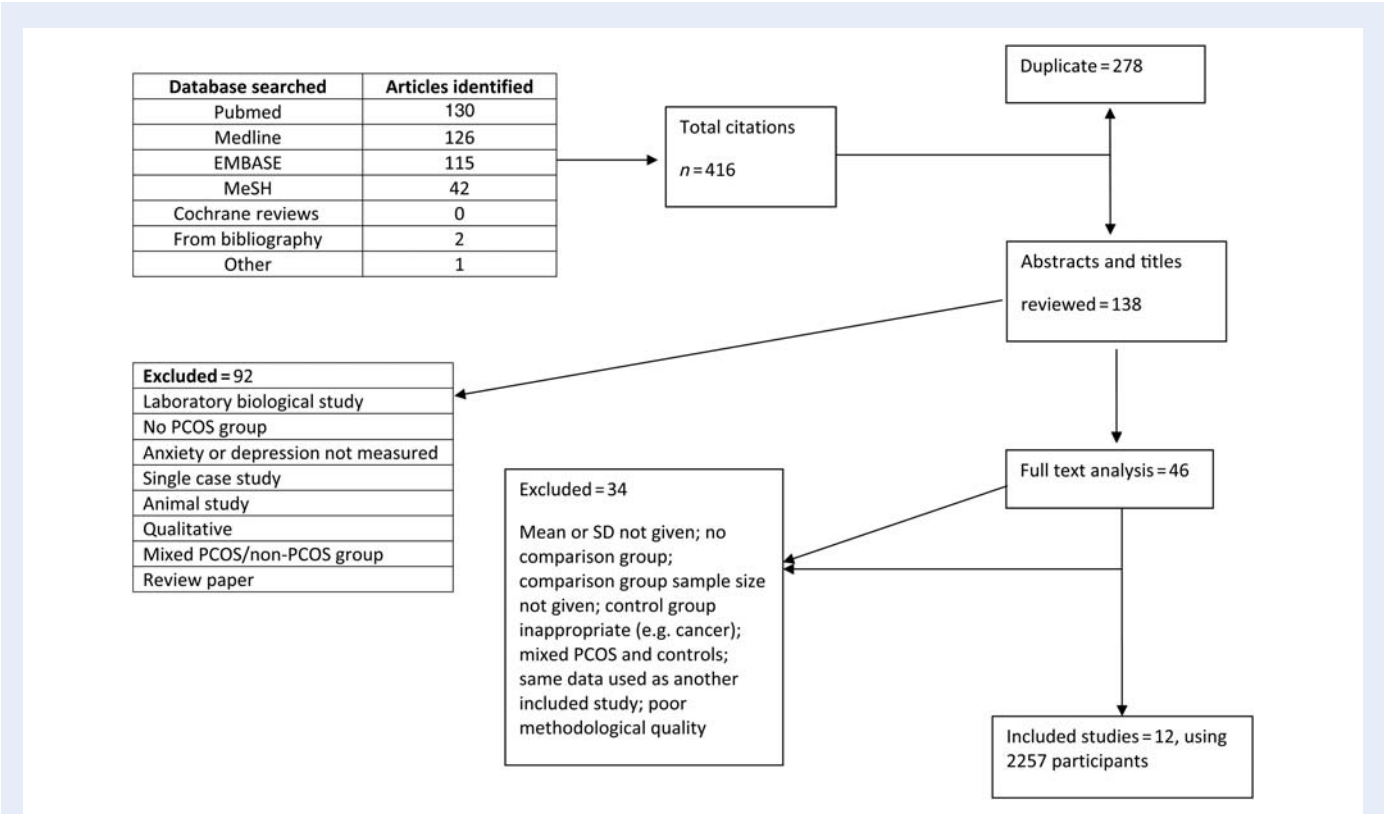
Papers with titles or abstracts that indicated that they were not relevant (for example, reviews, single case studies etc.) were excluded. A table of excluded studies (Supplementary data, Table SI) and tables of descriptive statistics for anxiety and depression for the included studies (Supplementary data, Table SII and SIII) are available online on the *Human Reproduction* website.

