BMJ Open

# Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: A systematic review and meta-analysis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2014-006592 |
| Article Type: | Research |
| Date Submitted by the Author: | 11-Sep-2014 |
| Complete List of Authors: | Frederiksen, Yoon; Aarhus University, Department of Psychology and Social Sciences<br>Farver-Vestergaard, Ingeborg; Aarhus University, Department of Psychology<br>Skovgård, Ninna; Aarhus University Hospital, Skejby Fertility Clinic<br>Ingerslev, Hans Jakob; Aarhus University Hospital, Center for Preimplantation Genetic Diagnosis/The Fertility Clinic<br>Zachariae, Robert; Aarhus University Hospital, Department of Oncology; Aarhus University, Department of Psychology |
| Primary Subject Heading: | Evidence based practice |
| Secondary Subject Heading: | Reproductive medicine |
| Keywords: | Infertility, Psychosocial intervention, distress, pregnancy |
| | |

# Title Page

| **Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: A systematic review and meta-analysis** |
|---|
| Yoon Frederiksen, Ingeborg Farver-Vestergaard, Ninna Grønhøj Skovgård, Hans Jakob Ingerslev, Robert Zachariae |
| Unit for Psychooncology and Health Psychology, Department of Psychology, University of Aarhus, 8000 Aarhus, Denmark Yoon Frederiksen MSc. Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, University of Aarhus, 8000 Aarhus, Denmark Ingeborg Farver-Vestergaard MSc., Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, Aarhus University, 8000 Aarhus, Denmark Ninna Grønhøj Skovgaard, research assistant, Skejby Fertility Clinic, Aarhus University Hospital, 8200 Aarhus Denmark. Hans Jakob Ingerslev, Professor, MD, DMSc, Unit for Psychooncology and Health Psychology, Department of Psychology, Aarhus University, 8000 Aarhus, Denmark Department of Oncology, Aarhus University Hospital, 8000 Aarhus Denmark Robert Zachariae, DMSci., professor. |
| Correspondence to: Yoon Frederiksen yoonf@psy.au.dk Phone no. +45 8716 5872 |
| Keywords: infertility/psychosocial intervention/distress/pregnancy |
| Word count: 4.852 |
|  |
| Competing interest: All authors have completed the Unified Competing Interest form and are available upon request from the Corresponding Author |

## 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 assessed. Effect sizes (Hedges *g*) were pooled using a random effect model. Heterogeneity was assessed using the *Q* statistic and $I^2$, and publication bias evaluated using Eggers' method. Possible moderators and mediators were explored with meta-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, marital function. Statistically significant and robust overall effects of psychosocial intervention were found for both clinical pregnancy (RR = 2.01; CI: 1.48-2.73; $p<0.001$) and psychological outcomes (Hedges $g=0.59$; CI: 0.38-0.80; $p=0.001$,). The pooled effect sizes (ES) for psychological outcomes were generally larger for women (*g*: 0.51-0.73) than men (0.13-0.34), but the difference only reached statistical significance for depressive symptoms ($p=0.004$). Cognitive behavioral therapy (CBT) ($g=1.15$) appeared more effective than mind-body interventions ($g=0.41$), but the difference did not reach statistical significance. Finally, meta-regression indicated that larger reductions in anxiety were associated with greater improvement in pregnancy rates (Slope: 0.19; $p=0.004$).

**Conclusion** The present meta-analysis suggests that psychosocial interventions for couples in treatment for infertility, in particular CBT, could be efficacious, both in reducing psychological distress and in improving clinical pregnancy rates.


## 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 an extended detailed methodological assessment
- Further analyses were performed to account for publication bias, yielding conservative effect sizes and thus strengthening the robustness of the estimates
- Substantial variation of the methodological quality may have influenced the interpretation of the outcomes
- Heterogeneity was observed for several of the outcomes

## 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, e.g. oxidative stress and inflammation, , [15,16] which may be promoted by psychological distress.[17,18] Such findings have lead several studies to investigate possible links between mental state and pregnancy outcome.[10,19-24] Although study 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.[25-27] Two recently published meta-analyses, however, report conflicting results.[28,29] Whereas one meta-analysis supported the conclusion that emotional distress may be critical to the success of fertility treatment outcome,[28] the other did not find sufficient support for

this hypothesis.[29] The different conclusions could be due to methodological issues, e.g. the chosen measures of distress and definitions of *pregnancy* (e.g. 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, possibly, optimize the chances of pregnancy.

So far, three systematic reviews and meta-analyses have presented results 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,[30] anxiety in particular. An effect of counseling 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, e.g. individual/couple vs. group setting.[31] Overall, the results indicated that both individual/couple and group interventions were effective in reducing emotional distress as well as possibly 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,[32] found no evidence for an effect of psychological interventions on emotional distress. An effect, however, was found for pregnancy rates, but only for 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 new psychosocial intervention approaches building on existing knowledge and targeting specif-

ic problems of infertile patients, e.g. mind/body interventions, web-based treatments, and online psycho-education programs, have been evaluated. Furthermore, the more recently published studies have generally used randomized controlled trial designs, a notable strength reducing the risk of bias and making the studies more easily comparable.[33] An updated review and meta-analysis is needed to determine to which 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 guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations.[34,35] 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 fertilization) and April 2014 was conducted, using a sensitive search strategy recommended for reviews by Higgins and Green.[36] When conducting the searches, we combined keywords from the two primary concepts, infertility and psychosocial treatment: (i) "infertil*", "childlessness", "IVF", "ICSI", "fertility treatment/problems" "assisted reproduction" and (ii) "psychological/psychosocial intervention", "social support", "couples therapy", "psycho-education", "internet-based intervention" and "behavioral therapy" (for a full search history, see 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 program 3) included both baseline and post-intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research approach. In general terms, infertility refers to not being able to conceive for more than one year without contraception (WHO, 2002). Despite this standard definition, a recent review has found considerable between-study variation in definitions.[37] Furthermore, infertility can be graded in relation to clinical diagnosis and duration. This present meta-analysis includes studies using various definitions of the term "infertile", i.e. all studies including patients diagnosed with infertility, but in different types and stages of ART treatments, such as intrauterine insemination, in vitro fertilization and intracytoplasmic sperm injection, as well as in different cycles. "Psychosocial interventions or supportive programs" were defined as all interventions with a psychosocial aim that did not include the prescription of medication nor had a primary physical focus, e.g. acupuncture or massage therapy. However, studies using e.g. relaxation, guided imagery or meditation exercises as part of a psychosocial program were included. The interventions could be delivered in individual-, group-, couples-, or internet-based format and did not need to involve face-to-face interaction. We included both controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines, commentaries, case reports, editorials, newspaper articles, newsletters, and books chapters. Neither did we include abstracts-only or conference posters. Our primary outcome was pregnancy rate, defined as *clinical pregnancy*. This clinical definition implies a visualization of at least one gestational sack and fetal heartbeat in approximately the 5$^{th}$ week after fertilization. Secondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalized 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 (IFV, NGS) and data extracted according to predefined criteria. Disagreements were discussed with a third author (YF) and resolved by consensus. If specification of 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,[38] a tool to evaluate methodological quality, e.g. use and adequate description of randomization- and blinding procedures, and description of drop-out rates (score range: 0-5). In addition to the 0-5 points possible on the original Jadad scale, one additional point was given for each of the following: (a) was a control group included (b) were both pre- and post-data presented (c) was any form of blinding of patients, or (d) researchers attempted, (e) was standardized and reliable outcome measure used, and (g) were the pre-post correlations provided. The modified scale yielded a total quality score ranging from 0-12. With respect to the modified Jadad score, the mean score difference (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). Kappa 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 effect sizes (ES) as this is generally discouraged.[39] Instead, associations between ESs and study quality indicators were explored with meta-ANOVAs (design) and meta-regression (modified Jadad-score). In cases where we were unable to retrieve articles from the authorized databases, authors were contacted between 1-3 times in order to amend the data collected.

**Calculating effect sizes**

The effect sizes 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 size.[40,41] A positive Hedges' $g$ indicates result in the expected direction, e.g. a reduction in distress in the intervention group compared to controls. A 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 (k=10) (k = number of studies). When possible, Hedges' *g* was calculated on the basis of reported means and SDs at pre and post-intervention or means and SDs of change scores. This was possible for 50 of 61 effect sizes. When required and available, the reported pre-post correlations were used in the calculation. This was the case for 5 ES's. When unavailable, the pre-post correlation was set to 0.50. When SD's were unavailable, two approaches were used. For STAI state anxiety scores, the average pre- and post SD (10.9 and 10.8) for the studies which reported the SD was used, as the SD's appeared to be highly comparable across the remaining studies. For other measures, ES's were estimated either on the basis of sample size and either p-value or Eta square. In one study reporting only medians,[42] the means and SD's were estimated following a previously suggested approach.[43]

**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).[44,45,45] In accordance with recommendations, a $p$-value $\leq 0.10$ was used to determine significant heterogeneity due to the general low statistical power of heterogeneity tests.[46] 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.[47] $I^2$ values of 0%, 25%, 50%, and 75% indicate no, low, moderate, and high heterogeneity, respectively.

**Analytical strategy**

All ESs 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 ESs for the individual outcome measures of depression, state anxiety, infertility-related distress, and marital function. This was done for the combined sample (women + men). If the results indicated

study heterogeneity, and if the number of studies in each category was sufficient (K≥3), possible between-study differences in ESs were explored by comparing the ESs of studies according to the following study characteristics: gender, study design, intervention type, and intervention format (mixed effect meta-ANOVAs), methodological quality (Jadad 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 recommended.[48] Based on the findings of the earlier meta-analysis, [32] we assumed to find a 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 alpha of 5% and a statistical power of 80%, with a total of only 9 studies, using a random-effects model. Based on these results, we considered it worthwhile to conduct the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2 (www.meta-analysis.com), SPSS-20, and various formulas in Excel.

**Publication bias**

The possibility of publication bias, a widespread problem when conducting meta-analyses, was evaluated with funnel plots,[49] Egger's method, and by calculating fail-safe numbers.[50,51] A funnel plot is a graphic illustration of study ESs in relation to study size or precision. Egger's test provides a statistic for the skewness of results.[52] 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).[53] If the results were suggestive of publication bias, an adjusted ES was calculated using Duval and Tweedie's trim and fill method,[54] which imputes ESs 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 "no access" policy from the university, and the authors did not respond to our enquiries.[55-58] Initially, the raters were uncertain or disagreed on 13 (8.3%) articles (inter-rater agreement: 0.78; $p < 0.001$ (Kappa statistic)) indicating "substantial agreement.[59] 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 authors provided unpublished additional data.[60-62] Figure 1 shows a flow chart of the study selection process.

(Insert Figure 1 near here)

## Study characteristics

Based on outcome, 29 of the studies were aimed at reducing negative emotional distress,[60-87] 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,[88-92] and 5 studies had included distress as well as pregnancy as outcome.[93-97] Twenty studies were randomized controlled trials,[63,71,72,74,76,78,86,91,94,96,98-107] eleven studies included control groups,[42,62,70,88-90,108-111] with most control groups receiving standardized care or being waiting-list controls. Only three studies had included an active/attention control condition, e.g. non-emotional writing or receiving an information booklet.[78,79,107] One study offered gift certificates to the control group participants if they responded to the follow-up questionnaires.[91] Relatively few studies were uncontrolled (k=8).[64-66,83,87,112-114] The reporting of the participants' medical treatment status was inconsistent. Seven

studies did not provide information on treatment status (whether or not in current ART treatment), 5 studies reported that some of the participants were in treatment, but not how many of them, and 27 studies reported that their participants were currently in ART treatment. Twenty-five studies had included only women, while the remaining 14 studies 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 was (32.7 yrs. SD 2.2) and (4.6 yrs. SD 2.1) and for control group participants (32.6 yrs. SD=1.7) and (5.1 yrs. SD=3.0). The intervention strategies mostly employed were cognitive behavioral therapy (k=9), supportive psycho-education (k=8), mind/body intervention (k=7), stress management (k=5), and general counselling (k=8). The number of sessions ranged from 1 to 24, lasting approximately from 20 minutes to 3 hours and the duration of psychosocial intervention ranged from 1 week to 28 months. The study characteristics are summarized in Table 1.

**Table 1**

General characteristics of included studies

| Author | Country | Participants (N) I: Intervention C: Control assigned (final analysis) (men %) | Study design[a] | Intervention category[b] | Intervention format (Group, Couples, Individual or Online) | Number of sessions | Intervention duration (weeks) | Outcome: Psychological[c] IS: Infertility stress A: Anxiety D: Depression MF: Marital function | Outcome: Pregnancy[d] (+/-) | Quality score[e] J: Jadad 0-5 MJ: Modified Jadad 0-12 J (MJ) |
|---|---|---|---|---|---|---|---|---|---|---|
| O'Moore et al. 1983 | Ireland, UK | I: 30 (22) (50 %) C: 20 (20) (50 %) | NRCT | MBI | Group | 8 | 8 | D: BDI A: STAI | - | 1 (4) |
| Lukse 1985 | USA | I: 29 (29 (14)) | UCT | CSG | Group | 6 | 6 | D: DES | - | 0 (3) |
| Sarrel and DeCherney 1985 | USA | I: 20 (10) C: 20 (9) | NRCT | CSG | Couples | 1 | 1 | | + | 0 (1) |
| Domar et al. 1990 | USA | I: 54 (54) | UCT | MBI | Group | 10 | 10 | A: STAI | - | 0 (3) |
| Domar et al. 1992 | USA | I: 52 (41) | UCT | MBI | Group | 10 | 10 | A: STAI | - | 1 (3) |
| Galletly et al. 1996 | Australia | I: 37 (37) | UCT | CSG | Group | 24 | 24 | D: HADS A: HADS | - | 1 (3) |
| McQueeney et al. 1997 | USA | I: 20 (20) C: 9 (9) | NRCT | CSG | Group | 6 | 6 | IS: ISD D: BDI | - | 3 (7) |
| Tuschen-Caffier et al. 1999 | Germany | I: 34 (22) C: 24 (24) | NRCT | CBT | Couples | 10-12 | 32 | IS: one question MF: one question | - | 1 (4) |
| Domar et al. 2000 | USA | I: 56 (20) C: 63 (14) | RCT | CBT | Group | 10 | 10 | D: BDI A: STAI | + | 4 (10) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Terzioglu 2001 | Turkey | I: 60 (60) (50 %) C: 60 (60) (50 %) | RCT | CSG | Individual | 5 | 5 | D: BDI A: STAI | + | 2 (5) |
| Hosaka et al. 2002 | Japan | I: 37 (37) C: 37 (37) | NRCT | CSG | Group | 5 | 5 | | + | 3 (6) |
| McNaughton-Cassill et al. 2002 | USA | I: 43 (43) (39.5 %) C: 37 (37) (48.6 %) | NRCT | CBT | Couples | 6 | 3 | D: BDI A: BAI | - | 2 (5) |
| Emery et al. 2003 | Switzerland | I: 158 (110) (34.8 %) C: 152 (131) (42.8 %) | RCT | CSG | Couples | 1 | 1 | D: BDI A: STAI | - | 3 (6) |
| Lee 2003 | Taiwan | I: 64 (64) C: 68(68) | RCT | MBI | Individual | 7 | 7 | D: SDS A: STAI | - | 1 (4) |
| De Klerk et al. 2005 | The Netherlands | I: 22 (18) C: 22 (15) | RCT | CSG | Group | 3 | 4-5 | D: HADS A: HADS | + | 3 (6) |
| Schmidt et al. 2005 | Denmark | I: 13 (13) C: 435 (435) | NRCT | CSG | Group | 5 | 6 | IS: COMPI | - | 1 (4) |
| Chan et al. 2006 | Hong Kong, China | I: 101 (69) C: 126 (115) | RCT | MBI | Group | 4 | 4 | A: STAI | - | 3 (7) |
| Levitas et al. 2006 | Israel | I: 89 (89) C: 96 (96) | NRCT | MBI | Individual | 1 | 1 | | + | 0 (1) |
| Nilforooshan et al. 2006 | Iran | I: 30 (30) (50 %) C: 30 (30) (50 %) | RCT | CBT | Group | 6 | 6 | D: BDI A: BAI | - | 2 (6) |
| Tuil et al. 2007 | The Netherlands | I: 108 (102) (50 %) C: 96 (78) (48.7 %) | RCT | CSG | Individual | infinite | 2 | D: BDI A: STAI | - | 3 (6) |
| Cousineau et al. 2008 | USA | I: 96 (49) C: 92 (49) | RCT | CSG | Online | 1-2 | 4 | IS: FPI MF: RDAS | - | 4 (8) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Faramarzi et al. 2008 | Iran | I: 42 (29) C: 40 (30) | RCT | CBT | Group | 10 | 10 | D: BDI A: Cattell | - | 3 (6) |
| Lancastle and Boivin 2008 | Wales, UK | XXX | RCT/UCT | CSG | Individual | 14 | 2 | IS: CIQ | - | 4 (8) |
| Noorbala et al. 2008 | Iran | I: 288 (288) (50 %) | UCT | CBT | Group | | 24 | D: BDI | - | 3 (8) |
| Mori 2009 | Japan | I: 85 (85) C: 40 (40) | RCT | CSG | Individual | 3 | 12 | D: HADS A: HADS | - | 4 (8) |
| Panagopoulou et al. 2009 | England, UK | I: 50 (50) C: 98 (98) | RCT | CSG | Individual | 3 | 1 | IS: ISS A: STAI | - | 3 (7) |
| Haemmerli et al. 2010 | Switzerland | I: 60 (46) C: 64 (41) | RCT | CSG | Online | 13 | 8 | IS: IDS D: CES-D A: STAI | - | 3 (6) |
| Sexton et al. 2010 | USA | I: 21 (15) C: 22 (16) | RCT | CSG | Individual | | 2 | IS: FPI | - | 3 (6) |
| Domar et al. 2011 | USA | I: 46 (46) C: 51(51) | RCT | MBI | Group | 10 | 10 | | + | 4 (6) |
| Hughes and Mann de Silva 2011 | Canada | I: 21 (21) | UCT | CSG | Group | 8 (2hrs) | 8 | D: BDI A: BAI | - | 0 (2) |
| Chan et al. 2012 | Hong Kong, China | I: 141 (141) C: 110 (110) | RCT | MBI | Group | 4 (3hrs) | 4 | A: STAI MF: C-KMS | + | 3 (6) |
| Gorayeb et al. 2012 | Brazil | I: 93 (93) C: 95 (95) | NRCT | CBT | Group | 5 (2hrs) | 5 | | + | 1 (4) |
| Koszycki et al. 2012 | Canada | I: 31 (23) | UCT | CSG | Individual | 12 (50min) | 12 | IS: FPI D: BDI HAM-D | - | 3 (7) |
| Matthiesen et al. 2012 | Denmark | I: 42 (15) C: 40 (16) | RCT | CSG | Individual | 3 (20min) | 1 | IS: COMPI | - | 4 (8) |
| Mosalanejad et al. 2012 | Iran | I: 32 (32) C: 33 (33) | RCT | CBT | Group | 12 (2hrs) | 12 | D: DASS A: DASS | - | 1 (4) |
| Mosalanejad et al. 2012b | Iran | I: 16 (16) C: 15 (15) | NRCT | CBT | Group | 15 (1,5hrs) | 16 | D: DASS A: DASS | - | 2 (5) |
| Catoire et al. 2013 | France | I: 50 (50) | UCT | MBI | Individual | 4 | 1 | A: STAI | - | 4 (7) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Galhardo et al. 2013 | Portugal | I: 55 (55) C: 37 (37) | NRCT | MBI | Group | 10 (2hrs) | 10 | IS: ISE D: BDI A: STAI | - | 1 (4) |
| Vizheh et al. 2013 | Iran | I: 86 (86) (50 %) C: 94 (86) (54.7 %) | RCT | CSG | Group | 3 (1.5hrs) | 3 | MF: MSQ | + | 4 (8) |

a) *RCT* Randomized controlled trial, *NRCT* non-randomized controlled trial, *UCT* uncontrolled pre-post trial, *NR* Not reported.

b) Intervention type: *MIB* Mind/body intervention: mindfulness, yoga, relaxation, imagery, hypnosis etc., *CBT* Cognitive behavioral therapy, *CSG* Counselling: psycho-education, supportive therapy, expressive writing intervention, brief therapy, emotion and problem focused therapy, and narrative therapy.

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

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

e) *Jadad range 0-5* an assessment tool rating the quality and methodology of the studies included[1] and the *modified Jadad range 0-12(total score)* included additional points for: inclusion of a control group, pre-post data, blinding of participants or researchers, use of standardized and reliable outcome measures and report of pre-post correlations.

**Effects of psychosocial intervention**

The results of the meta-analyses are summarized in Table 2.

