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

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5 Abstract

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

9 **Design:** Systematic review and meta-analysis.

10 **Data sources** PsycINFO, PubMed, Embase, CINAHL, Web of Science and The Cochrane Library
11 between 1978 and April 2014.

12 **Study selection** Studies were considered eligible if they evaluated the effect of any psychosocial
13 intervention on clinical pregnancy and/or distress in infertile participants, used a quantitative ap-
14 proach, and were published in English.

15 **Data extraction** Study characteristics and results were extracted and the methodological quality
16 assessed. Effect sizes (Hedges g) were pooled using a random effect model. Heterogeneity was as-
17 sessed using the Q statistic and I^2 , and publication bias evaluated using Eggers' method. Possible
18 moderators and mediators were explored with meta-ANOVAs and meta-regression.

19 **Results** We identified 39 eligible studies (total $N = 2746$ men and women) assessing the effects of
20 psychological treatment on pregnancy rates and/or adverse psychological outcomes, including de-
21 pressive symptoms, anxiety, infertility stress, marital function. Statistically significant and robust
22 overall effects of psychosocial intervention were found for both clinical pregnancy ($RR = 2.01$; CI :
23 $1.48-2.73$; $p < 0.001$) and psychological outcomes (Hedges $g = 0.59$; CI : $0.38-0.80$; $p = 0.001$). The
24 pooled effect sizes (ES) for psychological outcomes were generally larger for women (g : $0.51-0.73$)
25 than men ($0.13-0.34$), but the difference only reached statistical significance for depressive symp-
26 toms ($p = 0.004$). Cognitive behavioral therapy (CBT) ($g = 1.15$) appeared more effective than mind-
27 body interventions ($g = 0.41$), but the difference did not reach statistical significance. Finally, meta-
28 regression indicated that larger reductions in anxiety were associated with greater improvement in
29 pregnancy rates (Slope: 0.19 ; $p = 0.004$).

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

33 **Strengths and limitations of this study**

- 34 • A major strength of this study is the extensive search of various databases from 1978 to
- 35 April 2014, as well as an extended detailed methodological assessment
- 36 • Further analyses were performed to account for publication bias, yielding conservative ef-
- 37 fect sizes and thus strengthening the robustness of the estimates
- 38 • Substantial variation of the methodological quality may have influenced the interpretation of
- 39 the outcomes
- 40 • Heterogeneity was observed for several of the outcomes

41 Introduction

42 Fecundity has become a growing problem for many couples trying to conceive a child and although
43 not all couples choose to seek medical assistance, more than 10% of the childbearing population has
44 resorted to assisted reproductive technology (ART) to conceive.¹⁻⁵ Being involuntarily childless and
45 going through various ART procedures imposes considerable stress on the couple, and childlessness
46 is often perceived as a life crisis where the emotional strain equals that found for traumatic
47 events.^{2,6-10} Although infertile couples may be considered mentally healthy in general,¹¹ several
48 studies indicate that coping with infertility is associated with periodically heightened levels of psy-
49 chological symptoms of distress, depression and anxiety.^{12,13} Feelings of loss, grief, anger, and sad-
50 ness are not uncommon, and women often report bodily disparagement, lack of femininity, shame,
51 and self-blame.^{2,14} There is some evidence to suggest that dysregulation in the uterus microenvi-
52 ronment may influence the ability to conceive, e.g. oxidative stress and inflammation, ,^{15,16} which
53 may be promoted by psychological distress.^{17,18} Such findings have lead several studies to investi-
54 gate possible links between mental state and pregnancy outcome.^{10,19-24} Although study results have
55 been mixed, reviews of the literature have generally reached the conclusion that psychosocial fac-
56 tors such as depressive symptoms, anxiety, distress, and certain coping strategies are linked to re-
57 duced chances of pregnancy.²⁵⁻²⁷ Two recently published meta-analyses, however, report conflicting
58 results.^{28,29} Whereas one meta-analysis supported the conclusion that emotional distress may be
59 critical to the success of fertility treatment outcome,²⁸ the other did not find sufficient support for

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3 60 this hypothesis.²⁹ The different conclusions could be due to methodological issues, e.g. the chosen
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5 61 measures of distress and definitions of *pregnancy* (e.g. serum positive test, clinical pregnancy, or
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7 62 live birth).
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10 63 Nonetheless, the evidence indicating a considerable psychosocial burden associated with infertility
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12 64 and its treatment has inspired several researchers to explore the effect of various psychosocial inter-
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14 65 ventions in reducing distress, improving quality-of-life, and, possibly, optimize the chances of
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16 66 pregnancy.
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20 67 So far, three systematic reviews and meta-analyses have presented results of psychological inter-
21
22 68 ventions on mental health and pregnancy outcome. Again, the results have been mixed. The first
23
24 69 meta-analysis, published in 2003, concluded that psychological intervention appeared to have a
25
26 70 beneficial effect on negative emotions,³⁰ anxiety in particular. An effect of counseling was also
27
28 71 found for infertility-related distress, whereas no clear effect was seen on pregnancy rates. Although
29
30 72 the original systematic review identified 25 independent studies, the final meta-analysis only in-
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32 73 cluded 8–10 studies selected on the basis of their methodological quality. The second meta-analysis
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34 74 published in 2005 focused on differences in effects related to intervention format, e.g. individu-
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36 75 al/couple vs. group setting.³¹ Overall, the results indicated that both individual/couple and group
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38 76 interventions were effective in reducing emotional distress as well as possibly increasing the con-
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40 77 ception rate. In contrast to the two first meta-analyses, which had investigated both controlled and
41
42 78 uncontrolled studies, the third meta-analysis from 2009, which only included controlled studies,³²
43
44 79 found no evidence for an effect of psychological interventions on emotional distress. An effect,
45
46 80 however, was found for pregnancy rates, but only for couples not in ART.
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52 81 Taken together, while showing promising results, the findings of existing quantitative systematic
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54 82 reviews, the most recent published in 2009, are mixed. The literature within this field is expanding
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56 83 and new psychosocial intervention approaches building on existing knowledge and targeting specif-
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3 84 ic problems of infertile patients, e.g. mind/body interventions, web-based treatments, and online
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5 85 psycho-education programs, have been evaluated. Furthermore, the more recently published studies
6
7 86 have generally used randomized controlled trial designs, a notable strength reducing the risk of bias
8
9 87 and making the studies more easily comparable.³³ An updated review and meta-analysis is needed
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11 88 to determine to which degree psychosocial interventions may reduce infertility related distress relat-
12
13 89 ed to improvement of pregnancy chances during fertility treatment.

18 90 **Methods**

20
21 91 The present study was conducted in accordance with the guidelines of the preferred reporting items
22
23 92 for systematic reviews and meta-analysis (PRISMA) recommendations.^{34,35} An *a priori* designed
24
25 93 study protocol guided the literature search, study selection and data synthesis.

28 94 **Search strategy and criteria**

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31 95 A comprehensive and systematic search of the literature published between 1978 (first baby born
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33 96 after in vitro fertilization) and April 2014 was conducted, using a sensitive search strategy recom-
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35 97 mended for reviews by Higgins and Green.³⁶ When conducting the searches, we combined key-
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37 98 words from the two primary concepts, infertility and psychosocial treatment: (i) “infertil*”, “child-
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39 99 lessness”, “IVF”, “ICSI”, “fertility treatment/problems” “assisted reproduction” and (ii) “psycho-
40
41 100 logical/psychosocial intervention”, “social support”, “couples therapy”, “psycho-education”, “inter-
42
43 101 net-based intervention” and “behavioral therapy” (for a full search history, see appendix 1). We
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45 102 identified relevant records by electronic searches in general medical and psychological databases:
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47 103 PubMed, PsycINFO, The Cochrane Library, Embase, CINAHL, and Web of Science. Furthermore,
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49 104 we cross-examined reference lists of the retrieved papers and reviews for additional relevant stud-
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51 105 ies. We did not pursue the grey literature or trial registries, and limited our search to include only
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53 106 peer-reviewed articles published in English.