### Statistical analysis

Statistical analyses were performed using Review Manager, Version 5 (RevMan 5). Anxiety and depression scores were meta-analysed using the fixed effect or random effects model, as appropriate. The inverse variance method was used. Heterogeneity was assessed using  $I^2$  and  $\chi^2$  statistics.  $I^2$  values of 30% or above were considered likely to represent moderate heterogeneity, and  $\chi^2$  *P*-values of <0.10 were considered to represent significant heterogeneity, thus studies showing  $I^2$  values <30% and  $\chi^2$  *P*-values of >0.10 were analysed using fixed-effects models. The effect size was measured as the standard mean difference, calculated using Hedges' *g*. Like Cohen's *d*, a Hedges' *g* of 0.2 can be considered a small difference, 0.5 a moderate difference, and 0.8 or more a large difference between groups. It should be noted that these values indicate statistical differences measured in terms of effect size; clinical differences must be assessed by reference to scores on clinical measures of anxiety and depression (see Supplementary data, Table SII and Table SIII on the *Human Reproduction* website).

## Results

Studies of anxiety and/or depression in PCOS (*n* = 138) were retrieved, mostly from the electronic databases (Fig. 1). Of these, 126 studies were excluded, thus 12 studies including 2257 participants (910 women with PCOS and 1347 controls), qualified for review according to the inclusion criteria. For all of these studies, those that measured depression also measured anxiety. There were no separate studies that examined only anxiety.



**Figure 1** Literature search and study selection for systematic review of studies of anxiety and depression in women with PCOS compared with controls.

Two of the included studies (Rocco et al., 1991; Weiner et al., 2004) used the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) and reported scores for both state and trait anxiety and depression. The results were similar on state and trait measures in both studies. Also the most frequently used measure of depression in the included studies was a measure of state depression, the Beck Depression Inventory (BDI; Beck et al., 1961), and for the sake of consistency only state anxiety and depression scores were included in the meta-analysis.

Himelein and Thatcher (2006) had two control groups, one infertility group and one community control. Because women with PCOS may experience problems with fertility, in the interests of maximizing between-group comparability, the infertility control group was included in the present analysis rather than the community control group.

Table I shows the characteristics of the included studies.

Table II shows the methodological quality of the included studies.

The funnel plots in Supplementary data, Fig. S1 (see online supplement) suggest that publication bias was probably not a significant problem for this meta-analysis. The plot on the right shows that all of the anxiety studies are (i) closely grouped, (ii) reasonably symmetrical and (iii) the larger studies (near the top of the graph) tend towards the mean more than the smaller studies. The plot on the left is less symmetrical than the plot on the right, indicating that the studies reporting on only depression (rather than anxiety and depression) may show signs of possible publication bias. Only 2 of the 12 studies included fewer than 50 participants, making the possibility of small study effects unlikely.

**Main outcomes**

Table III shows the results of the meta-analyses. Figures 2 and 3 show forest plots and test statistics for the main outcomes, depression and anxiety, respectively, and subgroup analyses are shown in Supplementary data, Figs SII–SVII (online supplement). Most analyses used fixed-effects models, except the three subgroups that used random effects models due to showing levels of heterogeneity outside the accepted limits for the use of fixed-effects models (Supplementary data, Figs SII, SV and SVI). The findings were fairly similar regardless of whether fixed or random effects models were applied.

The most commonly used outcome measure for assessing depression was the BDI, which was used in 8 of the 12 studies (see Supplementary data, Table SII). Six of these studies used comparable versions of the BDI, with mild depression being indicated when scores reach 11. For these six studies the mean BDI score for women with PCOS was 11.47, and for controls it was 7.31. This difference is statistically significant ( $Z = 5.94$ ,  $P < 0.00001$ ; Hedges'  $g = 0.60$ ; 95% CI 0.40–0.80) with 0% heterogeneity ( $I^2 = 0\%$ ). In clinical terms this represents the difference between, on average, mild depression in the PCOS groups and no depression in the control groups. For anxiety, the most commonly used outcome measure was the STAI-S (state anxiety measure), and was used in five of the six studies. In these five studies the women with PCOS indicated statistically significantly higher anxiety scores ( $Z = 3.47$ ,  $P < 0.0005$ ; Hedges'  $g = 0.46$ ; 95% CI 0.20–0.73) with little heterogeneity ( $I^2 = 14\%$ ). The control groups scored a mean of 34.6 on the STAI-S, which is slightly below

