Human Reproduction Update, Vol.18, No.6 pp. 638–651, 2012
Advanced Access publication on July 23, 2012 doi:10.1093/humupd/dms029

human reproduction update

Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies

Susanne M. Veltman-Verhulst[1], Jacky Boivin[2,*], Marinus J.C. Eijkemans[1,3], and Bart J.C.M. Fauser[1]

[1]Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands [2]Cardiff Fertility Studies Research Group, School of Psychology, Cardiff University, Tower Building, Park Place, Cardiff, Wales CF10 3AT, UK [3]Julius Center for Health Sciences and Primary Care, Center for Biostatistics, University Medical Center Utrecht, 85500, 3508 GA Utrecht, The Netherlands

Correspondence address. Tel: +44-2920-876707; Fax: +44-2920-874858; E-mail: boivin@cardiff.ac.uk

Submitted on December 22, 2011; resubmitted on May 20, 2012; accepted on June 8, 2012

TABLE OF CONTENTS

BACKGROUND: For a number of reasons, the results of previous meta-analyses may not fully reflect the mental health status of the average woman suffering from polycystic ovary syndrome (PCOS), or the causes of this distress. Our objective was to examine emotional distress and its associated features in women with PCOS.

METHODS: A comprehensive meta-analysis of comparative studies reporting measures of depression, anxiety or emotional-subscales of quality of life (emoQoL) was performed. PubMed, Embase, PsychInfo and the Cochrane trial register databases were searched up to November 2011 (see Supplementary Data for PUBMED search string). Unpublished data obtained through contact with authors were also included. The standardized mean difference (SMD) of distress scores was calculated. Subgroup analyses and meta-regression analysis of methodological and PCOS-related features were performed.

RESULTS: Twenty-eight studies (2384 patients and 2705 control women) were included. Higher emotional distress was consistently found for women with PCOS compared with control populations [main outcomes: depression: 26 studies, SMD 0.60 (95% confidence interval (CI) 0.47–0.73), anxiety: 17 studies, SMD of 0.49 (95% CI 0.36–0.63), emoQoL: 8 studies, SMD −0.66 (95% CI −0.92 to −0.41)]. However, heterogeneity was present (I^2 52–76%). Methodological and clinical aspects only partly explained effect size variation.

CONCLUSIONS: Women with PCOS exhibit significantly more emotional distress compared with women without PCOS. However, distress scores mostly remain within the normal range. The cause of emotional distress could only partly be explained by methodological or clinical features. Clinicians should be aware of the emotional aspects of PCOS, discuss these with patients and refer for appropriate support where necessary and in accordance with patient preference.

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

Introduction

Polycystic ovary syndrome (PCOS) is a common female health condition (prevalence ~12%) (March *et al.*, 2010) that is characterized by anovulation, hyperandrogenism and the presence of polycystic ovarian (PCO) morphology (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). PCOS has a great impact on the lives of women affected, mainly because of the associated problems, such as infertility, hirsutism, acne, obesity, metabolic syndrome, insulin resistance (IR), diabetes, dyslipidemia, hypertension and endometrial cancer (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). Not surprisingly, a high percentage of women report symptoms of depression and anxiety and a diminished quality of life (QoL) (Coffey *et al.*, 2006; Himelein and Thatcher, 2006; Benson *et al.*, 2009b). The present study is a systematic review and meta-analysis of the PCOS literature focused on the prevalence of emotional disorders and potential explanatory mechanisms.

In women diagnosed with PCOS, emotional distress could have psychosocial and/or pathophysiological causes (Farrell and Antoni, 2010). Visible features, such as hirsutism and acne, or potential consequences, such as infertility and obesity, are perceived as stigmatizing by many women and could cause distress (Sonino *et al.*, 1993; Cronin *et al.*, 1998; Jones *et al.*, 2004). Causes of PCOS or its physiological consequences could also overlap with the causes of depression. For example, emotional disorders have been linked to hyperandrogenism (Weiner *et al.*, 2004), obesity (Scott *et al.*, 2008), diabetes (Wiltink *et al.*, 2011), metabolic syndrome (Skilton *et al.*, 2007; Vanhala *et al.*, 2009) and low-grade inflammation (Pasco *et al.*, 2010).

The prevalence of depression and anxiety in PCOS has been investigated in different patient populations (Himelein and Thatcher, 2006; Bhattacharya and Jha, 2010; Jedel *et al.*, 2010; Rassi *et al.*, 2010). Recently, three meta-analyses of emotional distress (Barry *et al.*, 2011b; Dokras *et al.*, 2011a, b) and one meta-analysis of health-related QoL (Li *et al.*, 2011) in PCOS have been published. Although there is overall convergence among these previously published meta-analyses that women with PCOS are at increased risk of depression, anxiety and lower QoL, questions regarding the magnitude of distress and its clinical relevance remain, warranting further analysis of the PCOS literature. First, a substantial number of studies were not included in existing meta-analyses because of selection criteria and/or exclusion of studies with incomplete reporting, and this may have inadvertently affected effect size estimates. Second, previous meta-analyses did not carry out sensitivity analyses to determine whether the pooled effect size was robust to variations in study methodology. This is an important process in meta-analysis, especially when methods are as heterogeneous as those of the PCOS literature. Sensitivity analyses can improve future research by pointing out factors that can over- or under-estimate differences between PCOS and control populations. Finally, the subgroup analyses reported thus far were concerned only with obesity and use of anti-androgens, whereas the literature also points to other potential explanations for why there is an association between PCOS and distress (e.g. infertility and hirsutism). These issues mean that the previous meta-analyses may not fully reflect the mental health status of the average woman suffering with PCOS or the causes of distress. This possibility, together with the contrasting clinical recommendations from past meta-analyses, suggested the need for a more comprehensive meta-analysis with in-depth analysis of the available evidence. We, therefore, performed a meta-analysis of comparative studies of depression and anxiety and emotional subscales of QoL (emoQoL) in women with PCOS, including both published and unpublished data obtained through contact with authors. We investigated potential explanatory mechanisms and causes of heterogeneity by performing focal subgroup and sensitivity analyses. It was expected that this comprehensive analysis would help to put the available evidence in perspective and to formulate appropriate care plans for this population.

Methods

Search strategy

The following electronic databases were searched up to November 2011: PubMed, Embase, PsychInfo and the Cochrane trial register. Search terms

for PCOS (MeSH, PCOS, PCOD, hyperandrogenism, hirsutism) and emotional distress (depression, anxiety, QoL, mood disorder, emotion, mental health, psychosocial, psychology and emotional distress) were used. We did not apply any restriction on date, type of publication or language. All reference lists of relevant articles and reviews were hand searched and authors were contacted if articles, translations or data were not available.

Criteria for inclusion

All studies including an assessment of emotional distress in women diagnosed with PCOS were considered for inclusion. Two authors (J.B. and S.M.V.) independently performed study selection and data extraction using a standardized data-extraction form. All eligible studies were discussed and methodological quality was assessed by J.B. and S.M.V. The following inclusion criteria were employed (i) adequate diagnosis of PCOS (see below) and (ii) data on at least one measure of emotional distress in a group of patients with PCOS and a control population without PCOS.

A diagnosis of PCOS had to be established by the presence of a combination of oligo- or anovulation, hyperandrogenism [clinical (hirsutism) or biochemical] and PCO morphology, which corresponds to the National Institutes of Health (NIH) criteria (Zawadski and Dunaif, 1992), the Rotterdam-criteria (2004), the Androgen Excess PCOS Society (AE&PCOS) (Azziz *et al.*, 2006) or a variation of these criteria.

Emotional distress was defined as any measure of feelings of depression or anxiety assessed by valid questionnaire or structured psychological interview. An instrument was considered valid if evidence of its satisfactory psychometric properties had been previously published (Bowling, 1995) or if adequate performance was presented in the included publication. Emotional (psychological) subscales from QoL questionnaires were included as an 'emotional quality of life subscale' (emoQoL). The emotional subscale of the disease specific quality of life questionnaire (PCOSQ) (Cronin *et al.*, 1998) was excluded because questions regarding emotional distress in the PCOSQ are confounded with possible symptoms of the disorder (e.g. 'Do you feel sad because of fertility problems?') and is therefore not an independent measure of emotion.

Studies were excluded if PCOS was induced by valproate or if the psychological data concerned behavioural disorders (e.g. eating disorders, obsessive compulsive disorders, sexual satisfaction) that encompass more than emotional aspects of functioning.