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3 107 **Study selection**
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5 108 Studies were considered eligible if they 1) reported data on infertile participants 2) presented data
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7 109 on a psychosocial intervention or a supportive program 3) included both baseline and post-
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9 110 intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research ap-
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11 111 proach. In general terms, infertility refers to not being able to conceive for more than one year
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13 112 without contraception (WHO, 2002). Despite this standard definition, a recent review has found
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15 113 considerable between-study variation in definitions.³⁷ Furthermore, infertility can be graded in rela-
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17 114 tion to clinical diagnosis and duration. This present meta-analysis includes studies using various
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19 115 definitions of the term “infertile”, i.e. all studies including patients diagnosed with infertility, but in
20
21 116 different types and stages of ART treatments, such as intrauterine insemination, in vitro fertilization
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23 117 and intracytoplasmic sperm injection, as well as in different cycles. “Psychosocial interventions or
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25 118 supportive programs” were defined as all interventions with a psychosocial aim that did not include
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27 119 the prescription of medication nor had a primary physical focus, e.g. acupuncture or massage thera-
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29 120 py. However, studies using e.g. relaxation, guided imagery or meditation exercises as part of a psy-
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31 121 chosocial program were included. The interventions could be delivered in individual-, group-, cou-
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33 122 ples-, or internet-based format and did not need to involve face-to-face interaction. We included
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35 123 both controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines,
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37 124 commentaries, case reports, editorials, newspaper articles, newsletters, and books chapters. Neither
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39 125 did we include abstracts-only or conference posters. Our primary outcome was pregnancy rate, de-
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41 126 fined as *clinical pregnancy*. This clinical definition implies a visualization of at least one gestational
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43 127 sack and fetal heartbeat in approximately the 5th week after fertilization. Secondary outcome
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45 128 measures were psychological ratings of depressive symptoms, anxiety, generalized stress, specific
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47 129 infertility stress, and interpersonal functioning assessed through self-reported questionnaires.
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130 **Data extraction and quality assessment**

131 All full-text articles were read by two independent review authors (IFV, NGS) and data extracted
132 according to predefined criteria. Disagreements were discussed with a third author (YF) and re-
133 solved by consensus. If specification of any outcome was missing or if clarifications were needed,
134 authors were contacted for further information. Each study was assessed for methodological quality
135 using the Jadad criteria,³⁸ a tool to evaluate methodological quality, e.g. use and adequate descrip-
136 tion of randomization- and blinding procedures, and description of drop-out rates (score range: 0-5).
137 In addition to the 0-5 points possible on the original Jadad scale, one additional point was given for
138 each of the following: (a) was a control group included (b) were both pre- and post-data presented
139 (c) was any form of blinding of patients, or (d) researchers attempted, (e) was standardized and reli-
140 able outcome measure used, and (g) were the pre-post correlations provided. The modified scale
141 yielded a total quality score ranging from 0-12. With respect to the modified Jadad score, the mean
142 score difference (Rater 1 and 2 means (SD): 5.2 (1.8) and 5.6 (2.0)) did not reach statistical signifi-
143 cance ($t(77) = 1.1$; $p = 0.28$), and the inter-rater score correlation was $r = 0.83$ ($p < 0.001$). Kappa
144 statistic was not used, as this assumes the nominal data and no natural ordering of ratings. Quality
145 ratings were not used as weights when calculating aggregated effect sizes (ES) as this is generally
146 discouraged.³⁹ Instead, associations between ESs and study quality indicators were explored with
147 meta-ANOVAs (design) and meta-regression (modified Jadad-score). In cases where we were una-
148 ble to retrieve articles from the authorized databases, authors were contacted between 1-3 times in
149 order to amend the data collected.

150 **Calculating effect sizes**

151 The effect sizes used were the risk ratio (RR) for pregnancy and Hedges g for psychological out-
152 comes. Hedges' g is a variation of Cohen's d which enables correction of potential bias due to small
153 sample size.^{40,41} A positive Hedges' g indicates result in the expected direction, e.g. a reduction in
154 distress in the intervention group compared to controls. A $RR > 1.0$ indicates a greater proportion of

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3 155 pregnancies in the intervention group. RRs were based on pregnancy rates and total N in the inter-
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5 156 vention and control groups ($k=10$) (k = number of studies). When possible, Hedges' g was calculat-
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7 157 ed on the basis of reported means and SDs at pre and post-intervention or means and SDs of change
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9 158 scores. This was possible for 50 of 61 effect sizes. When required and available, the reported pre-
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11 159 post correlations were used in the calculation. This was the case for 5 ES's. When unavailable, the
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13 160 pre-post correlation was set to 0.50. When SD's were unavailable, two approaches were used. For
14
15 161 STAI state anxiety scores, the average pre- and post SD (10.9 and 10.8) for the studies which re-
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17 162 ported the SD was used, as the SD's appeared to be highly comparable across the remaining studies.
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19 163 For other measures, ES's were estimated either on the basis of sample size and either p -value or Eta
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21 164 square. In one study reporting only medians,⁴² the means and SD's were estimated following a pre-
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23 165 viously suggested approach.⁴³

27 28 166 **Heterogeneity**

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30 167 Heterogeneity was assessed using Q and I^2 statistics. Heterogeneity tests are aimed at determining
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32 168 whether results reflect genuine between-study differences (heterogeneity), or whether the variation
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34 169 is due to chance (homogeneity).^{44,45} In accordance with recommendations, a p -value ≤ 0.10 was
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36 170 used to determine significant heterogeneity due to the general low statistical power of heterogeneity
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38 171 tests.⁴⁶ The I^2 quantity provides a measure of the degree of inconsistency by estimating the amount
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40 172 of variance in a pooled ES that can be accounted for by heterogeneity in the sample of studies.⁴⁷ I^2
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42 173 values of 0%, 25%, 50%, and 75% indicate no, low, moderate, and high heterogeneity, respectively.

45 46 174 **Analytical strategy**

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48 175 All ESs were weighted with the inverse variance and combined with a random effects model. First,
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50 176 the overall ES of the effect of psychosocial interventions on pregnancy rates was calculated. Then
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52 177 the overall ES for the combined psychological outcomes was calculated together with the overall
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54 178 ESs for the individual outcome measures of depression, state anxiety, infertility-related distress, and
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56 179 marital function. This was done for the combined sample (women + men). If the results indicated

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3 180 study heterogeneity, and if the number of studies in each category was sufficient ($K \geq 3$), possible
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5 181 between-study differences in ESs were explored by comparing the ESs of studies according to the
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7 182 following study characteristics: gender, study design, intervention type, and intervention format
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9 183 (mixed effect meta-ANOVAs), methodological quality (Jadad score), mean age of the sample, in-
10
11 184 tervention duration, and number of sessions (mixed effect meta-regression).

14
15 185 Prior to the search, statistical power analyses were conducted as recommended.⁴⁸ Based on the find-
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17 186 ings of the earlier meta-analysis,³² we assumed to find a RR of 1.4 for pregnancy rates and an aver-
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19 187 age sample size of $N=76$. We expected to be able to detect a similar small ES (Hedges $g = 0.28$ or
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21 188 $RR = 1.4$) with an alpha of 5% and a statistical power of 80%, with a total of only 9 studies, using a
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23 189 random-effects model. Based on these results, we considered it worthwhile to conduct the meta-
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25 190 analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2
26
27 191 (www.meta-analysis.com), SPSS-20, and various formulas in Excel.

31 192 **Publication bias**

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33 193 The possibility of publication bias, a widespread problem when conducting meta-analyses, was
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35 194 evaluated with funnel plots,⁴⁹ Egger's method, and by calculating fail-safe numbers.^{50,51} A funnel
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37 195 plot is a graphic illustration of study ESs in relation to study size or precision. Egger's test provides
38
39 196 a statistic for the skewness of results.⁵² Calculation of fail-safe numbers is aimed at achieving an
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41 197 indication of the number of unpublished studies with null-findings that would reduce the result to
42
43 198 statistical non-significance ($p > 0.05$). It has been suggested that a reasonable level is achieved if the
44
45 199 fail-safe number exceeds $5K+10$ ($K = N$ studies in the meta-analysis).⁵³ If the results were sugges-
46
47 200 tive of publication bias, an adjusted ES was calculated using Duval and Tweedie's trim and fill
48
49 201 method,⁵⁴ which imputes ESs of missing studies and recalculates the ES accordingly.

202 Results

203 Study selection

204 In a first screening, duplicates were identified, and titles and abstracts reviewed. A total of 157 stud-
205 ies were found potentially relevant and reviewed independently by two raters. Four articles could
206 not be retrieved due to “no access” policy from the university, and the authors did not respond to
207 our enquiries.⁵⁵⁻⁵⁸ Initially, the raters were uncertain or disagreed on 13 (8.3%) articles (inter-rater
208 agreement: 0.78; $p < 0.001$ (Kappa statistic)) indicating “substantial agreement.”⁵⁹ After negotiation,
209 5 of these were included, resulting in 41 potentially eligible articles. One additional study was ex-
210 cluded due to the combination of psychological intervention with a psychoactive drug, and one
211 study had insufficient statistical data and the authors did not respond to our enquiry. We thus in-
212 cluded a total of 39 studies in the present review. On three occasions authors provided unpublished
213 additional data.⁶⁰⁻⁶² Figure 1 shows a flow chart of the study selection process.