**Table 2**

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

| | Sample size | | Heterogeneity[a] | | | | Global effect sizes | | | Failsafe N[c] | Criterion[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | K | N | Q | df | *p* | $I^2$ | Hedges g[b] | 95 % CI | *p* | | |
| **MAIN EFFECTS** | | | | | | | | | | | |
| Pregnancy | | | | | | | | | | | |
| Pregnancy, women | 10 | 1194 | 22.0 | 9 | =0.009 | 59.0 | 2.01 (RR) | 1.48 – 2.73 | <0.001 | 130 | 60 |
| *Adjusted for publication bias* | *(13)* | - | - | - | - | - | *1.57 (RR)* | *1.10 – 2.25* | *<0.05* | - | - |
| Psych. combined, women+men | 35 | 2746 | 259.2 | 34 | <0.001 | 86.9 | 0.59 | 0.38 – 0.80 | <0.001 | 1552 | 185 |
| *Adjusted for publication bias* | *(42)*[e] | - | - | - | - | - | *0,31* | *0.07 – 0.56* | *<0.05* | - | - |
| Psych. combined, women | 28 | 2076 | 130.8 | 27 | <0.001 | 76.4 | 0.51 | 0.32 – 0.70 | <0.001 | 798 | 150 |
| *Adjusted for publication bias* | *(34)*[e] | - | - | - | - | - | *0.30* | *0.09 – 0.51* | *<0.05* | - | - |
| Psych. combined, men | 7 | 347 | 8,9 | 6 | =0.178 | 32.8 | 0.34 | 0.08 – 0.59 | =0.010 | 12 | 45 |
| Between-group[f] (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 – 0.50 | ns | - | - |
| Infertility distress, women | 6 | 371 | 17.8 | 5 | =0.003 | 71.8 | 0.37 | -0.06 – 0.79 | ns | - | - |
| Depressive symptoms | | | | | | | | | | | |
| Depression symp., women+men | 21 | 1558 | 367.5 | 20 | <0.001 | 94.6 | 1.00 | 0.54 – 1.45 | <0.001 | 1022 | 115 |
| *Adjusted for publication bias* | *(25)*[e] | - | - | - | - | - | *0.31* | *-0.20 – 0.84* | *ns* | - | - |
| Depressive symp.,women | 17 | 992 | 107.7 | 16 | <0.001 | 85.1 | 0.73 | 0.41 – 1.06 | <0.001 | 393 | 95 |
| *Adjusted for publication bias* | *(23)*[e] | - | - | - | - | - | *0.29* | *-0.07 – 0.65* | *ns* | - | - |
| Depressive symp., men | 5 | 243 | 1.9 | 4 | =0.749 | 0.00 | 0.13 | -0.11 – 0.37 | ns | - | - |
| Between-group[f] (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 – 0.71 | <0.001 | 760 | 135 |
| *Adjusted for publication bias* | *(29)*[e] | - | - | - | - | - | *0.31* | *0.07 – 0.54* | *<0.05* | - | - |
| Anxiety, women | 23 | 1737 | 114.3 | 22 | <0.001 | 80.8 | 0.53 | 0.32 – 0.73 | <0.001 | 631 | 125 |
| *Adjusted for publication bias* | *(27)*[e] | - | - | - | - | - | *0.32* | *0.08 – 0.57* | *<0.05* | - | - |
| Anxiety, men | 5 | 246 | 8.7 | 4 | =0.070 | 53.8 | 0.32 | -0.04 – 0.67 | ns | - | - |
| Between-group[f] (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 – 0.41 | ns | - | - |
| Marital function, women | 4 | 587 | 14.5 | 3 | =0.002 | 79.3 | 0.08 | -0.30 – 0.46 | ns | - | - |
| **MODERATOR ANALYSES** | | | | | | | | | | | |
| **Pregnancy (women)** | | | | | | | | | | | |
| **Study design**[h] | | | | | | | | | | | |
| RCT | 5 | 668 | 11.5 | 4 | =0.066 | 62.1 | 1.70 (RR) | 1.06 – 2.72 | < 0.05 | 12 | 35 |
| NRCT | 5 | 656 | 8.1 | 4 | =0.032 | 54.7 | 2.37 (RR) | 1.57 – 3.60 | < 0.001 | 46 | 35 |
| Between group[f] | 10 | 1324 | 1.1 | 1 | ns | - | - | - | - | - | - |
| **Intervention format** | | | | | | | | | | | |
| Group | 5 | 691 | 10.9 | 4 | =0.027 | 63.4 | 2.03 (RR) | 1.29 – 3.20 | < 0.01 | 28 | 35 |
| Individual | 4 | 433 | 2.2 | 3 | =0.531 | 0.0 | 1.65 (RR) | 1.26 – 2.17 | < 0.001 | 8 | 30 |
| Between group[f] | 9 | 1124 | 0.5 | 1 | ns | - | - | - | - | - | - |
| **Psychological outcomes combined (women+men)** | | | | | | | | | | | |
| **Study design**[h] | | | | | | | | | | | |
| RCT | 20 | 2185 | 232.4 | 19 | <0.001 | 91.8 | 0.70 | 0.36 – 1.03 | <0.001 | 642 | 110 |
| *Adjusted for publication bias* | *(24)*[e] | - | - | - | - | - | *0.26* | *-0.10 – 0.68* | *ns* | - | - |
| NRCT | 8 | 450 | 14.9 | 7 | =0.037 | 53.1 | 0.28 | -0.00 – 0.57 | ns | - | - |
| UCT | 7 | 215 | 6.0 | 6 | =0.424 | 0.0 | 0.55 | 0.40 – 0.70 | <0.001 | 90 | 45 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.51* | *0.36 – 0.66* | *<0.05* | - | - |
| Between group[f] | 35 | 2850 | 3.9 | 2 | ns | - | - | - | - | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Intervention types** | | | | | | | | | | | |
| CBT | 8 | 602 | 67.8 | 7 | <0.001 | 89.7 | 1.15 | 0.53 – 1.78 | <0.001 | 190 | 50 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.66* | *-0.01 – 1.33* | *ns* | - | - |
| MBI | 7 | 733 | 21.2 | 6 | =0.002 | 71.0 | 0.41 | 0.17 – 0.65 | <0.001 | 76 | 45 |
| *Adjusted for publication bias* | *(8)*[e] | - | - | - | - | - | *0.36* | *0.11 – 0.62* | *<0.05* | - | - |
| Counselling | 10 | 891 | 121.0 | 9 | <0.001 | 92.6 | 0.45 | -0.11 – 1.00 | ns | - | - |
| Between group[f] | 25 | 1624 | 4.4 | 2 | ns | - | - | - | - | - | |
| **Intervention format** | | | | | | | | | | | |
| Group | 20 | 1484 | 87.2 | 19 | <0.001 | 78.2 | 0.76 | 0.55 – 0.98 | <0.001 | 959 | 110 |
| *Adjusted for publication bias* | *(26)*[e] | - | - | - | - | - | *0.50* | *0.25 – 0.75* | *<0.05* | - | - |
| Individual | 9 | 834 | 17.7 | 8 | =0.023 | 54.9 | 0.13 | -0.08 – 0.35 | ns | - | - |
| Couples | 3 | 284 | 92.3 | 2 | <0.001 | 97.8 | 1.07 | -1.02 – 3.16 | ns | - | - |
| Online | 3 | 248 | 1.2 | 2 | =0.541 | 0.00 | 0.03 | -0.22 – 0.28 | ns | - | -- |
| Between group[f] | 35 | 2850 | 24.5 | 3 | <0.001 | - | - | - | - | - | |

[a] Q-statistic: *p*-values < 0.1 taken to suggest heterogeneity. $I^2$ statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity), 75% (high heterogeneity).
[b] ESR = Hedges g. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size in the hypothesized direction, i.e. reduced pain or relative smaller increased in pain in the intervention group. All ES's were combined using a random effects model. To ensure independency, if a study reported results for more than one pain measure, the ES's were combined (mean), ensuring that only one ES per study was used in the calculation.
[c] Failsafe N = number of non-significant studies that would bring the p-value to non-significant (p > 0.05);
[d] A Failsafe N exceeding the criterion (5 x k + 10) indicates a robust result [1].

[e] If analyses indicated the possibility of publication bias, missing studies were imputed and an adjusted ESR calculated (italics) RW:ERROR - Unable to find reference:1076. (K) indicates number of published studies + number of imputed studies.

[f] Meta-ANOVA (between-study comparisons)

[h] RCT (randomized controlled trial),NRCT (Non-randomized Controlled Trial), UCT (uncontrolled trial (pre-post))

*Pregnancy rates*

A statistically significant and robust effect size (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 risk ratio was somewhat lower (1.57).

*Combined psychological outcomes*

Combining the effect sizes of the 35 studies which had included one or more psychological outcomes revealed a statistically significant, robust [53], medium [40]effect size (g= 0.59). The results indicated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger published ESs. When imputing missing ESs, [54] 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.

*Infertility-related distress*

Only ten studies had included infertility-related distress as an outcome. Small ESs 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 reduced to a non-significant 0.29 after adjusting for possible publication bias. For men alone, the ES (0.13) did not reach statistically significance.

*State anxiety*

Twenty-five studies had included state anxiety as 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 5 studies (N = 633) had included measures of marital function, and 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, we explored, when a sufficient number of studies were available for each analysis, possible sources of heterogeneity and analyzed whether the ESs 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 2.

*Study design*

The ESs found for pregnancy outcomes were statistically significant for both randomized controlled trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.4). The difference did not reach statistical significance. For psychological outcomes, the pooled ES for RCT's (g= 0.70) was larger than for both NRCT's (0.28) and uncontrolled trials (UCT) (0.55) and the only statistically significant result. When adjusting for publication bias, the ES for RCTs (0.26) was smaller than for NRCTs and UCTs. 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 effects were found for both cognitive behavioral therapies (CBT) and mind/body interventions (MBI), with the largest ES for CBT (g=1.15), followed by MBI (0.41). Counseling did not reach statistically significance. The failsafe numbers exceeded the criterion, indicating rather robust results. The between-group differences did not reach statistical significance.

*Intervention format*

For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats. Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group difference did not reach statistical significance. For the combined psychological outcomes, a statistically significant effect was found for Group format (g= 0.76) ($p < 0.001$). Intervention formats such as Individual, Couples, and Online did not reach statistical significance. The overall between-group difference for intervention formats was statistical 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 (Jadad scores) were analyzed with meta-regression. As seen in Table 3, no significant effects were found for any of the moderators for either pregnancy or the combined psychological outcomes. A total of 6 studies had examined effects on both 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 ESs for anxiety and pregnancy, indicating that the greater the reduction in anxiety, the greater the likelihood of achieving pregnancy (see Table 3).

**Table 3**

Results of meta-regression analyses

| Dependent variable | Independent variable | K | Beta[a] | 95% CI | *p* |
|---|---|---|---|---|---|
| Pregnancy | ES- Anxiety | 6 | 0.19 | 0.06 – 0..31 | **0.004** |
| | Mean age | 9 | -0.05 | -0.19 – 0.10 | 0.534 |
| | Intervention duration | 9 | 0.01 | -0.03 – 0.06 | 0.669 |
| | Number of sessions | 9 | -0.00 | -0.08 – 1.07 | 0.922 |
| | Study quality (Jadad scores)[b] | 10 | -0.02 | -0.09 – 0.04 | 0.477 |
| Psych.Combined | Mean age | 32 | -0.05 | -0.12 - -0.02 | 0.214 |
| | Intervention duration | 32 | 0.01 | -0.02 – 0.04 | 0.518 |
| | Number of sessions | 27 | 0.03 | -0.01 – 0.07 | 0.150 |
| | Study quality (Jadad scores) [b,c] | 35 | -0.02 | -0.06 – 0.02 | 0.415 |

[a)] Mixed effects regression: unrestricted maximum likelihood; [b)] Modified Jadad-score; [c)] P-values for individual psychological outcomes; 0.09 (anxiety) – 0.58 (depression).

# 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 to controls receiving standardized care or active control intervention. Although the results of the 10 currently available studies appeared robust, there were some indications of publication bias in favor of studies with larger positive effect sizes. It should also be noted that the precision of the effect size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. Although the between-group difference did not reach statistical significance, NRCT's yielded greater effects (RR: 2.4 (95 % CI: 1.57 – 3.60)) than RCT's (RR: 1.7 (95 % CI: 1.06 – 2.72)). 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 confidence interval is substantial. While the results could be considered surprising, we have no good 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 effect sizes (0.5 and 1.0). As 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 effect size 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 of a total of 3401 women (3064) and men (347). The participants received various psychosocial interventions lasting from one week to six months, including cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions. The present review evaluates almost twice the number of studies included in the most recent previous review,[32] which reported mixed results of the efficacy of psychosocial intervention. 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.[32] In line with the second review from 2005,[31] we found more credible results for group intervention than for other formats, e.g. online interventions, individual and couples intervention.[115] The first review published in 2003 also highlighted group interventions as more effective, especially if the interventions emphasized education and skills training, such as relaxation. Our results concurred with those observations, and distinguishing between CBT, MBI, and counseling in general, our findings suggest that interventions delivered in groups may be more effective in reducing distress. The recently conducted studies included in the present review have contributed by increasing the size of the available dataset considerably, and taken together the currently available evidence suggests that offering psychosocial interventions may improve both chances of pregnancy and 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.[35] In order to limit the possibility of selection bias, we encouraged authors of eligible studies to elaborate on their results if the data reported was insufficient, and asked authors of papers written in foreign language to submit their results to us in English. The included studies represented a range of different countries, has used comparable outcome measures, and provided fairly comprehensive descriptions of the interventions studied. In addition, we conducted a detailed evaluation of the methodological quality, 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 were not as homogeneous as could be wished for. A small number of infertile participants did not receive treatment with ART, and it was not consistently reported what type of ART procedure the participants received and what phase or treatment they were in. Nonetheless, as suggested by the failsafe numbers, the reductions in anxiety and depressive symptoms appeared quite robust. Secondly, the methodological quality varied considerably across the included studies, which may have weakened the interpretability of the outcomes, as suggested by the greater ESs found for pregnancy outcomes for NRCSs compared with RCTs. On the other hand, we found no statistical significant associations between study quality scores for either pregnancy or psychological outcomes. A third possible limitation is the high level of heterogeneity indicated by Q and $I^2$ statistics and the pooled effect sizes reported in the present review should thus be viewed as an estimate of the average expected effect across a range of different settings. Fourth, the indications of publication bias for several results suggest the possibility of a "file drawer problem", i.e. the existence of relevant unpublished null-findings, a common problem when conducting systematic reviews. Finally, due to inconsistencies in the reporting of causes of infertility, we are unable to evaluate the possible associations between effect sizes 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 the heterogeneity and methodological limitations of the existing 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 involuntarily childlessness, and rumination about the involuntary childlessness may persist, even when psychosocial intervention improves general psychological wellbeing. Of special 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.[116,117] However, our meta-regression was conducted for the mean age of the *sample* and the mean age across study samples only showed little variation (Mean age: 32.7; SD: 2.4). A rather narrow age interval 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. This could be explained by various reasons. Firstly, group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3) than individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive impact of

"group settings" i.e. the sense-of-community between participants, reducing the feelings of isolation or alienation and sharing with individuals in the same life situation etc.[118-121]

**Recommendations for future research**

Despite the overall positive effects of psychosocial interventions, there is generally a need for studies with more rigorous methodology, including more strict reporting of causes of infertility, the types of ART used, and which phases of treatment participants are in. 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.[122] Also needed are studies testing hypotheses concerning possible moderating and mediating mechanisms of the effects if interventions on distress as well as pregnancy outcomes. For example, what psychosocial factors do we need to target to optimize effects on distress and pregnancy rates, and which biomarkers affected by psychosocial interventions, e.g. 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 intervention, in particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety and depressive symptoms 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.

## Acknowledgements

We would like to thank Gina Bay, Librarian at the Institute Library, Institute of Psychology and Behavioral Sciences, School of Business and Social Sciences, Aarhus University for valuable and tireless assistance throughout the database search process. We would also like to give our most grateful thanks to the researchers who provided us with additional data on their studies or aided us in other ways.

Contributors: RZ and YF designed the protocol. YF developed search strategies and IFV, NGS and YF performed the searches and study selection. YF and IFV undertook data extraction and quality assessments. RZ were responsible for analyzing the data. YF drafted the manuscript and IFV, NGS, HJI and RZ contributed to the manuscript throughout the process. All authors provided input and were involved with the interpretation of this review. YF is the study guarantor.

Funding: This study has not received funding but Y.F. was supported by a research grant from The Danish Agency for Science Technology and Innovation based on a PhD-fellowship.

Competing interests: None declared

Ethical approval**:** None required

Data sharing: No additional data available

**What is already known on this topic**

Previous reviews have been inconclusive concerning the efficacy of psychosocial interventions for reducing distress and improving clinical pregnancy chances.

**What this study adds**

Synthesizing the currently available evidence suggests that psychosocial interventions, in particular cognitive behavioral therapy (CBT), could provide clinically meaningful benefits for infertile wom-

en and men. Psychosocial intervention leads to reductions in anxiety and depressive symptoms and larger reductions in anxiety appear to be associated with increased fertility rates for women in treatment for infertility.

## References

1. Hart VA. Infertility and the role of psychotherapy. *Issues Ment Health Nurs*. 2002;23(1):31-41.

2. Oddens BJ, den Tonkelaar I, Nieuwenhuyse H. Psychosocial experiences in women facing fertility problems--a comparative survey. *Hum Reprod*. 1999;14(1):255-261.

3. Cwikel J, Gidron Y, Sheiner E. Psychological interactions with infertility among women. *Eur J Obstet Gynecol Reprod Biol*. 2004;117(2):126-131.

4. Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: An analysis of 101 studies published 1934-1996. *Environ Health Perspect*. 2000;108(10):961-966.

5. Skakkebaek NE, Jorgensen N, Main KM, et al. Is human fecundity declining? *Int J Androl*. 2006;29(1):2-11.

6. Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005;1:293-319.

7. Benyamini Y, Gozlan M, Kokia E. Variability in the difficulties experienced by women undergoing infertility treatments. *Fertil Steril*. 2005;83(2):275-283.

8. Alesi R. Infertility and its treatment--an emotional roller coaster. *Aust Fam Physician*. 2005;34(3):135-138.

9. Merari D, Chetrit A, Modan B. Emotional reactions and attitudes prior to in vitro fertilization: An inter-spouse study. *Psychol Health*. 2002;17(5):629-640.

10. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertil Steril*. 2001;76(4):675-687.

11. Edelmann RJ, Connolly KJ, Bartlett H. Coping strategies and psychological adjustment of couples presenting for IVF. *J Psychosom Res*. 1994;38(4):355-364.

12. Eugster A, Vingerhoets AJ. Psychological aspects of in vitro fertilization: A review. *Soc Sci Med*. 1999;48(5):575-589.

13. Stanton AL, Dunkel-Schetter C, eds. *Psychological adjustment to infertility: An overview of conceptual approaches.* Stanton, Annette L.; Dunkel-Schetter, Christine . Infertility: Perspectives from stress and coping research. The Plenum series on stress and coping. (pp. 3-16). New York, NY, US: Plenum Press; 1991Infertility: Perspectives from stress and coping research.

14. Benyamini Y, Gozlan M, Kokia E. Women's and men's perceptions of infertility and their associations with psychological adjustment: A dyadic approach. *British Journal of Health Psychology*. 2009;14:1-16. doi: 10.1348/135910708X279288.

15. du Plessis S,S., Makker K, Desai NR, Agarwal A. Impact of oxidative stress on IVF. *Expert Review of Obstetrics & Gynecology*. 2008;3(4):539-554. http://dx.doi.org/10.1586/17474108.3.4.539. doi: 10.1586/17474108.3.4.539.

16. Agarwal A, Allamaneni SS. Role of free radicals in female reproductive diseases and assisted reproduction. *Reprod Biomed Online*. 2004;9:338-347.

17. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853-859. doi: 10.1038/nature01321 [doi].

514 18. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: New
515 perspectives from psychoneuroimmunology. *Annu Rev Psychol*. 2002;53:83-107. doi:
516 10.1146/annurev.psych.53.100901.135217 [doi].

517 19. Csemiczky G, Landgren BM, Collins A. The influence of stress and state anxiety on the out-
518 come of IVF-treatment: Psychological and endocrinological assessment of swedish women entering
519 IVF-treatment. *Acta Obstet Gynecol Scand*. 2000;79(2):113-118.

520 20. Stoleru S, Teglas JP, Fermanian J, Spira A. Psychological factors in the aetiology of infertility:
521 A prospective cohort study. *Hum Reprod*. 1993;8(7):1039-1046.

522 21. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of
523 coping influence the outcome of in vivro fertilization through stress responses. *Psychoneuroendo-*
524 *crinology*. 1992;17(6):655-665. doi: http://dx.doi.org/10.1016/0306-4530(92)90024-2.

525 22. Sanders KA, Bruce NW. Psychosocial stress and treatment outcome following assisted repro-
526 ductive technology. *Human Reproduction*. 1999;14(6):1656-1662. doi: 10.1093/humrep/14.6.1656.

527 23. Smeenk JM, Verhaak CM, Vingerhoets AJ, et al. Stress and outcome success in IVF: The role
528 of self-reports and endocrine variables. *Hum Reprod*. 2005;20(4):991-996.

529 24. Ebbesen SM, Zachariae R, Mehlsen MY, et al. Stressful life events are associated with a poor
530 in-vitro fertilization (IVF) outcome: A prospective study. *Hum Reprod*. 2009;24(9):2173-2182. doi:
531 10.1093/humrep/dep185; 10.1093/humrep/dep185.

532 25. Eugster A, Vingerhoets AJJM. Psychological aspects of in vitro fertilization: A review. *Soc Sci*
533 *Med*. 1999;48(5):575-589.

26. Klonoff-Cohen H. Female and male lifestyle habits and IVF: What is known and unknown. *Hum Reprod Update*. 2005;11(2):179-203.

27. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: A review. *Hum Reprod Update*. 2007;13(3):209-223. doi: 10.1093/humupd/dml056.

28. Matthiesen SM, Frederiksen Y, Ingerslev HJ, Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): A meta-analysis. *Hum Reprod*. 2011;26(10):2763-2776. doi: 10.1093/humrep/der246; 10.1093/humrep/der246.

29. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: Meta-analysis of prospective psychosocial studies. *BMJ*. 2011;342:d223. doi: 10.1136/bmj.d223.

30. Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med*. 2003;57(12):2325-2341.

31. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Hum Reprod*. 2005;20(5):1324-1332.

32. Haemmerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: A meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279-295. doi: 10.1093/humupd/dmp002.

33. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi: 10.1136/bmj.g1687.

34. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. http://dx.doi.org/10.1371%2Fjournal.pmed.1000100.

35. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. http://dx.doi.org/10.1371%2Fjournal.pmed.1000097.

36. Higgins J, Green S, eds. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0 [updated March 2011] ed. The Cochrance Collaboration; 2011. Available from www.cochrane-handbook.org.

37. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. *Hum Reprod Update*. 2011;17(5):575-588.

38. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.

39. Greenland S, O'rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics*. 2001;2(4):463-471. doi: 10.1093/biostatistics/2.4.463.

40. Cohen J. *Statistical power analysis for the behavioral sciences.* Hillsdale, N.J.: Lawrence Erlbaum Associates; 1988.

41. Hedges L, Olkin I. *Statistical methods for meta-analysis.* New York: Acedemic Press; 1985.

42. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. *Psychother Psychosom*. 1999;68(1):15-21.

43. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology*. 2005;5(1):13. http://www.biomedcentral.com/1471-2288/5/13.

44. Sterne JA, Egger M, Moher D. Addressing reporting biases. In: *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons, Ltd; 2008; 2008:297-333. 10.1002/9780470712184.ch10.

45. Koszycki D, Bisserbe J, Blier P, Bradwejn J, Markowitz J. Interpersonal psychotherapy versus brief supportive therapy for depressed infertile women: First pilot randomized controlled trial. *Archives of Womens Mental Health*. 2012;15(3):193-201. doi: 10.1007/s00737-012-0277-z.

46. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *American Journal of Epidemiology*. 1999;150(5):469-475.

47. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi: 10.1136/bmj.327.7414.557.

48. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods*. 2001;6(3):203-217.

49. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *CMAJ*. 2007;176(8):1091-1096. doi: 10.1503/cmaj.060410.

50. Copas J, Shi JQ. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics*. 2000;1(3):247-262. doi: 10.1093/biostatistics/1.3.247.

595 51. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample
596 size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*.
597 2005;58(9):882-893. doi: 10.1016/j.jclinepi.2005.01.016.

598 52. Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder. Bias in meta-
599 analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:
600 10.1136/bmj.315.7109.629.

601 53. Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull*.
602 1979;86(3):638-641. doi: 10.1037/0033-2909.86.3.638.

603 54. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting
604 for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

605 55. Gutierrez K. Group psychological intervention in assisted human reproduction. *Rev Iberoam*
606 *Fertil Reprod Humana*. 2008;25(SUPPL. 1):47-54.

607 56. Bjornsen K. Opening the door to fertility. retreat to fertile ground: Sometimes the secret to get-
608 ting pregnant lies in just getting away from it all. *ALTERN MED*. 2006(88):80-81.
609 http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009216983&site=ehost-live.

610 57. Pengelly P, Inglis M, Cudmore L. Infertility: Couples' experiences and the use of counselling in
611 treatment centres. *Psychodynamic Counselling*. 1995;1(4):507-524.

612 58. A prospective study of the effectiveness of brief professionally-led support groups for infertility
613 patients. *Int J Psychiatry Med*. 1992(2):173.

614 59. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*.
615 1977;33(1):159-174.

60. Galhardo A, Cunha M, Pinto-Gouveia J. Developing mindfulness and acceptance skills in infertility: The mindfulness based program for infertility. *Aten Prim*. 2013;45:143.

61. Nilforooshan P, Ahmadi A, Abedi MR, Ahmadi M. Counseling based on interacting cognitive subsystems and its effect on anxiety of infertile couples. *Pakistan Journal of Psychological Research*. 2006;21(3-4):95-103. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/621710509?accountid=14468.

62. Schmidt L, Holstein BE, Christensen U, Boivin J. Communication and coping as predictors of fertility problem stress: Cohort study of 816 participants who did not achieve a delivery after 12 months of fertility treatment. *Hum Reprod*. 2005;20(11):3248-3256. doi: 10.1093/humrep/dei193.

63. Faramarzi M, Kheirkhah F, Esmaelzadeh S, Alipour A, Hjiahmadi M, Rahnama J. Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2008;141(1):49-53.

64. Lukse MP. The effect of group counseling on the frequency of grief reported by infertile couples. *JOGNN*. 1985;14(6):67S-70s. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=1986045607&site=ehost-live. doi: 10.1111/j.1552-6909.1985.tb02804.x.