**Table 1** Characteristics of the 12 included studies of anxiety and depression in PCOS compared with controls.

Study	Age (years)		BMI (kg/m <sup>2</sup> )		Control group features	Controls: ovarian cysts excluded?	Psychiatric cases excluded	Diagnosis PCOS	Medication status		Duration on medication	Variables controlled <sup>a,b</sup>	Outcome measure
	PCOS	Control	PCOS	Control					Metformin	OCP			
Rocco <i>et al.</i> (1991)	20.2 (2.75)	21.7 (2.21)	22.7 (1.81)	21.01 (0.95)	Healthy medical students	Yes	No	Three symptoms	Not stated	Not stated	Not stated	Age, culture	MMPI, STAI
Weiner <i>et al.</i> (2004)	28.19 (4.84)	30.07 (6.48)	37.7 (3.46)	36.89 (7.24)	Advert. Normal menstruation and Testosterone	No	Yes	Three symptoms; some self-report	None	None	Off minimum 2 months	Age, BMI, ethnicity, education	DACL, STAI
Himelein and Thatcher (2006)	32.1 (5.5) (all participants)		33.8 (8.5)	23.4 (3.6)	2 groups; infertile & healthy. 98% all Participants White	Yes, in infertility control group	No	Rotterdam-like <sup>f</sup>	78% PCOS report receiving 'some type of treatment for PCOS'		Not stated	Fertility. Also age, demographics	BDI-SF
Hollinrake <i>et al.</i> (2007)	29.8 (6.2)	30.7 (8.5)	34.9 (8.5)	24.5 (4.7)	Healthy	No	No	Rotterdam	Not stated	Same rate in both groups	Not stated	Age, demographics	BDI-II
Barnard <i>et al.</i> (2007) No AA <sup>g</sup>	31 (6.5)	31 (7.9)	31 (10.23)	25 (5.12)	Internet	No	No	Rotterdam (self-report)	none	none	Not stated	AA	Zung
Barnard <i>et al.</i> (2007) AA <sup>g</sup>	29 (5.6)	26 (5.11)	32 (9.4)	23 (4.3)	Internet	No	No	Rotterdam (self-report)	AA	AA	Not stated	AA	Zung
Soyupek <i>et al.</i> (2008)	24.1 (6.1)	26.1 (5.7)	24.5 (6.5)	22.5 (2.6)	Healthy	No	No	Rotterdam	No PCOS on meds for PCOS. Not stated controls.		Not stated	Age <sup>d</sup>	BDI
Adali <i>et al.</i> (2008)	23.54 (3.13)	24.45 (2.47)	28.42 (4.3)	24.11 (4.14)	No PCOS features	Yes	Yes	Rotterdam	All Ps clear for minimum 6 months			Age, demographics	BDI
Benson <i>et al.</i> (2008)	28.9 (0.7)	29.9 (1.2)	29.6 (1.0)	23.6 (0.7)	Advert.	No	No	Rotterdam	Not stated	Not stated	Not stated	Age	BDI
Özenli <i>et al.</i> (2008)	27.58 (7.66)	26.54 (5.16)	25.43 (5.58)	24.76 (5.37)	Friends and family of staff	No	Yes <sup>e</sup>	Rotterdam	None	Not stated	PCOS off for minimum 3 months	BMI, age, demographics	BDI, STAI
Benson <i>et al.</i> (2009)	30.1 (0.9)	31.5 (1.1)	29.8 (1.6)	28.7 (1.5)	Advert; healthy	No	Yes	Rotterdam	44% PCOS; controls?	0% controls; PCOS?	Not stated	BMI, age, demographics, psych. problems	BDI, STAI
Laggari <i>et al.</i> (2009)	16.95 (2.0)	17.04 (2.16)	24.63 (6.42)	20.7 (2.97)	Schools, colleges	No	No	Rotterdam	Not stated	none	Never	Age	BDI, STAI
Barry <i>et al.</i> (2011)	28.8 (4.81)	35.12 (4.37)	27.87 (7.36)	24.69 (7.08)	Subfertility	No	Severe psychiatric cases excluded	Rotterdam	76% PCOS & 11% controls on AA. Status of 33% of total sample unknown.		Not stated	Infertility <sup>c</sup>	HADS

<sup>a</sup>Variables controlled prior to statistical manipulation.

<sup>b</sup>Demographics here indicates that one or more of the following were controlled or were not significantly different in each group: race, education, income. Other demographics factors may be included in some studies, e.g. religion, city or rural dwelling.

<sup>c</sup>Barry *et al.* (2011) has also performed a subgroup analysis controlling for age and BMI but because medians were presented for depression, data from the total group analysis is presented here.

<sup>d</sup>Groups were matched for age. Although age was significantly different in both groups, the difference was not of clinical significance.

<sup>e</sup>Infertile women with PCOS were not included in the study because infertility imputes depressive characters for these patients (Özenli *et al.*, 2008, p. 191).