214 (Insert Figure 1 near here)

215 Study characteristics

216 Based on outcome, 29 of the studies were aimed at reducing negative emotional distress,⁶⁰⁻⁸⁷ with
217 the targeted outcomes being: infertility-related distress ($k=10$), depression ($k=21$), anxiety ($k=25$),
218 and marital function ($k=5$). Five studies focused solely on the outcome of pregnancy,⁸⁸⁻⁹² and 5
219 studies had included distress as well as pregnancy as outcome.⁹³⁻⁹⁷ Twenty studies were randomized
220 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}
221 with most control groups receiving standardized care or being waiting-list controls. Only three stud-
222 ies had included an active/attention control condition, e.g. non-emotional writing or receiving an
223 information booklet.^{78,79,107} One study offered gift certificates to the control group participants if
224 they responded to the follow-up questionnaires.⁹¹ Relatively few studies were uncontrolled ($k=$
225 8).^{64-66,83,87,112-114} The reporting of the participants’ medical treatment status was inconsistent. Seven

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3 226 studies did not provide information on treatment status (whether or not in current ART treatment), 5
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5 227 studies reported that some of the participants were in treatment, but not how many of them, and 27
6
7 228 studies reported that their participants were currently in ART treatment. Twenty-five studies had
8
9 229 included only women, while the remaining 14 studies had included both women and men. The in-
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11 230 cluded studies had reported data for a total of 3401 participants (3064 women and 347 men). The
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13 231 mean age and mean duration of infertility for intervention group participants was (32.7 yrs. SD 2.2)
14
15 232 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).
16
17 233 The intervention strategies mostly employed were cognitive behavioral therapy (k=9), supportive
18
19 234 psycho-education (k=8), mind/body intervention (k=7), stress management (k=5), and general
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21 235 counselling (k=8). The number of sessions ranged from 1 to 24, lasting approximately from 20
22
23 236 minutes to 3 hours and the duration of psychosocial intervention ranged from 1 week to 28 months.
24
25 237 The study characteristics are summarized in Table 1.
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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)

1																			
2																			
3																			
4	Faramarzi	et	al.	Iran	I: 42 (29)	RCT	CBT	Group	10	10		D: BDI	-	3 (6)					
5	2008				C: 40 (30)							A: Cattell							
6	Lancastle	and	Boivin	Wales, UK	XXX	RCT/UCT	CSG	Individual	14	2		IS: CIQ	-	4 (8)					
7	2008																		
8	Noorbala	et	al.	Iran	I: 288 (288)	UCT	CBT	Group		24		D: BDI	-	3 (8)					
9	2008				(50 %)														
10	Mori			Japan	I: 85 (85)	RCT	CSG	Individual	3	12		D: HADS	-	4 (8)					
11	2009				C: 40 (40)							A: HADS							
12	Panagopoulou	et	al.	England, UK	I: 50 (50)	RCT	CSG	Individual	3	1		IS: ISS	-	3 (7)					
13	2009				C: 98 (98)							A: STAI							
14	Haemmerli	et	al.	Switzerland	I: 60 (46)	RCT	CSG	Online	13	8		IS: IDS	-	3 (6)					
15	2010				C: 64 (41)							D: CES-D							
16												A: STAI							
17	Sexton	et	al.	USA	I: 21 (15)	RCT	CSG	Individual		2		IS: FPI	-	3 (6)					
18	2010				C: 22 (16)														
19	Domar	et	al.	USA	I: 46 (46)	RCT	MBI	Group	10	10			+	4 (6)					
20	2011				C: 51(51)														
21	Hughes and Mann de Silva			Canada	I: 21 (21)	UCT	CSG	Group	8 (2hrs)	8		D: BDI	-	0 (2)					
22	2011											A: BAI							
23	Chan	et	al.	Hong Kong, China	I: 141 (141)	RCT	MBI	Group	4 (3hrs)	4		A: STAI	+	3 (6)					
24	2012				C: 110 (110)							MF: C-KMS							
25	Gorayeb	et	al.	Brazil	I: 93 (93)	NRCT	CBT	Group	5 (2hrs)	5			+	1 (4)					
26	2012				C: 95 (95)														
27	Koszycki	et	al.	Canada	I: 31 (23)	UCT	CSG	Individual	12 (50min)	12		IS: FPI	-	3 (7)					
28	2012											D: BDI							
29												HAM-D							
30	Matthiesen	et	al.	Denmark	I: 42 (15)	RCT	CSG	Individual	3 (20min)	1		IS: COMPI	-	4 (8)					
31	2012				C: 40 (16)														
32	Mosalanejad	et	al.	Iran	I: 32 (32)	RCT	CBT	Group	12 (2hrs)	12		D: DASS	-	1 (4)					
33	2012				C: 33 (33)							A: DASS							
34	Mosalanejad	et	al.	Iran	I: 16 (16)	NRCT	CBT	Group	15 (1,5hrs)	16		D: DASS	-	2 (5)					
35	2012b				C: 15 (15)							A: DASS							
36	Catoire	et	al.	France	I: 50 (50)	UCT	MBI	Individual	4	1		A: STAI	-	4 (7)					
37	2013																		

Galhardo 2013	et al.	Portugal	I: 55 (55) C: 37 (37)	NRCT	MBI	Group	10 (2hrs)	10	IS: D: A: STAI	ISE - BDI	1 (4)
Vizheh 2013	et al.	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 Depression 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 included¹ 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.

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3 253 **Effects of psychosocial intervention**
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6 254 The results of the meta-analyses are summarized in Table 2.
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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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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											

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3												
4	Anxiety, women+men	25	2159	144.4	24	<0.001	83.4	0.51	0.31 – 0.71	<0.001	760	135
5	<i>Adjusted for publication bias</i>	(29) ^e	-	-	-	-	-	0.31	0.07 – 0.54	<0.05	-	-
6	Anxiety, women	23	1737	114.3	22	<0.001	80.8	0.53	0.32 – 0.73	<0.001	631	125
7	<i>Adjusted for publication bias</i>	(27) ^e	-	-	-	-	-	0.32	0.08 – 0.57	<0.05	-	-
8	Anxiety, men	5	246	8.7	4	=0.070	53.8	0.32	-0.04 – 0.67	ns	-	-
9	Between-group ^f (women vs. men)	28	1983	1.0	1	ns	-	-	-	-	-	-
10	Marital function											
11	Marital function, women+men	5	633	14.6	4	=0.006	72.6	0.09	-0.23 – 0.41	ns	-	-
12	Marital function, women	4	587	14.5	3	=0.002	79.3	0.08	-0.30 – 0.46	ns	-	-
13	MODERATOR ANALYSES											
14	Pregnancy (women)											
15	Study design^h											
16	RCT	5	668	11.5	4	=0.066	62.1	1.70 (RR)	1.06 – 2.72	< 0.05	12	35
17	NRCT	5	656	8.1	4	=0.032	54.7	2.37 (RR)	1.57 – 3.60	< 0.001	46	35
18	Between group ^f	10	1324	1.1	1	ns	-	-	-	-	-	-
19	Intervention format											
20	Group	5	691	10.9	4	=0.027	63.4	2.03 (RR)	1.29 – 3.20	< 0.01	28	35
21	Individual	4	433	2.2	3	=0.531	0.0	1.65 (RR)	1.26 – 2.17	< 0.001	8	30
22	Between group ^f	9	1124	0.5	1	ns	-	-	-	-	-	-
23	Psychological outcomes combined (women+men)											
24	Study design^h											
25	RCT	20	2185	232.4	19	<0.001	91.8	0.70	0.36 – 1.03	<0.001	642	110
26	<i>Adjusted for publication bias</i>	(24) ^e	-	-	-	-	-	0.26	-0.10 – 0.68	ns	-	-
27	NRCT	8	450	14.9	7	=0.037	53.1	0.28	-0.00 – 0.57	ns	-	-
28	UCT	7	215	6.0	6	=0.424	0.0	0.55	0.40 – 0.70	<0.001	90	45
29	<i>Adjusted for publication bias</i>	(10) ^e	-	-	-	-	-	0.51	0.36 – 0.66	<0.05	-	-
30	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
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.66</i>	<i>-0.01 – 1.33</i>	<i>ns</i>	-	-
MBI	7	733	21.2	6	=0.002	71.0	0.41	0.17 – 0.65	<0.001	76	45
<i>Adjusted for publication bias</i>	<i>(8)^e</i>	-	-	-	-	-	<i>0.36</i>	<i>0.11 – 0.62</i>	<i><0.05</i>	-	-
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
<i>Adjusted for publication bias</i>	<i>(26)^e</i>	-	-	-	-	-	<i>0.50</i>	<i>0.25 – 0.75</i>	<i><0.05</i>	-	-
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. I² 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))

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4 266 *Pregnancy rates*

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6 267 A statistically significant and robust effect size (RR = 2.01) was found for the 10 studies which had
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8 268 investigated effects of psychosocial intervention on clinical pregnancy rates, with the chance of
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10 269 becoming pregnant being doubled in the intervention group. Adjusting for possible publication bias,
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12 270 the risk ratio was somewhat lower (1.57).