65. Domar AD, Seibel MM, Benson H. The mind/body program for infertility: A new behavioral treatment approach for women with infertility. *Fertil Steril*. 1990;53(2):246-249.

66. Domar AD, Zuttermeister PC, Seibel M, Benson H. Psychological improvement in infertile women after behavioral treatment - a replication. *Fertil Steril*. 1992;58(1):144-147.

67. Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile women following a group treatment program: An open pilot study. *Gen Hosp Psychiatry*.

1996;18(3):192-195. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/618849278?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1016/0163-8343(96)00006-0.

68. McQueeney DA, Stanton AL, Sigmon S. Efficacy of emotion-focused and problem-focused group therapies for women with fertility problems. *J Behav Med*. 1997;20(4):313-331. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/619146790?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1023/A:1025560912766.

69. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. *Psychother Psychosom*. 1999;68(1):15-21. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/619405653?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1159/000012305.

70. McNaughton-Cassill M, Bostwick JM, Arthur NJ, Robinson RD, Neal GS. Efficacy of brief couples support groups developed to manage the stress of in vitro fertilization treatment. *Mayo Clin Proc*. 2002;77(10):1060-1066. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2003034100&site=ehost-live.

71. M E, MD B, J D, et al. Results from a prospective, randomized, controlled study evaluating the acceptability and effects of routine pre-IVF counselling. In: *Human reproduction (oxford, england)*. Vol 18. ; 2003:2647-2653. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/003/CN-00463003/frame.html.

72. Lee S. Effects of using a nursing crisis intervention program on psychosocial responses and coping strategies of infertile women during in vitro fertilization. *J NURS RES*. 2003;11(3):197-207. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2004076404&site=ehost-live.

73. Chan CHY, Ng EHY, Chan CLW, Ho PC, Chan THY. Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: A randomized controlled study. *Fertil Steril*. 2006;85(2):339-346. doi: 10.1016/j.fertnstert.2005.07.1310.

74. Tuil WS, Verhaak CM, Braat DD, de Vries Robbe PF, Kremer JA. Empowering patients undergoing in vitro fertilization by providing internet access to medical data. *Fertil Steril*. 2007;88(2):361-368. doi: 10.1016/j.fertnstert.2006.11.197.

75. TM C, TC G, E C, et al. Online psychoeducational support for infertile women: A randomized controlled trial. In: *Human reproduction (oxford, england)*. Vol 23. ; 2008:554-566. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/885/CN-00628885/frame.html.

76. Lancastle D, Boivin J. A feasibility study of a brief coping intervention (PRCI) for the waiting period before a pregnancy test during fertility treatment. *Hum Reprod*. 2008;23(10):2299-2307.

77. Noorbala AA, Ramazanzadeh F, Malekafzali H, et al. Effects of a psychological intervention on depression in infertile couples. *International Journal of Gynecology & Obstetrics*. 2008;101(3):248-252. doi: 10.1016/j.ijgo.2007.12.010.

78. Mori A. Supporting stress management for women undergoing the early stages of fertility treatment: A cluster-randomized controlled trial. *JAPAN J NURS SCI*. 2009;6(1):37-49. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2010359009&site=ehost-live.

79. E P, A M, B T. Experimental emotional disclosure in women undergoing infertility treatment: Are drop outs better off? In: *Social science & medicine (1982)*. Vol 69. ; 2009:678-681. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/736/CN-00719736/frame.html. 10.1016/j.socscimed.2009.06.031.

80. Haemmerli K, Znoj H, Berger T. Internet-based support for infertile patients: A randomized controlled study. *J Behav Med*. 2010;33(2):135-146. doi: 10.1007/s10865-009-9243-2.

81. Sexton MB, Byrd MR, O'Donohue WT, Jacobs NN. Web-based treatment for infertility-related psychological distress. *Arch Women's Ment Health*. 2010;13(4):347-358.

82. Hughes EG, da Silva AM. A pilot study assessing art therapy as a mental health intervention for subfertile women. *Human Reproduction*. 2011;26(3):611-615. doi: 10.1093/humrep/deq385.

83. D K, J-C B, P B, J B, J M. Interpersonal psychotherapy versus brief supportive therapy for depressed infertile women: First pilot randomized controlled trial. In: *Archives of women's mental health.* Vol 15. ; 2012:193-201. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/922/CN-00834922/frame.html.

84. Matthiesen S, Klonoff-Cohen H, Zachariae R, et al. The effect of an expressive writing intervention (EWI) on stress in infertile couples undergoing assisted reproductive technology (ART) treatment: A randomized controlled pilot study. *Br J Health Psychol*. 2012;17(2):362-378. doi: 10.1111/j.2044-8287.2011.02042.x; 10.1111/j.2044-8287.2011.02042.x.

85. Mosalanejad L, Koolaee AK, Shoyokh F. Does spiritual group psychotherapy impact on the rate of pregnancy? A case report. *Iran J Psychiatr Behav Sci*. 2012;6(1):78-81.

86. L M, AK K, S J. Effect of cognitive behavioral therapy in mental health and hardiness of infertile women receiving assisted reproductive therapy (ART). In: *Iranian journal of reproductive medicine.* Vol 10. ; 2012:483-488. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/752/CN-00852752/frame.html.

87. Catoire P, Delaunay L, Dannappel T, et al. Hypnosis versus diazepam for embryo transfer: A randomized controlled study. *Am J Clin Hypn*. 2013;55(4):378-386. doi: 10.1080/00029157.2012.747949.

88. Sarrel PM, DeCherney AH. Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertil Steril*. 1985;43(6):897-900.

89. Hosaka T, Matsubayashi H, Sugiyama Y, Izumi S, Makino T. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. *Gen Hosp Psychiatry*. 2002;24(5):353-356.

90. Levitas E, Parmet A, Lunenfeld E, et al. Impact of hypnosis during embryo transfer on the outcome of in vitro fertilization-embryo transfer: A case-control study. *Fertil Steril*. 2006;85(5):1404-1408. doi: 10.1016/j.fertnstert.2005.10.035.

91. AD D, KL R, B W, et al. Impact of a group mind/body intervention on pregnancy rates in IVF patients. In: *Fertility and sterility*. Vol 95. ; 2011:2269-2273. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/060/CN-00788060/frame.html. 10.1016/j.fertnstert.2011.03.046.

92. Gorayeb R, Borsari AC, Rosa-e-Silva AC, Ferriani RA. Brief cognitive behavioral intervention in groups in a brazilian assisted reproduction program. *Behav Med*. 2012;38(2):29-35. doi: 10.1080/08964289.2012.654834; 10.1080/08964289.2012.654834.

93. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychology*. 2000;19(6):568-575. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/619538260?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1037/0278-6133.19.6.568.

94. Terzioglu F. Investigation into effectiveness of counseling on assisted reproductive techniques in turkey. *J Psychosom Obstet Gynecol*. 2001;22(3):133-141.

95. de Klerk C, Hunfeld JA, Duivenvoorden HJ, et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: A randomized controlled trial. *Hum Reprod*. 2005;20(5):1333-1338.

96. Vizheh M, Pakgohar M, Babaei G, Ramezanzadeh F. Effect of counseling on quality of marital relationship of infertile couples: A randomized, controlled trial (RCT) study. *Arch Gynecol Obstet*. 2013;287(3):583-589.

97. Chan CHY, Chan CLW, Ng EHY, et al. Incorporating spirituality in psychosocial group intervention for women undergoing in vitro fertilization: A prospective randomized controlled study. *Psychology and Psychotherapy: Theory, Research and Practice*. 2012;85(4):356-373. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/1230614341?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1111/j.2044-8341.2011.02040.x.

98. AD D, D C, EA S, J D, B K, M F. Impact of group psychological interventions on pregnancy rates in infertile women. In: *Fertility and sterility.* Vol 73. ; 2000:805-811. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/593/CN-00276593/frame.html.

99. de Klerk C, Hunfeld JAM, Duivenvoorden HJ, et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: A randomized controlled trial. *Hum Reprod*. 2005;20(5):1333-1338.

100. CH C, EH N, CL C, null H, TH C. Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: A randomized controlled study. In: *Fertility and sterility.* Vol 85. ; 2006:339-346.

http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/041/CN-00556041/frame.html.
10.1016/j.fertnstert.2005.07.1310.

101. Nilforooshan P, Ahmadi A, Abedi MR, Ahmadi M. Counseling based on interacting cognitive subsystems and its effect on anxiety of infertile couples. *Pakistan Journal of Psychological Research*. 2006;21(3-4):95-103.

102. Cousineau TM, Green TC, Corsini E, et al. Online psychoeducational support for infertile women: A randomized controlled trial. *Hum Reprod*. 2008;23(3):554-566.

103. Panagopoulou E, Montgomery A, Tarlatzis B. Experimental emotional disclosure in women undergoing infertility treatment: Are drop outs better off? *Soc Sci Med*. 2009;69(5):678-681.

104. Haemmerli K, Znoj H, Berger T. Internet-based support for infertile patients: A randomized controlled study. *Journal of Behavioral Medicine*. 2010;33(2):135-146.

105. Sexton MB, Byrd MR, O'Donohue WT, Jacobs NN. Web-based treatment for infertility-related psychological distress. *Archives of Women's Mental Health*. 2010;13(4):347-358.

106. Chan CH, Chan CL, Ng EH, et al. Incorporating spirituality in psychosocial group intervention for women undergoing in vitro fertilization: A prospective randomized controlled study. *Psychol Psychother*. 2012;85(4):356-373. doi: 10.1111/j.2044-8341.2011.02040.x; 10.1111/j.2044-8341.2011.02040.x.

107. Matthiesen S, Klonoff-Cohen H, Zachariae R, et al. The effect of an expressive writing intervention (EWI) on stress in infertile couples undergoing assisted reproductive technology (ART) treatment: A randomized controlled pilot study. *British Journal of Health Psychology*. 2012;17(2):362-378.

766 108. O'Moore AM, O'Moore RR, Harrison RF. Psychosomatic aspects in idiopathic infertility: Ef-
767 fects of treatment with autogenic training. *J Psychosom Res*. 1983;27(2):145-151.

768 109. McQueeney DA, Stanton AL, Sigmon S. Efficacy of emotion-focused and problem-focused
769 group therapies for women with fertility problems. *J Behav Med*. 1997;20(4):313-331.

770 110. Gorayeb R, Borsari ACT, Rosa-e-Silva, Ana Carolina J. S., Ferriani RA. Brief cognitive be-
771 havioral intervention in groups in a brazilian assisted reproduction program. *Behavioral Medicine*.
772 2012;38(2):29-35.

773 111. Mosalanejad L, Koolaee AK, Behbahani BM. Looking out for the secret wound: The effect of
774 E-cognitive group therapy with emotional disclosure on the status of mental health in infertile
775 women. *International Journal of Fertility & Sterility*. 2012;6(2):87-94.

776 112. Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile
777 women following a group treatment program: An open pilot study. *General Hospital Psychiatry*.
778 1996;18(3):192-195.

779 113. Noorbala AA, Ramazanzadeh F, Malekafzali H, et al. Effects of a psychological intervention
780 on depression in infertile couples. *Int J Gynecol Obstet*. 2008;101(3):248-252.

781 114. Hughes EG, Da Silva AM. A pilot study assessing art therapy as a mental health intervention
782 for subfertile women. *Hum Reprod*. 2011;26(3):611-615.

783 115. de Liz T, Strauss B. Differential efficacy of group and individual/couple psychotherapy with
784 infertile patients. *Human Reproduction*. 2005;20(5):1324-1332. doi: 10.1093/humrep/deh743.

116. Navot D, Bergh RA, Williams MA, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *The Lancet*. 1991;337(8754):1375-1377. doi: http://dx.doi.org/10.1016/0140-6736(91)93060-M.

117. Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. *Human Reproduction*. 2002;17(5):1399-1403. doi: 10.1093/humrep/17.5.1399.

118. Van den Broeck U, Emery M, Wischmann T, Thorn P. Counselling in infertility: Individual, couple and group interventions. *Patient Educ Couns*. 2010;81(3):422-428. doi: 10.1016/j.pec.2010.10.009.

119. Burns LH(, Covington SN(. *Infertility counseling: A comprehensive handbook for clinicians.* New York, NY, US: Parthenon Publishing Group; 1999:xvii.

120. Boivin J, Appleton TC, Baetens P, et al. Guidelines for counselling in infertility: Outline version. *Hum Reprod*. 2001;16(6):1301-1304.

121. Boivin J, Kentenich H, eds. *Guidelines for counselling in infertility.* ESHRE Monographs: Oxford University Press; 2002.

122. Gameiro S, Boivin J, Domar A. Optimal in vitro fertilization in 2020 should reduce treatment burden and enhance care delivery for patients and staff. *Fertil Steril*. 2013;100(2):302-309. doi: 10.1016/j.fertnstert.2013.06.015 [doi].

803

## 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-behavio* therapy” | 13.914 | 1259 | 3706 | 32.160 | 13.056 | 2358 |

| | | | | | | |
|---|---|---|---|---|---|---|
| #20 ”cognitive-behavio* 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 searhes

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

- Additional records identified n=6

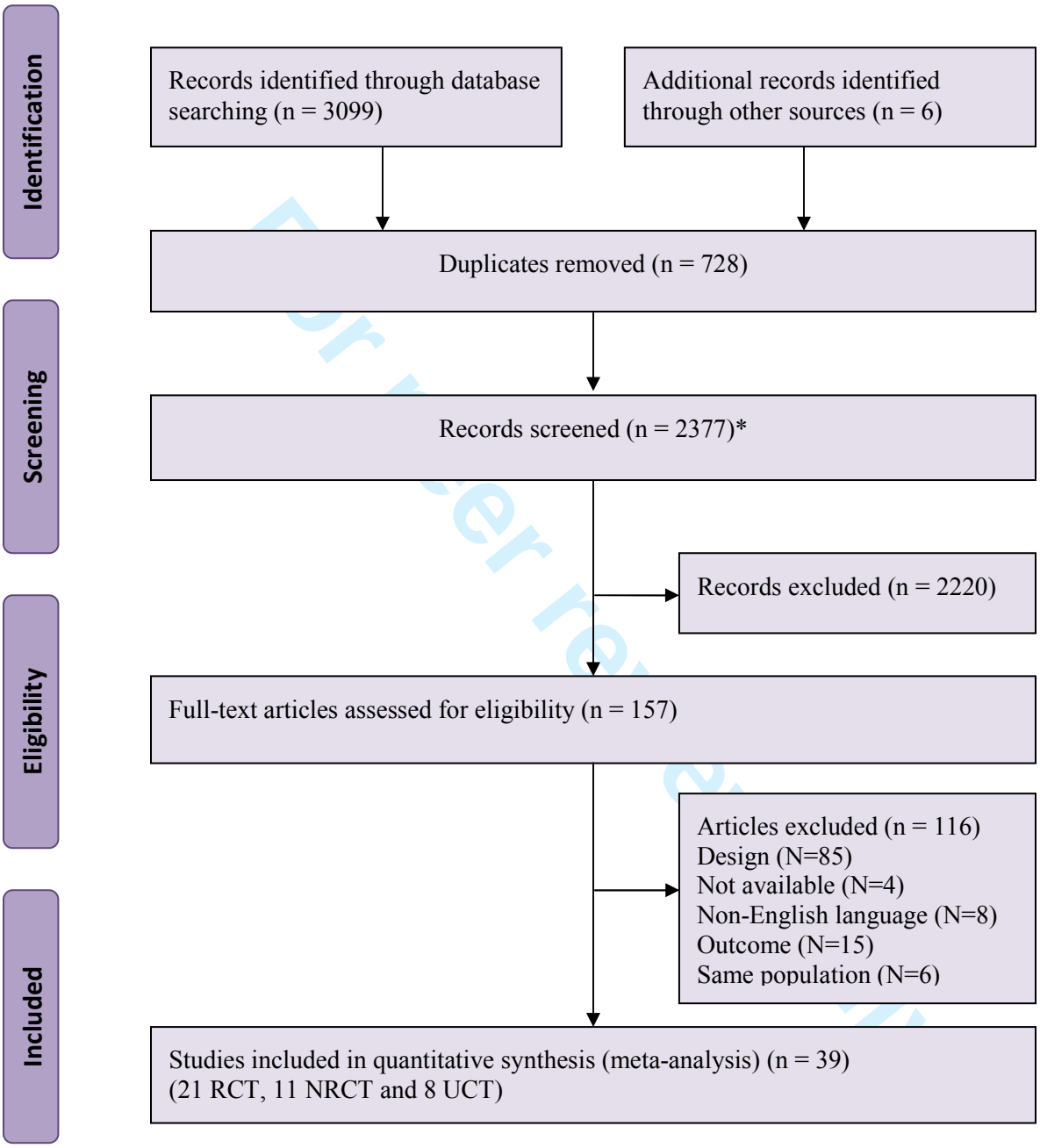
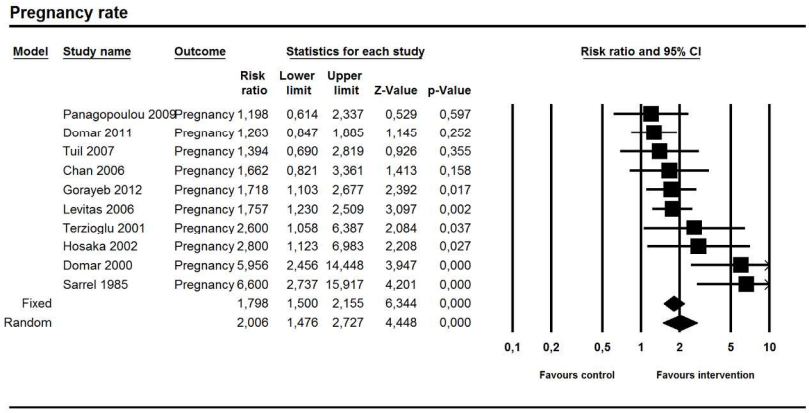
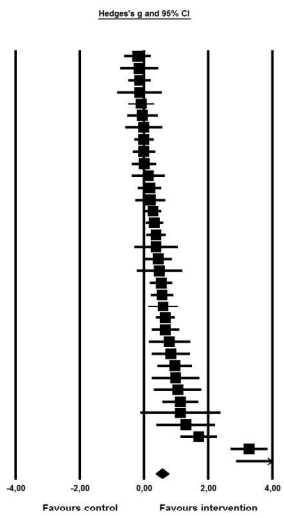



**Fig 1** PRISMA flowchart.*Screened according to the exclusion criteria presented in the Methods section.



**Psychological outcomes combined**

| Model | Study name | Outcome | Hedges's g | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|---|---|
| | Catoire 2013 | Anxiety | -0,195 | 0,207 | 0,043 | -0,601 | 0,210 | -0,945 | 0,345 |
| | Schmidt 2005 | Infertility distress | -0,148 | 0,302 | 0,091 | -0,740 | 0,443 | -0,492 | 0,622 |
| | Lee 2003 | Combined | -0,141 | 0,173 | 0,030 | -0,481 | 0,199 | -0,811 | 0,417 |
| | Sexton 2010 | Infertility distress | -0,139 | 0,350 | 0,123 | -0,826 | 0,548 | -0,397 | 0,691 |
| | Cousineau 2008 | Combined | 0,088 | 0,201 | 0,040 | -0,482 | 0,305 | 0,440 | 0,660 |
| | McNaughton-Cassill 2007 | Combined | -0,048 | 0,237 | 0,056 | -0,513 | 0,416 | -0,204 | 0,838 |
| | Tuschen-Caffier 1999 | Combined | -0,005 | 0,291 | 0,084 | -0,575 | 0,565 | -0,017 | 0,986 |
| | Tuil 2007 | Combined | -0,004 | 0,150 | 0,022 | -0,298 | 0,289 | -0,027 | 0,978 |
| | Panagopoulou 2009 | Combined | -0,003 | 0,174 | 0,030 | -0,343 | 0,338 | -0,015 | 0,988 |
| | Mori 2009 | Combined | 0,006 | 0,191 | 0,036 | -0,368 | 0,380 | 0,033 | 0,974 |
| | Terzioglu 2001 | Combined | 0,136 | 0,259 | 0,067 | -0,371 | 0,643 | 0,525 | 0,599 |
| | Haemmerli 2010 | Combined | 0,177 | 0,183 | 0,033 | -0,181 | 0,536 | 0,970 | 0,332 |
| | Hosaka 2002 | Combined | 0,195 | 0,231 | 0,053 | -0,257 | 0,647 | 0,844 | 0,399 |
| | Chan 2012 | Combined | 0,281 | 0,128 | 0,016 | 0,031 | 0,532 | 2,200 | 0,028 |
| | Domar 1992 | Anxiety | 0,326 | 0,138 | 0,019 | 0,056 | 0,596 | 2,367 | 0,018 |
| | Chan 2006 | Anxiety | 0,374 | 0,154 | 0,024 | 0,071 | 0,676 | 2,422 | 0,015 |
| | De Klerk 2005 | Combined | 0,375 | 0,344 | 0,119 | -0,300 | 1,050 | 1,090 | 0,276 |
| | Galhardo 2013 | Combined | 0,444 | 0,213 | 0,046 | 0,026 | 0,862 | 2,081 | 0,037 |
| | Matthiesen 2012 | Infertility distress | 0,482 | 0,355 | 0,126 | -0,215 | 1,178 | 1,356 | 0,175 |
| | Galletly 1996 | Combined | 0,536 | 0,174 | 0,030 | 0,195 | 0,878 | 3,075 | 0,002 |
| | Noorbala 2008 | Depression | 0,561 | 0,174 | 0,030 | 0,220 | 0,902 | 3,223 | 0,001 |
| | Hughes 2011 | Combined | 0,603 | 0,220 | 0,063 | 0,143 | 1,062 | 2,686 | 0,010 |
| | Domar 1990 | Anxiety | 0,663 | 0,150 | 0,022 | 0,369 | 0,957 | 4,423 | 0,000 |
| | Vizheh 2013 | Marital function | 0,666 | 0,215 | 0,046 | 0,245 | 1,088 | 3,098 | 0,002 |
| | O'Moore 1983 | Anxiety | 0,791 | 0,325 | 0,106 | 0,153 | 1,429 | 2,431 | 0,015 |
| | Lancaste & Boivin 2008 | Infertility distress | 0,835 | 0,297 | 0,088 | 0,253 | 1,417 | 2,812 | 0,005 |
| | Nilforooshan 2006 | Combined | 0,956 | 0,269 | 0,073 | 0,428 | 1,485 | 3,549 | 0,000 |
| | Koszycki 2012 | Combined | 0,983 | 0,373 | 0,139 | 0,251 | 1,714 | 2,634 | 0,008 |
| | Mosalanejad 2012b | Combined | 1,048 | 0,376 | 0,141 | 0,311 | 1,785 | 2,786 | 0,005 |
| | Faramarzi 2008 | Combined | 1,130 | 0,280 | 0,079 | 0,581 | 1,679 | 4,033 | 0,000 |
| | Lukse 1985 | Depression | 1,134 | 0,634 | 0,402 | -0,110 | 2,377 | 1,787 | 0,074 |
| | McQueeney 1997 | Combined | 1,300 | 0,461 | 0,212 | 0,396 | 2,203 | 2,820 | 0,005 |
| | Mosalanejad 2012 | Combined | 1,704 | 0,288 | 0,083 | 1,141 | 2,268 | 5,927 | 0,000 |
| | Emery 2003 | Combined | 3,267 | 0,290 | 0,084 | 2,699 | 3,835 | 11,266 | 0,000 |
| | Domar 2000 | Combined | 4,069 | 0,613 | 0,376 | 2,868 | 5,271 | 6,638 | 0,000 |
| Random | | | 0,555 | 0,103 | 0,011 | 0,354 | 0,756 | 5,412 | 0,000 |



# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5-6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ for each meta-analysis. | 7-9 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 10-11 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 11 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 12-13 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 13-14 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 14 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16-17 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-18 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 19 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

# Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: A systematic review and meta-analysis



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2014-006592.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 28-Nov-2014 |
| Complete List of Authors: | Frederiksen, Yoon; Aarhus University, Department of Psychology and Social Sciences<br>Farver-Vestergaard, Ingeborg; Aarhus University, Department of Psychology<br>Skovgård, Ninna; Aarhus University Hospital, Skejby Fertility Clinic<br>Ingerslev, Hans Jakob; Aarhus University Hospital, Center for Preimplantation Genetic Diagnosis/The Fertility Clinic<br>Zachariae, Robert; Aarhus University Hospital, Department of Oncology; Aarhus University, Department of Psychology |
| Primary Subject Heading: | Evidence based practice |
| Secondary Subject Heading: | Reproductive medicine |
| Keywords: | Infertility, Psychosocial intervention, distress, pregnancy |
| | |

# Title Page

| **Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: A systematic review and meta-analysis** |
|---|
| Yoon Frederiksen, Ingeborg Farver-Vestergaard, Ninna Grønhøj Skovgård, Hans Jakob Ingerslev, Robert Zachariae |
| Unit for Psychooncology and Health Psychology, Department of Psychology, University of Aarhus, 8000 Aarhus, Denmark Yoon Frederiksen MSc. Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, University of Aarhus, 8000 Aarhus, Denmark Ingeborg Farver-Vestergaard MSc., Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, Aarhus University, 8000 Aarhus, Denmark Ninna Grønhøj Skovgaard, research assistant, Skejby Fertility Clinic, Aarhus University Hospital, 8200 Aarhus Denmark. Hans Jakob Ingerslev, Professor, MD, DMSc, Unit for Psychooncology and Health Psychology, Department of Psychology, Aarhus University, 8000 Aarhus, Denmark Department of Oncology, Aarhus University Hospital, 8000 Aarhus Denmark Robert Zachariae, DMSci., professor. |
| Correspondence to: Yoon Frederiksen yoonf@psy.au.dk Phone no. +45 8716 5872 |
| Keywords: infertility/psychosocial intervention/distress/pregnancy |
| Word count: 5.877 |
|  |
| Competing interest: All authors have completed the Unified Competing Interest form and are available upon request from the Corresponding Author |

## 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 assessed. Effect sizes (Hedges *g*) were pooled using a random effect model. Heterogeneity was assessed using the *Q* statistic and $I^2$, and publication bias evaluated using Eggers' method. Possible moderators and mediators were explored with meta-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 (RR = 2.01; CI: 1.48-2.73; $p<0.001$) and combined psychological outcomes (Hedges $g=0.59$; CI: 0.38-0.80; $p=0.001$,). The pooled effect sizes (ES) for psychological outcomes were generally larger for women (*g*: 0.51-0.73) than men (0.13-0.34), 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 behavioral therapy (CBT) ($g=0.84$), mind-body interventions (0.61), and other intervention types (0.50).

