

BMJ Open Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the evidence on the efficacy of psychosocial interventions for improving pregnancy rates and reducing distress for couples in treatment with assisted reproductive technology (ART).

Design: Systematic review and meta-analysis.

Data sources: PsycINFO, PubMed, EMBASE, CINAHL, Web of Science and The Cochrane Library between 1978 and April 2014.

Study selection: Studies were considered eligible if they evaluated the effect of any psychosocial intervention on clinical pregnancy and/or distress in infertile participants, used a quantitative approach and were published in English.

Data extraction: Study characteristics and results were extracted and the methodological quality was assessed. Effect sizes (ES; Hedges *g*) were pooled using a random effects model. Heterogeneity was assessed using the *Q* statistic and *I*², and publication bias was evaluated using Egger's method. Possible moderators and mediators were explored with meta-analyses of variances (ANOVAs) and meta-regression.

Results: We identified 39 eligible studies (total *N*=2746 men and women) assessing the effects of psychological treatment on pregnancy rates and/or adverse psychological outcomes, including depressive symptoms, anxiety, infertility stress and marital function. Statistically significant and robust overall effects of psychosocial intervention were found for both clinical pregnancy (risk ratio=2.01; CI 1.48 to 2.73; *p*<0.001) and combined psychological outcomes (Hedges *g*=0.59; CI 0.38 to 0.80; *p*=0.001). The pooled ES for psychological outcomes were generally larger for women (*g*: 0.51 to 0.73) than men (0.13 to 0.34), but the difference only reached statistical significance for depressive symptoms (*p*=0.004). Meta-regression indicated that larger reductions in anxiety were associated with greater improvement in pregnancy rates (Slope 0.19; *p*=0.004). No clear-cut differences were found between effects of cognitive-behavioural therapy (CBT; *g*=0.84), mind-body interventions (0.61) and other intervention types (0.50).

Conclusions: The present meta-analysis suggests that psychosocial interventions for couples in treatment for infertility, in particular CBT, could be efficacious, both

Strengths and limitations of this study

- A major strength of this study is the extensive search of various databases from 1978 to April 2014, as well as a comprehensive methodological assessment.
- Further analyses were performed to account for publication bias, yielding conservative effect sizes and thus strengthening the robustness of the estimates.
- Heterogeneity and indications of publication bias were observed for several of the outcomes.
- A substantial variation of the methodological quality and missing information on fertility and assisted reproductive technology (ART) treatment may limit the interpretability of the outcomes.

in reducing psychological distress and in improving clinical pregnancy rates.

INTRODUCTION

Fecundity has become a growing problem for many couples trying to conceive a child, and although not all couples choose to seek medical assistance, more than 10% of the childbearing population has resorted to assisted reproductive technology (ART) to conceive.^{1–5} Being involuntarily childless and going through various ART procedures imposes considerable stress on the couple, and childlessness is often perceived as a life crisis where the emotional strain equals that found for traumatic events.^{2 6–10} Although infertile couples may be considered mentally healthy in general,¹¹ several studies indicate that coping with infertility is associated with periodically heightened levels of psychological symptoms of distress, depression and anxiety.^{12 13} Feelings of loss, grief, anger and sadness are not uncommon, and women

often report bodily disparagement, lack of femininity, shame and self-blame.^{2 14} There is some evidence to suggest that dysregulation in the uterus microenvironment may influence the ability to conceive, for example, oxidative stress and inflammation,^{15 16} which may be promoted by psychological distress.^{17 18} Such findings have led several studies to investigate possible links between mental state and pregnancy outcome.^{10 19–24} Although the results have been mixed, reviews of the literature have generally reached the conclusion that psychosocial factors such as depressive symptoms, anxiety, distress and certain coping strategies are linked to reduced chances of pregnancy.^{12 25 26} Two recently published meta-analyses, however, report conflicting results.^{27 28} Whereas one meta-analysis supported the conclusion that emotional distress may be critical to the success of fertility treatment outcome,²⁷ the other did not find sufficient support for this hypothesis.²⁸ The different conclusions could be due to between-study methodological differences, for example, in the chosen measures of distress and definitions of pregnancy (eg, serum positive test, clinical pregnancy or live birth).

Nonetheless, the evidence indicating a considerable psychosocial burden associated with infertility and its treatment has inspired several researchers to explore the effect of various psychosocial interventions in reducing distress, improving quality of life, and thereby possibly optimising the chances of pregnancy. So far, three meta-analyses have reviewed effects of psychological interventions on mental health and pregnancy outcome. Again, the results have been mixed. The first meta-analysis, published in 2003, concluded that psychological intervention appeared to have a beneficial effect on negative emotions,²⁹ particularly anxiety. An effect of counselling was also found for infertility-related distress, whereas no clear effect was seen on pregnancy rates. Although the original systematic review identified 25 independent studies, the final meta-analysis only included 8–10 studies selected on the basis of their methodological quality. The second meta-analysis published in 2005 focused on differences in effects related to intervention format, for example, individual/couple versus group setting.³⁰ Overall, the results suggested that both individual/couple and group interventions were effective in reducing emotional distress as well as increasing the conception rate. In contrast to the two first meta-analyses, which had investigated both controlled and uncontrolled studies, the third meta-analysis from 2009, which only included controlled studies,³¹ found no evidence for an effect of psychological interventions on emotional distress. An effect, however, was found for pregnancy rates, but only for infertile couples not in ART.

Taken together, while showing promising results, the findings of existing quantitative systematic reviews, the most recent published in 2009, are mixed. The literature within this field is expanding, and studies of new psychosocial intervention approaches building on existing knowledge and targeting specific problems of infertile

patients, for example, mind/body interventions (MBIs), internet-based treatments and online psychoeducation programmes, have since been published. Furthermore, the more recently published studies have generally used randomised controlled trial (RCT) designs, a notable strength reducing the risk of bias and making the studies more easily comparable.³² An updated review and meta-analysis is needed to determine to what degree psychosocial interventions may reduce infertility-related distress related to improvement of pregnancy chances during fertility treatment.

METHODS

The present study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations.^{33 34} An *a priori* designed study protocol guided the literature search, study selection and data synthesis.

Search strategy and criteria

A comprehensive and systematic search of the literature published between 1978 (first baby born after *in vitro* fertilisation (IVF)) and April 2014 was conducted, using a sensitive search strategy recommended for reviews by Higgins and Green.³⁵ When conducting the searches, we combined keywords representing the two primary concepts, infertility and psychosocial treatment: (1) “infertil*”, “childlessness”, “IVF”, “ICSI”, “fertility treatment/problems” “assisted reproduction” and (2) “psychological/psychosocial intervention”, “social support”, “couples therapy”, “psycho-education”, “internet-based intervention” and “behavioral therapy” (for a full search history, see online supplementary appendix 1). We identified relevant records by electronic searches in general medical and psychological databases: PubMed, PsycINFO, The Cochrane Library, EMBASE, CINAHL and Web of Science. Furthermore, we cross-examined reference lists of the retrieved papers and reviews for additional relevant studies. We did not pursue the grey literature or trial registries, and limited our search to include only peer-reviewed articles published in English.

Study selection

Studies were considered eligible if they (1) reported data on infertile participants (2) presented data on a psychosocial intervention or a supportive programme (3) included baseline and postintervention measures of stress, distress or pregnancy outcome and (4) used a quantitative research approach. In general terms, infertility refers to not being able to conceive for more than 1 year without contraception (WHO, 2002). Despite this standard definition, a recent review has found considerable between-study variation in definitions.³⁶ Furthermore, infertility can be graded in relation to clinical diagnosis and duration. The present meta-analysis reviews studies using several different definitions of the term ‘infertile’, and includes all studies of patients

diagnosed with different types of infertility and in different types and stages of ART treatments, for example, intrauterine insemination (IUI), IVF and intracytoplasmic sperm injection (ICSI). 'Psychosocial interventions or supportive programs' were defined as all interventions with a psychosocial aim that did not include the prescription of medication or had a primary physical focus, for example, acupuncture or massage therapy. However, studies using 'psychophysiological' approaches, for example, relaxation, guided imagery or meditation exercises as part of a psychosocial programme, were included. The interventions could be delivered in an individual-based, group-based, couples-based or internet-based format. We included controlled and uncontrolled trial (UCT) studies, but chose to exclude expert opinion, magazines, commentaries, case reports, editorials, newspaper articles, newsletters and book chapters. Neither did we include abstracts-only, doctoral theses or conference presentations. Our primary outcome was pregnancy rate, defined as *clinical pregnancy*. This clinical definition implies a visualisation of at least one gestational sac and fetal heartbeat in approximately the fifth week after fertilisation. Secondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalised stress, specific infertility stress and interpersonal functioning assessed through self-reported questionnaires.