Data extraction

The following data were extracted (where available): Study design, publication date, study period, country, sample size, diagnostic criteria for PCOS, time since diagnosis, patient and control selection procedures, participation rates, inclusion and exclusion criteria for cases and controls, use of (hormone) medication, presence of infertility (or an unfulfilled wish to conceive), age, BMI (kg/m^2), hirsutism [assessed by Ferriman–Gallwey (FG) scoring system; a score of >8 is considered hirsute] (Ferriman and Gallwey, 1961), testosterone concentrations (in nmol/l), IR (defined as homeostasis model of assessment-insulin resistance), low-grade inflammation markers (e.g. high-sensitive C-reactive protein), education level, marital status and methods of assessment of distress. Continent of origin was allocated by the geographical location of the country or institute where the study took place (United Nations, 2011).

To avoid multiple-publication bias, we excluded secondary publications with overlapping patient populations from the meta-analysis (see flowchart, Fig. 1). Where duplicate publications existed, the primary publication of comparative design reporting mean and standard deviation of emotional distress for the largest patient and control population was selected for inclusion.

Many studies reported outcomes on two or more distress measures. If multiple measures of the same outcome category were available in one study (e.g. multiple measures of depression), we prioritized a full questionnaire over subscales and state-emotion over trait-emotion (Fridhandler, 1986). Questionnaires measuring both types of emotional distress (e.g. Hospital Anxiety and Depression Scale) were included and depression and anxiety subscale scores were extracted. Authors were contacted to obtain separate depression or anxiety scores when only overall scores were published. The psychological score extracted from the Short Form-36 inventory was prioritized over the 'role emotional' subscale because the psychological score is a more reliable indicator of emoQoL than the individual subscales (Ware *et al.*, 1995).

Quality assessment

Study quality was assessed according to an adapted version of the Newcastle-Ottawa Quality Assessment Scale (Wells *et al.*, 2010) as presented in Supplementary data, Table SI.

Points were awarded if (i) the diagnosis of PCOS was assessed according to the NIH, Rotterdam or AE&PCOS criteria and clinically confirmed (1 point), (ii) sample size was larger than $n = 60$ per group, which is the minimum group size needed to detect a medium large difference in emotional distress score between cases and control groups with 80% power (calculated according to Cohen's D) (Erdfelder *et al.*, 1996) (1 point), (iii) selection bias was unlikely to be present because of random population selection technique or because cases and controls were selected from the same population (e.g. hospital controls if patients were recruited in the hospital) (1 point), (iv) PCOS was excluded in the control population by either full exclusion (all Rotterdam criteria) or partial exclusion (both received 1 point), (v) cases and controls were comparable on confounders when matched for age (1 point) and/or BMI (1 point), (vi) at least two predictors, such as BMI, hirsutism and infertility, were clinically assessed (1 point), (vii) emotional distress was assessed by a reliable and valid measure based on published psychometric properties of the questionnaire or structured interview (Bowling, 1995) (1 point). A study score of 0–2 points was considered low quality, 3–5 medium quality and 6–8 high quality.

Data analysis

We used Review Manager Version 5.0.25 for the meta-analysis and calculation of effect sizes, heterogeneity and forest plots (Review Manager, 2008). Meta-regression analyses were performed using 'metafor' package (version 0.5-5), R version 2.9.0. A P-value of < 0.05 was considered to be statistically significant.

Effect size and methodological aspects

The primary outcome measure was the pooled standardized mean difference (SMD) comparing emotional distress between women with PCOS and a control population [adjusted for small sample size using Hedges' g (Hedges, 1981)]. An effect size was calculated for all the three outcomes: depression, anxiety and emoQoL (where available). The SMD reflects the group difference relative to the pooled variability observed between groups. The meaning of the SMD magnitude is typically interpreted in statistical terms as defined by Cohen (1992): 0.20 (small), 0.50 (moderate) and 0.80 (large). This statistical interpretation may or may not translate into clinical relevance (see 'Discussion' section). We used a random effects model because of expected heterogeneity in the studied populations. A fixed effect model was also employed as sensitivity analysis (differences are reported). The SMD were pooled using the inverse-variance method. Effect size heterogeneity was evaluated using the chi-square statistic and calculation of the I^2 index (Higgins and Green, 2008). Positive effect sizes for depression and anxiety indicated greater emotional distress

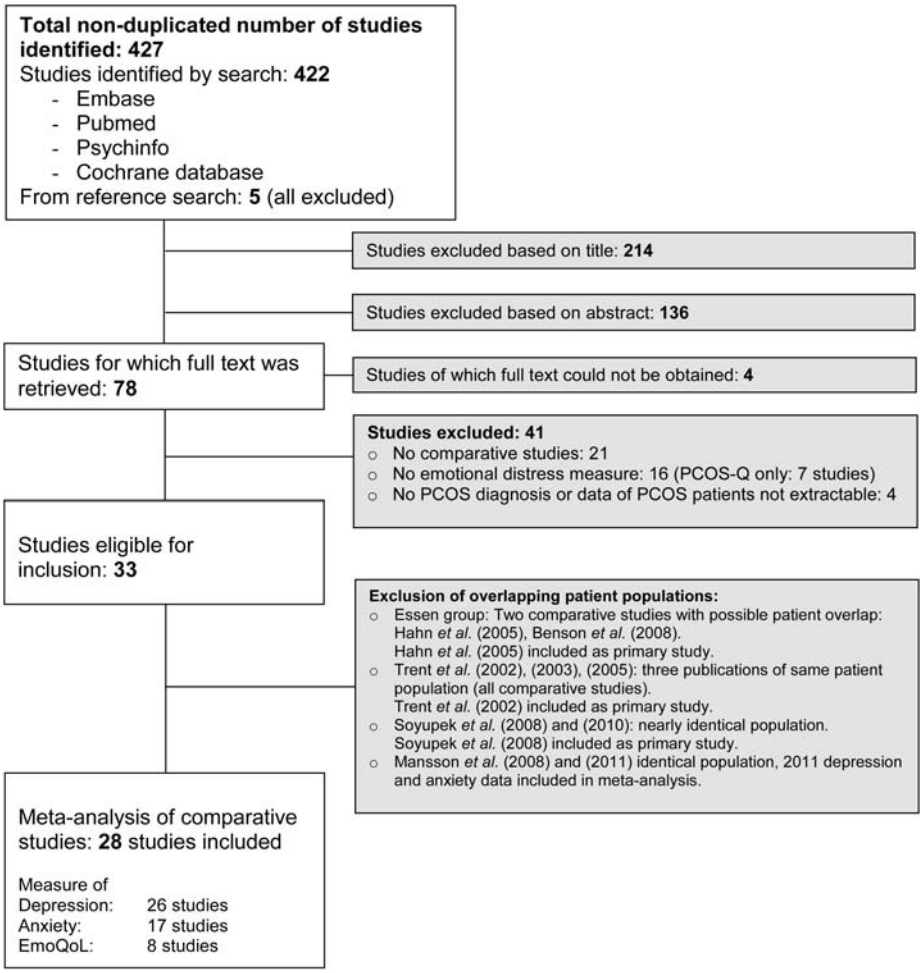

Figure 1 Flow chart of study selection for systematic review and meta-analysis of emotional distress in women with PCOS.

in the PCOS group. Owing to the scoring of emoQoL scales, negative effect sizes for emoQoL indicated more distress (i.e. less emotional QoL) in the PCOS group. Sensitivity analyses were performed to assess the robustness of the effect size according to pre-specified methodological factors. These were: overall study quality (low, medium, high), population recruitment (hospital, advertisement/internet, other), PCOS diagnosis (confirmed in study or not), diagnostic criteria (confirmed NIH, Rotterdam or AE&PCOS criteria) and PCOS exclusion in control selection (excluded, partly excluded by irregular menstruation only or not stated). We also performed sensitivity analyses according to age (youth 15–24 years, adult >24 years) (United Nations, 1981), marital status (partnered/married or not) and continent of study (America, Europe, Asia, Australia).

Publication bias was checked with visual inspection of funnel plots.