**Conclusion** The present meta-analysis suggests that psychosocial interventions for couples in treatment for infertility, in particular CBT, could be efficacious, both in reducing psychological distress and in improving clinical pregnancy rates.


## 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
- Substantial variation of the methodological quality and missing information on fertility and ART treatment may limit the interpretability of the outcomes

## 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, e.g. oxidative stress and inflammation,[15,16] which may be promoted by psychological distress.[17,18] Such findings have lead 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, e.g. in the chosen measures of distress and definitions of pregnancy (e.g. 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, optimize 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 counseling 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, e.g. individual/couple vs. 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, e.g. mind/body interventions, web-based treatments, and online psycho-education programs, have since been published. Furthermore, the more recently pub-

lished studies have generally used randomized controlled trial 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 which 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-analysis (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 fertilization) 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: (i) "infertil*", "childlessness", "IVF", "ICSI", "fertility treatment/problems" "assisted reproduction" and (ii) "psychological/psychosocial intervention", "social support", "couples therapy", "psycho-education", "internet-based intervention" and "behavioral therapy" (for a full search history, see 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 program 3) included both baseline and post-

intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research approach. In general terms, infertility refers to not being able to conceive for more than one 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, e.g. intrauterine insemination (IUI), in vitro fertilization (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 had a primary physical focus, e.g. acupuncture or massage therapy. However, studies using "psychophysiological" approaches, e.g. relaxation, guided imagery or meditation exercises as part of a psychosocial program, were included. The interventions could be delivered in individual-, group-, couples-, or internet-based format. We included both controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines, commentaries, case reports, editorials, newspaper articles, newsletters, and books 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 visualization of at least one gestational sack and fetal heartbeat in approximately the 5$^{th}$ week after fertilization. Secondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalized 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 (IFV, NGS) and the data 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, e.g. use and adequate description of randomization- and blinding procedures, and description of drop-out rates (score range: 0-5). In addition to the 0-5 points possible on the original Jadad scale, one additional point was given for each of the following: (a) *was a control group included*; in order to acknowledge whether the intervention group was compared with another group, although randomization was not used, (b) *were both pre- and post-data presented;* as including both pre- and post-intervention data will provide more accurate results. (c) *Was any form of blinding or masking of conditions to patients, or (d) blinding of researchers attempted*; acknowledging if the study had attempted to masking the active condition, (e) *was a standardized and reliable outcome measure used;* a criterion increasing the validity and comparability of the outcomes, and (f) *were pre-post correlations provided*; which could provide better estimates of the effect size. The modified scale yielded a total quality score ranging from 0-11. 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). Kappa 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 effect sizes (ES) as this is generally discouraged due to the risk of introducing additional bias.[38] Instead, associations between ESs and study quality indicators were explored with meta-ANOVAs (design) and meta-regression (modified quality-score). In cases where we were unable to retrieve articles from the authorized databases, authors were contacted between 1-3 times in order to amend the data collected.

**Calculating effect sizes**

The effect sizes (ESs) 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 size.[39,40] A positive Hedges' *g* indicates result in the expected direction, e.g. a reduction in distress in the intervention group compared to controls. A 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 (k=10) (k = number of studies). When possible, Hedges' *g* was calculated on the basis of reported means and SDs at pre and post-intervention or means and SDs of change scores. This was possible for 50 of 61 effect sizes. When required and available, the reported pre-post correlations were used in the calculation. This was the case for 5 ES's. When unavailable, the pre-post correlation was set to 0.50. When SDs were unavailable, two approaches were used. For STAI state anxiety scores, the average pre- and post SDs (10.9 and 10.8) for the studies which reported the SD was used, as the SDs appeared to be highly comparable across the remaining studies. For other measures, ESs were estimated either on the basis of sample size and either p-value or Eta square. 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 ESs 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 ESs for the individual outcome measures of depression, state anxiety, infertility-related distress, and marital function. This was done for the combined sample (women + men). If the results indicated study heterogeneity, and if the number of studies in each category was sufficient (K≥3), possible between-study differences in ESs were explored by comparing the ESs 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] Based on the findings of the earlier meta-analysis, [31] we expected to find a 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 alpha of 5% and a statistical power of 80%, with a total of only 9 studies, using a random-effects model. Based on these results, we considered it worthwhile to conduct the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2 (www.meta-analysis.com), IBM SPSS-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 ESs 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's trim and fill method,[52] which imputes ESs 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 "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; $p < 0.001$ (Kappa 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 authors provided unpublished additional data.[58-60] Figure 1 shows a flowchart of the study selection process.

(Insert Figure 1 near here)

### Study characteristics

The study characteristics are summarized in Table 1. Based on 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 5 studies had included distress as well as pregnancy as outcome.[78,91-94] Twenty-one studies were randomized controlled trials (RCTs),[58,61,65-72,74,75,83,85,89-95] and ten studies were non-randomized controlled studies (NRCTs),[41,59,60,76,79,80,86-88,96] with most control groups receiving standardized care or being waiting-list controls. Only three studies had included an active/attention control condition, e.g.

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 uncontrolled (UCT) (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 studies reported that some, but not how many, of the participants were in treatment, and 31 studies reported that their participants were currently in ART treatment, although not what kind of treatment e.g. 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 studies 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 was (32.7 yrs. SD 2.2) and (4.6 yrs. SD 2.1) and for control group participants (32.6 yrs. SD=1.7) and (5.1 yrs. SD=3.0). The specific intervention strategies mostly employed were cognitive behavioral therapy (k=8) and mind/body intervention (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 counseling. Some studies had included more than one approach, e.g. cognitive behavioral approaches supplemented with mind-body techniques such as relaxation. To be categorized as mind/body intervention, a study had to use such strategies as the general approach over the course of intervention. Thus, if studies had mainly used cognitive behavioral therapy strategies and only incorporated other approaches, e.g., relaxation exercises, in one or two sessions, they were categorized as cognitive behavioral therapy interventions. The number of sessions ranged from 1 to 24, lasting approximately from 20 minutes to 3 hours 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, dropout 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 ex-

plicitly 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, e.g. carrying last (baseline) observations forward or use of multilevel linear modeling.[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 ESs and uneven dropout in the intervention and control groups was analyzed for the 15 studies that reported dropout by regressing the difference in dropout rates on the overall ESs across all outcomes. The result indicated that larger dropouts in the intervention group compared were generally associated with smaller ES's (Slope = -0.02), but the association did not reach statistical significance (p = 0.268).

**Table 1. Characteristics of included studies**

| Author | Country | Participants (N) I: Intervention C: Control assigned (final analysis) (men %) | Study design[a] | Intervention type[b] | Intervention category[c] | Intervention format | Number of sessions | Intervention duration (weeks) | Outcome: Psychological[d] IS: Infertility stress A: Anxiety D: Depression MF: Marital function | Outcome: Pregnancy[e](+/-) | Quality score[f] J: Jadad 0-5 MJ: Modified Jadad 0-12 J (MJ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| O'Moore et al. 1983 | Ireland, UK | I: 30 (22) (50 %) C: 20 (20) (50 %) | NRCT | Autogenic training | MBI | Group | 8 | 8 | D: BDI A: STAI | - | 1 (4) |
| Lukse 1985 | USA | I: 29 (29 (14)) | UCT | Counseling | Other | Group | 6 | 6 | D: DES | - | 0 (3) |
| Sarrel and DeCherney 1985 | USA | I: 20 (10) C: 20 (9) | NRCT | Psychotherapeutic interview | Other | Couples | 1 | 1 | | + | 0 (1) |
| Domar et al. 1990 | USA | I: 54 (54) | UCT | Mind/Body program | MBI | Group | 10 | 10 | A: STAI | - | 0 (3) |
| Domar et al. 1992 | USA | I: 52 (41) | UCT | Behavioral Medicine Program for Infertility | MBI | Group | 10 | 10 | A: STAI | - | 1 (3) |
| Galletly et al. 1996 | Australia | I: 37 (37) | UCT | Treatment program | Other | Group | 24 | 24 | D: HADS A: HADS | - | 1 (3) |
| McQueeney et al. 1997 | USA | I: 20 (20) C: 9 (9) | NRCT | Emotion- and problem-focused therapies | Other | Group | 6 | 6 | IS: ISD D: BDI | - | 3 (7) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tuschen-Caffier et al. 1999 | Germany | I: 34 (22)<br>C: 24 (24) | NRCT | Cognitive-behavioral therapy | CBT | Couples | 10-12 | 32 | IS: one item<br>MF: one item | - | 1 (4) |
| Domar et al. 2000 | USA | I: 56 (20)<br>C: 63 (14) | RCT | Psychological intervention | MBI | Group | 10 | 10 | D: BDI<br>A: STAI | + | 4 (10) |
| Terzioglu 2001 | Turkey | I: 60 (60) (50 %)<br>C: 60 (60) (50 %) | RCT | Counseling | Other | Individual | 5 | 5 | D: BDI<br>A: STAI | + | 2 (5) |
| Hosaka et al. 2002 | Japan | I: 37 (37)<br>C: 37 (37) | NRCT | Structured intervention | MBI | Group | 5 | 5 | | + | 3 (6) |
| McNaughton-Cassill et al. 2002 | USA | I: 43 (43) (39.5 %)<br>C: 37 (37) (48.6 %) | NRCT | Couples support | CBT | Couples | 6 | 3 | D: BDI<br>A: BAI | - | 2 (5) |
| Emery et al. 2003 | Switzerland | I: 158 (110) (34.8 %)<br>C: 152 (131) (42.8 %) | RCT | Pre-IVF counseling | Other | Couples | 1 | 1 | D: BDI<br>A: STAI | - | 3 (6) |
| Lee 2003 | Taiwan | I: 64 (64)<br>C: 68(68) | RCT | Nursing crisis intervention program | MBI | Individual | 7 | 7 | D: SDS<br>A: STAI | - | 1 (4) |
| De Klerk et al. 2005 | The Netherlands | I: 22 (18)<br>C: 22 (15) | RCT | Counseling | Other | Group | 3 | 4-5 | D: HADS<br>A: HADS | + | 3 (6) |
| Schmidt et al. 2005 | Denmark | I: 13 (13)<br>C: 435 (435) | NRCT | Stress management | Other | Group | 5 | 6 | IS: COMPI | - | 1 (4) |
| Chan et al. 2006 | Hong Kong, China | I: 101 (69)<br>C: 126 (115) | RCT | The Eastern body-mind intervention | MBI | Group | 4 | 4 | A: STAI | - | 3 (7) |
| Levitas et al. 2006 | Israel | I: 89 (89)<br>C: 96 (96) | NRCT | Hypnosis | MBI | Individual | 1 | 1 | | + | 0 (1) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nilforooshan et al. 2006 | Iran | I: 30 (30) (50 %) C: 30 (30) (50 %) | RCT | Cognitive-behavioral counseling | CBT | Group | 6 | 6 | D: BDI A: BAI | - | 2 (6) |
| Tuil et al. 2007 | The Nether-lands | 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 et al. 2008 | USA | I: 96 (49) C: 92 (49) | RCT | Psycho-educational support | Other | Online | 1-2 | 4 | IS: FPI MF: RDAS | - | 4 (8) |
| Faramarzi et al. 2008 | Iran | I: 42 (29) C: 40 (30) | RCT | Cognitive-behavioral therapy | CBT | Group | 10 | 10 | D: BDI A: Cattell | - | 3 (6) |
| Lancastle and Boivin 2008 | Wales, UK | I:28 (28) C: 27 (27) | RCT | Brief coping intervention | Other | Individual | 14 | 2 | IS: CIQ | - | 4 (8) |
| Noorbala et al. 2008 | Iran | I: 288 (288) (50 %) | UCT | Cognitive-behavioral therapy | CBT | Group | | 24 | D: BDI | - | 3 (8) |
| Mori 2009 | Japan | I: 85 (85) C: 40 (40) | RCT | Stress man-agement | Other | Individual | 3 | 12 | D: HADS A: HADS | - | 4 (8) |
| Panagopoulou et al. 2009 | England, UK | I: 50 (50) C: 98 (98) | RCT | Expressive writing in-tervention | Other | Individual | 3 | 1 | IS: ISS A: STAI | - | 3 (7) |
| Haemmerli et al. 2010 | Switzer-land | I: 60 (46) C: 64 (41) | RCT | Coaching and support | Other | Online | 13 | 8 | IS: IDS D: CES-D A: STAI | - | 3 (6) |
| Sexton et al. 2010 | USA | I: 21 (15) C: 22 (16) | RCT | Web-based coping with infertility | Other | Individual | | 2 | IS: FPI | - | 3 (6) |
| Domar et al. 2011 | USA | I: 46 (46) C: 51(51) | RCT | Mind/body program for infertility | MBI | Group | 10 | 10 | | + | 4 (6) |
| Hughes and Mann de Silva | Canada | I: 21 (21) | UCT | Art therapy | Other | Group | 8 (2hrs) | 8 | D: BDI A: BAI | - | 0 (2) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 | | | | | | | | | | | |
| Chan et al. 2012 | Hong Kong, China | I: 141 (141) C: 110 (110) | RCT | Integrative body-mind-spirit intervention | MBI | Group | 4 (3hrs) | 4 | A: STAI MF: C-KMS | + | 3 (6) |
| Gorayeb et al. 2012 | Brazil | I: 93 (93) C: 95 (95) | RCT | Brief cognitive-behavioral intervention | CBT | Group | 5 (2hrs) | 5 | | + | 1 (4) |
| Koszycki et al. 2012 | Canada | I: 31 (23) | UCT | Interpersonal and supportive therapy | Other | Individual | 12 (50min) | 12 | IS: FPI D: BDI HAM-D | - | 3 (7) |
| Matthiesen et al. 2012 | Denmark | I: 42 (15) C: 40 (16) | RCT | Expressive writing intervention | Other | Individual | 3 (20min) | 1 | IS: COMPI | - | 4 (8) |
| Mosalanejad et al. 2012 | Iran | I: 32 (32) C: 33 (33) | RCT | Cognitive-behavioral treatment | CBT | Group | 12 (2hrs) | 12 | D: DASS A: DASS | - | 1 (4) |
| Mosalanejad et al. 2012b | Iran | I: 16 (16) C: 15 (15) | NRCT | Cognitive-behavioral therapy | CBT | Group | 15 (1,5hrs) | 16 | D: DASS A: DASS | - | 2 (5) |
| Catoire et al. 2013 | France | I: 50 (50) | UCT | Hypnosis | MBI | Individual | 4 | 1 | A: STAI | - | 4 (7) |
| Galhardo et al. 2013 | Portugal | I: 55 (55) C: 37 (37) | NRCT | Mindfulness-based program for infertility | MBI | Group | 10 (2hrs) | 10 | IS: ISE D: BDI A: STAI | - | 1 (4) |
| Vizheh et al. 2013 | Iran | I: 86 (86) (50 %) C: 94 (86) (54.7 %) | RCT | Marital counseling | Other | Group | 3 (1.5hrs) | 3 | MF: MSQ | + | 4 (8) |

a) *RCT* Randomized controlled trial, *NRCT* non-randomized controlled trial, *UCT* uncontrolled pre-post trial, *NR* Not reported.

b) Self-reported intervention type.

c) Intervention type: *CBT* (Cognitive behavioral therapy); *MBI* (Mind/body intervention): mindfulness, yoga, relaxation, imagery, hypnosis etc.; Other: all other intervention types, e.g. counseling, psycho-education, supportive therapy, expressive writing intervention, brief therapy, emotion and problem focused therapy, and narrative therapy.

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

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

f) *Jadad range 0-5* an assessment tool rating the quality and methodology of the studies included[37] 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 standardized and reliable outcome measures and report of pre-post correlations.

*Quality ratings*

All included studies were methodologically assessed with both 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.

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

| | Jadad criteria | | | | | | | Additional criteria | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | 1 | 2 | 3 | 4 | 5 | 6 | 7 | a | b | C | d | e | f | **Jadad** | **Total** |
| | **Randomized** | **Double blind** | **Withdrawals and drop-outs** | **Randomization (evaluation)** | **Blinding (evaluation)** | **Randomization (evaluation)** | **Blinding (evaluation)** | Control group | Pre- and post-assessment | Blinding (patients) | Blinding (researchers) | Standardized and reliable outcome | Pre-post correlation | **Jadad scores** | **Total scores** |
| O'Moore et al., 1983 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Lukse, 1985 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 1 | **0** | **3** |
| Sarrel et al., 1985 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **0** | **1** |
| Domar et al., 1990 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 1 | **0** | **3** |
| Domar et al., 1992 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **1** | **3** |
| Galletly et al., 1996 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **1** | **3** |
| McQueeney et al., 1997 | **1** | **0** | **0** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Tuschen-Caffier et al., 1999 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Domar et al., 2000 | **1** | **1** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 1 | 1 | 1 | 1 | **4** | **10** |
| Terzioglu, 2001 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **2** | **5** |
| Hosaka et al., 2002 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| McNaughton-Casill et al., 2002[a] | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **2** | **5** |
| Emery et al., 2003 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Lee et al., 2003 | **1** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| De Klerk et al., 2005 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Schmidt et al., 2005 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Chan et al., 2006 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **3** | **7** |
| Levitas et al., 2006 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **0** | **1** |
| Nilforooshan et al., 2006 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **2** | **6** |
| Tuil et al., 2007 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Cousineau et al., 2008 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Faramarzi et al., 2008 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **2** | **6** |
| Lancastle and Boivin, 2008 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Noorbala et al., 2008[a] | **1** | **0** | **0** | **1** | **1** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Mori, 2009 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Panagopoulou et al., 2009 | **1** | **0** | **1** | **0** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Haemmerli et al., 2010 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Sexton et al., 2010 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Domar et al., 2011 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 0 | 0 | 1 | 0 | 0 | **4** | **6** |
| Hughes and Mann de Silva, 2011 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **0** | **2** |
| Chan et al. 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Gorayeb et al., 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **3** | **4** |
| Koszycki et al., 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Matthiesen et al., 2012 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mosalanejad et al., 2012 | **1** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Mosalanejad et al., 2012b | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Catoire et al., 2013[a] | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 1 | 1 | 0 | **0** | **3** |
| Galhardo et al., 2013 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Vizeh et al., 2013 | **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 randomized;** 2**) Was the study described as double blind; 3) Was there a description of withdrawals and dropouts; 4) The method of randomization was described, and appropriate; 5) The method of blinding was described, and appropriate; 6) The method of randomization was described, but in inappropriate; 7) The method of blinding was described, but inappropriate;** a) The study included a control group; b) The study included pre- and post-assessment; 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 standardized and reliable outcome measures; f) The study reported pre-post correlation.

[a]) 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, e.g. 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.

**Effects of psychosocial intervention**

The results of the meta-analyses are shown in Table 3.

*Pregnancy rates*

A statistically significant and robust effect size (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 risk ratio was somewhat lower (1.57). A forest plot of the effects of psychological intervention on pregnancy outcomes are shown in Figure 2.

(Insert Figure 2 near here)

*Combined psychological outcomes*

Combining the effect sizes of the 35 studies which had included one or more psychological outcomes revealed a statistically significant, robust [51], medium [39]effect size (g= 0.59). The results indicated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger published ESs. When imputing missing ESs, [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.