<sup>f</sup>Rotterdam-like indicates that PCOS diagnosis was based on two of three PCOS symptoms, but not as defined by the Rotterdam criteria (2004).

<sup>g</sup>Barnard *et al.* (2007) has two rows, one for participants taking anti-androgen (AA) medication and one for those not taking AA.

AA, anti-androgen medication; OCPs, metformin, or other medication capable of reducing testosterone levels; OCP, oral contraceptive pill, or other anti-androgen; Metf., metformin, or other insulin sensitizer;

MMPI, Minnesota Multiphasic Personality Inventory; STAI, State-Trait Anxiety Inventory; DACL, Depression Adjective Check Lists;

BDI-SF, Beck Depression Inventory Short Form; BDI-II, Beck Depression Inventory;

Zung, Zung Self-Rating Depression Rating; HADS, Hospital Anxiety and Depression Scale.

**Table II** Evaluation of the methodological quality of the 12 studies included in the meta-analysis using the NOS.

Study	Case definition adequate	Representativeness of cases	Selection of controls	Definition of controls	Comparability of both groups	Ascertainment of diagnosis	Same ascertainment method for both groups	Non-response rate	NOS Score
Rocco <i>et al.</i> (1991)	*	x	*	* <sup>a</sup>	*	*	x	x	5
Monzani <i>et al.</i> (1994) <sup>b</sup>	*	x	x	x	*	x	x	x	2
Weiner <i>et al.</i> (2004)	x	*	*	*	**	x	x	x	5
Himelein and Thatcher (2006)	*	*	*	* <sup>a</sup>	*	*	x	*	7
Hollinrake <i>et al.</i> (2007)	*	*	x	*	*	*	x	*	6
Barnard <i>et al.</i> (2007)	x	x	*	x	**	x	*	x	4
Soyupek <i>et al.</i> (2008)	*	*	x	*	**	*	x	x	6
Adali <i>et al.</i> (2008)	*	*	x	* <sup>a</sup>	**	*	*	x	7
Benson <i>et al.</i> (2008)	*	x	*	*	*	*	*	x	6
Özenli <i>et al.</i> (2008)	*	x	*	*	**	*	x	x	6
Benson <i>et al.</i> (2009)	*	x	*	*	**	*	x	x	6
Laggari <i>et al.</i> (2009)	*	*	*	*	*	*	x	x	6
Barry <i>et al.</i> (2011)	*	x	*	*	*	*	x	*	6

<sup>a</sup>Controls screened for presence of polycystic ovaries.<sup>b</sup>Excluded from meta-analysis because of low NOS score.

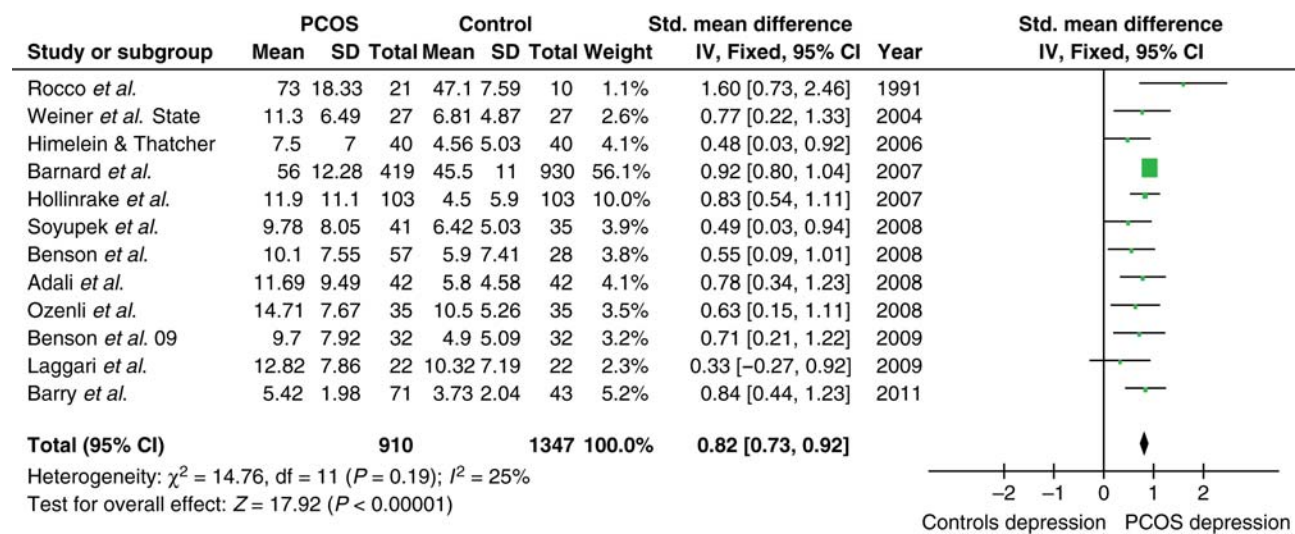
\* NOS quality assessment star.

x, No NOS quality assessment star.