Data extraction and quality assessment

All full-text articles were read by two independent review authors (IF-V, NGS) and the data were extracted according to predefined criteria. Disagreements were discussed with a third author (YF) and resolved by consensus. If information on any outcome was missing or if clarifications were needed, authors were contacted for further information. Each study was assessed for methodological quality using the Jadad criteria,³⁷ a commonly used tool to evaluate methodological quality, for example, use and adequate description of randomisation and blinding procedures, and description of dropout rates (score range 0–5). In addition to the 0–5 points possible on the original Jadad scale, 1 additional point was given for each of the following: (1) *was a control group included*, in order to acknowledge whether the intervention group was compared with another group, although randomisation was not used; (2) *were both predata and postdata presented*, as including preintervention and postintervention data will provide more accurate results; (3) *was any form of blinding or masking of conditions to patients or (4) blinding of researchers attempted*, acknowledging if the study had attempted to mask the active condition; (5) *was a standardised and reliable outcome measure used*, a criterion increasing the validity and comparability of the outcomes and (6) *were pre-post correlations provided*, which could provide better estimates of the effect size (ES). The modified scale yielded a total quality score ranging from 0 to 11. With respect to the modified quality score, the mean score difference between rater 1 and 2

(means (SD) 5.2 (1.8) and 5.6 (2.0)) did not reach statistical significance ($t(77)=1.1$; $p=0.28$), and the inter-rater score correlation was $r=0.83$ ($p<0.001$). The κ Statistic was not used, as this assumes the nominal data and no natural ordering of ratings. Quality ratings were not used as weights when calculating aggregated ES as this is generally discouraged due to the risk of introducing additional bias.³⁸ Instead, associations between ES and study quality indicators were explored with meta-analyses of variances (ANOVAs) and meta-regression (modified quality score). In cases where we were unable to retrieve articles from the authorised databases, authors were contacted between 1 and 3 times in order to amend the data collected.

Calculating ES

The ES used were the risk ratio (RR) for pregnancy and Hedges g for psychological outcomes. Hedges g is a variation of Cohen's d which enables correction of potential bias due to small sample sizes.^{39 40} A positive Hedges g indicates a result in the expected direction, for example, a reduction in distress in the intervention group compared with controls. An $RR>1.0$ indicates a greater proportion of pregnancies in the intervention group. RRs were based on pregnancy rates and total N in the intervention and control groups. When possible, Hedges g was calculated on the basis of reported means and SDs at preintervention and postintervention or means and SDs of change scores. This was possible for 50 of 61 ES. When required and available, the reported pre-post correlations were used in the calculation. This was the case for five ES. When unavailable, the pre-post correlation was set to 0.50. When SDs were unavailable, two approaches were used. For STAI (State-Trait Anxiety Inventory) state anxiety scores, the average pre-SDs and post-SDs (10.9 and 10.8, respectively) for the studies which reported the SD were used, as the SDs appeared to be highly comparable across the remaining studies. For other measures, ES were estimated either on the basis of sample size and either p value or η^2 . In one study reporting only medians,⁴¹ the means and SDs were estimated following a previously suggested approach.⁴²

Heterogeneity

Heterogeneity was assessed using Q and I^2 statistics. Heterogeneity tests are aimed at determining whether results reflect genuine between-study differences (heterogeneity), or whether the variation is due to chance (homogeneity).⁴³ In accordance with recommendations, a p value ≤ 0.10 was used to determine significant heterogeneity due to the general low statistical power of heterogeneity tests.⁴⁴ The I^2 quantity provides a measure of the degree of inconsistency by estimating the amount of variance in a pooled ES that can be accounted for by heterogeneity in the sample of studies.⁴⁵ I^2 values of 0%, 25%, 50% and 75% indicate no, low, moderate and high heterogeneity, respectively.

Analytical strategy

All ES were weighted with the inverse variance and combined with a random effects model. First, the overall ES of the effect of psychosocial interventions on pregnancy rates was calculated. Then the overall ES for the combined psychological outcomes was calculated together with the overall ES for the individual outcome measures of depression, state anxiety, infertility-related distress and marital function. This was performed for the combined sample (women+men). If the results indicated study heterogeneity, and if the number of studies in each category was sufficient ($K \geq 3$), possible between-study differences in ES were explored by comparing the ES of studies according to the following study characteristics: gender, study design, intervention type and intervention format (mixed effect meta-ANOVAs), methodological quality (modified quality score), mean age of the sample, intervention duration and number of sessions (mixed effect meta-regression).

Prior to the search, statistical power analyses were conducted as previously recommended.⁴⁶ On the basis of the findings of the earlier meta-analysis,³¹ we expected to find an RR of 1.4 for pregnancy rates and an average sample size of $N=76$. We expected to be able to detect a similar small ES (Hedges $g=0.28$ or $RR=1.4$) with an α of 5% and a statistical power of 80%, with a total of only nine studies, using a random effects model. On the basis of these results, we considered it worthwhile to conduct the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, V.2 (<http://www.meta-analysis.com>), IBM SPSS V.20 and various formulas in Microsoft Excel.

Publication bias

The possibility of publication bias, a widespread problem when conducting meta-analyses, was evaluated with funnel plots,⁴⁷ Egger's method and by calculating fail-safe numbers.^{48 49} A funnel plot is a graphic illustration of study ES in relation to study size or precision. Egger's test provides a statistic for the skewness of results.⁵⁰ Calculation of fail-safe numbers is aimed at achieving an indication of the number of unpublished studies with null findings that would reduce the result to statistical non-significance ($p > 0.05$). It has been suggested that a reasonable level is achieved if the fail-safe number exceeds $5K+10$ ($K=N$ studies in the meta-analysis).⁵¹ If the results were suggestive of publication bias, an adjusted ES was calculated using Duval and Tweedie's⁵² trim and fill method, which imputes ES of missing studies and recalculates the ES accordingly.

RESULTS

Study selection

In a first screening, duplicates were identified, and titles and abstracts reviewed. A total of 157 studies were found potentially relevant and reviewed independently by two raters. Four articles could not be retrieved due to the

'no access policy from the university, and the authors did not respond to our enquiries'.^{53–56} Initially, the raters were uncertain or disagreed on 13 (8.3%) articles (inter-rater agreement 0.78; $p < 0.001$ (κ statistic)) indicating 'substantial agreement'.⁵⁷ After negotiation, 5 of these were included, resulting in 41 potentially eligible articles. One additional study was excluded due to the combination of psychological intervention with a psychoactive drug, and one study had insufficient statistical data and the authors did not respond to our enquiry. We thus included a total of 39 studies in the present review. On three occasions, the authors provided unpublished additional data.^{58–60} Figure 1 shows a flow chart of the study selection process.

Study characteristics

The study characteristics are summarised in table 1. Based on the outcome, 29 of the studies were aimed at reducing negative emotional distress,^{41 58–85} with the targeted outcomes being infertility-related distress ($k=10$), depression ($k=21$), anxiety ($k=25$) and marital function ($k=5$). Five studies focused solely on the outcome of pregnancy,^{86–90} and five had included distress as well as pregnancy as the outcome.^{78 91–94} Twenty-one studies were RCTs,^{58 61 65–72 74 75 83 85 89–95} and 10 were non-RCTs (NRCTs),^{41 59 60 76 79 80 86–88 96} with most control groups receiving standardised care or being waiting list controls. Only three studies had included an active/attention control condition, for example, non-emotional writing or receiving an information booklet.^{70 71 74} One study offered gift certificates to the control group participants if they responded to the follow-up questionnaires.⁸⁹ Relatively few studies were UCTs ($k=8$).^{62–64 73 77 81 82 84} The reporting of the participants' medical treatment status was inconsistent. Five studies did not provide information on treatment status (whether or not in current ART treatment), 3 reported that some, but not how many, of the participants were in treatment, and 31 reported that their participants were currently in ART treatment, although not what kind of treatment, for example, IUI, IVF/ICSI or treatment cycle. The cause of infertility was also inconsistently reported, and some participants may still have been under evaluation during the study period. Twenty-five studies had included only women, while the remaining 14 had included both women and men. The included studies had reported data for a total of 3401 participants (3064 women and 347 men). The mean age and mean duration of infertility for intervention group participants were (32.7 years, 'SD' 2.2) and (4.6 years, 'SD' 2.1), and for control group participants (32.6 years, 'SD' 1.7) and (5.1 years, 'SD' 3.0), respectively. The specific intervention strategies mostly employed were cognitive-behavioural therapy (CBT; $k=8$) and MBI ($k=12$). The remaining studies had used a variety of interventions, including stress management, hypnosis, art therapy, expressive writing intervention, crisis intervention and various types of counselling. Some studies had included