**(**Insert Figure 3 near here)

*Infertility-related distress*

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

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

| | Sample size | | Heterogeneity[a] | | | | Global effect sizes | | | Failsafe N[c] | Criterion[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | K | N | Q | df | *P* | $I^2$ | Hedges g[b] | 95 % CI | *p* | | |
| **MAIN EFFECTS** | | | | | | | | | | | |
| Pregnancy | | | | | | | | | | | |
| Pregnancy, women | 10 | 1324 | 22.0 | 9 | =0.009 | 59.0 | 2.01 (RR) | 1.48 – 2.73 | <0.001 | 130 | 60 |
| *Adjusted for publication bias* | *(13)* | - | - | - | - | - | *1.57 (RR)* | *1.10 – 2.25* | *<0.05* | - | - |
| Psych. combined, women+men | 35 | 2746 | 259.2 | 34 | <0.001 | 86.9 | 0.59 | 0.38 – 0.80 | <0.001 | 1552 | 185 |
| *Adjusted for publication bias* | *(42)*[e] | - | - | - | - | - | *0,31* | *0.07 – 0.56* | *<0.05* | - | - |
| Psych. combined, women | 28 | 2076 | 130.8 | 27 | <0.001 | 76.4 | 0.51 | 0.32 – 0.70 | <0.001 | 798 | 150 |
| *Adjusted for publication bias* | *(34)*[e] | - | - | - | - | - | *0.30* | *0.09 – 0.51* | *<0.05* | - | - |
| Psych. combined, men | 7 | 347 | 8,9 | 6 | =0.178 | 32.8 | 0.34 | 0.08 – 0.59 | =0.010 | 12 | 45 |
| Between-group[f] (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 – 0.50 | ns | - | - |
| Infertility distress, women | 6 | 371 | 17.8 | 5 | =0.003 | 71.8 | 0.37 | -0.06 – 0.79 | ns | - | - |
| Depressive symptoms | | | | | | | | | | | |
| Depression symp., women+men | 21 | 1558 | 367.5 | 20 | <0.001 | 94.6 | 1.00 | 0.54 – 1.45 | <0.001 | 1022 | 115 |
| *Adjusted for publication bias* | *(25)*[e] | - | - | - | - | - | *0.31* | *-0.20 – 0.84* | *ns* | - | - |
| Depressive symp.,women | 17 | 992 | 107.7 | 16 | <0.001 | 85.1 | 0.73 | 0.41 – 1.06 | <0.001 | 393 | 95 |
| *Adjusted for publication bias* | *(23)*[e] | - | - | - | - | - | *0.29* | *-0.07 – 0.65* | *ns* | - | - |
| Depressive symp., men | 5 | 243 | 1.9 | 4 | =0.749 | 0.00 | 0.13 | -0.11 – 0.37 | ns | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Between-group[f] (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 – 0.71 | <0.001 | 760 | 135 |
| *Adjusted for publication bias* | *(29)*[e] | - | - | - | - | - | *0.31* | *0.07 – 0.54* | *<0.05* | - | - |
| Anxiety, women | 23 | 1737 | 114.3 | 22 | <0.001 | 80.8 | 0.53 | 0.32 – 0.73 | <0.001 | 631 | 125 |
| *Adjusted for publication bias* | *(27)*[e] | - | - | - | - | - | *0.32* | *0.08 – 0.57* | *<0.05* | - | - |
| Anxiety, men | 5 | 246 | 8.7 | 4 | =0.070 | 53.8 | 0.32 | -0.04 – 0.67 | ns | - | - |
| Between-group[f] (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 – 0.41 | ns | - | - |
| Marital function, women | 4 | 587 | 14.5 | 3 | =0.002 | 79.3 | 0.08 | -0.30 – 0.46 | ns | - | - |
| **MODERATOR ANALYSES** | | | | | | | | | | | |
| **Pregnancy (women)** | | | | | | | | | | | |
| **Study design**[h] | | | | | | | | | | | |
| RCT | 6 | 856 | 10.8 | 5 | =0.057 | 53.5 | 1.67 (RR) | 1.17 – 2.40 | < 0.05 | 22 | 40 |
| NRCT | 4 | 468 | 7.9 | 3 | =0.048 | 62.1 | 2.80 (RR) | 1.55 – 5.06 | < 0.001 | 31 | 30 |
| *Adjusted for publication bias* | *(6)*[e] | - | - | - | - | - | *1.93 (RR)* | *1.07 – 3.49* | *< 0.05* | - | - |
| Between group[f] | 10 | 1324 | 2.1 | 1 | Ns | - | - | - | - | - | - |
| **Intervention format** | | | | | | | | | | | |
| Group | 5 | 691 | 10.9 | 4 | =0.027 | 63.4 | 2.03 (RR) | 1.29 – 3.20 | < 0.01 | 28 | 35 |
| Individual | 4 | 433 | 2.2 | 3 | =0.531 | 0.0 | 1.65 (RR) | 1.26 – 2.17 | < 0.001 | 8 | 30 |
| Between group[f] | 9 | 1124 | 0.5 | 1 | Ns | - | - | - | - | - | - |
| **Psychological outcomes combined (women+men)** | | | | | | | | | | | |
| **Study design**[h] | | | | | | | | | | | |
| RCT | 20 | 2185 | 232.4 | 19 | <0.001 | 91.8 | 0.70 | 0.36 – 1.03 | <0.001 | 642 | 110 |
| *Adjusted for publication bias* | *(24)*[e] | - | - | - | - | - | *0.26* | *-0.10 – 0.68* | *ns* | - | - |
| NRCT | 8 | 450 | 14.9 | 7 | =0.037 | 53.1 | 0.28 | -0.00 – 0.57 | ns | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UCT | 7 | 215 | 6.0 | 6 | =0.424 | 0.0 | 0.55 | 0.40 – 0.70 | <0.001 | 90 | 45 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.51* | *0.36 – 0.66* | *<0.05* | - | - |
| Between group[f] | 35 | 2850 | 3.9 | 2 | Ns | - | - | - | - | - | - |
| **Intervention types** | | | | | | | | | | | |
| CBT | 7 | 475 | 39.0 | 6 | <0.001 | 84.6 | 0.84 | 0.33 – 1.35 | =0.001 | 107 | 45 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.37* | *-0.19 – 0.93* | *ns* | - | - |
| MBI | 9 | 841 | 57.7 | 8 | <0.001 | 86.1 | 0.61 | 0.17 – 0.65 | <0.001 | 158 | 55 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.42* | *0.01 – 0.84* | *<0.05* | - | - |
| Other | 19 | 1430 | 149.2 | 9 | <0.001 | 87.9 | 0.50 | 0.18 – 0.81 | =0.002 | 246 | 105 |
| *Adjusted for publication bias* | *(24)*[e] | - | - | - | - | - | *0.17* | *-0.20 – 0.54* | *ns* | - | - |
| Between group[f] | 35 | 2746 | 1.3 | 2 | Ns | - | - | - | - | - | |
| **Intervention format** | | | | | | | | | | | |
| Group | 20 | 1484 | 87.2 | 19 | <0.001 | 78.2 | 0.76 | 0.55 – 0.98 | <0.001 | 959 | 110 |
| *Adjusted for publication bias* | *(26)*[e] | - | - | - | - | - | *0.50* | *0.25 – 0.75* | *<0.05* | - | - |
| Individual | 9 | 834 | 17.7 | 8 | =0.023 | 54.9 | 0.13 | -0.08 – 0.35 | ns | - | - |
| Couples | 3 | 284 | 92.3 | 2 | <0.001 | 97.8 | 1.07 | -1.02 – 3.16 | ns | - | - |
| Online | 3 | 248 | 1.2 | 2 | =0.541 | 0.00 | 0.03 | -0.22 – 0.28 | ns | - | -- |
| Between group[f] | 35 | 2850 | 24.5 | 3 | <0.001 | - | - | - | - | - | |

[a)] Q-statistic: *p*-values < 0.1 taken to suggest heterogeneity. $I^2$ statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity), 75% (high heterogeneity).
[b)] ESR = Hedges g. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size in the hypothesized direction, i.e. reduced pain or relative smaller increased in pain in the intervention group. All ES's were combined using a random effects model. To ensure independency, if a study reported results for more than one pain measure, the ES's were combined (mean), ensuring that only one ES per study was used in the calculation.
[c)] Failsafe N = number of non-significant studies that would bring the p-value to non-significant ($p > 0.05$)
[d)] A Failsafe N exceeding the criterion (5 x k + 10) indicates a robust result [98].
[e)] If analyses indicated the possibility of publication bias, missing studies were imputed and an adjusted ESR calculated (italics), (K) indicates number of published studies + number of imputed studies.
[f)] Meta-ANOVA (between-study comparisons)
[h)] RCT (randomized controlled trial), NRCT (Non-randomized Controlled Trial), UCT (uncontrolled trial (pre-post))

*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 reduced to a non-significant 0.29 after adjusting for possible publication bias. For men alone, the ES (0.13) did not reach statistically significance.

*State anxiety*

Twenty-five studies had included state anxiety as 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 5 studies (N = 633) had included measures of marital function, and 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, we, when a sufficient number of studies were available for each analysis, explored possible sources of heterogeneity and analyzed whether the ESs 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 ESs found for pregnancy outcomes were statistically significant for both randomized controlled trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.8), with the ES for NRCT

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 both 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 failsafe 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, however, did not reach statistical significance. Furthermore, the results suggested the possibility of publication bias, and when adjusting for publication bias, all three ESs were reduced from medium to small.

*Intervention format*

For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats. Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group difference did not reach statistical significance. For the combined psychological outcomes, a statistically significant effect was found for Group format (g= 0.76) ($p < 0.001$). The ESs for intervention formats such as Individual, Couples, and Online did not reach statistical significance. The overall between-group difference for intervention formats was statistical 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 analyzed 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 6 studies had

examined effects on both 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 ESs for anxiety and pregnancy, indicating that the greater the reduction in anxiety, the greater the likelihood of achieving pregnancy (see Table 4).

**Table 4. Results of meta-regression analyses**

| Dependent variable | Independent variable | K | Beta[a] | 95% CI | *p* |
|---|---|---|---|---|---|
| Pregnancy | ES- Anxiety | 6 | 0.19 | 0.06 – 0..31 | **0.004** |
| | Mean age | 9 | -0.05 | -0.19 – 0.10 | 0.534 |
| | Intervention duration | 9 | 0.01 | -0.03 – 0.06 | 0.669 |
| | Number of sessions | 9 | -0.00 | -0.08 – 1.07 | 0.922 |
| | Study quality (Quality scores)[b] | 10 | -0.02 | -0.09 – 0.04 | 0.477 |
| Psych.Combined | Mean age | 32 | -0.05 | -0.12 - -0.02 | 0.214 |
| | Intervention duration | 32 | 0.01 | -0.02 – 0.04 | 0.518 |
| | Number of sessions | 27 | 0.03 | -0.01 – 0.07 | 0.150 |
| | Study quality (Quality scores) [b,c] | 35 | -0.02 | -0.06 – 0.02 | 0.415 |

[a)] Mixed effects regression: unrestricted maximum likelihood; [b)] Modified Jadad quality score; [c)] P-values for individual psychological outcomes; 0.09 (anxiety) – 0.58 (depression).

## 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 to controls receiving standardized 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 favor of studies with larger positive effect sizes. It should also be noted that the precision of the effect size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. Furthermore, although the between-group difference did not reach statistical significance, when disregarding the possibility of publication bias, NRCT's yielded greater effects (RR: 2.8 (95 % CI: 1.55 – 5.06)) than RCT's (RR: 1.7 (95 % CI: 1.17 – 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 confidence interval is substantial. While the results could be considered surprising, the available data do 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 effect sizes (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, effect size 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 of a total of 3401 women (3064) and men (347). The participants received various psychosocial interventions lasting from one week to six months, including cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions. 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. 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, e.g. online interventions, individual, and couples intervention.[30] The first review published in 2003 also highlighted group interventions as more effective, especially if the interventions emphasized 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. Here, it should be noted that the categorization of interventions may be somewhat ambiguous. For example, the study by Cousineau et al. (2000) [83] could have been categorized as a mind-body intervention, 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 categorized as MBI. The possible ambiguity and considerable variability in interventions forced us to categorize many studies as "other", which limits our understanding the possible mechanisms in psychosocial interventions. Taken together, the available data do not provide a clear basis for understanding 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 dataset considerably, and taken together, the currently available evidence suggests that offering psychosocial interventions may improve both chances of pregnancy and 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 was insufficient, and asked authors of papers written in foreign language to submit their results to us in English. The included studies represented a range of different countries, has 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 possible affect the accuracy of the effect sized 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, e.g. 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 RCT's, where randomization is expected to reduce their influence. Although the difference did not reach statistical significance, RCTs reported smaller ESs 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 statistical 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 failsafe numbers, improvements generally appeared quite robust. A second possible limitation is the high level of heterogeneity indicated by Q and $I^2$ statistics, and the pooled effect sizes 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 intention-to-treat analyses may have influenced the results, and it cannot be excluded that fertility- and treatment-related factors such as non-optimal fertilization, small number of eggs, etc. may have demotivated some participants and made them drop out 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 pos-

sibility of a "file drawer problem", i.e. the existence of relevant unpublished null-findings, a common problem when conducting systematic reviews. Finally, due to inconsistencies in the reporting of causes of infertility, we are unable to evaluate the possible associations between effect sizes 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 involuntarily childlessness, and rumination about the involuntary childlessness may persist, even when psychosocial intervention improves general psychological wellbeing. 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. Firstly, group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3)

than individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive impact of "group settings" i.e. 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 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 generalized 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 generalizability 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 not only dropouts and completers, but also 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 the 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 optimize effects on distress and pregnancy rates, and which biomarkers affected by psychosocial interventions, e.g. 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 intervention, in particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety and depressive symptoms 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.

## Acknowledgements

We would like to thank Gina Bay, Librarian at the Institute Library, Institute of Psychology and Behavioral Sciences, School of Business and Social Sciences, Aarhus University for valuable and tireless assistance throughout the database search process. We would also like to give our most grateful thanks to the researchers who provided us with additional data on their studies or aided us in other ways.

Contributors: RZ and YF designed the protocol. YF developed search strategies and IFV, NGS and YF performed the searches and study selection. YF and IFV undertook data extraction and quality assessments. RZ was responsible for analyzing the data. YF drafted the manuscript and IFV, NGS, HJI and RZ contributed to the manuscript throughout the process. All authors provided input and were involved with the interpretation of this review. YF is the study guarantor.

Funding: This specific study has not received funding, but Y.F. was supported by a research grant from The Danish Agency for Science Technology and Innovation.

Competing interests: None declared

Ethical approval**:** None required

Data sharing: No additional data available

**What is already known on this topic**

Previous reviews have been inconclusive concerning the efficacy of psychosocial interventions for reducing distress and improving clinical pregnancy chances.

**What this study adds**

Synthesizing the currently available evidence suggests that psychosocial interventions could provide clinically meaningful benefits for infertile women and men. Psychosocial intervention leads to reductions in anxiety and depressive symptoms, and larger reductions in anxiety appear to be associated with increased fertility rates for women in treatment for infertility.

**Legends to figures**

Figure 1. PRISMA flowchart of selection of studies

Figure 2. Effects of psychosocial intervention on pregnancy rates

Figure 3. Effects of psychosocial intervention on combined psychological outcomes

## References

1. Hart VA. Infertility and the role of psychotherapy. *Issues Ment Health Nurs*. 2002;23(1):31-41.

2. Oddens BJ, den Tonkelaar I, Nieuwenhuyse H. Psychosocial experiences in women facing fertility problems--a comparative survey. *Hum Reprod*. 1999;14(1):255-261.

3. Cwikel J, Gidron Y, Sheiner E. Psychological interactions with infertility among women. *Eur J Obstet Gynecol Reprod Biol*. 2004;117(2):126-131.

4. Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: An analysis of 101 studies published 1934-1996. *Environ Health Perspect*. 2000;108(10):961-966.

5. Skakkebaek NE, Jorgensen N, Main KM, et al. Is human fecundity declining? *Int J Androl*. 2006;29(1):2-11.

6. Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005;1:293-319.

7. Benyamini Y, Gozlan M, Kokia E. Variability in the difficulties experienced by women undergoing infertility treatments. *Fertil Steril*. 2005;83(2):275-283.

8. Alesi R. Infertility and its treatment--an emotional roller coaster. *Aust Fam Physician*. 2005;34(3):135-138.

9. Merari D, Chetrit A, Modan B. Emotional reactions and attitudes prior to in vitro fertilization: An inter-spouse study. *Psychol Health*. 2002;17(5):629-640.

10. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertil Steril*. 2001;76(4):675-687.

11. Edelmann RJ, Connolly KJ, Bartlett H. Coping strategies and psychological adjustment of couples presenting for IVF. *J Psychosom Res*. 1994;38(4):355-364.

12. Eugster A, Vingerhoets AJ. Psychological aspects of in vitro fertilization: A review. *Soc Sci Med*. 1999;48(5):575-589.

13. Stanton AL, Dunkel-Schetter C, eds. *Psychological adjustment to infertility: An overview of conceptual approaches.* Stanton, Annette L.; Dunkel-Schetter, Christine . Infertility: Perspectives

from stress and coping research. The Plenum series on stress and coping. (pp. 3-16). New York, NY, US: Plenum Press; 1991Infertility: Perspectives from stress and coping research.

14. Benyamini Y, Gozlan M, Kokia E. Women's and men's perceptions of infertility and their associations with psychological adjustment: A dyadic approach. *British Journal of Health Psychology*. 2009;14:1-16. doi: 10.1348/135910708X279288.

15. du Plessis S,S., Makker K, Desai NR, Agarwal A. Impact of oxidative stress on IVF. *Expert Review of Obstetrics & Gynecology*. 2008;3(4):539-554. http://dx.doi.org/10.1586/17474108.3.4.539. doi: 10.1586/17474108.3.4.539.

16. Agarwal A, Allamaneni SS. Role of free radicals in female reproductive diseases and assisted reproduction. *Reprod Biomed Online*. 2004;9:338-347.

17. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853-859. doi: 10.1038/nature01321 [doi].

18. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: New perspectives from psychoneuroimmunology. *Annu Rev Psychol*. 2002;53:83-107. doi: 10.1146/annurev.psych.53.100901.135217 [doi].

19. Csemiczky G, Landgren BM, Collins A. The influence of stress and state anxiety on the outcome of IVF-treatment: Psychological and endocrinological assessment of swedish women entering IVF-treatment. *Acta Obstet Gynecol Scand*. 2000;79(2):113-118.

20. Stoleru S, Teglas JP, Fermanian J, Spira A. Psychological factors in the aetiology of infertility: A prospective cohort study. *Hum Reprod*. 1993;8(7):1039-1046.

21. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of coping influence the outcome of in vivro fertilization through stress responses. *Psychoneuroendocrinology*. 1992;17(6):655-665. doi: http://dx.doi.org/10.1016/0306-4530(92)90024-2.

22. Sanders KA, Bruce NW. Psychosocial stress and treatment outcome following assisted reproductive technology. *Human Reproduction*. 1999;14(6):1656-1662. doi: 10.1093/humrep/14.6.1656.

23. Smeenk JM, Verhaak CM, Vingerhoets AJ, et al. Stress and outcome success in IVF: The role of self-reports and endocrine variables. *Hum Reprod*. 2005;20(4):991-996.

24. Ebbesen SM, Zachariae R, Mehlsen MY, et al. Stressful life events are associated with a poor in-vitro fertilization (IVF) outcome: A prospective study. *Hum Reprod*. 2009;24(9):2173-2182. doi: 10.1093/humrep/dep185; 10.1093/humrep/dep185.

25. Klonoff-Cohen H. Female and male lifestyle habits and IVF: What is known and unknown. *Hum Reprod Update*. 2005;11(2):179-203.

26. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: A review. *Hum Reprod Update*. 2007;13(3):209-223. doi: 10.1093/humupd/dml056.

27. Matthiesen SM, Frederiksen Y, Ingerslev HJ, Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): A meta-analysis. *Hum Reprod*. 2011;26(10):2763-2776. doi: 10.1093/humrep/der246; 10.1093/humrep/der246.

28. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: Meta-analysis of prospective psychosocial studies. *BMJ*. 2011;342:d223. doi: 10.1136/bmj.d223.

29. Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med*. 2003;57(12):2325-2341.

30. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Hum Reprod*. 2005;20(5):1324-1332.

31. Haemmerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: A meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279-295. doi: 10.1093/humupd/dmp002.

32. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi: 10.1136/bmj.g1687.

33. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. http://dx.doi.org/10.1371%2Fjournal.pmed.1000100.

34. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. http://dx.doi.org/10.1371%2Fjournal.pmed.1000097.

35. Higgins J, Green S, eds. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0 [updated March 2011] ed. The Cochrance Collaboration; 2011. Available from www.cochrane-handbook.org.

36. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. *Hum Reprod Update*. 2011;17(5):575-588.

37. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.

38. Greenland S, O'rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics*. 2001;2(4):463-471. doi: 10.1093/biostatistics/2.4.463.

39. Cohen J. *Statistical power analysis for the behavioral sciences.* Hillsdale, N.J.: Lawrence Erlbaum Associates; 1988.

40. Hedges L, Olkin I. *Statistical methods for meta-analysis.* New York: Acedemic Press; 1985.

41. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. *Psychother Psychosom*. 1999;68(1):15-21.

42. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology*. 2005;5(1):13. http://www.biomedcentral.com/1471-2288/5/13.

43. Sterne JAC, Egger M, Moher D. Addressing reporting biases. In: John Wiley & Sons, Ltd; 2008:297-333. http://dx.doi.org/10.1002/9780470712184.ch10. 10.1002/9780470712184.ch10.

44. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *American Journal of Epidemiology*. 1999;150(5):469-475.

45. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi: 10.1136/bmj.327.7414.557.

46. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods*. 2001;6(3):203-217.

679 47. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in me-
680 ta-analyses: A large survey. *CMAJ*. 2007;176(8):1091-1096. doi: 10.1503/cmaj.060410.

681 48. Copas J, Shi JQ. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics*.
682 2000;1(3):247-262. doi: 10.1093/biostatistics/1.3.247.

683 49. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample
684 size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*.
685 2005;58(9):882-893. doi: 10.1016/j.jclinepi.2005.01.016.

686 50. Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder. Bias in meta-
687 analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:
688 10.1136/bmj.315.7109.629.

689 51. Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull*.
690 1979;86(3):638-641. doi: 10.1037/0033-2909.86.3.638.

691 52. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting
692 for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

693 53. Gutierrez K. Group psychological intervention in assisted human reproduction. *Rev Iberoam*
694 *Fertil Reprod Humana*. 2008;25(SUPPL. 1):47-54.

695 54. Bjornsen K. Opening the door to fertility. retreat to fertile ground: Sometimes the secret to get-
696 ting pregnant lies in just getting away from it all. *ALTERN MED*. 2006(88):80-81.
697 http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009216983&site=ehost-live.

698 55. Pengelly P, Inglis M, Cudmore L. Infertility: Couples' experiences and the use of counselling in
699 treatment centres. *Psychodynamic Counselling*. 1995;1(4):507-524.

56. Stewart DE, Boydell KM, McCarthy K, Swerdlyk S, Redmond C, Cohrs W. A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. *Int J Psychiatry Med*. 1992;22(2):173-182.

57. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-174.

58. Nilforooshan P, Ahmadi A, Abedi MR, Ahmadi M. Counseling based on interacting cognitive subsystems and its effect on anxiety of infertile couples. *Pakistan Journal of Psychological Research*. 2006;21(3-4):95-103. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/621710509?accountid=14468.

59. Schmidt L, Holstein BE, Christensen U, Boivin J. Communication and coping as predictors of fertility problem stress: Cohort study of 816 participants who did not achieve a delivery after 12 months of fertility treatment. *Hum Reprod*. 2005;20(11):3248-3256. doi: 10.1093/humrep/dei193.

60. Galhardo A, Cunha M, Pinto-Gouveia J. Mindfulness-based program for infertility: Efficacy study. *Fertil Steril*. 2013.

61. Faramarzi M, Kheirkhah F, Esmaelzadeh S, Alipour A, Hjiahmadi M, Rahnama J. Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2008;141(1):49-53.

62. Lukse MP. The effect of group counseling on the frequency of grief reported by infertile couples. *JOGNN*. 1985;14(6):67S-70s. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=1986045607&site=ehost-live. doi: 10.1111/j.1552-6909.1985.tb02804.x.

63. Domar AD, Seibel MM, Benson H. The mind/body program for infertility: A new behavioral treatment approach for women with infertility. *Fertil Steril*. 1990;53(2):246-249.

64. Domar AD, Zuttermeister PC, Seibel M, Benson H. Psychological improvement in infertile women after behavioral treatment - a replication. *Fertil Steril*. 1992;58(1):144-147.

65. Emery M, Béran M-, Darwiche J, et al. Results from a prospective, randomized, controlled study evaluating the acceptability and effects of routine pre-IVF counselling. *Human Reproduction*. 2003;18(12):2647-2653. doi: 10.1093/humrep/deg501.

66. Lee S. Effects of using a nursing crisis intervention program on psychosocial responses and coping strategies of infertile women during in vitro fertilization. *J NURS RES*. 2003;11(3):197-207. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2004076404&site=ehost-live.