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15 271 *Combined psychological outcomes*

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17 272 Combining the effect sizes of the 35 studies which had included one or more psychological out-
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19 273 comes revealed a statistically significant, robust⁵³, medium⁴⁰ effect size ($g = 0.59$). The results indi-
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21 274 cated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger pub-
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23 275 lished ESs. When imputing missing ESs,⁵⁴ the resulting adjusted pooled ES was smaller (0.31), but
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25 276 remained statistically significant. Taking gender into consideration, the ES (0.51) remained statisti-
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27 277 cally significant for women, still suggesting a robust effect. The ES was smaller for men (0.34) and
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29 278 did not reach statistical significance.

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33 279 *Infertility-related distress*

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35 280 Only ten studies had included infertility-related distress as an outcome. Small ESs were found for
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37 281 women and men combined (0.24) and women alone (0.37), and did not reach statistical signifi-
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43 283 *Depression*

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45 284 Twenty-one studies had assessed depressive symptoms. A statistically significant ES (1.00) was
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47 285 found for women and men combined. However, when adjusting for possible publication bias, the
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49 286 results changed dramatically to a small, non-significant ES of 0.31. Similar results were found for
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51 287 women alone with a statistically significant ES of 0.73 reduced to a non-significant 0.29 after ad-
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53 288 justing for possible publication bias. For men alone, the ES (0.13) did not reach statistically signifi-
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55 289 cance.

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3 290 *State anxiety*

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5 291 Twenty-five studies had included state anxiety as outcome. A statistically significant, robust medi-
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7 um ES (0.51) was found for women and men combined. Adjusting for possible publication bias led
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9 292 to a smaller, but statistically significant, ES (0.31). For women, the ES of 0.53 was statistically sig-
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11 293 nificant, but smaller (0.32) and non-significant when adjusting for publication bias. For men only,
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13 294 the analysis produced a small, non-significant ES of 0.32.
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17 296 *Marital function*

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19 297 Only 5 studies (N = 633) had included measures of marital function, and only very small (ES: 0.09-
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21 298 0.08) non-significant effects were found.
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25 299 **Possible moderators**

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27 300 As the Q -statistics were generally statistically significant ($p < 0.10$) and the I^2 -statistic indicated low
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29 301 to medium heterogeneity, we explored, when a sufficient number of studies were available for each
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31 302 analysis, possible sources of heterogeneity and analyzed whether the ESs for pregnancy and com-
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33 303 bined psychological outcomes varied according to between-study differences in study design and
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35 304 intervention characteristics (type and format). The results are shown in Table 2.
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39 305 *Study design*

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41 306 The ESs found for pregnancy outcomes were statistically significant for both randomized controlled
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43 307 trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.4). The difference did not
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45 308 reach statistical significance. For psychological outcomes, the pooled ES for RCT's ($g = 0.70$) was
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47 309 larger than for both NRCT's (0.28) and uncontrolled trials (UCT) (0.55) and the only statistically
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49 310 significant result. When adjusting for publication bias, the ES for RCTs (0.26) was smaller than for
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51 311 NRCTs and UCTs. Between-group differences did not reach statistical significance.
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3 312 *Intervention type*

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5 313 The number of studies for each intervention type was insufficient to explore differences in pregnan-
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7 314 cy outcomes. For the combined psychological outcomes, statistically significant effects were found
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9 315 for both cognitive behavioral therapies (CBT) and mind/body interventions (MBI), with the largest
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11 316 ES for CBT ($g=1.15$), followed by MBI (0.41). Counseling did not reach statistical significance.
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14 317 The failsafe numbers exceeded the criterion, indicating rather robust results. The between-group
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16 318 differences did not reach statistical significance.

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19 319 *Intervention format*

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21 320 For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats.
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23 321 Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group differ-
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25 322 ence did not reach statistical significance. For the combined psychological outcomes, a statistically
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27 323 significant effect was found for Group format ($g= 0.76$) ($p < 0.001$). Intervention formats such as
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29 324 Individual, Couples, and Online did not reach statistical significance. The overall between-group
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31 325 difference for intervention formats was statistical significant ($p < 0.001$).
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35 326 *Other study characteristics*

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37 327 The possible moderating influence of the continuously assessed study characteristics of mean age,
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39 328 intervention duration, number or sessions, and study quality (Jadad scores) were analyzed with me-
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41 329 ta-regression. As seen in Table 3, no significant effects were found for any of the moderators for
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43 330 either pregnancy or the combined psychological outcomes. A total of 6 studies had examined ef-
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45 331 fects on both pregnancy and anxiety. When examining the possible role of anxiety reduction as a
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47 332 mediator of the effect on pregnancy outcome with meta-regression, a statistically significant associ-
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49 333 ation was found between the ESs for anxiety and pregnancy, indicating that the greater the reduc-
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51 334 tion in anxiety, the greater the likelihood of achieving pregnancy (see Table 3).
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56 335 **Table 3**

Results of meta-regression analyses

Dependent variable	Independent variable	K	Beta ^a	95% CI	<i>p</i>
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

336 ^{a)} Mixed effects regression: unrestricted maximum likelihood; ^{b)} Modified Jadad-score; ^{c)} P-values for individual psy-
 337 chological outcomes; 0.09 (anxiety) – 0.58 (depression).

338 Discussion

339 Primary findings

340 Our meta-analysis of the available evidence suggests that women who receive some form of psy-
 341 chological intervention are approximately twice as likely to become pregnant when compared to
 342 controls receiving standardized care or active control intervention. Although the results of the 10
 343 currently available studies appeared robust, there were some indications of publication bias in favor
 344 of studies with larger positive effect sizes. It should also be noted that the precision of the effect
 345 size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. Although the between-
 346 group difference did not reach statistical significance, NRCT's yielded greater effects (RR: 2.4 (95
 347 % CI: 1.57 – 3.60)) than RCT's (RR: 1.7 (95 % CI: 1.06 – 2.72)). Compared with other types of
 348 interventions that historically have been introduced to improve pregnancy rates in ART (improved
 349 culture media, new hormone stimulation regimens etc.), even an effect corresponding to the lower
 350 limit of the confidence interval is substantial. While the results could be considered surprising, we
 351 have no good reasons to reject this finding, which is further supported by the results of the meta-
 352 regression showing that larger reductions in anxiety were associated with improved pregnancy out-
 353 comes. With respect to the psychological outcomes currently reported in the literature, the results

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3 354 suggest that psychological intervention could be effective in reducing anxiety (25 studies) as well as
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5 355 depressive symptoms (21 studies) with the effects corresponding to medium and large effect sizes
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7 356 (0.5 and 1.0). As for pregnancy outcomes, there were indications of publication bias in the direction
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9 357 of larger positive effects, and adjusting for publication bias resulted in a considerably smaller statis-
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11 358 tically non-significant effect size for depressive symptoms. The pooled results did not reach statisti-
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13 359 cal significance for the 10 studies which had investigated effects on infertility-related distress and
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15 360 the 5 studies which had included measures of marital function.

19 361 **Comparing with results of previous reviews**

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21 362 The present review included 39 studies of a total of 3401 women (3064) and men (347). The partic-
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23 363 ipants received various psychosocial interventions lasting from one week to six months, including
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25 364 cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions.
26
27 365 The present review evaluates almost twice the number of studies included in the most recent previ-
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29 366 ous review,³² which reported mixed results of the efficacy of psychosocial intervention. Whereas
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31 367 the former review found no evidence for attenuating distress, there was promising support of psy-
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33 368 chological intervention increasing pregnancy chances for women not receiving ART.³² In line with
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35 369 the second review from 2005,³¹ we found more credible results for group intervention than for other
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37 370 formats, e.g. online interventions, individual and couples intervention.¹¹⁵ The first review published
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39 371 in 2003 also highlighted group interventions as more effective, especially if the interventions em-
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41 372 phasized education and skills training, such as relaxation. Our results concurred with those observa-
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43 373 tions, and distinguishing between CBT, MBI, and counseling in general, our findings suggest that
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45 374 interventions delivered in groups may be more effective in reducing distress. The recently conduct-
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47 375 ed studies included in the present review have contributed by increasing the size of the available
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49 376 dataset considerably, and taken together the currently available evidence suggests that offering psy-
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51 377 chosocial interventions may improve both chances of pregnancy and quality-of-life for infertile pa-
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53 378 tients going through fertility treatment.