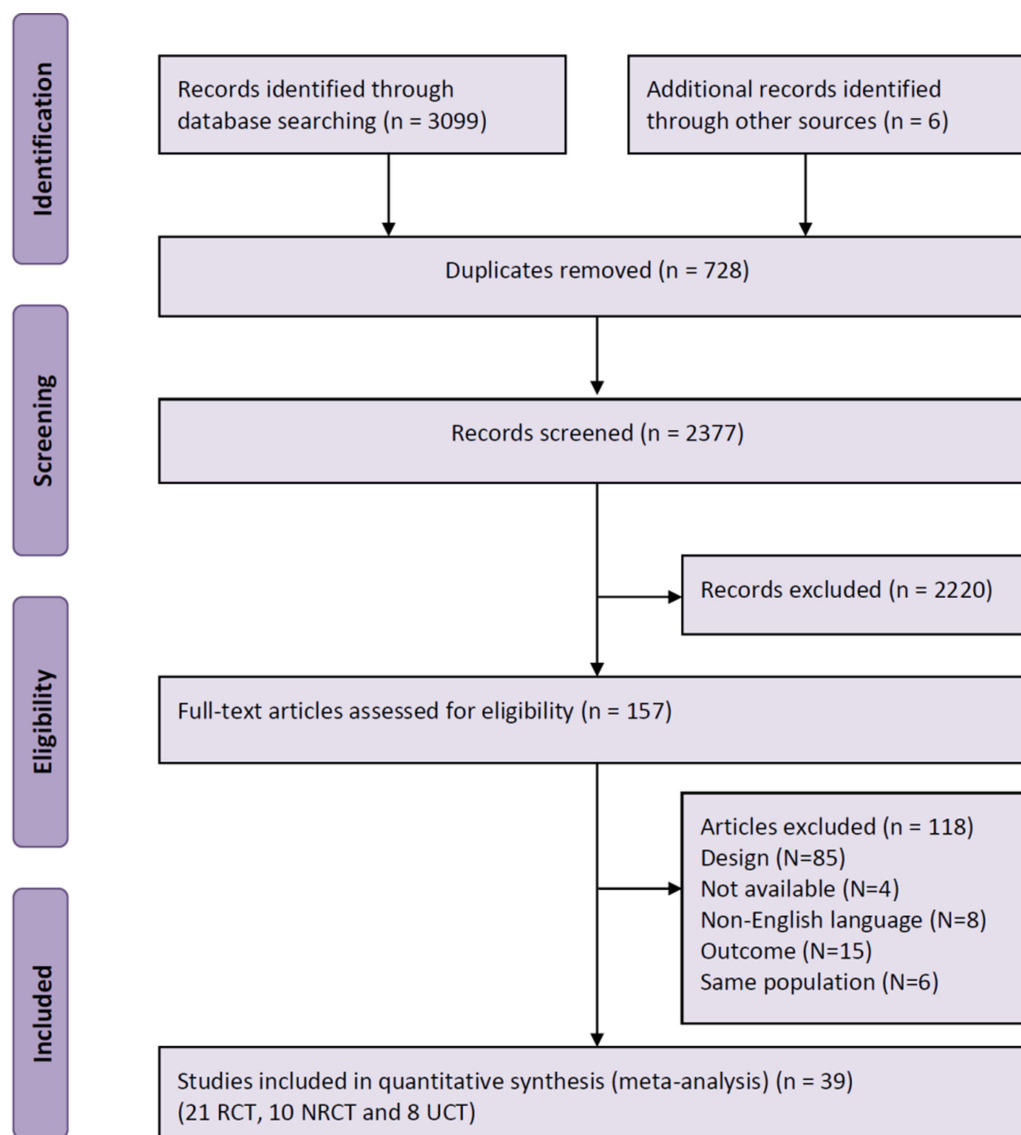


Figure 1 PRISMA flow chart of selection of studies (NRCT, non-randomised controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; UCT, uncontrolled trial).

more than one approach, for example, cognitive-behavioural approaches supplemented with mind-body techniques such as relaxation. To be categorised as MBI, a study had to use such strategies as the general approach over the course of intervention. Thus, if studies had mainly used CBT strategies and only incorporated other approaches, for example, relaxation exercises, in one or two sessions, they were categorised as CBT interventions. The number of sessions ranged from 1 to 24, lasting approximately from 20 min to 3 h, and the duration of psychosocial intervention ranged from 1 week to 28 months.

Attrition

A total of 15 studies reported the number of participants at baseline and then again at follow-up, and as seen in [table 1](#), the number of dropouts varied across studies. Although the dropout rates in the intervention groups

were somewhat higher (mean 30.5% (SD 20.2)) than in controls (24.9% (24.8)), the difference did not reach statistical significance ($t(28) 0.68, p=0.50$). Furthermore, only four studies explicitly stated that the analysis was based on an intention-to-treat (ITT) approach.^{70 72 83 92} Two additional studies used methods comparable to ITT, for example, carrying last (baseline) observations forward or use of multilevel linear modelling.^{69 97} Four studies stated that there were no differences between completers and dropouts without specifying this further,^{41 64 81 85} and the remaining studies failed to report whether there were dropouts or how such missing data were dealt with. The possible association between ES and uneven dropouts in the intervention and control groups was analysed for the 15 studies that reported dropouts by regressing the difference in dropout rates on the overall ES across all outcomes. The result indicated that larger dropouts in the intervention group

Table 1 Characteristics of included studies

Author	Country	Participants (N) I: intervention C: control assigned (final analysis) (men %)	Study design	Intervention type*	Intervention category†	Intervention format	Number of sessions	Intervention duration (weeks)	Outcome: psychological‡ IS: infertility stress A: anxiety D: depression MF: marital function	Outcome: pregnancy§ (+/-)	Quality score¶ J: Jadad 0–5 MJ: modified Jadad 0–12 J (MJ)
O'Moore <i>et al</i> ⁷⁹	Ireland, UK	I: 30 (22) (50%) C: 20 (20) (50%)	NRCT	Autogenic training	MBI	Group	8	8	D: BDI A: STAI	–	1 (4)
Lukse ⁶²	USA	I: 29 (29 (14))	UCT	Counselling	Other	Group	6	6	D: DES	–	0 (3)
Sarrel and DeCherney ⁸⁶	USA	I: 20 (10) C: 20 (9)	NRCT	Psychotherapeutic interview	Other	Couples	1	1		+	0 (1)
Domar <i>et al</i> ⁶³	USA	I: 54 (54)	UCT	Mind/body programme	MBI	Group	10	10	A: STAI	–	0 (3)
Domar <i>et al</i> ⁶⁴	USA	I: 52 (41)	UCT	Behavioural medicine programme for infertility	MBI	Group	10	10	A: STAI	–	1 (3)
Galletly <i>et al</i> ⁸²	Australia	I: 37 (37)	UCT	Treatment programme	Other	Group	24	24	D: HADS A: HADS	–	1 (3)
McQueeney <i>et al</i> ⁸⁰	USA	I: 20 (20) C: 9 (9)	NRCT	Emotion-focused and problem-focused therapies	Other	Group	6	6	IS: ISD D: BDI	–	3 (7)
Tuschen-Caffier <i>et al</i> ⁴¹	Germany	I: 34 (22) C: 24 (24)	NRCT	CBT	CBT	Couples	10–12	32	IS: one item MF: one item	–	1 (4)
Domar <i>et al</i> ^{78 95}	USA	I: 56 (20) C: 63 (14)	RCT	Psychological intervention	MBI	Group	10	10	D: BDI A: STAI	+	4 (10)
Terzioglu ⁹¹	Turkey	I: 60 (60) (50%) C: 60 (60) (50%)	RCT	Counselling	Other	Individual	5	5	D: BDI A: STAI	+	2 (5)
Hosaka <i>et al</i> ⁸⁷	Japan	I: 37 (37) C: 37 (37)	NRCT	Structured intervention	MBI	Group	5	5		+	3 (6)
McNaughton-Cassill <i>et al</i> ⁸⁶	USA	I: 43 (43)(39.5%) C: 37 (37)(48.6%)	NRCT	Couples' support	CBT	Couples	6	3	D: BDI A: BAI	–	2 (5)
Emery <i>et al</i> ⁶⁵	Switzerland	I: 158 (110) (34.8%) C: 152 (131) (42.8%)	RCT	Pre-IVF counselling	Other	Couples	1	1	D: BDI A: STAI	–	3 (6)
Lee ⁶⁶	Taiwan	I: 64 (64) C: 68 (68)	RCT	Nursing crisis intervention programme	MBI	Individual	7	7	D: SDS A: STAI	–	1 (4)
De Klerk <i>et al</i> ⁸²	The Netherlands	I: 22 (18) C: 22 (15)	RCT	Counselling	Other	Group	3	4–5	D: HADS A: HADS	–	3 (6)
Schmidt <i>et al</i> ⁶⁹	Denmark	I: 13 (13) C: 435 (435)	NRCT	Stress management	Other	Group	5	6	IS: COMPI	–	1 (4)
Chan <i>et al</i> ⁶⁷	Hong Kong, China	I: 101 (69) C: 126 (115)	RCT	The Eastern body–mind intervention	MBI	Group	4	4	A: STAI	–	3 (7)
Levitas <i>et al</i> ⁸⁸	Israel	I: 89 (89) C: 96 (96)	NRCT	Hypnosis	MBI	Individual	1	1		+	0 (1)
Nilforooshan <i>et al</i> ⁶⁸	Iran	I: 30 (30)(50%) C: 30 (30)(50%)	RCT	Cognitive–behavioural counselling	CBT	Group	6	6	D: BDI A: BAI	–	2 (6)
Tuil <i>et al</i> ⁶⁸	The Netherlands	I: 108 (102) (50%) C: 96 (78) (48.7%)	RCT	Internet-based health record	Other	Individual	Infinite	2	D: BDI A: STAI	+	3 (6)
Cousineau <i>et al</i> ⁸³	USA	I: 96 (49) C: 92 (49)	RCT	Psycho-educational support	Other	Online	1–2	4	IS: FPI MF: RDAS	–	4 (8)
Faramarzi <i>et al</i> ⁶¹	Iran	I: 42 (29) C: 40 (30)	RCT	CBT	CBT	Group	10	10	D: BDI A: Cattell	–	3 (6)
Lancastle and Boivin ⁶⁹	Wales, UK	I: 28 (28) C: 27 (27)	RCT	Brief coping intervention	Other	Individual	14	2	IS: CIQ	–	4 (8)