67. Chan CHY, Ng EHY, Chan CLW, Ho, Chan THY. Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: A randomized controlled study. *Fertil Steril*. 2006;85(2):339-346.

68. Tuil WS, Verhaak CM, Braat DD, de Vries Robbe PF, Kremer JA. Empowering patients undergoing in vitro fertilization by providing internet access to medical data. *Fertil Steril*. 2007;88(2):361-368. doi: 10.1016/j.fertnstert.2006.11.197.

69. Lancastle D, Boivin J. A feasibility study of a brief coping intervention (PRCI) for the waiting period before a pregnancy test during fertility treatment. *Hum Reprod*. 2008;23(10):2299-2307.

70. Mori A. Supporting stress management for women undergoing the early stages of fertility treatment: A cluster-randomized controlled trial. *Jpn J Nurs Sci*. 2009;6(1):37-49.

71. Panagopoulou E, Montgomery A, Tarlatzis B. Experimental emotional disclosure in women undergoing infertility treatment: Are drop outs better off? *Soc Sci Med*. 2009;69(5):678-681.

72. Haemmerli K, Znoj H, Berger T. Internet-based support for infertile patients: A randomized controlled study. *Journal of Behavioral Medicine*. 2010;33(2):135-146.

73. Hughes EG, Da Silva AM. A pilot study assessing art therapy as a mental health intervention for subfertile women. *Hum Reprod*. 2011;26(3):611-615.

74. Matthiesen S, Klonoff-Cohen H, Zachariae R, et al. The effect of an expressive writing intervention (EWI) on stress in infertile couples undergoing assisted reproductive technology (ART) treatment: A randomized controlled pilot study. *Br J Health Psychol*. 2012;17(2):362-378. doi: 10.1111/j.2044-8287.2011.02042.x; 10.1111/j.2044-8287.2011.02042.x.

75. Mosalanejad L, Koolaee AK, Behbahani BM. Looking out for the secret wound: The effect of E-cognitive group therapy with emotional disclosure on the status of mental health in infertile women. *Int J Fertil Steril*. 2012;6(2):87-94.

76. Mosalanejad L, Koolaee AK, Jamali S. Effect of cognitive behavioral therapy in mental health and hardiness of infertile women receiving assisted reproductive therapy (ART). *Iranian Journal of Reproductive Medicine*. 2012;10(5):483-488.

77. Catoire P, Delaunay L, Dannappel T, et al. Hypnosis versus diazepam for embryo transfer: A randomized controlled study. *Am J Clin Hypn*. 2013;55(4):378-386. doi: 10.1080/00029157.2012.747949.

78. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychology*. 2000;19(6):568-575. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/619538260?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1037/0278-6133.19.6.568.

79. O'Moore AM, O'Moore RR, Harrison RF. Psychosomatic aspects in idiopathic infertility: Effects of treatment with autogenic training. *J Psychosom Res*. 1983;27(2):145-151.

80. McQueeney D, Stanton A, Sigmon S. Efficacy of emotion-focused and problem-focused group therapies for women with fertility problems. *J Behav Med*. 1997;20(4):313-331. doi: 10.1023/A:1025560912766.

81. Koszycki D, Bisserbe J, Blier P, Bradwejn J, Markowitz J. Interpersonal psychotherapy versus brief supportive therapy for depressed infertile women: First pilot randomized controlled trial. *Archives of Women's Mental Health*. 2012;15(3):193-201.

82. Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile women following a group treatment program: An open pilot study. *General Hospital Psychiatry*. 1996;18(3):192-195.

83. Cousineau TM, Green TC, Corsini E, et al. Online psychoeducational support for infertile women: A randomized controlled trial. *Hum Reprod*. 2008;23(3):554-566.

84. Noorbala AA, Ramazanzadeh F, Malekafzali H, et al. Effects of a psychological intervention on depression in infertile couples. *Int J Gynecol Obstet*. 2008;101(3):248-252.

85. Sexton MB, Byrd MR, O'Donohue WT, Jacobs NN. Web-based treatment for infertility-related psychological distress. *Arch Women's Ment Health*. 2010;13(4):347-358.

86. Sarrel PM, DeCherney AH. Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertil Steril*. 1985;43(6):897-900.

87. Hosaka T, Matsubayashi H, Sugiyama Y, Izumi S, Makino T. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. *Gen Hosp Psychiatry*. 2002;24(5):353-356.

88. Levitas E, Parmet A, Lunenfeld E, et al. Impact of hypnosis during embryo transfer on the outcome of in vitro fertilization-embryo transfer: A case-control study. *Fertil Steril*. 2006;85(5):1404-1408. doi: 10.1016/j.fertnstert.2005.10.035.

89. Domar AD, Rooney KL, Wiegand B, et al. Impact of a group mind/body intervention on pregnancy rates in IVF patients. *Fertil Steril*. 2011;95(7):2269-2273. doi: http://dx.doi.org/10.1016/j.fertnstert.2011.03.046.

90. Gorayeb R, Borsari AC, Rosa-e-Silva AC, Ferriani RA. Brief cognitive behavioral intervention in groups in a brazilian assisted reproduction program. *Behav Med*. 2012;38(2):29-35. doi: 10.1080/08964289.2012.654834; 10.1080/08964289.2012.654834.

91. Terzioglu F. Investigation into effectiveness of counseling on assisted reproductive techniques in turkey. *J Psychosom Obstet Gynecol*. 2001;22(3):133-141.

92. de Klerk C, Hunfeld JAM, Duivenvoorden HJ, et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: A randomized controlled trial. *Hum Reprod*. 2005;20(5):1333-1338.

93. Vizheh M, Pakgohar M, Babaei G, Ramezanzadeh F. Effect of counseling on quality of marital relationship of infertile couples: A randomized, controlled trial (RCT) study. *Arch Gynecol Obstet*. 2013;287(3):583-589.

94. Chan CH, Chan CL, Ng EH, et al. Incorporating spirituality in psychosocial group intervention for women undergoing in vitro fertilization: A prospective randomized controlled study. *Psychol Psychother*. 2012;85(4):356-373.

95. Domar A, Clapp D, Slawsby E, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril*. 2000;73(4):805-811. doi: 10.1016/S0015-0282(99)00493-8.

96. McNaughton-Cassill M, Bostwick JM, Arthur NJ, Robinson RD, Neal GS. Efficacy of brief couples support groups developed to manage the stress of in vitro fertilization treatment. *Mayo Clin Proc*. 2002;77(10):1060-1066. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2003034100&site=ehost-live.

97. Galhardo A, Cunha M, Pinto-Gouveia J. Developing mindfulness and acceptance skills in infertility: The mindfulness based program for infertility. *Aten Prim*. 2013;45:143.

98. Chen JH, Bierhals AJ, Prigerson HG, Kasl SV, Mazure CM, Jacobs S. Gender differences in the effects of bereavement-related psychological distress in health outcomes. *Psychol Med*. 1999;29(2):367-380.

99. Navot D, Bergh RA, Williams MA, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *The Lancet*. 1991;337(8754):1375-1377. doi: http://dx.doi.org/10.1016/0140-6736(91)93060-M.

100. Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. *Human Reproduction*. 2002;17(5):1399-1403. doi: 10.1093/humrep/17.5.1399.

101. Van den Broeck U, Emery M, Wischmann T, Thorn P. Counselling in infertility: Individual, couple and group interventions. *Patient Educ Couns*. 2010;81(3):422-428. doi: 10.1016/j.pec.2010.10.009.

102. Burns LH(, Covington SN(. *Infertility counseling: A comprehensive handbook for clinicians.* New York, NY, US: Parthenon Publishing Group; 1999:xvii.

103. Boivin J, Appleton TC, Baetens P, et al. Guidelines for counselling in infertility: Outline version. *Hum Reprod*. 2001;16(6):1301-1304.

104. Boivin J, Kentenich H, eds. *Guidelines for counselling in infertility.* ESHRE Monographs: Oxford University Press; 2002.

105. Gameiro S, Boivin J, Domar A. Optimal in vitro fertilization in 2020 should reduce treatment burden and enhance care delivery for patients and staff. *Fertil Steril*. 2013;100(2):302-309. doi: 10.1016/j.fertnstert.2013.06.015 [doi].

# Title Page

| |
|---|
| **Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: A systematic review and meta-analysis** |
| Yoon Frederiksen, Ingeborg Farver-Vestergaard, Ninna Grønhøj Skovgård, Hans Jakob Ingerslev, Robert Zachariae |
| Unit for Psychooncology and Health Psychology, Department of Psychology, University of Aarhus, 8000 Aarhus, Denmark Yoon Frederiksen MSc. Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, University of Aarhus, 8000 Aarhus, Denmark Ingeborg Farver-Vestergaard MSc., Psychology, PhD-fellow Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Science, Aarhus University, 8000 Aarhus, Denmark Ninna Grønhøj Skovgaard, research assistant, Skejby Fertility Clinic, Aarhus University Hospital, 8200 Aarhus Denmark. Hans Jakob Ingerslev, Professor, MD, DMSc, Unit for Psychooncology and Health Psychology, Department of Psychology, Aarhus University, 8000 Aarhus, Denmark Department of Oncology, Aarhus University Hospital, 8000 Aarhus Denmark Robert Zachariae, DMSci., professor. |
| Correspondence to: Yoon Frederiksen yoonf@psy.au.dk Phone no. +45 8716 5872 |
| Keywords: infertility/psychosocial intervention/distress/pregnancy |
| Word count: 4.852 |
|  |
| Competing interest: All authors have completed the Unified Competing Interest form and are available upon request from the Corresponding Author |

## 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 assessed. Effect sizes (Hedges *g*) were pooled using a random effect model. Heterogeneity was assessed using the *Q* statistic and $I^2$, and publication bias evaluated using Eggers' method. Possible moderators and mediators were explored with meta-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 (RR = 2.01; CI: 1.48-2.73; $p<0.001$) and combined psychological outcomes (Hedges $g=0.59$; CI: 0.38-0.80; $p=0.001$,). The pooled effect sizes (ES) for psychological outcomes were generally larger for women (*g*: 0.51-0.73) than men (0.13-0.34), 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 behavioral therapy (CBT) ($g=0.84$), mind-body interventions (0.61), and other intervention types (0.50).

**Conclusion** The present meta-analysis suggests that psychosocial interventions for couples in treatment for infertility, in particular CBT, could be efficacious, both in reducing psychological distress and in improving clinical pregnancy rates.


## 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
- Substantial variation of the methodological quality and missing information on fertility and ART treatment may limit the interpretability of the outcomes

## 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, e.g. oxidative stress and inflammation,[15,16] which may be promoted by psychological distress.[17,18] Such findings have lead 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, e.g. in the chosen measures of distress and definitions of pregnancy (e.g. 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, optimize 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 counseling 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, e.g. individual/couple vs. 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, e.g. mind/body interventions, web-based treatments, and online psycho-education programs, have since been published. Furthermore, the more recently pub-

lished studies have generally used randomized controlled trial 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 which 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-analysis (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 fertilization) 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: (i) "infertil*", "childlessness", "IVF", "ICSI", "fertility treatment/problems" "assisted reproduction" and (ii) "psychological/psychosocial intervention", "social support", "couples therapy", "psycho-education", "internet-based intervention" and "behavioral therapy" (for a full search history, see 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 program 3) included both baseline and post-

intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research approach. In general terms, infertility refers to not being able to conceive for more than one 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, e.g. intrauterine insemination (IUI), in vitro fertilization (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 had a primary physical focus, e.g. acupuncture or massage therapy. However, studies using "psychophysiological" approaches, e.g. relaxation, guided imagery or meditation exercises as part of a psychosocial program, were included. The interventions could be delivered in individual-, group-, couples-, or internet-based format. We included both controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines, commentaries, case reports, editorials, newspaper articles, newsletters, and books 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 visualization of at least one gestational sack and fetal heartbeat in approximately the 5$^{th}$ week after fertilization. Secondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalized 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 (IFV, NGS) and the data 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, e.g. use and adequate description of randomization- and blinding procedures, and description of drop-out rates (score range: 0-5). In addition to the 0-5 points possible on the original Jadad scale, one additional point was given for each of the following: (a) *was a control group included*; in order to acknowledge whether the intervention group was compared with another group, although randomization was not used, (b) *were both pre- and post-data presented;* as including both pre- and post-intervention data will provide more accurate results. (c) *Was any form of blinding or masking of conditions to patients, or (d) blinding of researchers attempted*; acknowledging if the study had attempted to masking the active condition, (e) *was a standardized and reliable outcome measure used;* a criterion increasing the validity and comparability of the outcomes, and (f) *were pre-post correlations provided*; which could provide better estimates of the effect size. The modified scale yielded a total quality score ranging from 0-11. 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). Kappa 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 effect sizes (ES) as this is generally discouraged due to the risk of introducing additional bias.[38] Instead, associations between ESs and study quality indicators were explored with meta-ANOVAs (design) and meta-regression (modified quality-score). In cases where we were unable to retrieve articles from the authorized databases, authors were contacted between 1-3 times in order to amend the data collected.

**Calculating effect sizes**

The effect sizes (ESs) 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 size.[39,40] A positive Hedges' *g* indicates result in the expected direction, e.g. a reduction in distress in the intervention group compared to controls. A 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 (k=10) (k = number of studies). When possible, Hedges' *g* was calculated on the basis of reported means and SDs at pre and post-intervention or means and SDs of change scores. This was possible for 50 of 61 effect sizes. When required and available, the reported pre-post correlations were used in the calculation. This was the case for 5 ES's. When unavailable, the pre-post correlation was set to 0.50. When SDs were unavailable, two approaches were used. For STAI state anxiety scores, the average pre- and post SDs (10.9 and 10.8) for the studies which reported the SD was used, as the SDs appeared to be highly comparable across the remaining studies. For other measures, ESs were estimated either on the basis of sample size and either p-value or Eta square. 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 ESs 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 ESs for the individual outcome measures of depression, state anxiety, infertility-related distress, and marital function. This was done for the combined sample (women + men). If the results indicated study heterogeneity, and if the number of studies in each category was sufficient (K≥3), possible between-study differences in ESs were explored by comparing the ESs 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] Based on the findings of the earlier meta-analysis, [31] we expected to find a 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 alpha of 5% and a statistical power of 80%, with a total of only 9 studies, using a random-effects model. Based on these results, we considered it worthwhile to conduct the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2 (www.meta-analysis.com), IBM SPSS-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 ESs 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's trim and fill method,[52] which imputes ESs 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 "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; $p < 0.001$ (Kappa 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 authors provided unpublished additional data.[58-60] Figure 1 shows a flow chart of the study selection process.

(Insert Figure 1 near here)

### Study characteristics

The study characteristics are summarized in Table 1. Based on 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 5 studies had included distress as well as pregnancy as outcome.[78,91-94] Twenty-one studies were randomized controlled trials (RCTs),[58,61,65-72,74,75,83,85,89-95] and ten studies were non-randomized controlled studies (NRCTs),[41,59,60,76,79,80,86-88,96] with most control groups receiving standardized care or being waiting-list controls. Only three studies had included an active/attention control condition, e.g.

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 uncontrolled (UCT) (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 studies reported that some, but not how many, of the participants were in treatment, and 31 studies reported that their participants were currently in ART treatment, although not what kind of treatment e.g. 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 studies 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 was (32.7 yrs. SD 2.2) and (4.6 yrs. SD 2.1) and for control group participants (32.6 yrs. SD=1.7) and (5.1 yrs. SD=3.0). The specific intervention strategies mostly employed were cognitive behavioral therapy (k=8) and mind/body intervention (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 counseling. Some studies had included more than one approach, e.g. cognitive behavioral approaches supplemented with mind-body techniques such as relaxation. To be categorized as mind/body intervention, a study had to use such strategies as the general approach over the course of intervention. Thus, if studies had mainly used cognitive behavioral therapy strategies and only incorporated other approaches, e.g., relaxation exercises, in one or two sessions, they were categorized as cognitive behavioral therapy interventions. The number of sessions ranged from 1 to 24, lasting approximately from 20 minutes to 3 hours 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, dropout 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 ex-

plicitly 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, e.g. carrying last (baseline) observations forward or use of multilevel linear modeling.[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 ESs and uneven dropout in the intervention and control groups was analyzed for the 15 studies that reported dropout by regressing the difference in dropout rates on the overall ESs across all outcomes. The result indicated that larger dropouts in the intervention group compared were generally associated with smaller ES's (Slope = -0.02), but the association did not reach statistical significance (p = 0.268).

**Table 1. Characteristics of included studies**

| Author | Country | Participants (N) I: Intervention C: Control assigned (final analysis) (men %) | Study design[a] | Intervention type[b] | Intervention category[c] | Intervention format | Number of sessions | Intervention duration (weeks) | Outcome: Psychological[d] IS: Infertility stress A: Anxiety D: Depression MF: Marital function | Outcome: Pregnancy[e](+/-) | Quality score[f] J: Jadad 0-5 MJ: Modified Jadad 0-12 J (MJ) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| O'Moore et al. 1983 | Ireland, UK | I: 30 (22) (50 %) C: 20 (20) (50 %) | NRCT | Autogenic training | MBI | Group | 8 | 8 | D: BDI A: STAI | - | 1 (4) |
| Lukse 1985 | USA | I: 29 (29 (14)) | UCT | Counseling | Other | Group | 6 | 6 | D: DES | - | 0 (3) |
| Sarrel and DeCherney 1985 | USA | I: 20 (10) C: 20 (9) | NRCT | Psychotherapeutic interview | Other | Couples | 1 | 1 | | + | 0 (1) |
| Domar et al. 1990 | USA | I: 54 (54) | UCT | Mind/Body program | MBI | Group | 10 | 10 | A: STAI | - | 0 (3) |
| Domar et al. 1992 | USA | I: 52 (41) | UCT | Behavioral Medicine Program for Infertility | MBI | Group | 10 | 10 | A: STAI | - | 1 (3) |
| Galletly et al. 1996 | Australia | I: 37 (37) | UCT | Treatment program | Other | Group | 24 | 24 | D: HADS A: HADS | - | 1 (3) |
| McQueeney et al. 1997 | USA | I: 20 (20) C: 9 (9) | NRCT | Emotion- and problem-focused therapies | Other | Group | 6 | 6 | IS: ISD D: BDI | - | 3 (7) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tuschen-Caffier et al. 1999 | Germany | I: 34 (22)<br>C: 24 (24) | NRCT | Cognitive-behavioral therapy | CBT | Couples | 10-12 | 32 | IS: one item<br>MF: one item | - | 1 (4) |
| Domar et al. 2000 | USA | I: 56 (20)<br>C: 63 (14) | RCT | Psychological intervention | MBI | Group | 10 | 10 | D: BDI<br>A: STAI | + | 4 (10) |
| Terzioglu 2001 | Turkey | I: 60 (60) (50 %)<br>C: 60 (60) (50 %) | RCT | Counseling | Other | Individual | 5 | 5 | D: BDI<br>A: STAI | + | 2 (5) |
| Hosaka et al. 2002 | Japan | I: 37 (37)<br>C: 37 (37) | NRCT | Structured intervention | MBI | Group | 5 | 5 | | + | 3 (6) |
| McNaughton-Cassill et al. 2002 | USA | I: 43 (43) (39.5 %)<br>C: 37 (37) (48.6 %) | NRCT | Couples support | CBT | Couples | 6 | 3 | D: BDI<br>A: BAI | - | 2 (5) |
| Emery et al. 2003 | Switzerland | I: 158 (110) (34.8 %)<br>C: 152 (131) (42.8 %) | RCT | Pre-IVF counseling | Other | Couples | 1 | 1 | D: BDI<br>A: STAI | - | 3 (6) |
| Lee 2003 | Taiwan | I: 64 (64)<br>C: 68(68) | RCT | Nursing crisis intervention program | MBI | Individual | 7 | 7 | D: SDS<br>A: STAI | - | 1 (4) |
| De Klerk et al. 2005 | The Netherlands | I: 22 (18)<br>C: 22 (15) | RCT | Counseling | Other | Group | 3 | 4-5 | D: HADS<br>A: HADS | + | 3 (6) |
| Schmidt et al. 2005 | Denmark | I: 13 (13)<br>C: 435 (435) | NRCT | Stress management | Other | Group | 5 | 6 | IS: COMPI | - | 1 (4) |
| Chan et al. 2006 | Hong Kong, China | I: 101 (69)<br>C: 126 (115) | RCT | The Eastern body-mind intervention | MBI | Group | 4 | 4 | A: STAI | - | 3 (7) |
| Levitas et al. 2006 | Israel | I: 89 (89)<br>C: 96 (96) | NRCT | Hypnosis | MBI | Individual | 1 | 1 | | + | 0 (1) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nilforooshan et al. 2006 | Iran | I: 30 (30) (50 %) C: 30 (30) (50 %) | RCT | Cognitive-behavioral counseling | CBT | Group | 6 | 6 | D: BDI A: BAI | - | 2 (6) |
| Tuil et al. 2007 | The Nether-lands | 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 et al. 2008 | USA | I: 96 (49) C: 92 (49) | RCT | Psycho-educational support | Other | Online | 1-2 | 4 | IS: FPI MF: RDAS | - | 4 (8) |
| Faramarzi et al. 2008 | Iran | I: 42 (29) C: 40 (30) | RCT | Cognitive-behavioral therapy | CBT | Group | 10 | 10 | D: BDI A: Cattell | - | 3 (6) |
| Lancastle and Boivin 2008 | Wales, UK | I:28 (28) C: 27 (27) | RCT | Brief coping intervention | Other | Individual | 14 | 2 | IS: CIQ | - | 4 (8) |
| Noorbala et al. 2008 | Iran | I: 288 (288) (50 %) | UCT | Cognitive-behavioral therapy | CBT | Group | | 24 | D: BDI | - | 3 (8) |
| Mori 2009 | Japan | I: 85 (85) C: 40 (40) | RCT | Stress man-agement | Other | Individual | 3 | 12 | D: HADS A: HADS | - | 4 (8) |
| Panagopoulou et al. 2009 | England, UK | I: 50 (50) C: 98 (98) | RCT | Expressive writing in-tervention | Other | Individual | 3 | 1 | IS: ISS A: STAI | - | 3 (7) |
| Haemmerli et al. 2010 | Switzer-land | I: 60 (46) C: 64 (41) | RCT | Coaching and support | Other | Online | 13 | 8 | IS: IDS D: CES-D A: STAI | - | 3 (6) |
| Sexton et al. 2010 | USA | I: 21 (15) C: 22 (16) | RCT | Web-based coping with infertility | Other | Individual | | 2 | IS: FPI | - | 3 (6) |
| Domar et al. 2011 | USA | I: 46 (46) C: 51(51) | RCT | Mind/body program for infertility | MBI | Group | 10 | 10 | | + | 4 (6) |
| Hughes and Mann de Silva | Canada | I: 21 (21) | UCT | Art therapy | Other | Group | 8 (2hrs) | 8 | D: BDI A: BAI | - | 0 (2) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 | | | | | | | | | | | |
| Chan et al. 2012 | Hong Kong, China | I: 141 (141) C: 110 (110) | RCT | Integrative body-mind-spirit intervention | MBI | Group | 4 (3hrs) | 4 | A: STAI MF: C-KMS | + | 3 (6) |
| Gorayeb et al. 2012 | Brazil | I: 93 (93) C: 95 (95) | RCT | Brief cognitive-behavioral intervention | CBT | Group | 5 (2hrs) | 5 | | + | 1 (4) |
| Koszycki et al. 2012 | Canada | I: 31 (23) | UCT | Interpersonal and supportive therapy | Other | Individual | 12 (50min) | 12 | IS: FPI D: BDI HAM-D | - | 3 (7) |
| Matthiesen et al. 2012 | Denmark | I: 42 (15) C: 40 (16) | RCT | Expressive writing intervention | Other | Individual | 3 (20min) | 1 | IS: COMPI | - | 4 (8) |
| Mosalanejad et al. 2012 | Iran | I: 32 (32) C: 33 (33) | RCT | Cognitive-behavioral treatment | CBT | Group | 12 (2hrs) | 12 | D: DASS A: DASS | - | 1 (4) |
| Mosalanejad et al. 2012b | Iran | I: 16 (16) C: 15 (15) | NRCT | Cognitive-behavioral therapy | CBT | Group | 15 (1,5hrs) | 16 | D: DASS A: DASS | - | 2 (5) |
| Catoire et al. 2013 | France | I: 50 (50) | UCT | Hypnosis | MBI | Individual | 4 | 1 | A: STAI | - | 4 (7) |
| Galhardo et al. 2013 | Portugal | I: 55 (55) C: 37 (37) | NRCT | Mindfulness-based program for infertility | MBI | Group | 10 (2hrs) | 10 | IS: ISE D: BDI A: STAI | - | 1 (4) |
| Vizheh et al. 2013 | Iran | I: 86 (86) (50 %) C: 94 (86) (54.7 %) | RCT | Marital counseling | Other | Group | 3 (1.5hrs) | 3 | MF: MSQ | + | 4 (8) |

a) *RCT* Randomized controlled trial, *NRCT* non-randomized controlled trial, *UCT* uncontrolled pre-post trial, *NR* Not reported.

b) Self-reported intervention type.

c) Intervention type: *CBT* (Cognitive behavioral therapy); *MBI* (Mind/body intervention): mindfulness, yoga, relaxation, imagery, hypnosis etc.; Other: all other intervention types, e.g. counseling, psycho-education, supportive therapy, expressive writing intervention, brief therapy, emotion and problem focused therapy, and narrative therapy.