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3 379 **Strengths and limitations**

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5 380 Our systematic review and meta-analysis has several strengths. We conducted a comprehensive
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7 381 search and performed the review in accordance with the recommended guidelines.³⁵ In order to lim-
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9 382 it the possibility of selection bias, we encouraged authors of eligible studies to elaborate on their
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11 383 results if the data reported was insufficient, and asked authors of papers written in foreign language
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13 384 to submit their results to us in English. The included studies represented a range of different coun-
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15 385 tries, has used comparable outcome measures, and provided fairly comprehensive descriptions of
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17 386 the interventions studied. In addition, we conducted a detailed evaluation of the methodological
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19 387 quality, explored heterogeneity, and made adjustments for possible publication bias, when required.
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21 388 Some limitations of the currently available data should also be noted. First, the samples investigated
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23 389 were not as homogeneous as could be wished for. A small number of infertile participants did not
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25 390 receive treatment with ART, and it was not consistently reported what type of ART procedure the
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27 391 participants received and what phase or treatment they were in. Nonetheless, as suggested by the
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29 392 failsafe numbers, the reductions in anxiety and depressive symptoms appeared quite robust. Second-
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31 393 ly, the methodological quality varied considerably across the included studies, which may have
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33 394 weakened the interpretability of the outcomes, as suggested by the greater ESs found for pregnancy
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35 395 outcomes for NRCSs compared with RCTs. On the other hand, we found no statistical significant
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37 396 associations between study quality scores for either pregnancy or psychological outcomes. A third
38
39 397 possible limitation is the high level of heterogeneity indicated by Q and I² statistics and the pooled
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41 398 effect sizes reported in the present review should thus be viewed as an estimate of the average ex-
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43 399 pected effect across a range of different settings. Fourth, the indications of publication bias for sev-
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45 400 eral results suggest the possibility of a “file drawer problem”, i.e. the existence of relevant un-
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47 401 published null-findings, a common problem when conducting systematic reviews. Finally, due to
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49 402 inconsistencies in the reporting of causes of infertility, we are unable to evaluate the possible asso-
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51 403 ciations between effect sizes and causes of infertility. Although meta-analysis remains the gold
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3 404 standard when evaluating the current evidence within a field of research, as is often the case with
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5 405 systematic reviews, qualitative as well as quantitative, the overall level of the evidence reported in
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7 406 our review may be challenged by the heterogeneity and methodological limitations of the existing
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9 407 studies.

12 408 **Clinical and practical implications**

14 409 We found evidence for improvement in general psychological symptoms such as anxiety and de-
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16 410 pression, but not for infertility-specific distress. A possible explanation for the latter could be the
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18 411 lack of sensitivity of the infertility-related distress measures used. The questions used in these
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20 412 measures are directly concerned with thoughts and feelings about involuntarily childlessness, and
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22 413 rumination about the involuntary childlessness may persist, even when psychosocial intervention
23
24 414 improves general psychological wellbeing. Of special interest is the result of our meta-regression
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26 415 analysis of the six studies which had included both pregnancy and anxiety as outcomes showing
27
28 416 that larger reductions in anxiety were associated with greater chances of pregnancy. Anxiety is a
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30 417 state of arousal, which over time is physically and mentally stressful for the individual.¹⁷ Reducing
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32 418 distress, anxiety in particular, may increase the physiological ability to cope with stress and advance
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34 419 the possibility of impregnation. We found no association between mean age and pregnancy rates
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36 420 outcomes, which may seem surprising, since age is the most important predictor of pregnancy out-
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38 421 comes of ART.^{116,117} However, our meta-regression was conducted for the mean age of the *sample*
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40 422 and the mean age across study samples only showed little variation (Mean age: 32.7; SD: 2.4). A
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42 423 rather narrow age interval may explain an apparent lack of association between age and chance of
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44 424 pregnancy. Our findings also suggest that group interventions appear to be more efficacious than
45
46 425 individual, couples or online interventions. This could be explained by various reasons. Firstly,
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48 426 group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3) than
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50 427 individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive impact of
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3 428 “group settings” i.e. the sense-of-community between participants, reducing the feelings of isolation
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5 429 or alienation and sharing with individuals in the same life situation etc.¹¹⁸⁻¹²¹
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7

8 430 **Recommendations for future research**

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10 431 Despite the overall positive effects of psychosocial interventions, there is generally a need for stud-
11
12 432 ies with more rigorous methodology, including more strict reporting of causes of infertility, the
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14 433 types of ART used, and which phases of treatment participants are in. Furthermore, it would be of
15
16 434 importance to develop clinically meaningful categories of distress with the purpose of improving
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18 435 interventions targeted to the various types and levels of distress experienced by the participants.
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20 436 Psychological well-being/distress fluctuates over time during fertility treatment and a stepped care
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22 437 approach could be potentially valuable in this population.¹²² Also needed are studies testing hypoth-
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24 438 eses concerning possible moderating and mediating mechanisms of the effects if interventions on
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26 439 distress as well as pregnancy outcomes. For example, what psychosocial factors do we need to tar-
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28 440 get to optimize effects on distress and pregnancy rates, and which biomarkers affected by psycho-
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30 441 social interventions, e.g. oxidative stress, inflammatory processes, can best explain the observed
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32 442 effects. This could assist in developing a more solid evidence base providing better guidance for
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34 443 patients, health professionals, and policy makers about “what works for whom” in infertile patients.
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41 444 **Conclusions**

42
43 445 In conclusion, the present meta-analysis of 39 studies suggests that psychosocial intervention, in
44
45 446 particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety
46
47 447 and depressive symptoms and for improving pregnancy outcomes of ART. Moreover, there is some
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49 448 preliminary evidence to suggest that reduction in anxiety achieved through psychological interven-
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51 449 tion may improve the chance of pregnancy. Despite the robust overall effect found, the considerable
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53 450 heterogeneity of the available studies with respect to methodological quality, intervention type and
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55 451 format still warrants caution as to the conclusions which can be drawn.
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460 assessments. RZ were responsible for analyzing the data. YF drafted the manuscript and IFV, NGS,
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468 **What is already known on this topic**

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

471 **What this study adds**

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

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3 474 en and men. Psychosocial intervention leads to reductions in anxiety and depressive symptoms and
4
5 475 larger reductions in anxiety appear to be associated with increased fertility rates for women in
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7 476 treatment for infertility.
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For peer review only

Complete search history

(1978 – April 2014)