Continued

Table 1 Continued

Author	Country	Participants (N) I: intervention C: control assigned (final analysis) (men %)	Study design	Intervention type*	Intervention category†	Intervention format	Number of sessions	Intervention duration (weeks)	Outcome: psychological‡ IS: infertility stress A: anxiety D: depression MF: marital function	Outcome: pregnancy§ (+/-)	Quality score¶ J: Jadad 0–5 MJ: modified Jadad 0–12 J (MJ)
Noorbala <i>et al</i> ⁶⁴	Iran	I: 288 (288)(50%)	UCT	CBT	CBT	Group		24	D: BDI	–	3 (8)
Mori ⁷⁰	Japan	I: 85 (85) C: 40 (40)	RCT	Stress management	Other	Individual	3	12	D: HADS A: HADS	–	4 (8)
Panagopoulou <i>et al</i> ⁷¹	England, UK	I: 50 (50) C: 98 (98)	RCT	Expressive writing intervention	Other	Individual	3	1	IS: ISS A: STAI	+	3 (7)
Haemmerli <i>et al</i> ⁷²	Switzerland	I: 60 (46) C: 64 (41)	RCT	Coaching and support	Other	Online	13	8	IS: IDS D: CES-D A: STAI	–	3 (6)
Sexton <i>et al</i> ⁶⁵	USA	I: 21 (15) C: 22 (16)	RCT	Web-based coping with infertility	Other	Individual		2	IS: FPI	–	3 (6)
Domar <i>et al</i> ⁶⁹	USA	I: 46 (46) C: 51 (51)	RCT	Mind/body programme for infertility	MBI	Group	10	10		+	4 (6)
Hughes and de Silva ⁷³	Canada	I: 21 (21)	UCT	Art therapy	Other	Group	8 (2 h)	8	D: BDI A: BAI	–	0 (2)
Chan <i>et al</i> ⁶⁴	Hong Kong, China	I: 141 (141) C: 110 (110)	RCT	Integrative body–mind– spirit intervention	MBI	Group	4 (3 h)	4	A: STAI MF: C-KMS	+	3 (6)
Gorayeb <i>et al</i> ⁶⁰	Brazil	I: 93 (93) C: 95 (95)	RCT	Brief cognitive– behavioural intervention	CBT	Group	5 (2 h)	5		+	1 (4)
Koszycski <i>et al</i> ⁶¹	Canada	I: 31 (23)	UCT	Interpersonal and supportive therapy	Other	Individual	12 (50 min)	12	IS: FPI D: BDI HAM-D	–	3 (7)
Matthiesen <i>et al</i> ⁷⁴	Denmark	I: 42 (15) C: 40 (16)	RCT	Expressive writing intervention	Other	Individual	3 (20 min)	1	IS: COMPI	–	4 (8)
Mosalanejad <i>et al</i> ^{75 76}	Iran	I: 32 (32) C: 33 (33)	RCT	Cognitive–behavioural treatment	CBT	Group	12 (2 h)	12	D: DASS A: DASS	–	1 (4)
Mosalanejad <i>et al</i> ^{75 76}	Iran	I: 16 (16) C: 15 (15)	NRCT	CBT	CBT	Group	15 (1.5 h)	16	D: DASS A: DASS	–	2 (5)
Catoire <i>et al</i> ⁷⁷	France	I: 50 (50)	UCT	Hypnosis	MBI	Individual	4	1	A: STAI	–	4 (7)
Galhardo <i>et al</i> ⁶⁷	Portugal	I: 55 (55) C: 37 (37)	NRCT	Mindfulness-based programme for infertility	MBI	Group	10 (2 h)	10	IS: ISE D: BDI A: STAI	–	1 (4)
Vizheh <i>et al</i> ⁶³	Iran	I: 86 (86) (50%) C: 94 (86) (54.7%)	RCT	Marital counselling	Other	Group	3 (1.5hrs)	3	MF: MSQ	–	4 (8)

*Self-reported intervention type.

†Intervention type: CBT; MBI: mindfulness, yoga, relaxation, imagery, hypnosis, etc; Other: all other intervention types, for example, counselling, psychoeducation, supportive therapy, expressive writing intervention, brief therapy, emotion and problem focused therapy, and narrative therapy.

‡Outcome measures: *Infertility stress*: CIQ, the Coping with Infertility Questionnaire; COMPI, the Copenhagen Multi-centre Psychosocial Infertility problem stress scale; FPI, Fertility Problem Index; IDS, Infertility Distress Scale; ISD, Infertility-Specific Distress and Well-being; ISE, Infertility Self-efficacy Scale; ISS, the Infertility and Strain Scale—*Depression*: BDI, the Beck Depression Inventory; CES-D, the Center for Epidemiologic Studies Depression—short version; DES, The Differential Emotion Scale; DASS, the Depression and Anxiety Stress Scale—depression; HADS, the Hospital Anxiety and Depression Scale; SDS, Zung's Self-administered Depression Scale—*Anxiety*: BAI, the Beck Anxiety Inventory; Cattell, Cattell Anxiety Inventory; DASS, the Depression and Anxiety Stress Scale—anxiety; HAM-D, Hamilton Depression Rating Scale—subscale anxiety; STAI, Spielberger State-Trait Anxiety Inventory—*Marital function*: C-KMS, Kansas Marital Satisfaction Scale—Chinese version RDAS (Revised Dyadic Adjustment Scale)—dyadic cohesion subscale; MSQ, Marital Satisfaction Questionnaire.

§*Pregnancy* is defined as a clinical pregnancy when the heartbeat of the fetal sac is evident in the uterus with an ultrasound scan.

¶*Jadad range 0–5* an assessment tool rating the quality and methodology of the studies included³⁷ and the *modified Jadad range 0–11 (total score)* included additional points for: inclusion of a control group, pre–post data, blinding of participants or researchers, use of standardised and reliable outcome measures and report of pre–post correlations.

CBT, cognitive–behavioural therapy; IVF, in vitro fertilisation; MBI, mind/body intervention; NRCT, non-randomised controlled trial; RCT, randomised controlled trial; UCT, uncontrolled trial (pre–post).

compared were generally associated with smaller ES (Slope=-0.02), but the association did not reach statistical significance ($p=0.268$).

Quality ratings

All included studies were methodologically assessed with the original Jadad scale and the additional methodological criteria. The original Jadad scores ranged from 0 to 4 with a mean of 2.28 (SD 1.36), and the modified total quality scores ranged from 1 to 10 with a mean of 5.36 (SD 2.05). The main methodological issue was that only very few studies attempted to blind or mask the intervention conditions to either patients or researchers. The quality ratings for each criterion for each study and total scores are shown in [table 2](#).

Effects of psychosocial intervention

The results of the meta-analyses are shown in [table 3](#).

Pregnancy rates

A statistically significant and robust ES (RR=2.01) was found for the 10 studies which had investigated effects of psychosocial intervention on clinical pregnancy rates, with the chance of becoming pregnant being doubled in the intervention group. Adjusting for possible publication bias, the RR was somewhat lower (1.57). A forest plot of the effects of psychological intervention on pregnancy outcomes is shown in [figure 2](#).

Combined psychological outcomes

Combining the ES of the 35 studies which had included one or more psychological outcomes revealed a statistically significant, robust,⁵¹ medium³⁹ ES ($g=0.59$). The results indicated possible publication bias (skewed funnel plot, Egger's test ($p<0.05$)) in favour of larger published ES. When imputing missing ES,⁵² the resulting adjusted pooled ES was smaller (0.31) but remained statistically significant. Taking gender into consideration, the ES (0.51) remained statistically significant for women, still suggesting a robust effect. The ES was smaller for men (0.34) and did not reach statistical significance. A forest plot of the effects of psychological intervention on the combined psychological outcomes is shown in [figure 3](#).

Infertility-related distress

Only 10 studies had included infertility-related distress as an outcome. Small ES were found for women and men combined (0.24) and women alone (0.37) and did not reach statistical significance.

Depression

Twenty-one studies had assessed depressive symptoms. A statistically significant ES (1.00) was found for women and men combined. However, when adjusting for possible publication bias, the results changed dramatically to a small, non-significant ES of 0.31. Similar results were found for women alone with a statistically

significant ES of 0.73, which was reduced to a non-significant 0.29 after adjusting for possible publication bias. For men alone, the ES (0.13) did not reach statistical significance.