Subgroup analyses

Focal subgroup analyses were performed to identify potential explanatory mechanisms for the difference in emotional distress between women with PCOS and controls and to identify causes of heterogeneity in effect size across studies. If a factor was implicated as a causal mechanism for variation in emotional distress in women with PCOS, then we expected the SMD to be lower in the subgroup where groups were matched on the investigated correlate (i.e. PCOS and controls are more similar). The focal subgroup analyses concerned the following questions, which were derived on the basis of theorized potential mechanisms and typical comparisons made in the included studies:

(1) Is there a difference in effect size between studies according to whether the proportion of infertility is equally present in comparison groups (e.g. patients and controls), equally absent or where infertility was significantly more prevalent in women with PCOS? Fertility status was defined and reported as in the primary study (using clinical diagnosis or self-report).
(2) Is there a difference in effect size when studies matched for BMI are compared with those where the BMI is significantly higher in PCOS patients versus controls? Does the effect size vary according to BMI values within the PCOS group?
(3) Is there a difference in effect size when studies matched for clinical hyperandrogenism (hirsutism) are compared with studies where clinical hyperandrogenism is significantly higher in PCOS patients? Does the effect size vary according to the magnitude of hirsutism within the PCOS group?
(4) Does the effect size vary according to the presence or absence of biochemical hyperandrogenism within the PCOS group?

In addition to these focal subgroup analyses, a random effects meta-regression analysis was performed. The association between the emotional distress SMD (as dependent variable) and the following

explanatory variables was assessed: age, BMI, percentage of infertility in PCOS population, FG score and testosterone values (independent variables). Only covariates with a univariate association with the dependent variable of $P < 0.30$ were included in the multivariate model.

Results

Search results

The database search yielded 427 non-duplicated articles (Fig. 1). References of all the included articles and relevant reviews and background articles were checked, which did not result in additional study inclusions. In 78 articles, the eligibility could not be determined by reading the abstract, and therefore, full text of the articles was read. Full text of four articles [one unpublished dissertation, one Italian and two Chinese studies (Monzani *et al.*, 1994; Castillo, 2008; Shi *et al.*, 2008; Wang *et al.*, 2009)] could not be obtained. We contacted 27 authors and received additional information on 11 studies and additional data for 8 studies. Thirty-three articles met the inclusion criteria (Adali *et al.*, 2008; Alvarez-Blasco *et al.*, 2010; Barnard *et al.*, 2007; Barry *et al.*, 2011a; Battaglia *et al.*, 2008; Bhattacharya and Jha, 2010; Benson *et al.*, 2008; Benson *et al.*, 2009a; Cinar *et al.*, 2011; Cipkala-Gaffin *et al.*, 2012; Deeks *et al.*, 2011; Drosdzol *et al.*, 2007; Elsenbruch *et al.*, 2003; Ghoreishi *et al.*, 2010; Hahn *et al.*, 2005; Himelein and Thatcher, 2006; Hollinrake *et al.*, 2007; Jedel *et al.*, 2010; Kumarapeli *et al.*, 2011; Laggari *et al.*, 2009; Mansson *et al.*, 2008; Mansson *et al.*, 2011; Moran *et al.*, 2010; Orenstein *et al.*, 1986; Ozenli *et al.*, 2008; Pastore *et al.*, 2011; Rocco *et al.*, 1991; Soyupek *et al.*, 2008; Soyupek *et al.*, 2010; Trent *et al.*, 2002; Trent *et al.*, 2003; Trent *et al.*, 2005; Weiner *et al.*, 2004). As a result of overlapping patient populations, only 28 of these studies could be included in the meta-analysis; 26 reporting on depression, 17 on anxiety and 8 on emoQoL.

The included studies generated information for 2384 women diagnosed with PCOS and 2705 controls, from 14 different countries. Study characteristics are presented in Supplementary data, Table SII. Population characteristics such as age and BMI were available in most studies as shown in Supplementary data, Table SIII. Measures of insulin resistance and other metabolic features were less often reported.

The quality assessment of the included studies is presented in Supplementary data, Table SI. One-third of the studies were of high quality, with an overall quality rating of 6 or more points.

Meta-analysis

Effect size and methodological aspects

Table I presents the pooled SMD effect size for the overall meta-analysis on each outcome (depression, anxiety, emoQoL) as well as the SMD for each sensitivity analysis computed.

Depression

The meta-analysis of 26 comparative studies reporting depression scores showed a significant SMD (by random effects model) of 0.60 [95% confidence interval (CI) 0.47–0.73] with substantial heterogeneity I^2 73%, $P < 0.001$ (Fig. 2). The fixed effects model showed a pooled SMD of 0.67 (95% CI 0.61–0.73). The pooled effect size corresponds to a moderate effect size according to Cohen (1992).

As shown in Table I, almost all the sensitivity analyses were significant and indicated that effect size variation could partly be accounted for by variation in methodological characteristics. Effect sizes were significantly higher for studies with lower methodological rigour. Further, smaller distress differences were found for younger populations. The marital status of participants did not account for effect size variation between studies. The sensitivity analyses also revealed that heterogeneity was eliminated (I^2 0%) for effect sizes drawn from subgroups where marital status or fertility status was equal between women with PCOS and controls, or from subgroups that included patients with increased mean FG scores. However, all effect sizes within individual subgroups remained significant.

Anxiety

The meta-analysis of 17 studies reporting anxiety showed an effect size of 0.49 (95% CI 0.36–0.63) ($P < 0.001$) (random effect, SMD) (Fig. 3). Heterogeneity was I^2 52%, $P < 0.05$. Similar results were obtained with a fixed effects model. The pooled effect size corresponds to a moderate effect size according to Cohen (1992). Sensitivity analyses (Table I) showed that methodological quality could significantly account for variation in effect size, with studies using recruitment through advertisements and studies of lower quality generating larger effect sizes. Subgroups based on continent of origin revealed lower anxiety scores for Americans and Europeans compared with Asian and Australian studies. It was also possible to generate subgroups with homogeneous effect sizes (I^2 0%) on the basis of methodological characteristics (i.e. hospital or advertisement recruitment), country of origin (American or Australian) and clinical aspects (grouping by diagnostic criteria used). However, all effect sizes within individual subgroups remained significant except for the subgroup of three studies of young women (<24 years).

Emotional-subscales of quality of life

A significantly smaller effect size, reflecting a lower QoL related to emotional distress, was present in women with PCOS compared with controls (Fig. 4): SMD of −0.66 (95% CI −0.92 to −0.41), with substantial heterogeneity, I^2 76% $P < 0.001$. Fixed effect analysis: −0.52 (95% CI −0.64 to −0.40). The pooled effect size corresponds to a moderate effect size according to Cohen (1992). Only eight studies reported an emoQoL, which resulted in small subgroups. The effect size varied significantly according to diagnostic criteria and age (NIH criteria and older age associated with poorer QoL). The differences among subgroups were not significant for study quality, confirmation of PCOS diagnosis and exclusion of PCOS in control groups. However, the effect sizes were in the expected direction. Heterogeneity was substantial for all sensitivity assessments and homogeneous subsets for emoQoL could not be identified.

Subgroup analysis

Focal subgroup analyses based on study variation in infertility, obesity and hyperandrogenism were performed (see results in Table II).

Infertility

Subgroups were created on the basis of fertility status of participants as reported in the original study. The subgroup analysis of depression showed no evidence of a significant difference between the three subgroups (e.g. equal percentage infertile, equally fertile women and

Table I Results of meta-analysis and sensitivity analysis of methodological aspects.