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

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

Total of all searches

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

- Additional records identified n=6

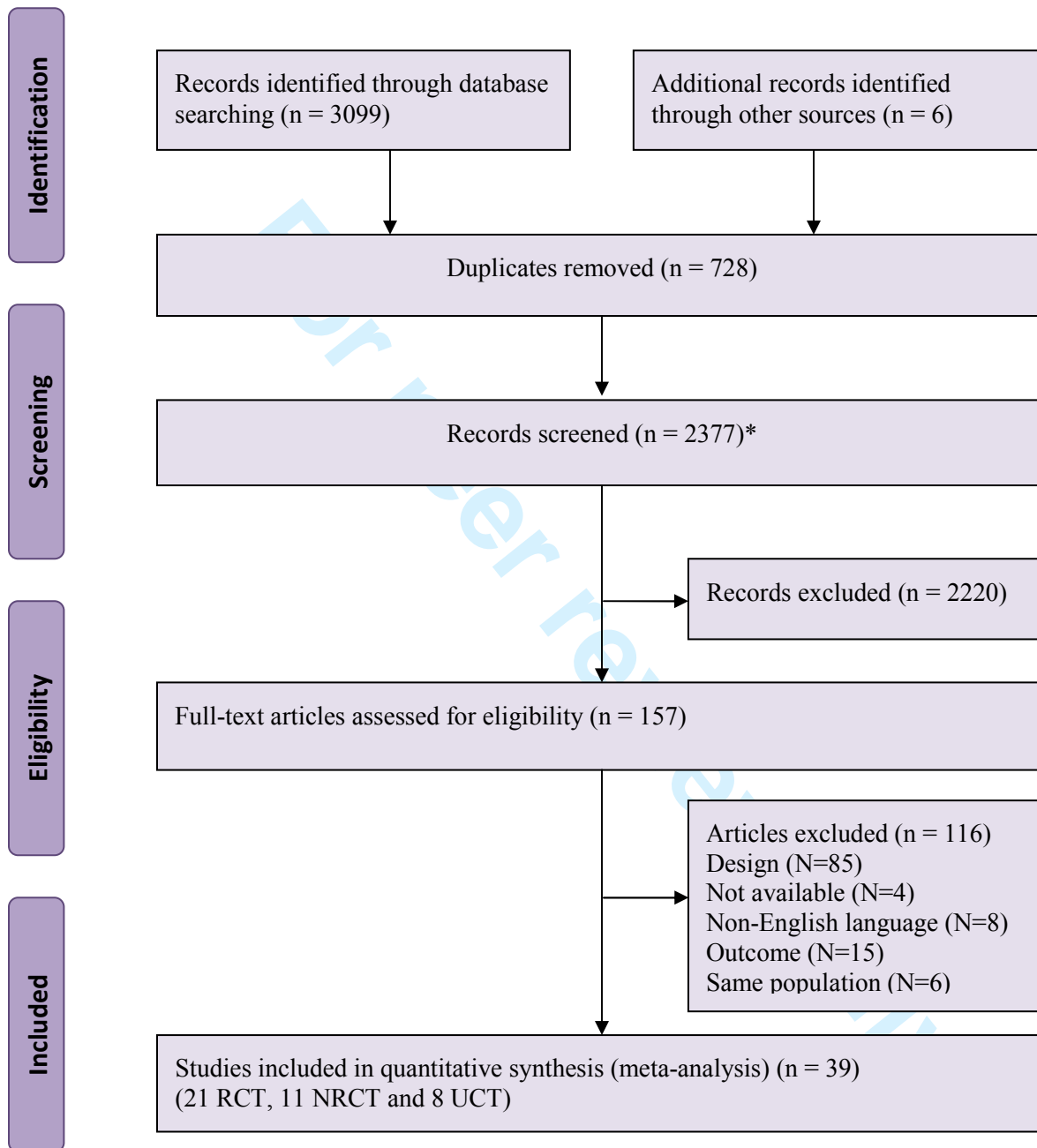
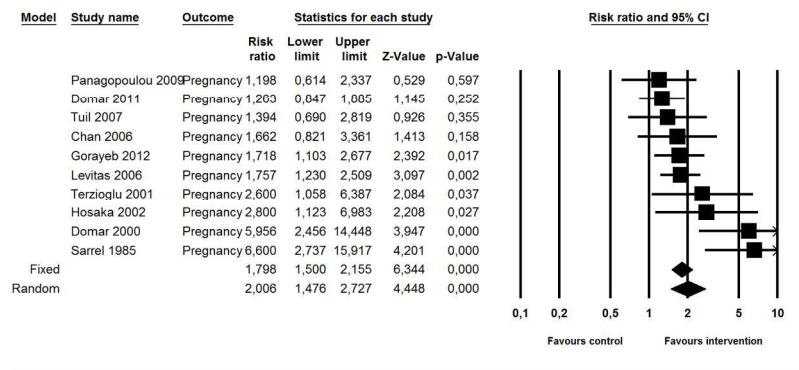


Fig 1 PRISMA flowchart.*Screened according to the exclusion criteria presented in the Methods section.

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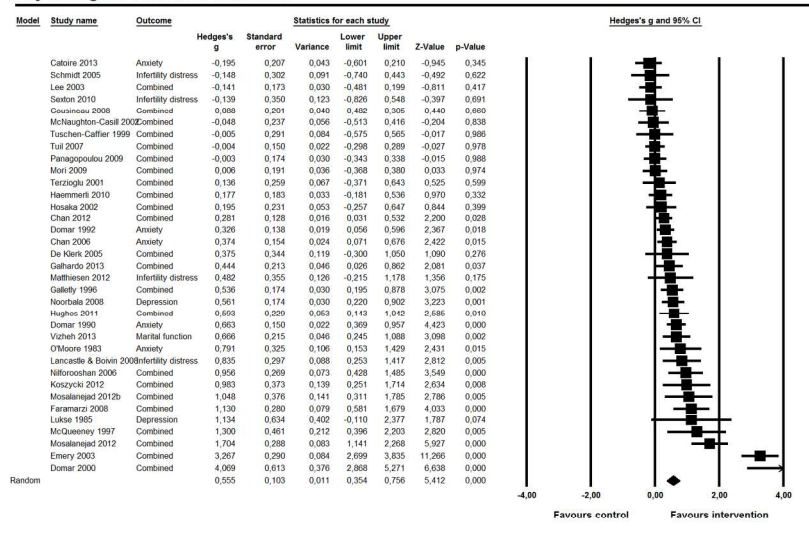
Pregnancy rate



Review only

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Psychological outcomes combined





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

Page 1 of 2

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.

Page 2 of 2
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BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Farver-Vestergaard, Ingeborg; Aarhus University, Department of Psychology Skovgård, Ninna; Aarhus University Hospital, Skejby Fertility Clinic Ingerslev, Hans Jakob; Aarhus University Hospital, Center for Preimplantation Genetic Diagnosis/The Fertility Clinic 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

SCHOLARONE™
Manuscripts

Only

1 **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

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Keywords: infertility/psychosocial intervention/distress/pregnancy

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5 Abstract

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

9 **Design:** Systematic review and meta-analysis.

10 **Data sources** PsycINFO, PubMed, Embase, CINAHL, Web of Science and The Cochrane Library
11 between 1978 and April 2014.

12 **Study selection** Studies were considered eligible if they evaluated the effect of any psychosocial
13 intervention on clinical pregnancy and/or distress in infertile participants, used a quantitative ap-
14 proach, and were published in English.

15 **Data extraction** Study characteristics and results were extracted and the methodological quality
16 assessed. Effect sizes (Hedges g) were pooled using a random effect model. Heterogeneity was as-
17 sessed using the Q statistic and I^2 , and publication bias evaluated using Eggers' method. Possible
18 moderators and mediators were explored with meta-ANOVAs and meta-regression.

19 **Results** We identified 39 eligible studies (total $N = 2746$ men and women) assessing the effects of
20 psychological treatment on pregnancy rates and/or adverse psychological outcomes, including de-
21 pressive symptoms, anxiety, infertility stress, and marital function. Statistically significant and ro-
22 bust overall effects of psychosocial intervention were found for both clinical pregnancy ($RR = 2.01$;
23 $CI: 1.48-2.73$; $p < 0.001$) and combined psychological outcomes (Hedges $g = 0.59$; $CI: 0.38-0.80$;
24 $p = 0.001$). The pooled effect sizes (ES) for psychological outcomes were generally larger for wom-
25 en ($g: 0.51-0.73$) than men ($0.13-0.34$), but the difference only reached statistical significance for
26 depressive symptoms ($p = 0.004$). Meta-regression indicated that larger reductions in anxiety were
27 associated with greater improvement in pregnancy rates (Slope: 0.19 ; $p = 0.004$). No clear-cut differ-
28 ences were found between effects of cognitive behavioral therapy (CBT) ($g = 0.84$), mind-body in-
29 terventions (0.61), and other intervention types (0.50).

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

33 **Strengths and limitations of this study**

- 34 • A major strength of this study is the extensive search of various databases from 1978 to
- 35 April 2014, as well as a comprehensive methodological assessment
- 36 • Further analyses were performed to account for publication bias, yielding conservative ef-
- 37 fect sizes and thus strengthening the robustness of the estimates
- 38 • Heterogeneity and indications of publication bias were observed for several of the outcomes
- 39 • Substantial variation of the methodological quality and missing information on fertility and
- 40 ART treatment may limit the interpretability of the outcomes

41 **Introduction**

42 Fecundity has become a growing problem for many couples trying to conceive a child and although
43 not all couples choose to seek medical assistance, more than 10% of the childbearing population has
44 resorted to assisted reproductive technology (ART) to conceive.¹⁻⁵ Being involuntarily childless and
45 going through various ART procedures imposes considerable stress on the couple, and childlessness
46 is often perceived as a life crisis where the emotional strain equals that found for traumatic
47 events.^{2,6-10} Although infertile couples may be considered mentally healthy in general,¹¹ several
48 studies indicate that coping with infertility is associated with periodically heightened levels of psy-
49 chological symptoms of distress, depression and anxiety.^{12,13} Feelings of loss, grief, anger, and sad-
50 ness are not uncommon, and women often report bodily disparagement, lack of femininity, shame,
51 and self-blame.^{2,14} There is some evidence to suggest that dysregulation in the uterus microenvi-
52 ronment may influence the ability to conceive, e.g. oxidative stress and inflammation,^{15,16} which
53 may be promoted by psychological distress.^{17,18} Such findings have lead several studies to investi-
54 gate possible links between mental state and pregnancy outcome.^{10,19-24} Although the results have
55 been mixed, reviews of the literature have generally reached the conclusion that psychosocial fac-
56 tors such as depressive symptoms, anxiety, distress, and certain coping strategies are linked to re-
57 duced chances of pregnancy.^{12,25,26} Two recently published meta-analyses, however, report conflict-
58 ing results.^{27,28} Whereas one meta-analysis supported the conclusion that emotional distress may be
59 critical to the success of fertility treatment outcome,²⁷ the other did not find sufficient support for