State anxiety

Twenty-five studies had included state anxiety as an outcome. A statistically significant, robust medium ES (0.51) was found for women and men combined. Adjusting for possible publication bias led to a smaller but statistically significant ES (0.31). For women, the ES of 0.53 was statistically significant, but smaller (0.32) and non-significant when adjusting for publication bias. For men only, the analysis produced a small, non-significant ES of 0.32.

Marital function

Only five studies (N=633) had included measures of marital function, but only very small (ES 0.09–0.08), non-significant effects were found.

Possible moderators

As the Q statistics were generally statistically significant ($p<0.10$) and the I^2 statistic indicated low-to-medium heterogeneity, when a sufficient number of studies were available for each analysis, we explored possible sources of heterogeneity and analysed whether the ES for pregnancy and combined psychological outcomes varied according to between-study differences in study design and intervention characteristics (type and format). The results are shown in [table 3](#).

Study design

The ES found for pregnancy outcomes were statistically significant for RCTs (RR=1.7) and NRCTs (2.8), with the ES for NRCTs being considerably smaller (1.9) when adjusting for publication bias. The difference did not reach statistical significance. For psychological outcomes, statistically significant results were found for RCTs ($g=0.70$) and UCTs (0.55), but not for NRCTs (0.28). When adjusting for publication bias, the ES for RCTs was considerably reduced (0.26). Furthermore, between-group differences did not reach statistical significance.

Intervention type

The number of studies for each intervention type was insufficient to explore differences in pregnancy outcomes. For the combined psychological outcomes, statistically significant and, as indicated by the large fail-safe numbers, robust effects were found for all three intervention categories with the largest ES found for CBT ($g=0.84$), followed by MBI (0.61) and other intervention types (0.50). The between-group differences, did not reach statistical significance. Furthermore, the results suggested the possibility of publication bias, and when adjusting for publication bias, all three ES were reduced from medium to small.

Table 2 Modified Jadad scores (original Jadad criteria +6 additional criteria)

Study	Jadad criteria							Additional criteria						Jadad scores	Total scores
	1	2	3	4	5	6	7	a	b	c	d	e	f		
	Randomised	Double blind	Withdrawals and dropouts	Randomisation (evaluation)	Blinding (evaluation)	Randomisation (evaluation)	Blinding (evaluation)	Control group	Preassessment and postassessment	Blinding (patients)	Blinding (researchers)	Standardised and reliable outcome	Pre-post correlation		
O'Moore <i>et al</i> ⁷⁹	0	0	1	0	0	0	0	1	1	0	0	1	0	1	4
Lukse ⁶²	0	0	0	0	0	0	0	0	1	0	0	1	1	0	3
Sarrel and DeCherney ⁸⁶	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Domar <i>et al</i> ⁶³	0	0	0	0	0	0	0	0	1	0	0	1	1	0	3
Domar <i>et al</i> ⁶⁴	0	0	1	0	0	0	0	0	1	0	0	1	0	1	3
Galletly <i>et al</i> ⁸²	0	0	1	0	0	0	0	0	1	0	0	1	0	1	3
McQueeney <i>et al</i> ⁸⁰	1	0	0	1	1	0	0	1	1	1	0	1	0	3	7
Tuschen-Caffier <i>et al</i> ⁴¹	0	0	1	0	0	0	0	1	1	0	0	1	0	1	4
Domar <i>et al</i> ^{78 95}	1	1	1	1	0	0	0	1	1	1	1	1	1	4	10
Terzioglu ⁹¹	1	0	1	0	0	0	0	1	1	0	0	1	0	2	5
Hosaka <i>et al</i> ⁸⁷	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
McNaughton-Casill <i>et al</i> ^{86*}	1	0	1	0	0	0	0	1	1	0	0	1	0	2	5
Emery <i>et al</i> ⁶⁵	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Lee ⁸⁶	1	0	0	0	0	0	0	1	1	0	0	1	0	1	4
De Klerk <i>et al</i> ⁸²	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Schmidt <i>et al</i> ⁸⁹	0	0	1	0	0	0	0	1	1	0	0	1	0	1	4
Chan <i>et al</i> ⁸⁷	1	0	1	1	0	0	0	1	1	0	0	1	1	3	7
Levitas <i>et al</i> ⁸⁸	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Nilforooshan <i>et al</i> ⁸⁸	1	0	1	0	0	0	0	1	1	0	0	1	1	2	6
Tuil <i>et al</i> ⁸⁸	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Cousineau <i>et al</i> ⁸³	1	0	1	1	1	0	0	1	1	1	0	1	0	4	8
Faramarzi <i>et al</i> ⁶¹	1	0	1	0	0	0	0	1	1	0	0	1	1	2	6
Lancastle and Boivin ⁶⁹	1	0	1	1	1	0	0	1	1	1	0	1	0	4	8
Noorbala <i>et al</i> ^{84*}	1	0	0	1	1	0	0	1	1	0	0	1	0	3	6
Mori ⁷⁰	1	0	1	1	1	0	0	1	1	1	0	1	0	4	8
Panagopoulou <i>et al</i> ⁷¹	1	0	1	0	1	0	0	1	1	1	0	1	0	3	7
Haemmerli <i>et al</i> ⁷²	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Sexton <i>et al</i> ⁸⁵	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Domar <i>et al</i> ⁸⁹	1	0	1	1	1	0	0	1	0	0	1	0	0	4	6
Hughes and de Silva ⁷³	0	0	0	0	0	0	0	0	1	0	0	1	0	0	2
Chan <i>et al</i> ⁸⁴	1	0	1	1	0	0	0	1	1	0	0	1	0	3	6
Gorayeb <i>et al</i> ⁹⁰	1	0	1	1	0	0	0	1	0	0	0	0	0	3	4
Koszycki <i>et al</i> ⁸¹	1	0	1	1	0	0	0	1	1	1	0	1	0	3	7
Matthiesen <i>et al</i> ⁷⁴	1	0	1	1	1	0	0	1	1	1	0	1	0	4	8
Mosalanejad <i>et al</i> ^{75 76}	1	0	0	0	0	0	0	1	1	0	0	1	0	1	4
Mosalanejad <i>et al</i> ^{75 76}	0	0	1	0	0	0	0	1	1	0	0	1	0	1	4
Catoire <i>et al</i> ^{77*}	0	0	0	0	0	0	0	0	1	0	1	1	0	0	3
Galhardo <i>et al</i> ⁸⁷	0	0	1	0	0	0	0	1	1	0	0	1	0	1	4
Vizheh <i>et al</i> ⁸³	1	0	1	1	1	0	0	1	1	0	1	1	0	4	8

Criteria 1–7 in bold font are the original Jadad scores, a–f are the additional criteria. (1) Was the study described as randomised; (2) Was the study described as double blind; (3) Was there a description of withdrawals and dropouts; (4) The method of randomisation was described, and appropriate; (5) The method of blinding was described, and appropriate; (6) The method of randomisation was described, but inappropriate; (7) The method of blinding was described, but inappropriate; (a) The study included a control group; (b) The study included preassessment and postassessment; (c) There was an attempt of blinding or masking the active condition to patients; (d) There was an attempt of blinding the researchers; (e) The study used standardised and reliable outcome measures and (f) The study reported pre-post correlation.

*In these studies, the original Jadad score and the modified quality score relate to the methodological quality of the published study. For the purpose of the meta-analyses, some of the groups were collapsed or omitted, for example, if they compared two or more interventions or compared a psychological intervention with a medical treatment, thereby changing design status as shown in table 1.

Table 3 Results of meta-analyses of effects of psychosocial intervention on psychological outcomes and pregnancy rates among infertile couples