**Table III** Results of meta-analyses for all included studies and the subgroups for women with PCOS compared with controls.

Analysis	Number of studies	Hedges' g [95% CI] <sup>a</sup>	Z (P)	$\chi^2$ (P)	I <sup>2</sup> (%)
Depression	12	0.82 [0.73, 0.92]	17.92 (P < 0.00001)	14.76 (P = 0.19)	25
Depression <sup>b</sup>	13	0.82 [0.61, 1.03]	7.65 (P < 0.00001)	40.14 (P = 0.0001)	70
Anxiety	6	0.54 [0.33, 0.75]	5.03 (P < 0.00001)	5.45 (P = 0.36)	8
Anxiety <sup>b</sup>	7	0.76 [0.35, 1.17]	3.64 (P = 0.0003)	23.03 (P = 0.0008)	74
Depression on AA <sup>c,d</sup>	5	0.84 [0.64, 1.04]	8.20 (P < 0.00001)	7.55 (P = 0.11)	47
Depression no AA <sup>c</sup>	5	0.74 [0.61, 0.88]	10.76 (P < 0.00001)	2.36 (P = 0.67)	0
Depression matched BMI	3	0.65 [0.37, 0.94]	4.48 (P < 0.00001)	0.54 (P = 0.76)	0
Depression BMI unmatched <sup>d</sup>	9	0.77 [0.62, 0.93]	9.64 (P < 0.00001)	12.61 (P = 0.13)	37
Anxiety matched BMI <sup>d</sup>	3	0.48 [0.08, 0.87]	2.38 (P = 0.02)	3.60 (P = 0.17)	44
Anxiety BMI unmatched	3	0.63 [0.33, 0.93]	4.11 (P < 0.0001)	1.28 (P = 0.53)	0

<sup>a</sup>95% CI = 95% confidence intervals.<sup>b</sup>These results show the effect on heterogeneity of including data from Monzani *et al.* (1994); I<sup>2</sup> is increased above 30% and the  $\chi^2$  P-value becomes significant, thus the random effects model has been used. This study also had a low score for methodological quality and was excluded from the meta-analysis based on the criteria described by Xiong *et al.* (2010).<sup>c</sup>AA = anti-androgen medication, i.e. medication commonly used to treat PCOS, mostly metformin or oral contraceptives.<sup>d</sup>The random effects model was used, as I<sup>2</sup> was >30% and the  $\chi^2$  P-value was almost 0.10.**Figure 2** Forest plot of all included studies of depression in women with PCOS compared with controls.

the norm of 36.2 for women of this age group (Spielberger, 1983), and the mean score for women with PCOS was 40.7, which is mildly elevated.

Table III shows a slightly larger difference in depression scores between women with PCOS and controls for women with PCOS were taking anti-androgen medication (Hedges' g = 0.84; 95% CI 0.64–1.04) than for women with PCOS were not taking anti-androgen medication (Hedges' g = 0.74; 95% CI 0.61–0.88).

## Discussion

Analysis of the 12 studies and subgroups revealed differences in the scores for anxiety and depression, which were significantly higher in

the PCOS groups compared with controls. These findings support those of the previous research reviewed by Farrell and Antoni (2010). The confidence intervals for the included studies were generally narrow and showed effect sizes which may be clinically relevant. Of the 18 results (12 depression and 6 anxiety), 4 confidence intervals encompassed a zero value, which suggests that overall (14 of the 18 studies) the results were representative of those likely to be seen in the general population of women with PCOS and healthy women.