	Depression					Anxiety					EmoQoL				
	K	*n*	SMD (95% CI)	I^2 (%)		*K*	*n*	SMD (95% CI)	I^2 (%)		*K*	*n*	SMD (95% CI)	I^2 (%)	
Meta-analysis															
Random effect model	26	4716	0.60 (0.47, 0.73)*	73*		17	2120	0.49 (0.36, 0.63)*	52#		8	1208	−0.66 (−0.92, −0.41)*	76*	
Fixed effect model	26	4716	0.67 (0.61, 0.73)*	73*		17	2120	0.47 (0.38, 0.55)*	52#		8	1208	−0.52 (−0.64, −0.40)*	76*	
Sensitivity analyses of methodological aspects															
Quality assessment															
High-quality studies	9	1278	0.60 (0.45, 0.76)*	34		4	530	0.49 (0.23, 0.76)*	43		4	565	−0.54 (−0.83, −0.24)*	56	
Medium quality	9	1474	0.54 (0.31, 0.78)*	77*		9	1085	0.41 (0.23, 0.59)*	46		4	643	−0.77 (−1.23, −0.32)*	85*	
Low quality	6	1964	0.80 (0.65, 0.95)*	31		4	505	0.69 (0.49, 0.88)*	40		0	0	Not estimable		
Subgroup					$P < 0.0001$					$P = 0.007$					$P = 0.13$
Population recruitment															
Hospital	7	847	0.63 (0.40, 0.86)*	58#		2	209	0.46 (0.18, 0.74)#	0		4	561	−0.66 (−1.09, −0.24)#	79#	
Advertisement or Internet	4	1770	0.80 (0.60, 1.00)*	49		3	411	0.79 (0.59, 1.00)*	0		0	0	Not estimable		
Mixed/other	15	2099	0.54 (0.37, 0.71)*	68*		12	1500	0.42 (0.26, 0.57)*	45#		4	647	−0.67 (−1.06, −0.28)*	79#	
Subgroup					$P < 0.0001$					$P = 0.002$					—
PCOS diagnosis confirmation															
Confirmed by study	18	2233	0.55 (0.39, 0.71)*	67*		12	1302	0.51 (0.37, 0.65)*	27		5	774	−0.62 (−0.91, −0.33)*	70#	
Not confirmed by study	8	2483	0.71 (0.52, 0.90)*	72*		5	818	0.42 (0.10, 0.75)#	77#		3	434	−0.75 (−1.40, −0.11)*	76*	
Subgroup					$P < 0.0001$					$P = 0.38$					$P = 0.98$
PCOS criteria															
NIH	3	374	0.44 (0.13, 0.76)*	52		2	270	0.32 (0.06, 0.57)#	0		3	374	−0.77 (−1.02, −0.52)*	16	
Rotterdam	12	1614	0.57 (0.39, 0.75)*	64*		7	787	0.62 (0.47, 0.77)*	0		2	400	−0.41 (−0.80, −0.01)#	63	
Subgroup					$P = 0.29$					$P = 0.05$					$P = 0.004$
Control status															
PCOS excluded	11	1457	0.68 (0.54, 0.82)*	32		8	960	0.51 (0.34, 0.68)*	29		6	835	−0.65 (−0.91, −0.39)*	66#	
Partly excluded	7	813	0.51 (0.19, 0.82)*	76*		3	173	0.53 (0.19, 0.87)#	12		1	283	−0.25 (−0.50, −0.00)	—	
Not stated	8	2446	0.60 (0.35, 0.85)*	84*		6	987	0.47 (0.19, 0.74)*	64*		1	90	−1.23 (−1.68, −0.78)*	—	
Subgroup					$P = 0.008$					$P = 0.78$					—
Age															
Youth	5	520	0.54 (0.16, 0.93)#	74#		3	235	0.48 (0.00, 0.96)	56		2	367	−0.41 (−0.81, −0.02)#	61	
Adult	21	4196	0.62 (0.49, 0.76)*	71*		14	1885	0.50 (0.36, 0.65)*	53#		6	841	−0.75 (−1.08, −0.43)*	76*	
Subgroup					$P = 0.008$					$P = 0.30$					$P = 0.05$
Marital status															
Similar % married	12	1409	0.68 (0.57, 0.79)*	0		6	559	0.43 (0.22, 0.64)*	31		6	821	−0.76 (−1.09, −0.43)*	78*	

Continued

Table I *Continued*

	Depression				Anxiety				EmoQoL			
	K	*n*	SMD (95% CI)	I^2 (%)	*K*	*n*	SMD (95% CI)	I^2 (%)	*K*	*n*	SMD (95% CI)	I^2 (%)
Not similar % married	1	100	0.78 (0.37, 1.20)*	n/a	0	0	Not estimable		0	0	Not estimable	—
Not stated	14	3207	0.60 (0.34, 0.78)*	85*	11	1561	0.52 (0.34, 0.71)*	61#	2	387	−0.39 (−0.75, −0.04)#	55
Subgroup			$P = 0.83$					—				—
Continent of origin												
America	6	956	0.54 (0.25, 0.83)*	77*	3	460	0.22 (0.04, 0.40)#	0	1	283	−0.25 (−0.50, −0.00)	—
Europe	11	2195	0.64 (0.42, 0.87)*	71	8	689	0.45 (0.27, 0.62)*	16	5	525	−0.87 (−1.09, −0.64)*	29
Asia	7	1214	0.58 (0.38, 0.79)*	63#	4	620	0.57 (0.26, 0.87)*	64#	2	400	−0.41 (−0.80, −0.01)#	63
Australia	2	351	0.69 (0.46, 0.91)*	0	2	351	0.77 (0.55, 1.00)*	0	0	0	Not estimable	—
Subgroup			$P = 0.0003$					$P = 0.002$				—

K, number of studies; *n*, number of participants; SMD, standardized mean difference, pooled by inverse-variance method (random effects model, unless stated otherwise); I^2, test for heterogeneity; PCOS, polycystic ovary syndrome; NIH, National Institutes of Health.
Subgroup difference: test (χ^2) for subgroup differences, $P < 0.05$ is considered to be significant.

PCOS with significantly more infertile women), $P = 0.44$. For anxiety and emoQoL, this subgroup analysis could not be computed.

Obesity

Studies matched on BMI had significantly smaller depression SMDs (0.55, 95% CI 0.26–0.83) compared with studies with significantly higher BMI in PCOS patients (0.68, 95% CI 0.55–0.81). Anxiety scores were similar for populations matched and unmatched on BMI. The opposite was found for emoQoL, showing poorest QoL scores for studies matched on BMI ($P = 0.003$).

Higher depression scores were observed in subgroups with higher mean BMI, whereas the highest anxiety score was observed in the low-weight category. EmoQol was not related to obesity category.

Clinical hyperandrogenism

No studies matched cases and controls on clinical hyperandrogenism (hirsutism). Fourteen studies described the hirsutism status of their patients and only 9 of the 28 included studies reported the FG score of patient and control groups. In the latter studies, hirsutism scores were higher in the PCOS population. Subgroup analyses showed significantly higher depression scores for studies with higher mean hirsutism scores. For emoQoL, a similar but non-significant effect was found. Subgroup analysis of the effect of hirsutism on anxiety could not be performed.

Biochemical hyperandrogenism

Not surprisingly, there were no studies including controls with high androgen levels or studies matched on hyperandrogenism. Separate assessment of the influence of the presence or absence of biochemical hyperandrogenism could therefore not be performed.

Meta-regression

A series of random effects meta-regression analyses were conducted with emotional distress SMDs (depression, anxiety, emoQoL) as dependent variables and differences in the continuous variables of BMI, age, percentage of infertility, hirsutism score or testosterone as independent variables to ascertain whether variations in these features could explain effect size variation. None of the variables was significantly associated with distress scores.

Publication bias

The funnel plot on emotional distress (depression and anxiety) (see Supplementary data) showed a nearly symmetrical scattering, except for one outlier linked to a small study with a significant effect size (Rocco *et al.*, 1991). This suggests that a small study with negative non-significant effect could be missing, pointing towards a possible, but likely minimal, publication bias.

Summary of previous meta-analyses

A summary of the pooled results of the four previously published meta-analyses of emotional distress in PCOS (Barry *et al.*, 2011b; Dokras *et al.*, 2011a, b; Li *et al.*, 2011) alongside the results of the present meta-analysis is given in Table III.