	Sample size		Heterogeneity*		p Value	I ²	Global ES		p Value	Fail-safe numbers‡	Criterion§
	K	N	Q	df			Hedges g†	95% CI			
Main effects											
Pregnancy											
Pregnancy, women	10	1324	22.0	9	0.009	59.0	2.01 (RR)	1.48 to 2.73	<0.001	130	60
Adjusted for publication bias	(13)	—	—	—	—	—	1.57 (RR)	1.10 to 2.25	<0.05	—	—
Psych. combined, women+men	35	2746	259.2	34	<0.001	86.9	0.59	0.38 to 0.80	<0.001	1552	185
Adjusted for publication bias	(42)¶	—	—	—	—	—	0.31	0.07 to 0.56	<0.05	—	—
Psych. combined, women	28	2076	130.8	27	<0.001	76.4	0.51	0.32 to 0.70	<0.001	798	150
Adjusted for publication bias	(34)¶	—	—	—	—	—	0.30	0.09 to 0.51	<0.05	—	—
Psych. combined, men	7	347	8.9	6	0.178	32.8	0.34	0.08 to 0.59	0.010	12	45
Between-group** (women vs men)	35	2110	1.2	1	NS	—	—	—	—	—	—
Infertility distress											
Infertility distress, women+men	10	615	21.4	9	0.01	58.0	0.24	−0.02 to 0.50	NS	—	—
Infertility distress, women	6	371	17.8	5	0.003	71.8	0.37	−0.06 to 0.79	NS	—	—
Depressive symptoms											
Depression symptom, women+men	21	1558	367.5	20	<0.001	94.6	1.00	0.54 to 1.45	<0.001	1022	115
Adjusted for publication bias	(25)¶	—	—	—	—	—	0.31	−0.20 to 0.84	NS	—	—
Depressive symptom, women	17	992	107.7	16	<0.001	85.1	0.73	0.41 to 1.06	<0.001	393	95
Adjusted for publication bias	(23)¶	—	—	—	—	—	0.29	−0.07 to 0.65	NS	—	—
Depressive symptom, men	5	243	1.9	4	0.749	0.00	0.13	−0.11 to 0.37	NS	—	—
Between-group** (women vs men)	22	1235	8.5	1	<0.004	—	—	—	—	—	—
Anxiety											
Anxiety, women+men	25	2159	144.4	24	<0.001	83.4	0.51	0.31 to 0.71	<0.001	760	135
Adjusted for publication bias	(29)¶	—	—	—	—	—	0.31	0.07 to 0.54	<0.05	—	—
Anxiety, women	23	1737	114.3	22	<0.001	80.8	0.53	0.32 to 0.73	<0.001	631	125
Adjusted for publication bias	(27)¶	—	—	—	—	—	0.32	0.08 to 0.57	<0.05	—	—
Anxiety, men	5	246	8.7	4	0.070	53.8	0.32	−0.04 to 0.67	NS	—	—
Between-group** (women vs men)	28	1983	1.0	1	NS	—	—	—	—	—	—
Marital function											
Marital function, women+men	5	633	14.6	4	0.006	72.6	0.09	−0.23 to 0.41	NS	—	—
Marital function, women	4	587	14.5	3	0.002	79.3	0.08	−0.30 to 0.46	NS	—	—
Moderator analyses											
Pregnancy (women)											
Study design††											
RCT	6	856	10.8	5	0.057	53.5	1.67 (RR)	1.17 to 2.40	<0.05	22	40
NRCT	4	468	7.9	3	0.048	62.1	2.80 (RR)	1.55 to 5.06	<0.001	31	30
Adjusted for publication bias	(6)¶	—	—	—	—	—	1.93 (RR)	1.07 to 3.49	<0.05	—	—
Between-group**	10	1324	2.1	1	NS	—	—	—	—	—	—
Intervention format											
Group	5	691	10.9	4	0.027	63.4	2.03 (RR)	1.29 to 3.20	<0.01	28	35
Individual	4	433	2.2	3	0.531	0.0	1.65 (RR)	1.26 to 2.17	<0.001	8	30
Between-group**	9	1124	0.5	1	NS	—	—	—	—	—	—

Continued

Table 3 Continued

	Sample size K	N	Heterogeneity*		p Value	I ²	Global ES		p Value	Fail-safe numbers‡	Criterion§
			Q	df			Hedges g†	95% CI			
Psychological outcomes combined (women+men)											
Study design††											
RCT	20	2185	232.4	19	<0.001	91.8	0.70	0.36 to 1.03	<0.001	642	110
<i>Adjusted for publication bias</i>	<i>(24)¶</i>	—	—	—	—	—	<i>0.26</i>	<i>−0.10 to 0.68</i>	<i>NS</i>	—	—
NRCT	8	450	14.9	7	0.037	53.1	0.28	−0.00 to 0.57	NS	—	—
UCT	7	215	6.0	6	0.424	0.0	0.55	0.40 to 0.70	<0.001	90	45
<i>Adjusted for publication bias</i>	<i>(10)¶</i>	—	—	—	—	—	<i>0.51</i>	<i>0.36 to 0.66</i>	<i><0.05</i>	—	—
Between-group**	35	2850	3.9	2	NS	—	—	—	—	—	—
Intervention types											
CBT	7	475	39.0	6	<0.001	84.6	0.84	0.33 to 1.35	0.001	107	45
<i>Adjusted for publication bias</i>	<i>(10)¶</i>	—	—	—	—	—	<i>0.37</i>	<i>−0.19 to 0.93</i>	<i>NS</i>	—	—
MBI	9	841	57.7	8	<0.001	86.1	0.61	0.17 to 0.65	<0.001	158	55
<i>Adjusted for publication bias</i>	<i>(10)¶</i>	—	—	—	—	—	<i>0.42</i>	<i>0.01 to 0.84</i>	<i><0.05</i>	—	—
Other	19	1430	149.2	9	<0.001	87.9	0.50	0.18 to 0.81	0.002	246	105
<i>Adjusted for publication bias</i>	<i>(24)¶</i>	—	—	—	—	—	<i>0.17</i>	<i>−0.20 to 0.54</i>	<i>NS</i>	—	—
Between-group**	35	2746	1.3	2	NS	—	—	—	—	—	—
Intervention format											
Group	20	1484	87.2	19	<0.001	78.2	0.76	0.55 to 0.98	<0.001	959	110
<i>Adjusted for publication bias</i>	<i>(26)¶</i>	—	—	—	—	—	<i>0.50</i>	<i>0.25 to 0.75</i>	<i><0.05</i>	—	—
Individual	9	834	17.7	8	0.023	54.9	0.13	−0.08 to 0.35	NS	—	—
Couples	3	284	92.3	2	<0.001	97.8	1.07	−1.02 to 3.16	NS	—	—
Online	3	248	1.2	2	0.541	0.00	0.03	−0.22 to 0.28	NS	—	—
Between-group**	35	2850	24.5	3	<0.001	—	—	—	—	—	—

*Q statistic: p values<0.1 taken to suggest heterogeneity. I² statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity) and 75% (high heterogeneity).

†ESR=Hedges g. Standardised mean difference, adjusting for small sample bias. A positive value indicates an ES in the hypothesised direction, that is, reduced pain or relatively smaller increase in pain in the intervention group. All ES were combined using a random effects model. To ensure independency, if a study reported results for more than one pain measure, the ES were combined (mean), ensuring that only one ES per study was used in the calculation.

‡Fail-safe number=number of non-significant studies that would bring the p value to non-significant (p>0.05).

§A fail-safe number exceeding the criterion (5×k+10) indicates a robust result.⁹⁸

¶If analyses indicated the possibility of publication bias, missing studies were imputed and an adjusted ESR was calculated (italics); (K) indicates the number of published studies+number of imputed studies.

**Meta-ANOVA (between-study comparisons).

††RCT, NRCT and UCT.

ANOVA, analysis of variance; CBT, cognitive-behavioural therapy; ES, effect size; MBI, mind/body intervention; NRCT, non-randomised controlled trial; NS, not significant; Psych, psychological outcomes; RCT, randomised controlled trial; RR, risk ratio; UCT, uncontrolled trial (pre-post).

Pregnancy rates

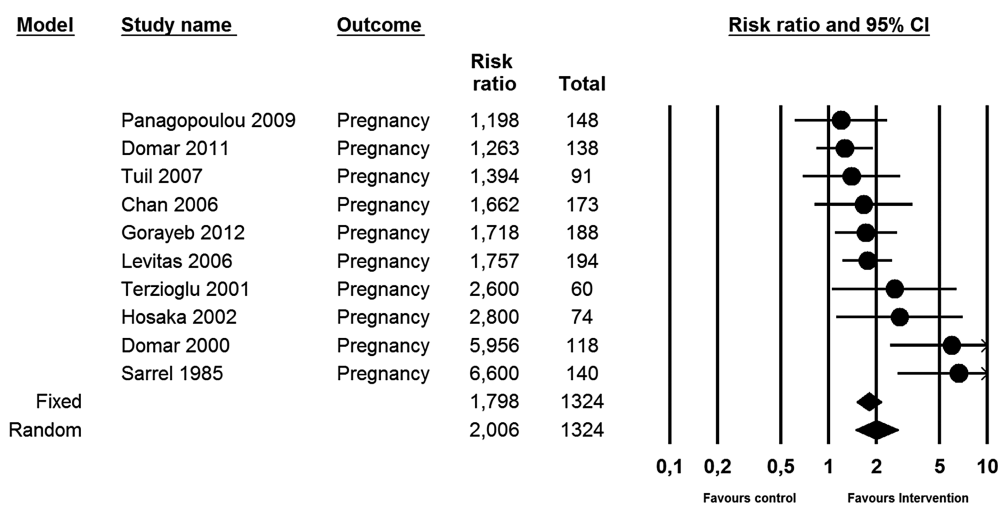


Figure 2 Effects of psychosocial intervention on pregnancy rates.