This meta-analysis helps to quantify the impact of BMI on anxiety and depression, and suggests that BMI has a small effect on anxiety and depression in PCOS. The three studies that controlled for BMI (Weiner *et al.*, 2004; Özenli *et al.*, 2008; Benson *et al.*, 2009) found on average a smaller difference in depression between women with

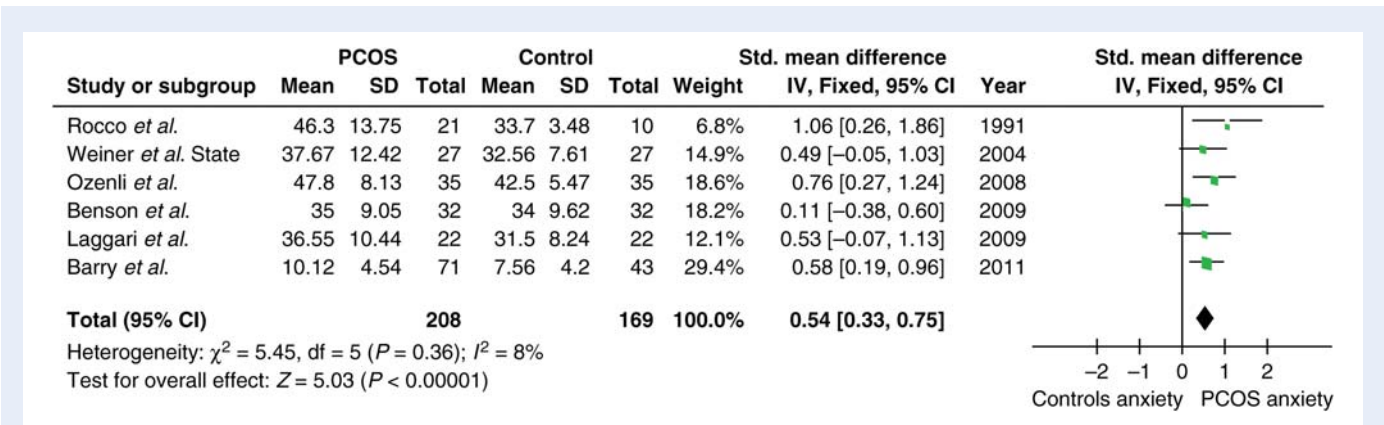


Figure 3 Forest plot of all included studies of anxiety in women with PCOS compared with controls.

PCOS and controls (Hedges'  $g = 0.65$ ) than the eight studies that did not control for BMI (Hedges'  $g = 0.77$ ), a rather small difference in effect size ( $g = 0.12$ ). This finding lends modest support to previous research suggesting an impact of obesity on depression (Rasgon *et al.*, 2003) and perhaps also QoL (Jones *et al.*, 2008). For anxiety, the three studies that controlled for BMI also found on average a smaller difference between women with PCOS and controls (Hedges'  $g = 0.48$ ) than the three studies that did not control for BMI (Hedges'  $g = 0.63$ ). The difference in anxiety when controlling for BMI represents a small effect size ( $g = 0.15$ ), similar to the impact of BMI on depression.

The differences between women with PCOS and controls for anxiety and depression were statistically significant, but what is the clinical significance of these findings? The most commonly used outcome measure for assessing depression, the BDI, found that women with PCOS scored statistically significantly higher than women without PCOS. In clinical terms this represents the difference between, on average, mild depression in the PCOS group and no depression in the control group. This appears to suggest that the difference between the groups is, on average, of only limited clinical significance. However, the SDs in Supplementary data, Table SII indicates that some proportion of the women in these studies had depression scores of greater clinical interest, especially in the PCOS groups. For example, Benson *et al.* (2008) found a mean PCOS BDI score of 10.1 with an SD of 7.55; given that these scores passed tests of normality of distribution, and given the properties of the normal distribution, we can infer that roughly 15% of women with PCOS in this study had depression scores of 18 or more, which places them in the range of moderate to severe depression. It should also be noted that although the cut-offs for BDI scores offer guidance on depression severity, interpretation of scores should be based on clinical judgement (Beck *et al.*, 1988).

For anxiety, the most commonly used outcome measure was the STAI-S (state anxiety measure), used in five of the six studies. The control groups scored slightly below the norm, and the PCOS groups' score was mildly elevated. Although this is perhaps only a modest clinical difference in anxiety scores, any increase in anxiety might be clinically significant in PCOS because of the potential impact of anxiety on testosterone levels; given that stress activates the adrenal glands via the hypothalamic–pituitary–adrenal axis

(HPA) (Reiche *et al.*, 2004) and that women produce roughly 25% of the testosterone from their adrenal glands (Burger, 2002) the level of stress that a woman experiences in her daily life may potentially increase her testosterone levels, thus exacerbating the symptoms of PCOS. Furthermore, there is evidence that women with PCOS show a stronger HPA response to a stressor than healthy women (Gallinelli *et al.*, 2000; Benson *et al.*, 2009) which suggests that the elevations in anxiety ratings seen in the studies reviewed in the present meta-analysis are of special relevance. The potential impact of anxiety and stress on testosterone levels in PCOS is clearly of importance and could be explored in future research.