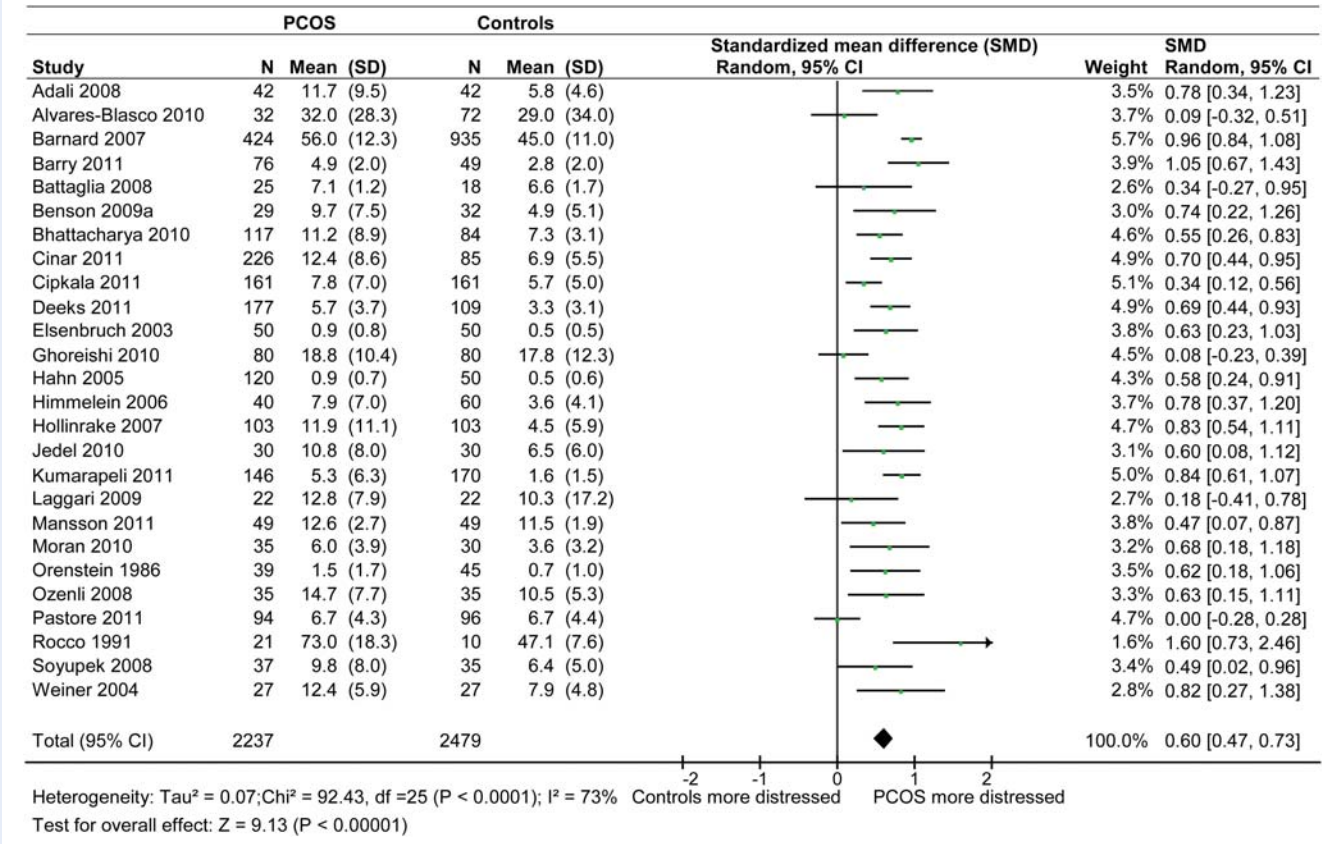

Figure 2 Forest plot of depression score in women with PCOS and controls. SMD, standardized mean difference; CI, confidence interval.

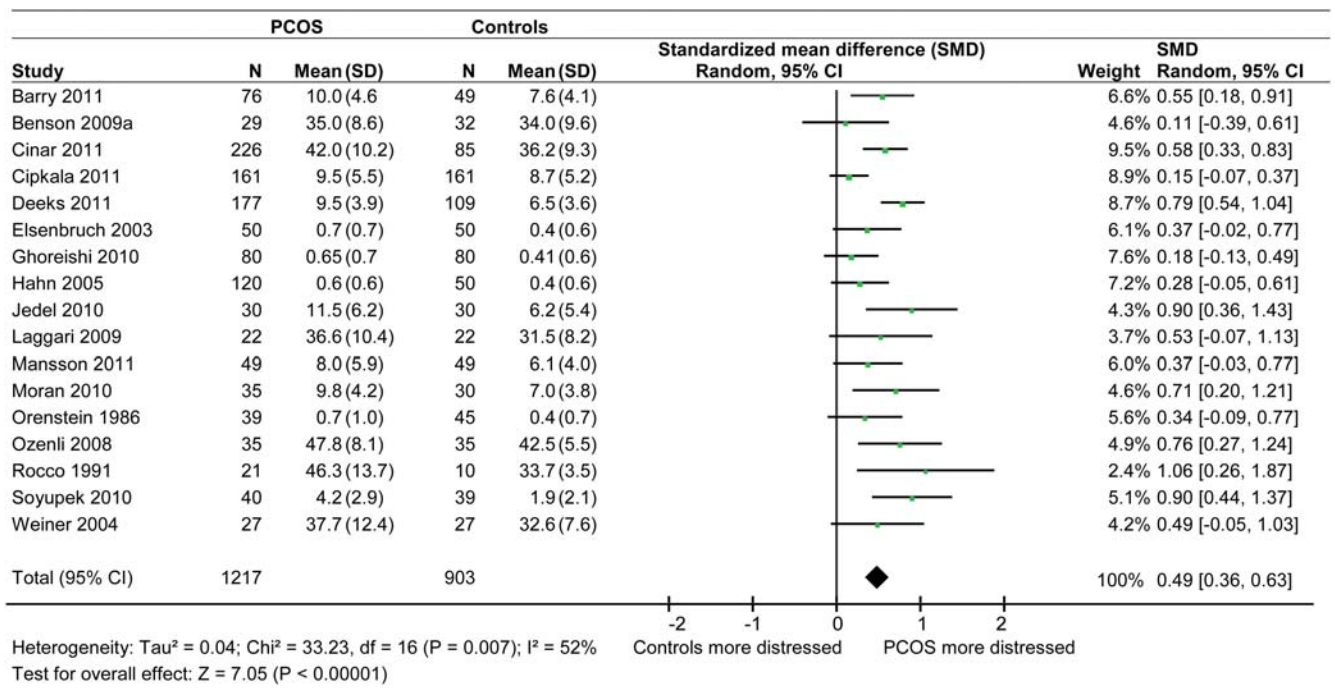

Figure 3 Forest plot of anxiety score in women with PCOS and controls.

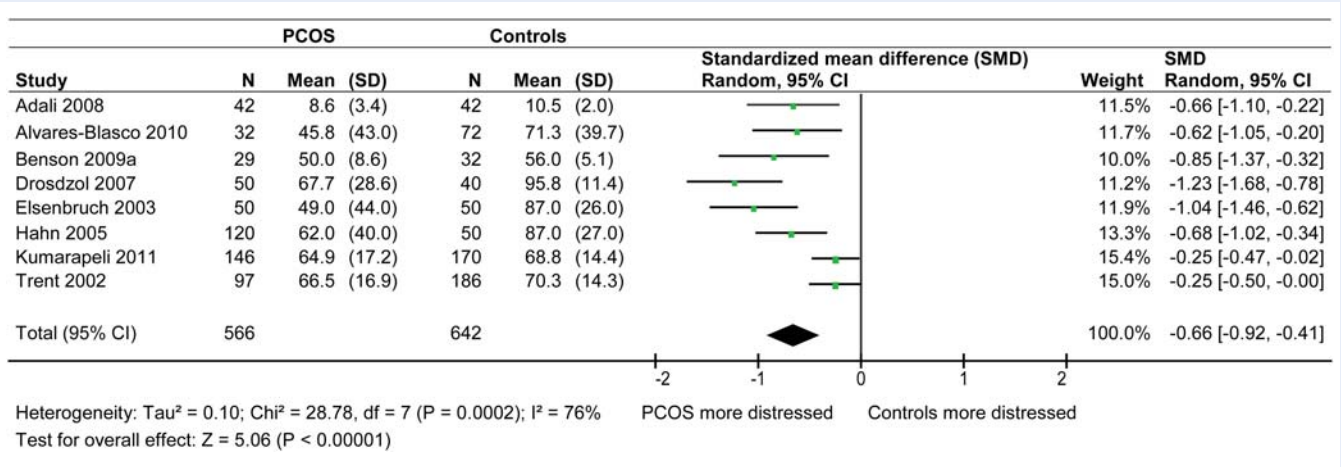

Figure 4 Forest plot of emotional (psychological) subscales from quality of life score in women with PCOS and controls.

Discussion

The current meta-analysis of 28 comparative studies of 2384 patients and 2705 control women provides compelling evidence of greater emotional distress in women with PCOS compared with controls. This meta-analysis included twice the number of studies and patients compared with previous meta-analyses and therefore represents the most comprehensive meta-analysis of emotional disorders in PCOS to date. Higher emotional distress was consistently found in PCOS patients in all the three examined emotional distress domains; i.e. depression, anxiety and the emoQoL measures. Sensitivity analyses showed that the effect size was robust to numerous variations in study design (e.g. study quality, population recruitment). Subgroup analyses did not offer definitive explanations for why PCOS and emotional distress are so strongly related but do suggest that the stigmatizing aspects of the disorder (e.g. hirsutism, obesity) warrant further investigation. The results indicate that women with PCOS should be forewarned of their elevated risk of emotional distress.