Combined psychological outcomes

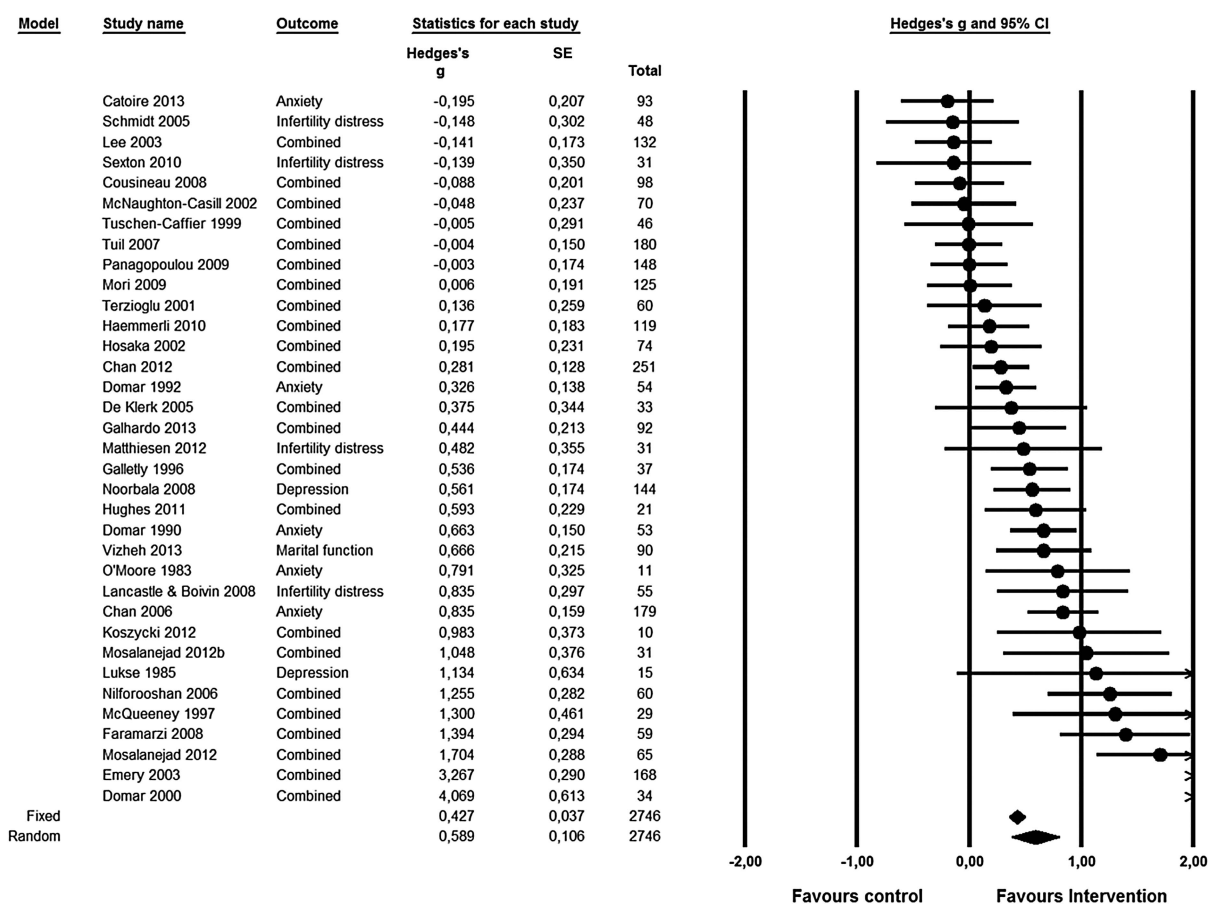


Figure 3 Effects of psychosocial intervention on combined psychological outcomes.

Intervention format

For pregnancy outcomes, the number of studies was sufficient for group and individual formats. Both formats yielded statistically significant ES (RR 2.03 and 1.65), and the between-group difference did not reach statistical significance. For the combined psychological outcomes, a statistically significant effect was found for the Group format ($g=0.76$; $p<0.001$). The ES for intervention formats such as individual, couples and online did not reach statistical significance. The overall between-group difference for intervention formats was statistically significant ($p<0.001$).

Other study characteristics

The possible moderating influence of the continuously assessed study characteristics of mean age, intervention duration, number or sessions, and study quality (modified quality scores) were analysed with meta-regression. As seen in table 4, no significant effects were found for any of the moderators for either pregnancy or the combined psychological outcomes. A total of six studies had examined the effects on pregnancy and anxiety. When examining the possible role of anxiety reduction as a mediator of the effect on pregnancy outcome with meta-regression, a statistically significant association was found between the ES for anxiety and pregnancy, indicating that the greater the reduction in anxiety, the greater the likelihood of achieving pregnancy (see table 4).

DISCUSSION

Primary findings

Our meta-analysis of the available evidence suggests that women who receive some form of psychological intervention are approximately twice as likely to become pregnant when compared with controls receiving standardised care or active control intervention. Although the results of the 10 currently available studies taken together appeared robust, there were some indications of publication bias in favour of studies with larger positive ES. It should also be noted that the precision of the

ES estimate is limited, with possible RRs ranging from approximately 1.5 to 2.7. Furthermore, although the between-group difference did not reach statistical significance when disregarding the possibility of publication bias, NRCTs yielded greater effects (RR 2.8 (95% CI 1.55 to 5.06)) than RCTs (RR 1.7 (95% CI 1.17 to 2.40)). Compared with other types of interventions that historically have been introduced to improve pregnancy rates in ART (improved culture media, new hormone stimulation regimens, etc), even an effect corresponding to the lower limit of the CI is substantial. While the results could be considered surprising, the available data do not provide any clear-cut reasons to reject this finding, which is further supported by the results of the meta-regression showing that larger reductions in anxiety were associated with improved pregnancy outcomes. With respect to the psychological outcomes currently reported in the literature, the results suggest that psychological intervention could be effective in reducing anxiety (25 studies) as well as depressive symptoms (21 studies) with the effects corresponding to medium and large ES (0.5 and 1.0). As seen for pregnancy outcomes, there were indications of publication bias in the direction of larger positive effects, and adjusting for publication bias resulted in a considerably smaller, statistically non-significant, ES for depressive symptoms. The pooled results did not reach statistical significance for the 10 studies which had investigated effects on infertility-related distress and the 5 studies which had included measures of marital function.

Comparing with results of previous reviews

The present review included 39 studies with a total of 3401 women (3064) and men (347). The participants received various psychosocial interventions lasting from 1 week to 6 months, including CBT, emotional disclosure, psychoeducation and MBIs. The present review evaluates almost twice the number of studies included in the most recent previous review,³¹ which reported mixed results of the efficacy of psychosocial intervention.

Table 4 Results of meta-regression analyses

Dependent variable	Independent variable	K	β^*	95% CI	p Value
Pregnancy	ES—anxiety	6	0.19	0.06 to 0.31	0.004
	Mean age	9	−0.05	−0.19 to 0.10	0.534
	Intervention duration	9	0.01	−0.03 to 0.06	0.669
	Number of sessions	9	−0.00	−0.08 to 1.07	0.922
	Study quality (quality scores)†	10	−0.02	−0.09 to 0.04	0.477
Psych. combined	Mean age	32	−0.05	−0.12 to −0.02	0.214
	Intervention duration	32	0.01	−0.02 to 0.04	0.518
	Number of sessions	27	0.03	−0.01 to 0.07	0.150
	Study quality (quality scores)†‡	35	−0.02	−0.06 to 0.02	0.415

*Mixed effects regression: unrestricted maximum likelihood.

†Modified Jadad quality score.

‡p Values for individual psychological outcomes; 0.09 (anxiety)–0.58 (depression).

Bold typeface indicates a significant result.

ES, effect size; Psych, psychological outcomes.

Whereas the former review found no evidence for attenuating distress, there was promising support of psychological intervention increasing pregnancy chances for women not receiving ART.³¹ In line with the second review from 2005,³⁰ we found more credible results for group intervention than for other formats, for example, online, individual and couples interventions.³⁰ The first review published in 2003 also highlighted group interventions as more effective, especially if the interventions emphasised education and skills training, such as relaxation. Our results concurred with these earlier observations, suggesting that interventions delivered in groups may be more effective in reducing distress. Moreover, although the comparison did not reach statistical significance, prior to adjusting for publication bias, the intervention type of CBT appeared to be more effective than MBI and other types of interventions. It should be noted that the categorisation of interventions may be somewhat ambiguous. For example, the study by Cousineau *et al*⁸³ could have been categorised as an MBI, as the authors had provided a website that directed attention towards relaxation exercises. However, as there was no reporting of whether the participants were engaged in weekly or daily training, we chose to interpret relaxation as an optional feature, and hence the study was not categorised as an MBI. The possible ambiguity and considerable variability in interventions forced us to categorise many studies as 'other', which limits our understanding of the possible mechanisms in psychosocial interventions. Taken together, the available data do not provide a clear basis for understanding the possible differences between effects of different intervention types, and the results should be interpreted with caution. The more recently conducted studies included in the present review have contributed by increasing the size of the available data set considerably, and taken together, the currently available evidence suggests that offering psychosocial interventions may improve both the chances of pregnancy and the quality of life for infertile patients going through fertility treatment.

Strengths and limitations

Our systematic review and meta-analysis has several strengths. We conducted a comprehensive search and performed the review in accordance with the recommended guidelines.³⁴ In order to limit the possibility of selection bias, we encouraged authors of eligible studies to elaborate on their results if the data reported were insufficient, and asked authors of papers written in a foreign language to submit their results to us in English. The included studies represented a range of different countries, have used comparable outcome measures, and provided fairly comprehensive descriptions of the interventions studied. In addition, we conducted a detailed evaluation of the methodological quality in order to detect any issues that could possibly affect the accuracy of the ES calculated. While not all characteristics, in particular reproductive, could be assessed; most

general methodological aspects were covered. We also explored heterogeneity and made adjustments for possible publication bias, when required.