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3 60 this hypothesis.²⁸ The different conclusions could be due to between-study methodological differ-
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5 61 ences, e.g. in the chosen measures of distress and definitions of pregnancy (e.g. serum positive test,
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7 62 clinical pregnancy, or live birth).
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10 63 Nonetheless, the evidence indicating a considerable psychosocial burden associated with infertility
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12 64 and its treatment has inspired several researchers to explore the effect of various psychosocial inter-
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14 65 ventions in reducing distress, improving quality-of-life, and thereby, possibly, optimize the chances
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16 66 of pregnancy. So far, three meta-analyses have reviewed effects of psychological interventions on
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18 67 mental health and pregnancy outcome. Again, the results have been mixed. The first meta-analysis,
19
20 68 published in 2003, concluded that psychological intervention appeared to have a beneficial effect on
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22 69 negative emotions,²⁹ particularly anxiety. An effect of counseling was also found for infertility-
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24 70 related distress, whereas no clear effect was seen on pregnancy rates. Although the original system-
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26 71 atic review identified 25 independent studies, the final meta-analysis only included 8–10 studies
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28 72 selected on the basis of their methodological quality. The second meta-analysis published in 2005
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30 73 focused on differences in effects related to intervention format, e.g. individual/couple vs. group
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32 74 setting.³⁰ Overall, the results suggested that both individual/couple and group interventions were
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34 75 effective in reducing emotional distress as well as increasing the conception rate. In contrast to the
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36 76 two first meta-analyses, which had investigated both controlled and uncontrolled studies, the third
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38 77 meta-analysis from 2009, which only included controlled studies,³¹ found no evidence for an effect
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40 78 of psychological interventions on emotional distress. An effect, however, was found for pregnancy
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42 79 rates, but only for infertile couples not in ART.
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49 80 Taken together, while showing promising results, the findings of existing quantitative systematic
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51 81 reviews, the most recent published in 2009, are mixed. The literature within this field is expanding,
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53 82 and studies of new psychosocial intervention approaches building on existing knowledge and target-
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55 83 ing specific problems of infertile patients, e.g. mind/body interventions, web-based treatments, and
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57 84 online psycho-education programs, have since been published. Furthermore, the more recently pub-
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3 85 lished studies have generally used randomized controlled trial designs, a notable strength reducing
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5 86 the risk of bias and making the studies more easily comparable.³² An updated review and meta-
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7 87 analysis is needed to determine to which degree psychosocial interventions may reduce infertility
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10 88 related distress related to improvement of pregnancy chances during fertility treatment.

11 12 13 14 89 **Methods**

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16 90 The present study was conducted in accordance with the preferred reporting items for systematic
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18 91 reviews and meta-analysis (PRISMA) recommendations.^{33,34} An *a priori* designed study protocol
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21 92 guided the literature search, study selection, and data synthesis.

22 23 24 93 **Search strategy and criteria**

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26 94 A comprehensive and systematic search of the literature published between 1978 (first baby born
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28 95 after in vitro fertilization) and April 2014 was conducted, using a sensitive search strategy recom-
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30 96 mended for reviews by Higgins and Green.³⁵ When conducting the searches, we combined key-
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32 97 words representing the two primary concepts, infertility and psychosocial treatment: (i) “infertil*”,
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34 98 “childlessness”, “IVF”, “ICSI”, “fertility treatment/problems” “assisted reproduction” and (ii) “psy-
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36 99 chological/psychosocial intervention”, “social support”, “couples therapy”, “psycho-education”,
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39 100 “internet-based intervention” and “behavioral therapy” (for a full search history, see appendix 1).
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41 101 We identified relevant records by electronic searches in general medical and psychological data-
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43 102 bases: PubMed, PsycINFO, The Cochrane Library, Embase, CINAHL, and Web of Science. Fur-
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45 103 thermore, we cross-examined reference lists of the retrieved papers and reviews for additional rele-
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47 104 vant studies. We did not pursue the grey literature or trial registries, and limited our search to in-
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49 105 clude only peer-reviewed articles published in English.

50 51 52 53 106 **Study selection**

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55 107 Studies were considered eligible if they 1) reported data on infertile participants 2) presented data
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57 108 on a psychosocial intervention or a supportive program 3) included both baseline and post-
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3 109 intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research ap-
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5 110 proach. In general terms, infertility refers to not being able to conceive for more than one year
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7 111 without contraception (WHO, 2002). Despite this standard definition, a recent review has found
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9 112 considerable between-study variation in definitions.³⁶ Furthermore, infertility can be graded in rela-
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11 113 tion to clinical diagnosis and duration. The present meta-analysis reviews studies using several dif-
12
13 114 ferent definitions of the term “infertile”, and includes all studies of patients diagnosed with different
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15 115 types of infertility and in different types and stages of ART treatments, e.g. intrauterine insemina-
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17 116 tion (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). “Psychosocial
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19 117 interventions or supportive programs” were defined as all interventions with a psychosocial aim that
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21 118 did not include the prescription of medication had a primary physical focus, e.g. acupuncture or
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23 119 massage therapy. However, studies using “psychophysiological” approaches, e.g. relaxation, guided
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25 120 imagery or meditation exercises as part of a psychosocial program, were included. The interven-
26
27 121 tions could be delivered in individual-, group-, couples-, or internet-based format. We included both
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29 122 controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines, commen-
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31 123 taries, case reports, editorials, newspaper articles, newsletters, and books chapters. Neither did we
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33 124 include abstracts-only, doctoral theses, or conference presentations. Our primary outcome was
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35 125 pregnancy rate, defined as *clinical pregnancy*. This clinical definition implies a visualization of at
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37 126 least one gestational sack and fetal heartbeat in approximately the 5th week after fertilization. Sec-
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39 127 ondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalized
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41 128 stress, specific infertility stress, and interpersonal functioning assessed through self-reported ques-
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43 129 tionnaires.
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50 **Data extraction and quality assessment**

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52 131 All full-text articles were read by two independent review authors (IFV, NGS) and the data extract-
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54 132 ed according to predefined criteria. Disagreements were discussed with a third author (YF) and re-
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56 133 solved by consensus. If information on any outcome was missing or if clarifications were needed,
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3 134 authors were contacted for further information. Each study was assessed for methodological quality
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5 135 using the Jadad criteria,³⁷ a commonly used tool to evaluate methodological quality, e.g. use and
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7 136 adequate description of randomization- and blinding procedures, and description of drop-out rates
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10 137 (score range: 0-5). In addition to the 0-5 points possible on the original Jadad scale, one additional
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12 138 point was given for each of the following: (a) *was a control group included*; in order to
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14 139 acknowledge whether the intervention group was compared with another group, although randomi-
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16 140 zation was not used, (b) *were both pre- and post-data presented*; as including both pre- and post-
17
18 141 intervention data will provide more accurate results. (c) *Was any form of blinding or masking of*
19
20 142 *conditions to patients, or (d) blinding of researchers attempted*; acknowledging if the study had
21
22 143 attempted to masking the active condition, (e) *was a standardized and reliable outcome measure*
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24 144 *used*; a criterion increasing the validity and comparability of the outcomes, and (f) *were pre-post*
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26 145 *correlations provided*; which could provide better estimates of the effect size. The modified scale
27
28 146 yielded a total quality score ranging from 0-11. With respect to the modified quality score, the mean
29
30 147 score difference between Rater 1 and 2 (means (SD): 5.2 (1.8) and 5.6 (2.0)) did not reach statistical
31
32 148 significance ($t(77) = 1.1$; $p = 0.28$), and the inter-rater score correlation was $r = 0.83$ ($p < 0.001$).
33
34 149 Kappa statistic was not used, as this assumes the nominal data and no natural ordering of ratings.
35
36 150 Quality ratings were not used as weights when calculating aggregated effect sizes (ES) as this is
37
38 151 generally discouraged due to the risk of introducing additional bias.³⁸ Instead, associations between
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40 152 ESs and study quality indicators were explored with meta-ANOVAs (design) and meta-regression
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42 153 (modified quality-score). In cases where we were unable to retrieve articles from the authorized
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44 154 databases, authors were contacted between 1-3 times in order to amend the data collected.
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155 **Calculating effect sizes**