The main finding of this systematic review and meta-analysis is the high consistency in evidence showing higher emotional distress (on average a 0.5 SD, moderate effect size) in women with PCOS compared with control populations. However, in the clinical context, the moderate effect size for depression would correspond to an approximate 4-point difference in total score on the Beck Depression Inventory scale (scale range 0–63), which was the most commonly used measure of depression (reported in $n = 8$ studies) (Beck and Steer, 1984). Scores for women with PCOS were on average in the non-clinical range in 50% of the included studies and in the mild depression range for the remaining studies. None of the studies reported average scores in the severe or clinical depression range. Similarly, results for the Spielberger State Anxiety Inventory (most common anxiety measure) corresponded to a mildly elevated anxiety score. These results concur with the smaller previous meta-analysis (Barry *et al.*, 2011b) of anxiety indicating higher but non-clinical levels of emotional distress in women with PCOS. In contrast, Dokras reported a 4- and 6-fold higher prevalence of depression and anxiety (respectively) and Barry *et al.* (2011b) large effect size for depression (SMD >0.80, see Table III) in women with PCOS compared with control populations (Dokras *et al.*, 2011a, b). However, these results were derived from meta-analyses that exclusively concerned studies focusing on elevated distress, which would overestimate the risk of high scores relative to the total pool of available studies. On the basis of currently available evidence, we conclude that emotional distress is significantly higher in women with PCOS but the magnitude of distress is likely to vary within the non-clinical range for the average woman with PCOS.

The evidence for a higher prevalence of emotional distress in PCOS is compelling but none of the meta-analyses (Barry *et al.*, 2011b; Dokras *et al.*, 2011a, b; Li *et al.*, 2011), including our own, provides a definitive explanation for the cause of this association. Many women perceive the visible features of PCOS (e.g. hirsutism) and its common correlates (e.g. infertility and obesity) as stigmatizing and a source of distress (Sonino *et al.*, 1993; Conaglen and Conaglen, 2003; Chachamovich *et al.*, 2010). Our significant sub-group analyses of these visible aspects support the hypothesis that distress is a reaction to the stigma of the condition. However, the sub-group analyses also showed that hirsutism, infertility and obesity did not fully or consistently account for the association between PCOS and emotional distress. Thus, depression was present in obese and infertile women as well as in lean and fertile patients with PCOS. The PCOS emotional distress association could also be explained via common underlying causes. Testosterone was the only pathophysiological feature that could be studied as mediator between PCOS and distress but testosterone was not significantly related to effect size variation in meta-regression. Mediators related to other concomitants of PCOS (e.g. diabetes, metabolic syndrome, low-grade inflammation) could not be studied because of insufficient reporting in primary studies (e.g. insulin resistance) or presence only in patients with PCOS (e.g. biochemical hyperandrogenism). Therefore, the explanation of common underlying causes needs to be investigated further. Finally, we tested the robustness of the overall effect size in sensitivity analyses of diverse methodological features as these too could explain why PCOS and emotional distress are related. As expected, effect size was overestimated in poorer quality studies (e.g. PCOS status not confirmed, internet recruitment). These analyses also identified demographic correlates that need further investigation, such as age, cultural background and social environment. However, as was the case for

Table II Results of subgroup analyses of explanatory mechanisms.

	Depression					Anxiety					EmoQoL				
	K	*n*	SMD (95% CI)	I^2(%)		*K*	*n*	SMD (95% CI)	I^2(%)		*K*	*n*	SMD (95% CI)	I^2(%)	
Infertility															
Equal infertile	2	123	0.47 (0.11, 0.83)**	0		0	0	Not estimable	—		0	0	Not estimable	—	
Equal fertile	4	671	0.72 (0.56, 0.88)*	0		1	70	0.76 (0.27, 1.24)	—		2	400	−0.41 (−0.80, −0.01)**	63	
More infertility in PCOS	6	966	0.59 (0.28, 0.90)*	66**		3	556	0.50 (0.15, 0.85)*	60		4	464	−0.87 (−1.15, −0.60)*	46	
Subgroup					$P = 0.44$					—					—
Obesity															
Matched for BMI	8	824	0.55 (0.26, 0.83)*	68**		6	677	0.49 (0.22, 0.75)*	53		3	255	−0.90 (−1.26, −0.53)*	46	
Higher BMI in PCOS	15	3548	0.68 (0.55, 0.81)*	64*		9	1289	0.50 (0.30, 0.69)*	61**		5	953	−0.54 (−0.82, −0.26)*	75**	
Subgroup					$P = 0.0004$					$P = 0.98$					$P = 0.003$
Obesity category															
Mean BMI <25	3	432	0.58 (0.20, 0.96)**	60		3	434	0.64 (0.43, 0.85)*	0		1	316	−0.25 (−0.47, −0.02)**	—	
Mean BMI 25–30	6	895	0.61 (0.40, 0.83)*	56**		4	610	0.39 (0.14, 0.65)**	52		1	84	−0.66 (−1.10, −0.22)**	—	
Mean BMI >30	6	2221	0.79 (0.64, 0.93)*	43		3	556	0.50 (0.15, 0.85)**	71**		3	553	−0.63 (−1.09, −0.18)**	83**	
Subgroup					$P = 0.001$					$P = 0.03$					$P = 0.10$
Hirsutism															
Mean FG >8	8	1145	0.70 (0.58, 0.83)*	0		5	702	0.44 (0.22, 0.66)*	40		7	1104	−0.67 (−0.96, −0.38)*	79*	
Subgroup															
Biochemical hyperandrogenism															
Equal in case and control	0	0	n.a.	n.a.		0	0	Not estimable	—		0	0	Not estimable	—	

K, number of studies; *n*, number of participants; SMD, standardized mean difference, pooled by inverse-variance method (random effects model); I^2, test for heterogeneity; FG: Ferriman–Gallwey.
Subgroup difference: test (χ^2) for subgroup differences. $P < 0.05$ is considered to be significant.
*$P < 0.001$.
**$P < 0.05$.

Table III Summary of pooled effect size of previous and present meta-analysis of studies of emotional distress in women with PCOS.

Study	Depression	Anxiety	Emotional quality of life
Barry *et al.* (2011)	SMD 0.82 (95% CI 0.73–0.92) ($n = 12$)	SMD 0.54 (95% CI 0.33–0.75) ($n = 6$)	—
Dokras *et al.* (2011a)	OR 4.03 (95% CI 2.96–5.50) ($n = 10$)	—	—
Dokras *et al.* (2011b)	—	OR 6.88 (95% CI 2.5–18.9) ($n = 4$)	—
Li *et al.* (2011)	—	—	Emotional role function: MD −13.83 (95% CI −27.51 to − 20.21) ($n = 4$) Mental Health: MD −13.83 (95% CI −16.13 to −11.53) ($n = 5$)
Veltman-Verhulst (present meta-analysis)	SMD 0.60 (95% CI 0.47–0.73) ($n = 26$)	SMD 0.49 (95% CI 0.36–0.63) ($n = 17$)	SMD −0.66 (95% CI −0.92 to −0.41) ($n = 8$)

SMD (standardized mean difference), calculated using Hedges'g. SMD expresses the difference between two groups in terms of standard deviation units above or below the mean. It is used when the outcome measures are based on different units of measurement. OR random effects model, calculated using the Mantel–Haenszel method. OR expresses the probability of the occurrence of an outcome related to the probability of this outcome in another group. MD (mean difference), calculated using the DerSimonian–Laird method. MD expresses the difference between two groups in the original outcome measurement units. n = number of studies. All meta-analyses used the Cochrane Review Manager software to conduct the analyses.

analyses related to psychosocial or physiological explanations, none of the sensitivity analyses fully explained the association between PCOS and emotional disorders (i.e. reduced SMD to zero). In light of the result of the current meta-analysis the focus of future studies should now go beyond describing that the association exists to trying to explain why PCOS and emotional disorders are so strongly related. Future studies should control for the design features that were shown in the present meta-analysis to increase (e.g. online recruitment) or decrease (e.g. PCOS verification in study) the effect size in order to achieve the most reliable estimate of the difference between PCOS and control populations. Further, the goal of identifying explanatory mechanisms may better be achieved by comparing the different PCOS phenotypes while controlling for known consequences (e.g. infertility, obesity).