Some limitations of the currently available data should also be noted. First, the samples investigated may not have been as homogeneous as could be wished for. A small number of infertile participants did not receive treatment with ART, and furthermore, it was not consistently reported what type of ART procedure the participants received, what phase or treatment they were in, or the causes of infertility. This information is clearly important when interpreting the outcomes, and unknown between-study and within-study between-group differences, for example, in numbers of cycles, idiopathic infertility and embryo transfer, may have influenced the results, in particular for pregnancy outcomes. However, such differences are likely to be less important in RCTs, where randomisation is expected to reduce their influence. Although the difference did not reach statistical significance, RCTs reported smaller ES for pregnancy outcomes than NRCTs, which could be interpreted as supporting the concern that infertility and treatment characteristics may have been unevenly distributed between psychological treatment arms, thus increasing the risk for misattribution of outcomes to intervention, at least for NRCTs. On the other hand, we found no statistically significant associations between study quality scores and either pregnancy or psychological outcomes, no statistically significant differences in dropout rates between intervention and control groups, and, as suggested by the large fail-safe numbers, the improvements generally appeared quite robust. A second possible limitation is the high level of heterogeneity indicated by the Q and I^2 statistics, and the pooled ES reported in the present review should thus be viewed as an estimate of the average expected effect across a wide range of different settings. A third issue is that the considerable dropout rates and lack of ITT analyses may have influenced the results, and it cannot be excluded that fertility-related and treatment-related factors such as non-optimal fertilisation, small number of eggs, etc, may have demotivated some participants and made them dropout of the study, while individuals who progressed through the treatment phases with more satisfactory outcomes were more likely to complete the study. Fourth, the indications of publication bias found for several results suggest the possibility of a 'file drawer problem', that is, the existence of relevant unpublished null findings, a common problem when conducting systematic reviews. Finally, owing to inconsistencies in the reporting of causes of infertility, we are unable to evaluate the possible associations between ES and causes of infertility. Although meta-analysis remains the gold standard when evaluating the current evidence within a field of research, as is often the case with systematic reviews, qualitative as well as quantitative, the overall level of the evidence reported in our review may be challenged by publication bias and the heterogeneity and methodological limitations of the available published studies.

Clinical and practical implications

We found evidence for improvement in general psychological symptoms such as anxiety and depression, but not for infertility-specific distress. A possible explanation for the latter could be the lack of sensitivity of the infertility-related distress measures used. The questions used in these measures are directly concerned with thoughts and feelings about involuntary childlessness, and rumination about the involuntary childlessness may persist even when psychosocial intervention improves general psychological well-being. Of particular interest is the result of our meta-regression analysis of the six studies which had included both pregnancy and anxiety as outcomes showing that larger reductions in anxiety were associated with greater chances of pregnancy. Anxiety is a state of arousal, which over time is physically and mentally stressful for the individual.¹⁷ Reducing distress, anxiety in particular, may increase the physiological ability to cope with stress and advance the possibility of impregnation. We found no association between mean age and pregnancy rates outcomes, which may seem surprising, since age is the most important predictor of pregnancy outcomes of ART.^{99 100} However, our meta-regression was conducted for the mean age of the *samples*, and the mean age across study samples showed little variation (mean age 32.7; SD 2.4). The rather narrow age interval across study samples may explain an apparent lack of association between age and chance of pregnancy. Our findings also suggest that group interventions appear to be more efficacious than individual, couples or online interventions. There could be various reasons for this. First, group interventions had a longer duration (mean 9.5 weeks) and involved more sessions (8.3) than individual interventions (mean 5.3 and 4.4), and second, there is evidence of a positive impact of 'group settings', that is, the sense of community between participants, reducing the feelings of isolation or alienation and sharing with individuals in the same life situation, etc.^{101–104}

Recommendations for future research

Despite the overall positive effects of psychosocial interventions found in the literature, our results suggest a need for further studies with more rigorous methodology, including more strict reporting of causes of infertility, the types of ART used, and which phases of treatment the participants are in. Also, most of the studies were conducted in high-income countries; it is therefore important to note that the assertions made here cannot be generalised to low-income and developing countries. There is thus a need for research in low-income or developing countries as well. Another aspect pertaining to generalisability is the challenge of comparing volunteering infertile participants in psychosocial efficacy studies with the general population of infertile individuals. The response rates in this area are moderate, and it seems important in future studies to explore and compare characteristics of dropouts and completers, as well as of

non-responders and responders. Furthermore, it would be of importance to develop clinically meaningful categories of distress with the purpose of improving interventions targeted to the various types and levels of distress experienced by the participants. Psychological well-being/distress fluctuates over time during fertility treatment and a stepped care approach could be potentially valuable in this population.¹⁰⁵ It is also possible that interventions aimed at relieving distress conducted at different phases in treatment may obtain different psychological outcome results. This calls for improved reporting and comparability of the timing of psychosocial interventions and greater precision and comparability of the timing of outcome assessments. Also needed are studies testing specific hypotheses concerning possible moderating and mediating mechanisms of the effects of interventions on distress and pregnancy outcomes. For example, which psychosocial factors do we need to target to optimise effects on distress and pregnancy rates, and which biomarkers affected by psychosocial interventions, for example, oxidative stress, inflammatory processes, can best explain the observed effects? This could assist in developing a more solid evidence base providing better guidance for patients, health professionals and policy-makers about 'what works for whom' in infertile patients.

CONCLUSIONS

In conclusion, the present meta-analysis of 39 studies suggests that psychosocial interventions, in particular CBT and MBI interventions, are beneficial for reducing distress and for improving pregnancy outcomes of ART. Moreover, there is some preliminary evidence to suggest that reduction in anxiety achieved through psychological intervention may improve the chance of pregnancy. Despite the robust overall effect found, the considerable heterogeneity of the available studies with respect to methodological quality, intervention type and format still warrants caution as to the conclusions which can be drawn.

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Contributors RZ and YF designed the protocol. YF developed search strategies and IF-V, NGS and YF performed the searches and study selection. YF and IF-V undertook data extraction and quality assessments. RZ was responsible for analysing the data. YF drafted the manuscript and IF-V, NGS, HJL and RZ contributed to the manuscript throughout the process. All authors provided inputs and were involved with the interpretation of this review. YF is the study guarantor.

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Complete search history

(1978 – April 2014)

	PsycInfo	Pubmed	Cochrane	Embase	Web of Science	Cinahl
Search 1:						
#1 infertil*	1686	69.582	2878	143.265	45.208	4425
#2 childlessness	427	557	9	715	767	113
#3 "IVF"	321	17.130	2505	27.748	19.434	651
#4 "ICSI"	54	5489	1106	14.179	7453	135
#5 "fertility treatment"	78	664	70	1215	747	149
#6 "fertility Problems"	78	89	44	862	674	79
#7 "in vitro fertil*"	412	8742	1894	101.673	22.836	761
#8 "intracytoplasmic sperm injection"	30	4889	723	13.027	7683	146
#9 "assisted reproduction"	176	4623	613	10.218	5963	277
#10 "assisted reproductive techn*"	218	6903	280	10.913	6250	505
#11 (#1 - #10:OR)	2560	91.369	5752	202.041	75.747	5571
Search 2:						
#12 "psychological intervention"	1330	1040	537	1807	1300	339
#13 "psychosocial intervention"	1047	1002	486	1504	1230	376
#14 "social support"	30.469	58.658	3454	61.497	36.355	10.702
#15 "couples therapy"	1895	495	114	2543	477	75
#16 psychoeducation	3551	1285	486	4419	1835	1560
#17 psychotherapy	119.862	159.004	7493	180.754	47.223	12.808
#18 "CBT"	5663	5017	2131	10.338	6326	1360
#19 "cognitive-behavior* therapy"	13.914	1259	3706	32.160	13.056	2358

#20 "cognitive-behavior* intervention"	750	9	389	18	791	194
#21 mindfulness	2912	1743	536	2555	3156	854
#22 "acceptance and commitment therapy"	512	214	95	387	382	64
#23 "emotion-focused"	1377	796	83	969	1063	448
#24 psychoanalysis	51.485	11.421	81	28432	16.717	627
# 25 "relational therapy"	82	20	2	31	32	4
#26 relaxation	9334	107.502	6121	116.625	305.797	6933
#27 hypnosis	10.571	12.898	1063	11.503	7490	1850
#28 hypnotherapy	3506	13.068	217	1206	1122	226
#29 "internet-based therapy"	26	22	12	36	29	6
#30 "internet-based intervention"	107	121	66	124	129	32
#31 "web-based therapy"	15	7	2	12	14	3
#32 "web-based intervention"	135	218	117	249	257	68
#33 (#12 - #32:OR)	219.898	327.062	20.473	379.392	429.409	36.993
Search 3:	311	593	77	1708	328	82

Total of all searches

	Initial search (combination 1+2)	Additional records	Excluded (due to duplicates)	Excluded (due to title + abstract)	Final** (articles coded individually)
All databases	3099	6	728	2220	157

- Additional records identified n=6