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

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

f) *Jadad range 0-5* an assessment tool rating the quality and methodology of the studies included[37] 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 standardized and reliable outcome measures and report of pre-post correlations.

*Quality ratings*

All included studies were methodologically assessed with both 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.

289 **Table 1 Modified Jadad scores (original Jadad criteria + 6 additional criteria)**

| | Jadad criteria | | | | | | | Additional criteria | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | 1 | 2 | 3 | 4 | 5 | 6 | 7 | a | b | C | d | e | f | **Jadad** | **Total** |
| | **Randomized** | **Double blind** | **Withdrawals and drop-outs** | **Randomization (evaluation)** | **Blinding (evaluation)** | **Randomization (evaluation)** | **Blinding (evaluation)** | Control group | Pre- and post-assessment | Blinding (patients) | Blinding (researchers) | Standardized and reliable outcome | Pre-post correlation | **Jadad scores** | **Total scores** |
| O'Moore et al., 1983 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Lukse, 1985 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 1 | **0** | **3** |
| Sarrel et al., 1985 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **0** | **1** |
| Domar et al., 1990 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 1 | **0** | **3** |
| Domar et al., 1992 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **1** | **3** |
| Galletly et al., 1996 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **1** | **3** |
| McQueeney et al., 1997 | **1** | **0** | **0** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Tuschen-Caffier et al., 1999 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Domar et al., 2000 | **1** | **1** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 1 | 1 | 1 | 1 | **4** | **10** |
| Terzioglu, 2001 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **2** | **5** |
| Hosaka et al., 2002 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| McNaughton-Casill et al., 2002[a] | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **2** | **5** |
| Emery et al., 2003 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Lee et al., 2003 | **1** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| De Klerk et al., 2005 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Schmidt et al., 2005 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Chan et al., 2006 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **3** | **7** |
| Levitas et al., 2006 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **0** | **1** |
| Nilforooshan et al., 2006 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **2** | **6** |
| Tuil et al., 2007 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Cousineau et al., 2008 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Faramarzi et al., 2008 | **1** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 1 | **2** | **6** |
| Lancastle and Boivin, 2008 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Noorbala et al., 2008[a] | **1** | **0** | **0** | **1** | **1** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Mori, 2009 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |
| Panagopoulou et al., 2009 | **1** | **0** | **1** | **0** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Haemmerli et al., 2010 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Sexton et al., 2010 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Domar et al., 2011 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 0 | 0 | 1 | 0 | 0 | **4** | **6** |
| Hughes and Mann de Silva, 2011 | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 0 | 1 | 0 | **0** | **2** |
| Chan et al. 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **3** | **6** |
| Gorayeb et al., 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 0 | 0 | 0 | 0 | 0 | **3** | **4** |
| Koszycki et al., 2012 | **1** | **0** | **1** | **1** | **0** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **3** | **7** |
| Matthiesen et al., 2012 | **1** | **0** | **1** | **1** | **1** | **0** | **0** | 1 | 1 | 1 | 0 | 1 | 0 | **4** | **8** |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mosalanejad et al., 2012 | **1** | **0** | **0** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Mosalanejad et al., 2012b | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Catoire et al., 2013[a] | **0** | **0** | **0** | **0** | **0** | **0** | **0** | 0 | 1 | 0 | 1 | 1 | 0 | **0** | **3** |
| Galhardo et al., 2013 | **0** | **0** | **1** | **0** | **0** | **0** | **0** | 1 | 1 | 0 | 0 | 1 | 0 | **1** | **4** |
| Vizeh et al., 2013 | **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 randomized; 2) Was the study described as double blind; 3) Was there a description of withdrawals and dropouts; 4) The method of randomization was described, and appropriate; 5) The method of blinding was described, and appropriate; 6) The method of randomization was described, but in inappropriate; 7) The method of blinding was described, but inappropriate;** a) The study included a control group; b) The study included pre- and post-assessment; 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 standardized and reliable outcome measures; f) The study reported pre-post correlation.

[a]) 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, e.g. 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.

**Effects of psychosocial intervention**

The results of the meta-analyses are shown in Table 3.

*Pregnancy rates*

A statistically significant and robust effect size (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 risk ratio was somewhat lower (1.57). A forest plot of the effects of psychological intervention on pregnancy outcomes are shown in Figure 2.

(Insert Figure 2 near here)

*Combined psychological outcomes*

Combining the effect sizes of the 35 studies which had included one or more psychological outcomes revealed a statistically significant, robust [51], medium [39]effect size (g= 0.59). The results indicated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger published ESs. When imputing missing ESs, [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.

(Insert Figure 3 near here)

*Infertility-related distress*

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

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

| | Sample size | | Heterogeneity[a] | | | | Global effect sizes | | | Failsafe N[c] | Criterion[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | K | N | Q | df | *P* | $I^2$ | Hedges g[b] | 95 % CI | *p* | | |
| **MAIN EFFECTS** | | | | | | | | | | | |
| Pregnancy | | | | | | | | | | | |
| Pregnancy, women | 10 | 1324 | 22.0 | 9 | =0.009 | 59.0 | 2.01 (RR) | 1.48 – 2.73 | <0.001 | 130 | 60 |
| *Adjusted for publication bias* | *(13)* | - | - | - | - | - | *1.57 (RR)* | *1.10 – 2.25* | *<0.05* | - | - |
| Psych. combined, women+men | 35 | 2746 | 259.2 | 34 | <0.001 | 86.9 | 0.59 | 0.38 – 0.80 | <0.001 | 1552 | 185 |
| *Adjusted for publication bias* | *(42)*[e] | - | - | - | - | - | *0,31* | *0.07 – 0.56* | *<0.05* | - | - |
| Psych. combined, women | 28 | 2076 | 130.8 | 27 | <0.001 | 76.4 | 0.51 | 0.32 – 0.70 | <0.001 | 798 | 150 |
| *Adjusted for publication bias* | *(34)*[e] | - | - | - | - | - | *0.30* | *0.09 – 0.51* | *<0.05* | - | - |
| Psych. combined, men | 7 | 347 | 8,9 | 6 | =0.178 | 32.8 | 0.34 | 0.08 – 0.59 | =0.010 | 12 | 45 |
| Between-group[f] (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 – 0.50 | ns | - | - |
| Infertility distress, women | 6 | 371 | 17.8 | 5 | =0.003 | 71.8 | 0.37 | -0.06 – 0.79 | ns | - | - |
| Depressive symptoms | | | | | | | | | | | |
| Depression symp., women+men | 21 | 1558 | 367.5 | 20 | <0.001 | 94.6 | 1.00 | 0.54 – 1.45 | <0.001 | 1022 | 115 |
| *Adjusted for publication bias* | *(25)*[e] | - | - | - | - | - | *0.31* | *-0.20 – 0.84* | *ns* | - | - |
| Depressive symp.,women | 17 | 992 | 107.7 | 16 | <0.001 | 85.1 | 0.73 | 0.41 – 1.06 | <0.001 | 393 | 95 |
| *Adjusted for publication bias* | *(23)*[e] | - | - | - | - | - | *0.29* | *-0.07 – 0.65* | *ns* | - | - |
| Depressive symp., men | 5 | 243 | 1.9 | 4 | =0.749 | 0.00 | 0.13 | -0.11 – 0.37 | ns | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Between-group[f] (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 – 0.71 | <0.001 | 760 | 135 |
| *Adjusted for publication bias* | *(29)[e]* | - | - | - | - | - | *0.31* | *0.07 – 0.54* | *<0.05* | - | - |
| Anxiety, women | 23 | 1737 | 114.3 | 22 | <0.001 | 80.8 | 0.53 | 0.32 – 0.73 | <0.001 | 631 | 125 |
| *Adjusted for publication bias* | *(27)[e]* | - | - | - | - | - | *0.32* | *0.08 – 0.57* | *<0.05* | - | - |
| Anxiety, men | 5 | 246 | 8.7 | 4 | =0.070 | 53.8 | 0.32 | -0.04 – 0.67 | ns | - | - |
| Between-group[f] (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 – 0.41 | ns | - | - |
| Marital function, women | 4 | 587 | 14.5 | 3 | =0.002 | 79.3 | 0.08 | -0.30 – 0.46 | ns | - | - |
| **MODERATOR ANALYSES** | | | | | | | | | | | |
| **Pregnancy (women)** | | | | | | | | | | | |
| **Study design[h]** | | | | | | | | | | | |
| RCT | 6 | 856 | 10.8 | 5 | =0.057 | 53.5 | 1.67 (RR) | 1.17 – 2.40 | < 0.05 | 22 | 40 |
| NRCT | 4 | 468 | 7.9 | 3 | =0.048 | 62.1 | 2.80 (RR) | 1.55 – 5.06 | < 0.001 | 31 | 30 |
| *Adjusted for publication bias* | *(6)[e]* | - | - | - | - | - | *1.93 (RR)* | *1.07 – 3.49* | *< 0.05* | - | - |
| Between group[f] | 10 | 1324 | 2.1 | 1 | Ns | - | - | - | - | - | - |
| **Intervention format** | | | | | | | | | | | |
| Group | 5 | 691 | 10.9 | 4 | =0.027 | 63.4 | 2.03 (RR) | 1.29 – 3.20 | < 0.01 | 28 | 35 |
| Individual | 4 | 433 | 2.2 | 3 | =0.531 | 0.0 | 1.65 (RR) | 1.26 – 2.17 | < 0.001 | 8 | 30 |
| Between group[f] | 9 | 1124 | 0.5 | 1 | Ns | - | - | - | - | - | - |
| **Psychological outcomes combined (women+men)** | | | | | | | | | | | |
| **Study design[h]** | | | | | | | | | | | |
| RCT | 20 | 2185 | 232.4 | 19 | <0.001 | 91.8 | 0.70 | 0.36 – 1.03 | <0.001 | 642 | 110 |
| *Adjusted for publication bias* | *(24)[e]* | - | - | - | - | - | *0.26* | *-0.10 – 0.68* | *ns* | - | - |
| NRCT | 8 | 450 | 14.9 | 7 | =0.037 | 53.1 | 0.28 | -0.00 – 0.57 | ns | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UCT | 7 | 215 | 6.0 | 6 | =0.424 | 0.0 | 0.55 | 0.40 – 0.70 | <0.001 | 90 | 45 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.51* | *0.36 – 0.66* | *<0.05* | - | - |
| Between group[f] | 35 | 2850 | 3.9 | 2 | Ns | - | - | - | - | - | - |
| **Intervention types** | | | | | | | | | | | |
| CBT | 7 | 475 | 39.0 | 6 | <0.001 | 84.6 | 0.84 | 0.33 – 1.35 | =0.001 | 107 | 45 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.37* | *-0.19 – 0.93* | *ns* | - | - |
| MBI | 9 | 841 | 57.7 | 8 | <0.001 | 86.1 | 0.61 | 0.17 – 0.65 | <0.001 | 158 | 55 |
| *Adjusted for publication bias* | *(10)*[e] | - | - | - | - | - | *0.42* | *0.01 – 0.84* | *<0.05* | - | - |
| Other | 19 | 1430 | 149.2 | 9 | <0.001 | 87.9 | 0.50 | 0.18 – 0.81 | =0.002 | 246 | 105 |
| *Adjusted for publication bias* | *(24)*[e] | - | - | - | - | - | *0.17* | *-0.20 – 0.54* | *ns* | - | - |
| Between group[f] | 35 | 2746 | 1.3 | 2 | Ns | - | - | - | - | - | |
| **Intervention format** | | | | | | | | | | | |
| Group | 20 | 1484 | 87.2 | 19 | <0.001 | 78.2 | 0.76 | 0.55 – 0.98 | <0.001 | 959 | 110 |
| *Adjusted for publication bias* | *(26)*[e] | - | - | - | - | - | *0.50* | *0.25 – 0.75* | *<0.05* | - | - |
| Individual | 9 | 834 | 17.7 | 8 | =0.023 | 54.9 | 0.13 | -0.08 – 0.35 | ns | - | - |
| Couples | 3 | 284 | 92.3 | 2 | <0.001 | 97.8 | 1.07 | -1.02 – 3.16 | ns | - | - |
| Online | 3 | 248 | 1.2 | 2 | =0.541 | 0.00 | 0.03 | -0.22 – 0.28 | ns | - | -- |
| Between group[f] | 35 | 2850 | 24.5 | 3 | <0.001 | - | - | - | - | - | |

[a)] Q-statistic: *p*-values < 0.1 taken to suggest heterogeneity. $I^2$ statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity), 75% (high heterogeneity).
[b)] ESR = Hedges g. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size in the hypothesized direction, i.e. reduced pain or relative smaller increased in pain in the intervention group. All ES's were combined using a random effects model. To ensure independency, if a study reported results for more than one pain measure, the ES's were combined (mean), ensuring that only one ES per study was used in the calculation.
[c)] Failsafe N = number of non-significant studies that would bring the p-value to non-significant ($p > 0.05$)
[d)] A Failsafe N exceeding the criterion (5 x k + 10) indicates a robust result [98].
[e)] If analyses indicated the possibility of publication bias, missing studies were imputed and an adjusted ESR calculated (italics), (K) indicates number of published studies + number of imputed studies.
[f)] Meta-ANOVA (between-study comparisons)
[h)] RCT (randomized controlled trial), NRCT (Non-randomized Controlled Trial), UCT (uncontrolled trial (pre-post))

*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 reduced to a non-significant 0.29 after adjusting for possible publication bias. For men alone, the ES (0.13) did not reach statistically significance.

*State anxiety*

Twenty-five studies had included state anxiety as 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 5 studies (N = 633) had included measures of marital function, and 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, we, when a sufficient number of studies were available for each analysis, explored possible sources of heterogeneity and analyzed whether the ESs 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 ESs found for pregnancy outcomes were statistically significant for both randomized controlled trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.8), with the ES for NRCT

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 both 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 failsafe 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, however, did not reach statistical significance. Furthermore, the results suggested the possibility of publication bias, and when adjusting for publication bias, all three ESs were reduced from medium to small.

*Intervention format*

For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats. Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group difference did not reach statistical significance. For the combined psychological outcomes, a statistically significant effect was found for Group format (g= 0.76) ($p < 0.001$). The ESs for intervention formats such as Individual, Couples, and Online did not reach statistical significance. The overall between-group difference for intervention formats was statistical 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 analyzed 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 6 studies had

examined effects on both 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 ESs for anxiety and pregnancy, indicating that the greater the reduction in anxiety, the greater the likelihood of achieving pregnancy (see Table 4).

**Table 4. Results of meta-regression analyses**

| Dependent variable | Independent variable | K | Beta[a] | 95% CI | *p* |
|---|---|---|---|---|---|
| Pregnancy | ES- Anxiety | 6 | 0.19 | 0.06 – 0..31 | **0.004** |
| | Mean age | 9 | -0.05 | -0.19 – 0.10 | 0.534 |
| | Intervention duration | 9 | 0.01 | -0.03 – 0.06 | 0.669 |
| | Number of sessions | 9 | -0.00 | -0.08 – 1.07 | 0.922 |
| | Study quality (Quality scores)[b] | 10 | -0.02 | -0.09 – 0.04 | 0.477 |
| Psych.Combined | Mean age | 32 | -0.05 | -0.12 - -0.02 | 0.214 |
| | Intervention duration | 32 | 0.01 | -0.02 – 0.04 | 0.518 |
| | Number of sessions | 27 | 0.03 | -0.01 – 0.07 | 0.150 |
| | Study quality (Quality scores) [b,c] | 35 | -0.02 | -0.06 – 0.02 | 0.415 |

[a)] Mixed effects regression: unrestricted maximum likelihood; [b)] Modified Jadad quality score; [c)] P-values for individual psychological outcomes; 0.09 (anxiety) – 0.58 (depression).

# 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 to controls receiving standardized 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 favor of studies with larger positive effect sizes. It should also be noted that the precision of the effect size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. Furthermore, although the between-group difference did not reach statistical significance, when disregarding the possibility of publication bias, NRCT's yielded greater effects (RR: 2.8 (95 % CI: 1.55 – 5.06)) than RCT's (RR: 1.7 (95 % CI: 1.17 – 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 confidence interval is substantial. While the results could be considered surprising, the available data do 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 effect sizes (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, effect size 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 of a total of 3401 women (3064) and men (347). The participants received various psychosocial interventions lasting from one week to six months, including cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions. 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. 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, e.g. online interventions, individual, and couples intervention.[30] The first review published in 2003 also highlighted group interventions as more effective, especially if the interventions emphasized 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. Here, it should be noted that the categorization of interventions may be somewhat ambiguous. For example, the study by Cousineau et al. (2000) [83] could have been categorized as a mind-body intervention, 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 categorized as MBI. The possible ambiguity and considerable variability in interventions forced us to categorize many studies as "other", which limits our understanding the possible mechanisms in psychosocial interventions. Taken together, the available data do not provide a clear basis for understanding 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 dataset considerably, and taken together, the currently available evidence suggests that offering psychosocial interventions may improve both chances of pregnancy and 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 was insufficient, and asked authors of papers written in foreign language to submit their results to us in English. The included studies represented a range of different countries, has 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 possible affect the accuracy of the effect sized 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, e.g. 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 RCT's, where randomization is expected to reduce their influence. Although the difference did not reach statistical significance, RCTs reported smaller ESs 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 statistical 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 failsafe numbers, improvements generally appeared quite robust. A second possible limitation is the high level of heterogeneity indicated by Q and $I^2$ statistics, and the pooled effect sizes 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 intention-to-treat analyses may have influenced the results, and it cannot be excluded that fertility- and treatment-related factors such as non-optimal fertilization, small number of eggs, etc. may have demotivated some participants and made them drop out 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 pos-

sibility of a "file drawer problem", i.e. the existence of relevant unpublished null-findings, a common problem when conducting systematic reviews. Finally, due to inconsistencies in the reporting of causes of infertility, we are unable to evaluate the possible associations between effect sizes 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 involuntarily childlessness, and rumination about the involuntary childlessness may persist, even when psychosocial intervention improves general psychological wellbeing. 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. Firstly, group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3)

than individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive impact of "group settings" i.e. 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 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 generalized 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 generalizability 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 not only dropouts and completers, but also 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 the 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 optimize effects on distress and pregnancy rates, and which biomarkers affected by psychosocial interventions, e.g. 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 intervention, in particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety and depressive symptoms 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.

## Acknowledgements

We would like to thank Gina Bay, Librarian at the Institute Library, Institute of Psychology and Behavioral Sciences, School of Business and Social Sciences, Aarhus University for valuable and tireless assistance throughout the database search process. We would also like to give our most grateful thanks to the researchers who provided us with additional data on their studies or aided us in other ways.

Contributors: RZ and YF designed the protocol. YF developed search strategies and IFV, NGS and YF performed the searches and study selection. YF and IFV undertook data extraction and quality assessments. RZ was responsible for analyzing the data. YF drafted the manuscript and IFV, NGS, HJI and RZ contributed to the manuscript throughout the process. All authors provided input and were involved with the interpretation of this review. YF is the study guarantor.

Funding: This specific study has not received funding, but Y.F. was supported by a research grant from The Danish Agency for Science Technology and Innovation.

Competing interests: None declared

Ethical approval**:** None required

Data sharing: No additional data available

**What is already known on this topic**

Previous reviews have been inconclusive concerning the efficacy of psychosocial interventions for reducing distress and improving clinical pregnancy chances.

**What this study adds**

Synthesizing the currently available evidence suggests that psychosocial interventions could provide clinically meaningful benefits for infertile women and men. Psychosocial intervention leads to reductions in anxiety and depressive symptoms, and larger reductions in anxiety appear to be associated with increased fertility rates for women in treatment for infertility.

Figure 1. PRISMA flowchart of selection of studies

Figure 2. Effects of psychosocial intervention on pregnancy rates

Figure 3. Effects of psychosocial intervention on combined psychological outcomes

## References

1. Hart VA. Infertility and the role of psychotherapy. *Issues Ment Health Nurs*. 2002;23(1):31-41.

2. Oddens BJ, den Tonkelaar I, Nieuwenhuyse H. Psychosocial experiences in women facing fertility problems--a comparative survey. *Hum Reprod*. 1999;14(1):255-261.

3. Cwikel J, Gidron Y, Sheiner E. Psychological interactions with infertility among women. *Eur J Obstet Gynecol Reprod Biol*. 2004;117(2):126-131.

4. Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: An analysis of 101 studies published 1934-1996. *Environ Health Perspect*. 2000;108(10):961-966.

5. Skakkebaek NE, Jorgensen N, Main KM, et al. Is human fecundity declining? *Int J Androl*. 2006;29(1):2-11.

6. Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005;1:293-319.

7. Benyamini Y, Gozlan M, Kokia E. Variability in the difficulties experienced by women undergoing infertility treatments. *Fertil Steril*. 2005;83(2):275-283.

8. Alesi R. Infertility and its treatment--an emotional roller coaster. *Aust Fam Physician*. 2005;34(3):135-138.

9. Merari D, Chetrit A, Modan B. Emotional reactions and attitudes prior to in vitro fertilization: An inter-spouse study. *Psychol Health*. 2002;17(5):629-640.

10. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertil Steril*. 2001;76(4):675-687.

11. Edelmann RJ, Connolly KJ, Bartlett H. Coping strategies and psychological adjustment of couples presenting for IVF. *J Psychosom Res*. 1994;38(4):355-364.

12. Eugster A, Vingerhoets AJ. Psychological aspects of in vitro fertilization: A review. *Soc Sci Med*. 1999;48(5):575-589.

13. Stanton AL, Dunkel-Schetter C, eds. *Psychological adjustment to infertility: An overview of conceptual approaches.* Stanton, Annette L.; Dunkel-Schetter, Christine . Infertility: Perspectives from stress and coping research. The Plenum series on stress and coping. (pp. 3-16). New York, NY, US: Plenum Press; 1991Infertility: Perspectives from stress and coping research.

14. Benyamini Y, Gozlan M, Kokia E. Women's and men's perceptions of infertility and their associations with psychological adjustment: A dyadic approach. *British Journal of Health Psychology*. 2009;14:1-16. doi: 10.1348/135910708X279288.