PCOS is a multifaceted disorder with multiple potential risk factors (e.g. infertility, diabetes, cardiovascular disease and metabolic syndrome). The main discourse between clinician and patient has therefore concerned risk communication about these potential effects, and prevention or treatment, where appropriate. This discourse should now extend to include discussion of the emotional aspects of the disorder. We recommend discussion rather than screening because it fulfils the responsibility of informing women about the potential future consequences while avoiding stigmatizing women who will generally report emotional distress in the non-clinical range. Further research in other health contexts shows that screening at a single point in time has minimal benefit on the overall management of patients at risk of depression in terms of physician symptom recognition, referral for intervention or prescription of anti-depressants (Gilbody *et al.*, 2008). Therefore, we recommend that clinicians be aware of the potential increased emotional distress in women with PCOS and discuss it with their patients. Referral for psychological intervention can be made when required in line with patient preferences. Dietary changes as well as patient support and cognitive-behavioural therapy are found to alleviate distress (Snyder, 2006; Galletly *et al.*, 2007; Percy *et al.*, 2009). Future research is required to identify the best method of risk communication and treatment for women with PCOS.

Overall, the strengths of this meta-analysis point to reliable and valid results despite some limitations. We have performed a systematic literature search and data-analysis that greatly reduces selection bias. Despite our efforts to obtain all available studies, abstracts and additional information through correspondence with authors, we were able to identify only few Chinese-Asian studies, of which full text could not be obtained. The overall quality of included studies was average and a possible bias related to patient selection procedures in the included studies could not be completely ruled out, because since diagnosis was sporadically reported, we could not assess the impact of disease duration on emotional distress. Inflation bias might be introduced by, for example, clinical interview by investigators that were not blind to study hypotheses (Kerchner *et al.*, 2009; Jedel *et al.*, 2010). Additionally, some general and social patient characteristics are known to contribute to the magnitude of emotional distress. For example, emotional distress can vary according to age (Jorm, 2000) and married couples are found to be at lower risk of developing depression (van de Velde *et al.*, 2010). Emotional distress can also vary according to ethnicity and socio-economic status (Simon *et al.*, 2002). Most comparative studies select their participants from the same population, which should minimize the effect of these general social factors. Nevertheless, these variables need to be taken into account when assessing emotional distress. The interpretation of the results of the meta-analysis was further challenged by the multiple measures of emotional distress. However, in all but one study, these were reliable and validated measures of emotional constructs. Finally, it should be noted that in the majority of studies women were attending a clinic (or participating in the research) because one or more PCOS symptoms were bothersome and this may make these women more distressed than those who do not come forward in this way.

In conclusion, women with PCOS exhibit significantly more emotional distress compared with women without PCOS. This result was robust in that it was consistently observed in the 28 studies included in this meta-analysis and across all outcomes investigated (anxiety, depression, poor emotional QoL). Methodological and clinical features explained some effect size variation but none could fully

account for the moderate relationship between emotional distress and PCOS. Clinicians should be aware of the emotional aspects of PCOS, discuss these with patients and provide referral for patients with concerns when appropriate in line with patient preference.

Supplementary data

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

Acknowledgements

We thank the authors of primary work for their responses to our correspondence. Many authors have provided us with additional information and data that were of great value for this review. Laurien Voorhuis, psychologist, is thanked for her assistance with data entry and study administration.

Authors' roles

S.M.V., J.B. and B.J.C.M.F. conceptualized the review. S.M.V. and J.B. searched databases, selected articles and performed data-extraction and statistical analysis. M.J.C.E. provided statistical support and data analysis. S.M.V. and J.B. took the lead in writing the review. B.J.C.M.F. revised several draft versions of the manuscript. All the authors approved the final version of the article.

Funding

B.J.C.M.F. has received fees and grant support from the following companies (in alphabetic order); Andromed, Ardana, Ferring, Genovum, Merck Serono, MSD, Organon, Pantharei Bioscience, PregLem, Schering, Schering Plough, Serono and Wyeth. J.B. received speaker fees from EMD Serono Inc. and Merck & Co. (then Schering Plough) and a research grant from Merck Serono S.A.

Conflict of interest

There are no other conflicts of interest to declare.

References

Adali E, Yildizhan R, Kurdoglu M, Kolusari A, Edirne T, Sahin HG, Yildizhan B, Kamaci M. The relationship between clinico-biochemical characteristics and psychiatric distress in young women with polycystic ovary syndrome. *J Int Med Res* 2008;**36**:1188–1196.

Alvarez-Blasco F, Luque-Ramirez M, Escobar-Morreale HF. Obesity impairs general health-related quality of life (HR-QoL) in premenopausal women to a greater extent than polycystic ovary syndrome (PCOS). *Clin Endocrinol (Oxf)* 2010; **73**:595–601.

Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod* 2012;**27**:14–24.

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE *et al*. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab* 2006;**91**:4237–4245.

Barnard L, Ferriday D, Guenther N, Strauss B, Balen AH, Dye L. Quality of life and psychological well being in polycystic ovary syndrome. *Hum Reprod* 2007; **22**:2279–2286.

Barry JA, Hardiman PJ, Saxby BK, Kuczmierczyk A. Testosterone and mood dysfunction in women with polycystic ovarian syndrome compared to subfertile controls. *J Psychosom Obstet Gynaecol* 2011a;**32**:104–111.

Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2011b; **26**:2442–2451.

Battaglia C, Nappi RE, Mancini F, Cianciosi A, Persico N, Busacchi P, Facchinetti F, Sisti G. PCOS, sexuality, and clitoral vascularisation: a pilot study. *J Sex Med* 2008; **5**:2886–2894.

Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol* 1984;**40**:1365–1367.

Benson S, Janssen OE, Hahn S, Tan S, Dietz T, Mann K, Pleger K, Schedlowski M, Arck PC, Elsenbruch S. Obesity, depression, and chronic low-grade inflammation in women with polycystic ovary syndrome. *Brain Behav Immun* 2008;**22**:177–184.

Benson S, Arck PC, Tan S, Hahn S, Mann K, Rifaie N, Janssen OE, Schedlowski M, Elsenbruch S. Disturbed stress responses in women with polycystic ovary syndrome. *Psychoneuroendocrinology* 2009a;**34**:727–735.

Benson S, Hahn S, Tan S, Mann K, Janssen OE, Schedlowski M, Elsenbruch S. Prevalence and implications of anxiety in polycystic ovary syndrome: results of an internet-based survey in Germany. *Hum Reprod* 2009b;**24**:1446–1451.

Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS). *Fertil Steril* 2010;**94**:357–359.

Bowling A. *Measuring Disease*, 2nd edn. Buckingham, UK: Open University Press, 1995.

Castillo Y. Understanding the social and emotional experiences of females with polycystic ovary syndrome (PCOS). *Diss Abstr Int A Humanit Soc Sci* 2008;**69**:2154.

Chachamovich JR, Chachamovich E, Ezer H, Fleck MP, Knauth D, Passos EP. Investigating quality of life and health-related quality of life in infertility: a systematic review. *J Psychosom Obstet Gynaecol* 2010;**31**:101–110.

Cinar N, Kizilarslanoglu MC, Harmanci A, Aksoy DY, Bozdag G, Demir B, Yildiz BO. Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome. *Hum Reprod* 2011;**26**:3339–3345.

Cipkala-Gaffin J, Talbott EO, Song MK, Bromberger J, Wilson J. Associations among depressive symptoms, anxiety, anger, hostility, and satisfaction with life in women with polycystic ovary syndrome. *J Womens Health (Larchmt)* 2012;**21**:179–187. [Epub 2011].

Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). *Gynecol Endocrinol* 2006;**22**:80–86.

Cohen J. A power primer. *Psychol Bull* 1992;**112**:155–159.

Conaglen HM, Conaglen JV. Sexual desire in women presenting for antiandrogen therapy. *J Sex Marital Ther* 2003;**29**:255–267.

Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, Cook D, Dunaif A. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J Clin Endocrinol Metab* 1998; **83**:1976–1987.

Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? *Hum Reprod* 2011;**26**:1399–1407.

Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Obstet Gynecol* 2011a;**117**:145–152.

Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. *Fertil Steril;* Advance Access published Nov 23rd, 2011b; doi:10.1016/j.fertnstert.2011.10.022.

Drosdzol A, Skrzypulec V, Mazur B, Pawlinska-Chmara R. Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. *Folia Histochem Cytobiol* 2007;**45**(Suppl 1):S93–S97.

Elsenbruch S, Hahn S, Kowalsky D, Offner AH, Schedlowski M, Mann K, Janssen OE. Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;**88**:5801–5807.

Erdfelder E, Faul F, Buchner A. GPOWER: a general power analysis program. *Behav Res Methods Instrum Comput* 1996;**28**:1–11.

Farrell K, Antoni MH. Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: biobehavioral mechanisms and interventions. *Fertil Steril* 2010;**94**:1565–1574.

Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961;**21**:1440–1447.