It should be noted that the control group participants from the included studies were drawn from a variety of sources, for example, the Internet, friends and family of the researchers, and medical students (Table I). Although the NOS criteria specify that community controls are preferable to hospital controls, the wide variety of control groups in the present review implies a heterogeneous selection process, which introduces uncertainty in interpretation of the findings because of the unknown influence of possible selection bias. Variation in the selection of participants is an issue often seen when reviewing comparative observational studies and the possible effects of this should be borne in mind when considering the findings of the present review. The NOS quality ratings of the included studies ranged from four to seven, out of a maximum of nine. Eleven of the 12 studies scored 5 or more, which indicates reasonably good methodological quality overall. The NOS criteria specify that community controls are preferable to hospital controls but it could be argued that in studies where women with PCOS were recruited from hospitals and clinics, a hospital or clinic control group may be the most appropriate comparison provided that the controls had medical conditions of comparable impact to PCOS. Nonetheless, in the interests of adherence to the NOS criteria, studies that used hospital control groups (Hollinrake *et al.*, 2007; Adali *et al.*, 2008; Barry *et al.*, 2011) lost an NOS quality assessment star. Where a study presented more than one control group, the one best matched to the PCOS group was used in the presented analysis. Thus Himelein and Thatcher's (2006) infertility control group was used, which had the effect of reducing the size of the difference in depression between women with PCOS and controls. The Barry *et al.* (2011) matched group was not used because the median rather than mean was given for the depression outcome.

Only three studies (Rocco *et al.*, 1991; Himelein and Thatcher, 2006; Adali *et al.*, 2008) tested for polycystic ovaries in control groups. Although the findings from the present study suggest that screening controls for polycystic ovaries is not essential (see below), the general lack of screening of controls for polycystic ovaries raises the question of whether a woman with polycystic ovaries can be classified as a control in a study of PCOS. Controls can be defined by excluding menstrual problems and hyperandrogenism (Rotterdam criteria i and ii; Rotterdam ESHRE/ASRM, 2004) without reference to polycystic ovaries, but this leaves open the possibility that women in the control groups had one of the diagnostic conditions (polycystic ovaries) for membership of the PCOS group. Polycystic ovary morphology (as seen on ultrasound) has been found in around 23% of regularly menstruating women (Polson *et al.*, 1988; Koivunen *et al.*, 1999), and although this may represent one end of the spectrum of symptom severity in genetically predisposed individuals, this single symptom in asymptomatic women is not generally considered to be of clinical importance. Theoretically therefore the failure to screen controls for polycystic ovaries could reduce group differences on outcomes related to PCOS, but in the present meta-analysis the three studies that excluded polycystic ovaries in their control groups had a slightly lower mean Hedge's *g* for depression than the other nine studies ( $g = 0.74$  versus  $0.83$ , respectively). The smaller difference in depression scores in these studies is not explained by other factors (study quality, BDI scores etc.), thus it could be concluded that screening for polycystic ovaries in control groups does not seem to be a confounding variable in studies of depression in PCOS. An assessment of the effect of screening for polycystic ovaries on anxiety scores cannot be made because only one of the three studies measured anxiety.

The finding that women with PCOS on medication for PCOS were slightly more depressed compared with controls than women with PCOS not on medication appears to suggest there is a small benefit in terms of depression of not taking PCOS medication, contradicting the finding by Rasgon *et al.* (2003) and supporting the finding of Barnard *et al.* (2007). However, because different outcome measures were used in the various studies (none of the on-medication PCOS groups used exactly the same scale), it is difficult to compare scores for the women with PCOS on medication to the women with PCOS not taking medication. Also the apparent benefit—relative to controls—of women with PCOS not taking anti-androgen medication is possibly caused in part by high depression scores in two of the control groups relative to their respective PCOS groups (Özenli *et al.*, 2008; Laggari *et al.*, 2009). Furthermore, medication use was not clearly defined in the studies (see below). For these reasons the very small apparent affect of medication use (Hedge's  $g = 0.1$ ) should be interpreted with caution. An assessment of the effect of medication for PCOS on anxiety scores cannot be made because, there were too few studies of anxiety that differentiated groups by medication status.