15. du Plessis S,S., Makker K, Desai NR, Agarwal A. Impact of oxidative stress on IVF. *Expert Review of Obstetrics & Gynecology*. 2008;3(4):539-554. http://dx.doi.org/10.1586/17474108.3.4.539. doi: 10.1586/17474108.3.4.539.

16. Agarwal A, Allamaneni SS. Role of free radicals in female reproductive diseases and assisted reproduction. *Reprod Biomed Online*. 2004;9:338-347.

17. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853-859. doi: 10.1038/nature01321 [doi].

18. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: New perspectives from psychoneuroimmunology. *Annu Rev Psychol*. 2002;53:83-107. doi: 10.1146/annurev.psych.53.100901.135217 [doi].

19. Csemiczky G, Landgren BM, Collins A. The influence of stress and state anxiety on the outcome of IVF-treatment: Psychological and endocrinological assessment of swedish women entering IVF-treatment. *Acta Obstet Gynecol Scand*. 2000;79(2):113-118.

20. Stoleru S, Teglas JP, Fermanian J, Spira A. Psychological factors in the aetiology of infertility: A prospective cohort study. *Hum Reprod*. 1993;8(7):1039-1046.

21. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of coping influence the outcome of in vivro fertilization through stress responses. *Psychoneuroendocrinology*. 1992;17(6):655-665. doi: http://dx.doi.org/10.1016/0306-4530(92)90024-2.

22. Sanders KA, Bruce NW. Psychosocial stress and treatment outcome following assisted reproductive technology. *Human Reproduction*. 1999;14(6):1656-1662. doi: 10.1093/humrep/14.6.1656.

23. Smeenk JM, Verhaak CM, Vingerhoets AJ, et al. Stress and outcome success in IVF: The role of self-reports and endocrine variables. *Hum Reprod*. 2005;20(4):991-996.

24. Ebbesen SM, Zachariae R, Mehlsen MY, et al. Stressful life events are associated with a poor in-vitro fertilization (IVF) outcome: A prospective study. *Hum Reprod*. 2009;24(9):2173-2182. doi: 10.1093/humrep/dep185; 10.1093/humrep/dep185.

25. Klonoff-Cohen H. Female and male lifestyle habits and IVF: What is known and unknown. *Hum Reprod Update*. 2005;11(2):179-203.

26. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: A review. *Hum Reprod Update*. 2007;13(3):209-223. doi: 10.1093/humupd/dml056.

27. Matthiesen SM, Frederiksen Y, Ingerslev HJ, Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): A meta-analysis. *Hum Reprod*. 2011;26(10):2763-2776. doi: 10.1093/humrep/der246; 10.1093/humrep/der246.

28. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: Meta-analysis of prospective psychosocial studies. *BMJ*. 2011;342:d223. doi: 10.1136/bmj.d223.

29. Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med*. 2003;57(12):2325-2341.

30. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. *Hum Reprod*. 2005;20(5):1324-1332.

31. Haemmerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: A meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279-295. doi: 10.1093/humupd/dmp002.

32. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi: 10.1136/bmj.g1687.

33. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. http://dx.doi.org/10.1371%2Fjournal.pmed.1000100.

34. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. http://dx.doi.org/10.1371%2Fjournal.pmed.1000097.

35. Higgins J, Green S, eds. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0 [updated March 2011] ed. The Cochrance Collaboration; 2011. Available from www.cochrane-handbook.org.

36. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. *Hum Reprod Update*. 2011;17(5):575-588.

37. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.

38. Greenland S, O'rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics*. 2001;2(4):463-471. doi: 10.1093/biostatistics/2.4.463.

39. Cohen J. *Statistical power analysis for the behavioral sciences.* Hillsdale, N.J.: Lawrence Erlbaum Associates; 1988.

40. Hedges L, Olkin I. *Statistical methods for meta-analysis.* New York: Acedemic Press; 1985.

41. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. *Psychother Psychosom*. 1999;68(1):15-21.

42. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology*. 2005;5(1):13. http://www.biomedcentral.com/1471-2288/5/13.

43. Sterne JAC, Egger M, Moher D. Addressing reporting biases. In: John Wiley & Sons, Ltd; 2008:297-333. http://dx.doi.org/10.1002/9780470712184.ch10. 10.1002/9780470712184.ch10.

44. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *American Journal of Epidemiology*. 1999;150(5):469-475.

45. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi: 10.1136/bmj.327.7414.557.

46. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods*. 2001;6(3):203-217.

47. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *CMAJ*. 2007;176(8):1091-1096. doi: 10.1503/cmaj.060410.

48. Copas J, Shi JQ. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics*. 2000;1(3):247-262. doi: 10.1093/biostatistics/1.3.247.

49. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*. 2005;58(9):882-893. doi: 10.1016/j.jclinepi.2005.01.016.

50. Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi: 10.1136/bmj.315.7109.629.

51. Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull*. 1979;86(3):638-641. doi: 10.1037/0033-2909.86.3.638.

52. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.

53. Gutierrez K. Group psychological intervention in assisted human reproduction. *Rev Iberoam Fertil Reprod Humana*. 2008;25(SUPPL. 1):47-54.

54. Bjornsen K. Opening the door to fertility. retreat to fertile ground: Sometimes the secret to get-ting pregnant lies in just getting away from it all. *ALTERN MED*. 2006(88):80-81. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2009216983&site=ehost-live.

55. Pengelly P, Inglis M, Cudmore L. Infertility: Couples' experiences and the use of counselling in treatment centres. *Psychodynamic Counselling*. 1995;1(4):507-524.

56. Stewart DE, Boydell KM, McCarthy K, Swerdlyk S, Redmond C, Cohrs W. A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. *Int J Psychiatry Med*. 1992;22(2):173-182.

57. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-174.

58. Nilforooshan P, Ahmadi A, Abedi MR, Ahmadi M. Counseling based on interacting cognitive subsystems and its effect on anxiety of infertile couples. *Pakistan Journal of Psychological Research*. 2006;21(3-4):95-103. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/621710509?accountid=14468.

59. Schmidt L, Holstein BE, Christensen U, Boivin J. Communication and coping as predictors of fertility problem stress: Cohort study of 816 participants who did not achieve a delivery after 12 months of fertility treatment. *Hum Reprod*. 2005;20(11):3248-3256. doi: 10.1093/humrep/dei193.

60. Galhardo A, Cunha M, Pinto-Gouveia J. Mindfulness-based program for infertility: Efficacy study. *Fertil Steril*. 2013.

61. Faramarzi M, Kheirkhah F, Esmaelzadeh S, Alipour A, Hjiahmadi M, Rahnama J. Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2008;141(1):49-53.

62. Lukse MP. The effect of group counseling on the frequency of grief reported by infertile couples. *JOGNN*. 1985;14(6):67S-70s. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=1986045607&site=ehost-live. doi: 10.1111/j.1552-6909.1985.tb02804.x.

63. Domar AD, Seibel MM, Benson H. The mind/body program for infertility: A new behavioral treatment approach for women with infertility. *Fertil Steril*. 1990;53(2):246-249.

64. Domar AD, Zuttermeister PC, Seibel M, Benson H. Psychological improvement in infertile women after behavioral treatment - a replication. *Fertil Steril*. 1992;58(1):144-147.

65. Emery M, Béran M-, Darwiche J, et al. Results from a prospective, randomized, controlled study evaluating the acceptability and effects of routine pre-IVF counselling. *Human Reproduction*. 2003;18(12):2647-2653. doi: 10.1093/humrep/deg501.

66. Lee S. Effects of using a nursing crisis intervention program on psychosocial responses and coping strategies of infertile women during in vitro fertilization. *J NURS RES*. 2003;11(3):197-207. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2004076404&site=ehost-live.

67. Chan CHY, Ng EHY, Chan CLW, Ho, Chan THY. Effectiveness of psychosocial group intervention for reducing anxiety in women undergoing in vitro fertilization: A randomized controlled study. *Fertil Steril*. 2006;85(2):339-346.

68. Tuil WS, Verhaak CM, Braat DD, de Vries Robbe PF, Kremer JA. Empowering patients undergoing in vitro fertilization by providing internet access to medical data. *Fertil Steril*. 2007;88(2):361-368. doi: 10.1016/j.fertnstert.2006.11.197.

69. Lancastle D, Boivin J. A feasibility study of a brief coping intervention (PRCI) for the waiting period before a pregnancy test during fertility treatment. *Hum Reprod*. 2008;23(10):2299-2307.

70. Mori A. Supporting stress management for women undergoing the early stages of fertility treatment: A cluster-randomized controlled trial. *Jpn J Nurs Sci*. 2009;6(1):37-49.

71. Panagopoulou E, Montgomery A, Tarlatzis B. Experimental emotional disclosure in women undergoing infertility treatment: Are drop outs better off? *Soc Sci Med*. 2009;69(5):678-681.

72. Haemmerli K, Znoj H, Berger T. Internet-based support for infertile patients: A randomized controlled study. *Journal of Behavioral Medicine*. 2010;33(2):135-146.

73. Hughes EG, Da Silva AM. A pilot study assessing art therapy as a mental health intervention for subfertile women. *Hum Reprod*. 2011;26(3):611-615.

74. Matthiesen S, Klonoff-Cohen H, Zachariae R, et al. The effect of an expressive writing intervention (EWI) on stress in infertile couples undergoing assisted reproductive technology (ART)

treatment: A randomized controlled pilot study. *Br J Health Psychol*. 2012;17(2):362-378. doi: 10.1111/j.2044-8287.2011.02042.x; 10.1111/j.2044-8287.2011.02042.x.

75. Mosalanejad L, Koolaee AK, Behbahani BM. Looking out for the secret wound: The effect of E-cognitive group therapy with emotional disclosure on the status of mental health in infertile women. *Int J Fertil Steril*. 2012;6(2):87-94.

76. Mosalanejad L, Koolaee AK, Jamali S. Effect of cognitive behavioral therapy in mental health and hardiness of infertile women receiving assisted reproductive therapy (ART). *Iranian Journal of Reproductive Medicine*. 2012;10(5):483-488.

77. Catoire P, Delaunay L, Dannappel T, et al. Hypnosis versus diazepam for embryo transfer: A randomized controlled study. *Am J Clin Hypn*. 2013;55(4):378-386. doi: 10.1080/00029157.2012.747949.

78. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychology*. 2000;19(6):568-575. http://search.proquest.com.ez.statsbiblioteket.dk:2048/docview/619538260?accountid=14468. doi: http://dx.doi.org.ez.statsbiblioteket.dk:2048/10.1037/0278-6133.19.6.568.

79. O'Moore AM, O'Moore RR, Harrison RF. Psychosomatic aspects in idiopathic infertility: Effects of treatment with autogenic training. *J Psychosom Res*. 1983;27(2):145-151.

80. McQueeney D, Stanton A, Sigmon S. Efficacy of emotion-focused and problem-focused group therapies for women with fertility problems. *J Behav Med*. 1997;20(4):313-331. doi: 10.1023/A:1025560912766.

81. Koszycki D, Bisserbe J, Blier P, Bradwejn J, Markowitz J. Interpersonal psychotherapy versus brief supportive therapy for depressed infertile women: First pilot randomized controlled trial. *Archives of Women's Mental Health*. 2012;15(3):193-201.

82. Galletly C, Clark A, Tomlinson L, Blaney F. Improved pregnancy rates for obese, infertile women following a group treatment program: An open pilot study. *General Hospital Psychiatry*. 1996;18(3):192-195.

83. Cousineau TM, Green TC, Corsini E, et al. Online psychoeducational support for infertile women: A randomized controlled trial. *Hum Reprod*. 2008;23(3):554-566.

84. Noorbala AA, Ramazanzadeh F, Malekafzali H, et al. Effects of a psychological intervention on depression in infertile couples. *Int J Gynecol Obstet*. 2008;101(3):248-252.

85. Sexton MB, Byrd MR, O'Donohue WT, Jacobs NN. Web-based treatment for infertility-related psychological distress. *Arch Women's Ment Health*. 2010;13(4):347-358.

86. Sarrel PM, DeCherney AH. Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertil Steril*. 1985;43(6):897-900.

87. Hosaka T, Matsubayashi H, Sugiyama Y, Izumi S, Makino T. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. *Gen Hosp Psychiatry*. 2002;24(5):353-356.

88. Levitas E, Parmet A, Lunenfeld E, et al. Impact of hypnosis during embryo transfer on the outcome of in vitro fertilization-embryo transfer: A case-control study. *Fertil Steril*. 2006;85(5):1404-1408. doi: 10.1016/j.fertnstert.2005.10.035.

89. Domar AD, Rooney KL, Wiegand B, et al. Impact of a group mind/body intervention on pregnancy rates in IVF patients. *Fertil Steril*. 2011;95(7):2269-2273. doi: http://dx.doi.org/10.1016/j.fertnstert.2011.03.046.

90. Gorayeb R, Borsari AC, Rosa-e-Silva AC, Ferriani RA. Brief cognitive behavioral intervention in groups in a brazilian assisted reproduction program. *Behav Med*. 2012;38(2):29-35. doi: 10.1080/08964289.2012.654834; 10.1080/08964289.2012.654834.

91. Terzioglu F. Investigation into effectiveness of counseling on assisted reproductive techniques in turkey. *J Psychosom Obstet Gynecol*. 2001;22(3):133-141.

92. de Klerk C, Hunfeld JAM, Duivenvoorden HJ, et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: A randomized controlled trial. *Hum Reprod*. 2005;20(5):1333-1338.

93. Vizheh M, Pakgohar M, Babaei G, Ramezanzadeh F. Effect of counseling on quality of marital relationship of infertile couples: A randomized, controlled trial (RCT) study. *Arch Gynecol Obstet*. 2013;287(3):583-589.

94. Chan CH, Chan CL, Ng EH, et al. Incorporating spirituality in psychosocial group intervention for women undergoing in vitro fertilization: A prospective randomized controlled study. *Psychol Psychother*. 2012;85(4):356-373.

95. Domar A, Clapp D, Slawsby E, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril*. 2000;73(4):805-811. doi: 10.1016/S0015-0282(99)00493-8.

96. McNaughton-Cassill M, Bostwick JM, Arthur NJ, Robinson RD, Neal GS. Efficacy of brief couples support groups developed to manage the stress of in vitro fertilization treatment. *Mayo Clin Proc*. 2002;77(10):1060-1066. http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2003034100&site=ehost-live.

97. Galhardo A, Cunha M, Pinto-Gouveia J. Developing mindfulness and acceptance skills in infertility: The mindfulness based program for infertility. *Aten Prim*. 2013;45:143.

98. Chen JH, Bierhals AJ, Prigerson HG, Kasl SV, Mazure CM, Jacobs S. Gender differences in the effects of bereavement-related psychological distress in health outcomes. *Psychol Med*. 1999;29(2):367-380.

99. Navot D, Bergh RA, Williams MA, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *The Lancet*. 1991;337(8754):1375-1377. doi: http://dx.doi.org/10.1016/0140-6736(91)93060-M.

100. Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. *Human Reproduction*. 2002;17(5):1399-1403. doi: 10.1093/humrep/17.5.1399.

101. Van den Broeck U, Emery M, Wischmann T, Thorn P. Counselling in infertility: Individual, couple and group interventions. *Patient Educ Couns*. 2010;81(3):422-428. doi: 10.1016/j.pec.2010.10.009.

102. Burns LH(, Covington SN(. *Infertility counseling: A comprehensive handbook for clinicians.* New York, NY, US: Parthenon Publishing Group; 1999:xvii.

103. Boivin J, Appleton TC, Baetens P, et al. Guidelines for counselling in infertility: Outline version. *Hum Reprod*. 2001;16(6):1301-1304.

104. Boivin J, Kentenich H, eds. *Guidelines for counselling in infertility.* ESHRE Monographs: Oxford University Press; 2002.

105. Gameiro S, Boivin J, Domar A. Optimal in vitro fertilization in 2020 should reduce treatment burden and enhance care delivery for patients and staff. *Fertil Steril*. 2013;100(2):302-309. doi: 10.1016/j.fertnstert.2013.06.015 [doi].

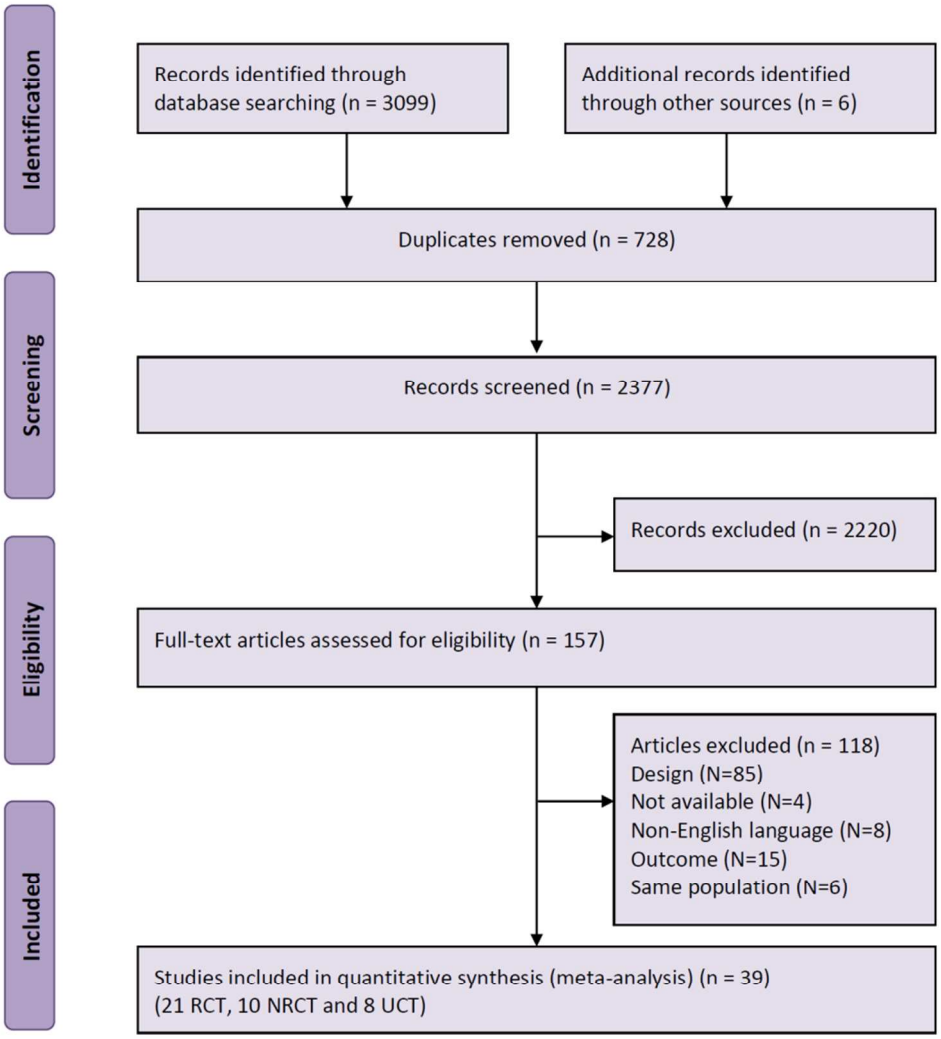



Figure 1. PRISMA flowchart of selection of studies
90x98mm (300 x 300 DPI)

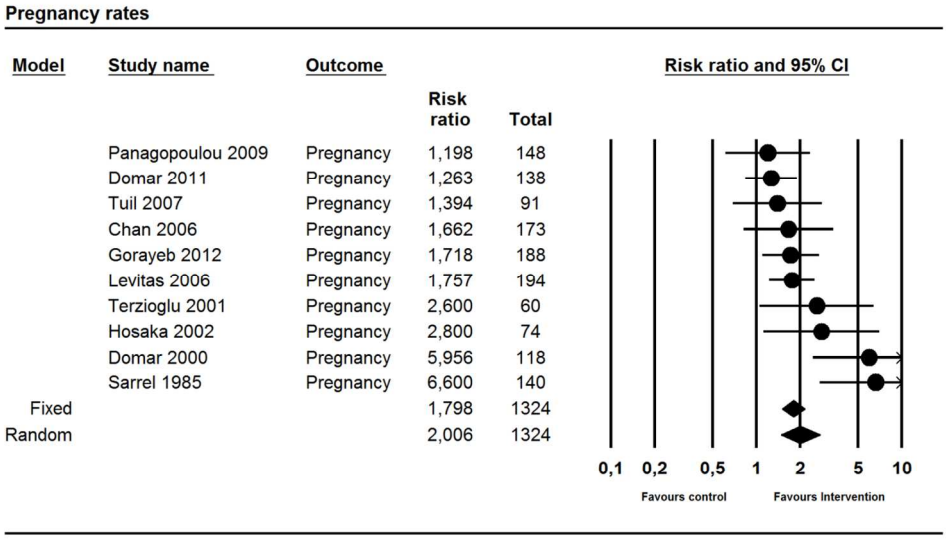



Figure 2. Effects of psychosocial intervention on pregnancy rates
154x90mm (300 x 300 DPI)

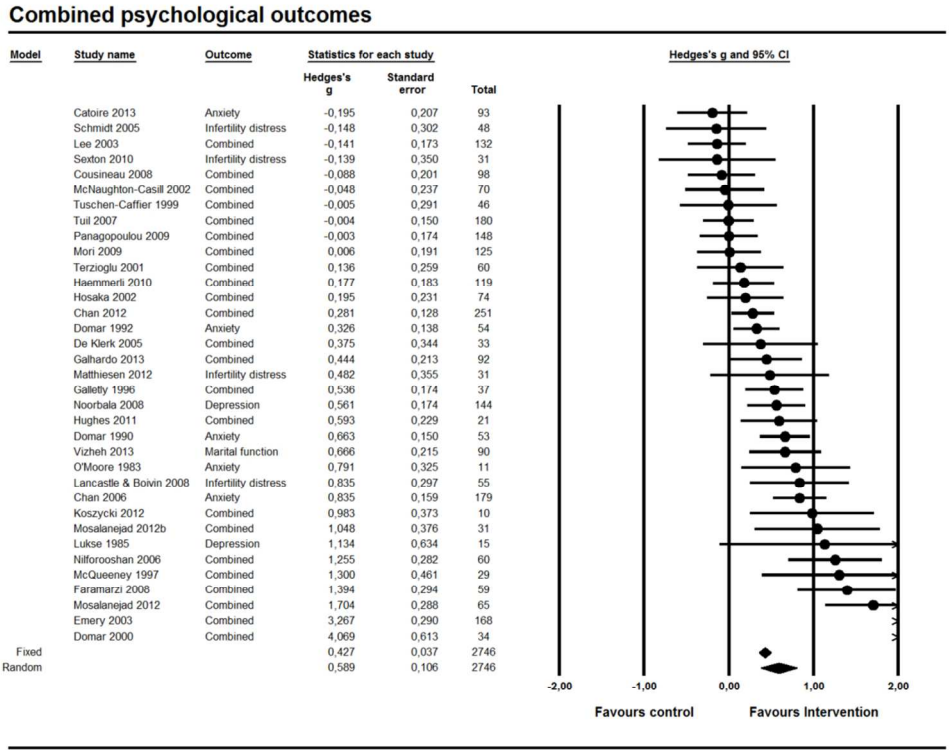



Figure 3. Effects of psychosocial intervention on combined psychological outcomes
112x90mm (300 x 300 DPI)

# 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-behavio* therapy” | 13.914 | 1259 | 3706 | 32.160 | 13.056 | 2358 |

| | | | | | | |
|---|---|---|---|---|---|---|
| #20 ”cognitive-behavio* 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 searhes

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

- Additional records identified n=6

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5-6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8-10 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 9-10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 9 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10-11 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10-11 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 13-17 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 19-20 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 22-28 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 26-28 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 26-28 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 28-29 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 30-32 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 32-33 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 34 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.