Fridhandler BM. Conceptual note on state, trait, and the state–trait distinction. *J Pers Soc Psychol* 1986;**50**:169–174.

Galletly C, Moran L, Noakes M, Clifton P, Tomlinson L, Norman R. Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome—a pilot study. *Appetite* 2007;**49**:590–593.

Ghoreishi A, Rahmanpour H, Mousavinasab N. Evaluation of psychological problems in teenagers suffering from polycystic ovary syndrome. *J Zanjan Univ of Med Sc* 2010;**18**:76–83.

Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ* 2008;**178**:997–1003.

Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, Kimmig R, Benson S, Balamitsa E, Elsenbruch S. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *Eur J Endocrinol* 2005;**153**:853–860.

Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Stat* 1981;**6**:107–128.

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.2 (updated September 2009). The Cochrane Collaboration. 2008. www.cochrane-handbook.org.

Himelein MJ, Thatcher SS. Depression and body image among women with polycystic ovary syndrome. *J Health Psychol* 2006;**11**:613–625.

Hollinrake E, Abreu A, Maifeld M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovary syndrome. *Fertil Steril* 2007;**87**:1369–1376.

Jedel E, Waern M, Gustafson D, Landen M, Eriksson E, Holm G, Nilsson L, Lind AK, Janson PO, Stener-Victorin E. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. *Hum Reprod* 2010;**25**:450–456.

Jones GL, Benes K, Clark TL, Denham R, Holder MG, Haynes TJ, Mulgrew NC, Shepherd KE, Wilkinson VH, Singh M *et al.* The polycystic ovary syndrome health-related quality of life questionnaire (PCOSQ): a validation. *Hum Reprod* 2004;**19**:371–377.

Jorm AF. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychol Med* 2000;**30**:11–22.

Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. *Fertil Steril* 2009;**91**:207–212.

Kumarapeli V, Seneviratne Rde A, Wijeyaratne C. Health-related quality of life and psychological distress in polycystic ovary syndrome: a hidden facet in South Asian women. *BJOG* 2011;**118**:319–328.

Laggari V, Diareme S, Christogiorgos S, Deligeoroglou E, Christopoulos P, Tsiantis J, Creatsas G. Anxiety and depression in adolescents with polycystic ovary syndrome and Mayer-Rokitansky-Kuster-Hauser syndrome. *J Psychosom Obstet Gynaecol* 2009;**30**:83–88.

Li Y, Li Y, Yu Ng EH, Stener-Victorin E, Hou L, Wu T, Han F, Wu X. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil Steril* 2011; **96**:452–458.

Mansson M, Holte J, Landin-Wilhelmsen K, Dahlgren E, Johansson A, Landen M. Women with polycystic ovary syndrome are often depressed or anxious—a case control study. *Psychoneuroendocrinology* 2008;**33**:1132–1138.

Mansson M, Norstrom K, Holte J, Landin-Wilhelmsen K, Dahlgren E, Landen M. Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls. *Eur J Obstet Gynecol Reprod Biol* 2011; **155**:161–165.

March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010;**25**:544–551.

Monzani F, Pucci F, Caraccio N, Bagnolesi A, Molli D, Fenu A, Prunetti C. Psychological and psychopathological correlates in the polycystic ovary syndrome (PCOS). *Medicina Psicosomatica* 1994;**39**:225–236.

Moran L, Gibson-Helm M, Teede H, Deeks A. Polycystic ovary syndrome: a biopsychosocial understanding in young women to improve knowledge and treatment options. *J Psychosom Obstet Gynaecol* 2010;**31**:24–31.

Orenstein H, Raskind MA, Wyllie D, Raskind WH, Soules MR. Polysymptomatic complaints and Briquet's syndrome in polycystic ovary disease. *Am J Psychiatry* 1986;**143**:768–771.

Ozenli Y, Haydardedeoglu B, Micozkadioglu I, Simsek E, Bulgan Kilicdag E, Bagis T. Anxiety, depression and ways of coping skills by women with polycystic ovary syndrome: a controlled study. *J Turkish-German Gynecol Assoc* 2008;**9**:190–194.

Pasco JA, Nicholson GC, Williams LJ, Jacka FN, Henry MJ, Kotowicz MA, Schneider HG, Leonard BE, Berk M. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry* 2010;**197**:372–377.

Pastore LM, Patrie JT, Morris WL, Dalal P, Bray MJ. Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women. *J Psychosom Res* 2011;**71**:270–276.

Percy CA, Gibbs T, Potter L, Boardman S. Nurse-led peer support group: experiences of women with polycystic ovary syndrome. *J Adv Nurs* 2009; **65**:2046–2055.

Rassi A, Veras AB, dos Reis M, Pastore DL, Bruno LM, Bruno RV, de Avila MA, Nardi AE. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. *Compr Psychiatry* 2010;**51**:599–602.

Review Manager. (Computer Program) Version 5.0. Copenhagen: The Cochrane Collaboration, 2008.

Rocco A, Falaschi P, Perrone G, Pancheri P, Rosa M, Zichella L. Psychoneuroendocrine aspects of polycystic ovary syndrome. *J Psychosom Obstet Gynaecol* 1991;**12**:169–180.

Scott KM, Bruffaerts R, Simon GE, Alonso J, Angermeyer M, de Girolamo G, Demyttenaere K, Gasquet I, Haro JM, Karam E *et al.* Obesity and mental disorders in the general population: results from the world mental health surveys. *Int J Obes (Lond)* 2008;**32**:192–200.

Shi X, Zhang L, Fu S. Psychiatric symptoms and monoamine neurotransmitter in serum of PCOS with infertility patients. [Chinese]. *Chin J Clin Psychol* 2008; **16**:294–296.

Simon GE, Goldberg DP, Von Korff M, Ustun TB. Understanding cross-national differences in depression prevalence. *Psychol Med* 2002;**32**:585–594.

Skilton MR, Moulin P, Terra JL, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatry* 2007;**62**:1251–1257.

Snyder BS. The lived experience of women diagnosed with polycystic ovary syndrome. *J Obstet Gynecol Neonatal Nurs* 2006;**35**:385–392.

Sonino N, Fava GA, Mani E, Belluardo P, Boscaro M. Quality of life of hirsute women. *Postgrad Med J* 1993;**69**:186–189.

Soyupek F, Guney M, Eris S, Cerci S, Yildiz S, Mungan T. Evaluation of hand functions in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2008; **24**:571–575.

Soyupek F, Yildiz S, Akkus S, Guney M, Mungan MT, Eris S. The frequency of fibromyalgia syndrome in patients with polycystic ovary syndrome. *J Musculoskeletal Pain* 2010;**31**:168–175.

The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Trent ME, Rich M, Austin SB, Gordon CM. Quality of life in adolescent girls with polycystic ovary syndrome. *Arch Pediatr Adolesc Med* 2002;**156**:556–560.

Trent ME, Rich M, Austin SB, Gordon CM. Fertility concerns and sexual behavior in adolescent girls with polycystic ovary syndrome: implications for quality of life. *J Pediatr Adolesc Gynecol* 2003;**16**:33–37.

Trent M, Austin SB, Rich M, Gordon CM. Overweight status of adolescent girls with polycystic ovary syndrome: body mass index as mediator of quality of life. *Ambul Pediatr* 2005;**5**:107–111.

United Nations. General Assembly, see A/36/215 and resolution 36/28 (1981) http://social.un.org/index/Youth/FAQ.aspx.

United Nations. United Nations Statistics Division, Geographical region and composition (2011) http://unstats.un.org/unsd/methods/m49/m49regin.htm.

van de Velde S, Bracke P, Levecque K. Gender differences in depression in 23 European countries. Cross-national variation in the gender gap in depression. *Soc Sci Med* 2010;**71**:305–313.

Vanhala M, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Koponen H. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. *Acta Psychiatr Scand* 2009;**119**:137–142.

Wang K, Liu Y, Zhang Q, Zhang M. Psychological symptoms and related factors in infertile women with polycystic ovary syndrome. [Chinese]. *Chin Mental Health J* 2009: **23**:22–26.

Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 1995;**33**:AS264–AS279.

Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. *Psychosom Med* 2004;**66**:356–362.

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (2010). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wiltink J, Beutel ME, Till Y, Ojeda FM, Wild PS, Munzel T, Blankenberg S, Michal M. Prevalence of distress, comorbid conditions and well being in the general population. *J Affect Disord* 2011;**130**:429–437.

Zawadski J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR (eds). *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific Publications, 1992.