A weakness of the present meta-analysis is that medication use was not clearly defined in the included studies. Whether oral contraceptives or other anti-androgenic medications were used by the control group is unclear in 7 of the 12 control groups, perhaps because these researchers did not hypothesize that healthy women would be affected by anti-androgen medication use. In the five studies classified as 'on medication', the numbers of women with PCOS taking

medication ranged from 100% to 44% (Table I). The study that most clearly stratified by medication use (100% on medication in Barnard *et al.*, 2007) relied on self-report, and as always self-report introduces uncertainty as to the exact numbers. The type of medication was not stratified in any of the studies making it impossible to assess whether, for example, insulin sensitizers affect women's mood differently than anti-androgens, as might be predicted based on the findings of Harborne *et al.* (2003). Four of the 12 studies stated the length of time that participants with PCOS had not been taking medication (minimum 2 months), and none stated the duration that the controls were on medication. Because the most common PCOS medications will have had their major effects within 6 months (Harborne *et al.*, 2003), it would be useful to know at least whether they had been taking medication for a longer or shorter period than 6 months. Future studies would be improved by stratifying findings by medication type, duration of medication, and dose.

Some studies controlled for age. All studies were of adult women of childbearing age, and apart from the Laggari *et al.* (2009) sample who were in their mid to late teens, all studies were of women aged on average in their mid twenties to early thirties. The Hedge's *g* for the Laggari *et al.* (2009) sample was smaller than the mean Hedge's *g* for the other studies for depression ( $g = 0.33$  versus  $0.84$ ) but was the same for anxiety ( $g = 0.54$  versus  $0.54$ ) suggesting that younger women with PCOS may be similarly anxious but less depressed than women with PCOS in their 20s and 30s. This finding undermines to some degree the suggestion that PCOS causes more distress to younger women because of the impact of PCOS on physical appearance (Farrell and Antoni, 2010) and fertility (Trent *et al.*, 2003). However, more studies with young women with PCOS are needed to help clarify this issue.

Five of the 12 studies screened for psychiatric illness, and these studies showed slightly smaller differences between depression scores in women with PCOS and controls (Hedge's  $g = 0.76$ ) compared with those with no screening (Hedge's  $g = 0.84$ ). This suggests that screening for psychiatric illness in studies of anxiety and depression in PCOS does not have a major impact on results. However, other factors that might affect mood in women with PCOS should also be accounted for in future research, e.g. the presence of hypoglycaemia (Kasim-Karakas *et al.*, 2007) or proinflammatory cytokines (González *et al.*, 2010).

Because of the possibility that state anxiety might be raised simply by being in a hospital context, future studies might also consider stating the context in which the questionnaires were completed. Although none of the included studies published data on this issue, the present authors know that 59% of the Barry *et al.* (2011) sample opted to fill in the questionnaire online, the remainder doing so at the clinic. However, context appeared to have little effect on Hospital Anxiety and Depression (HADS; Zigmond and Snaith, 1983) anxiety scores as there was no significant difference between those completing the survey at the clinic for the PCOS group, controls or both groups combined.

## Conclusion

PCOS is generally seen as a reproductive endocrine disorder, with symptoms of modest importance compared with other conditions with more obvious effects on wellbeing. However the results of this



systematic review highlight the psychological distress experienced by the 5–10% of women affected by PCOS. General practitioners, gynaecologists, endocrinologists and clinical psychologists should be more aware that levels of anxiety and depression are higher in women with PCOS than women without PCOS. The fact that differences in anxiety and depression scores between women with PCOS and controls are slightly lower when both groups have a similar BMI would suggest that mood in PCOS might be improved to some degree through weight control; a recent study found that the low GI diet has some advantages for women with PCOS (Marsh et al., 2010) therefore this diet might be considered a treatment option. Future studies in this field should also be directed at assessing the potential to alleviate psychological distress using anti-androgens and insulin sensitizers, currently used to treat physical symptoms of PCOS, as well as conventional antidepressant and anxiolytic therapy. A 'talking treatment', such as cognitive behavioural therapy or counselling, should be considered too.

## Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

## Authors' roles

J.A.B. conducted the literature search, assessed study characteristics, study quality assessment, conducted the data analysis, interpretation of statistics and drafted the paper. A.R.K. critically reviewed the paper, commenting on the clinical psychological interpretation of statistical findings. P.J.H. commented on clinical/biological aspects of the findings, and revised the paper. All authors approved the final version.

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