156 The effect sizes (ESs) used were the risk ratio (RR) for pregnancy and Hedges g for psychological
157 outcomes. Hedges' g is a variation of Cohen's d which enables correction of potential bias due to
158 small sample size.^{39,40} A positive Hedges' g indicates result in the expected direction, e.g. a reduc-
159 tion in distress in the intervention group compared to controls. A $RR > 1.0$ indicates a greater pro-
160 portion of pregnancies in the intervention group. RRs were based on pregnancy rates and total N in
161 the intervention and control groups ($k=10$) (k = number of studies). When possible, Hedges' g was
162 calculated on the basis of reported means and SDs at pre and post-intervention or means and SDs of
163 change scores. This was possible for 50 of 61 effect sizes. When required and available, the report-
164 ed pre-post correlations were used in the calculation. This was the case for 5 ES's. When unavaila-
165 ble, the pre-post correlation was set to 0.50. When SDs were unavailable, two approaches were
166 used. For STAI state anxiety scores, the average pre- and post SDs (10.9 and 10.8) for the studies
167 which reported the SD was used, as the SDs appeared to be highly comparable across the remaining
168 studies. For other measures, ESs were estimated either on the basis of sample size and either p -
169 value or Eta square. In one study reporting only medians,⁴¹ the means and SDs were estimated fol-
170 lowing a previously suggested approach.⁴²

171 **Heterogeneity**

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

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3 179 **Analytical strategy**
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5 180 All ESs were weighted with the inverse variance and combined with a random effects model. First,
6
7 181 the overall ES of the effect of psychosocial interventions on pregnancy rates was calculated. Then
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9 182 the overall ES for the combined psychological outcomes was calculated together with the overall
10
11 183 ESs for the individual outcome measures of depression, state anxiety, infertility-related distress, and
12
13 184 marital function. This was done for the combined sample (women + men). If the results indicated
14
15 185 study heterogeneity, and if the number of studies in each category was sufficient ($K \geq 3$), possible
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17 186 between-study differences in ESs were explored by comparing the ESs of studies according to the
18
19 187 following study characteristics: gender, study design, intervention type, and intervention format
20
21 188 (mixed effect meta-ANOVAs), methodological quality (modified quality score), mean age of the
22
23 189 sample, intervention duration, and number of sessions (mixed effect meta-regression).
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28 190 Prior to the search, statistical power analyses were conducted as previously recommended.⁴⁶ Based
29
30 191 on the findings of the earlier meta-analysis,³¹ we expected to find a RR of 1.4 for pregnancy rates
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32 192 and an average sample size of $N=76$. We expected to be able to detect a similar small ES (Hedges g
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34 193 = 0.28 or RR = 1.4) with an alpha of 5% and a statistical power of 80%, with a total of only 9 stud-
35
36 194 ies, using a random-effects model. Based on these results, we considered it worthwhile to conduct
37
38 195 the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2
39
40 196 (www.meta-analysis.com), IBM SPSS-20, and various formulas in Microsoft Excel.
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45 197 **Publication bias**

46 198 The possibility of publication bias, a widespread problem when conducting meta-analyses, was
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48 199 evaluated with funnel plots,⁴⁷ Egger's method, and by calculating fail-safe numbers.^{48,49} A funnel
49
50 200 plot is a graphic illustration of study ESs in relation to study size or precision. Egger's test provides
51
52 201 a statistic for the skewness of results.⁵⁰ Calculation of fail-safe numbers is aimed at achieving an
53
54 202 indication of the number of unpublished studies with null-findings that would reduce the result to
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56 203 statistical non-significance ($p > 0.05$). It has been suggested that a reasonable level is achieved if the
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3 204 fail-safe number exceeds $5K+10$ ($K = N$ studies in the meta-analysis).⁵¹ If the results were sugges-
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5 205 tive of publication bias, an adjusted ES was calculated using Duval and Tweedie's trim and fill
6
7 206 method,⁵² which imputes ESs of missing studies and recalculates the ES accordingly.

11 207 **Results**

15 208 **Study selection**

17 209 In a first screening, duplicates were identified, and titles and abstracts reviewed. A total of 157 stud-
18
19 210 ies were found potentially relevant and reviewed independently by two raters. Four articles could
20
21 211 not be retrieved due to "no access" policy from the university, and the authors did not respond to
22
23 212 our enquiries.⁵³⁻⁵⁶ Initially, the raters were uncertain or disagreed on 13 (8.3%) articles (inter-rater
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25 213 agreement: 0.78; $p < 0.001$ (Kappa statistic)) indicating "substantial agreement."⁵⁷ After negotiation,
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27 214 5 of these were included, resulting in 41 potentially eligible articles. One additional study was ex-
28
29 215 cluded due to the combination of psychological intervention with a psychoactive drug, and one
30
31 216 study had insufficient statistical data and the authors did not respond to our enquiry. We thus in-
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33 217 cluded a total of 39 studies in the present review. On three occasions authors provided unpublished
34
35 218 additional data.⁵⁸⁻⁶⁰ Figure 1 shows a flowchart of the study selection process.

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40 219 (Insert Figure 1 near here)

43 220 **Study characteristics**

45 221 The study characteristics are summarized in Table 1. Based on outcome, 29 of the studies were aimed at
46
47 222 reducing negative emotional distress,^{41,58-85} with the targeted outcomes being infertility-related distress
48
49 223 ($k=10$), depression ($k=21$), anxiety ($k=25$), and marital function ($k=5$). Five studies focused solely on the
50
51 224 outcome of pregnancy,⁸⁶⁻⁹⁰ and 5 studies had included distress as well as pregnancy as outcome.^{78,91-94} Twen-
52
53 225 ty-one studies were randomized controlled trials (RCTs),^{58,61,65-72,74,75,83,85,89-95} and ten studies were non-
54
55 226 randomized controlled studies (NRCTs),^{41,59,60,76,79,80,86-88,96} with most control groups receiving standardized
56
57 227 care or being waiting-list controls. Only three studies had included an active/attention control condition, e.g.

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3 228 non-emotional writing or receiving an information booklet.^{70,71,74} One study offered gift certificates to the
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5 229 control group participants if they responded to the follow-up questionnaires.⁸⁹ Relatively few studies were
6
7 230 uncontrolled (UCT) (k= 8).^{62-64,73,77,81,82,84} The reporting of the participants' medical treatment status was
8
9 231 inconsistent. Five studies did not provide information on treatment status (whether or not in current ART
10
11 232 treatment), 3 studies reported that some, but not how many, of the participants were in treatment, and 31
12
13 233 studies reported that their participants were currently in ART treatment, although not what kind of treatment
14
15 234 e.g. IUI, IVF/ICSI, or treatment cycle. The cause of infertility was also inconsistently reported, and some
16
17 235 participants may still have been under evaluation during the study period. Twenty-five studies had included
18
19 236 only women, while the remaining 14 studies had included both women and men. The included studies had
20
21 237 reported data for a total of 3401 participants (3064 women and 347 men). The mean age and mean duration
22
23 238 of infertility for intervention group participants was (32.7 yrs. SD 2.2) and (4.6 yrs. SD 2.1) and for control
24
25 239 group participants (32.6 yrs. SD=1.7) and (5.1 yrs. SD=3.0). The specific intervention strategies mostly em-
26
27 240 ployed were cognitive behavioral therapy (k=8) and mind/body intervention (k=12). The remaining studies
28
29 241 had used a variety of interventions, including stress management, hypnosis, art therapy, expressive writing
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31 242 intervention, crisis intervention, and various types of counseling. Some studies had included more than one
32
33 243 approach, e.g. cognitive behavioral approaches supplemented with mind-body techniques such as relaxation.
34
35 244 To be categorized as mind/body intervention, a study had to use such strategies as the general approach over
36
37 245 the course of intervention. Thus, if studies had mainly used cognitive behavioral therapy strategies and only
38
39 246 incorporated other approaches, e.g., relaxation exercises, in one or two sessions, they were categorized as
40
41 247 cognitive behavioral therapy interventions. The number of sessions ranged from 1 to 24, lasting approxi-
42
43 248 mately from 20 minutes to 3 hours and the duration of psychosocial intervention ranged from 1 week to 28
44
45 249 months.

48 250 *Attrition*

50
51 251 A total of 15 studies reported the number of participants at baseline and then again at follow-up, and
52
53 252 as seen in Table 1, dropout varied across studies. Although the dropout rates in the intervention
54
55 253 groups were somewhat higher (Mean: 30.5% (SD: 20.2)) than in controls (24.9% (24.8)), the differ-
56
57 254 ence did not reach statistical significance (t(28):0.68, p=0.50). Furthermore, only four studies ex-

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3 255 plicitly stated that the analysis was based on an intention-to-treat (ITT) approach.^{70,72,83,92} Two addi-
4
5 256 tional studies used methods comparable to ITT, e.g. carrying last (baseline) observations forward or
6
7 257 use of multilevel linear modeling.^{69,97} Four studies stated that there were no differences between
8
9 258 completers and dropouts without specifying this further,^{41,64,81,85} and the remaining studies failed to
10
11 259 report whether there were dropouts or how such missing data were dealt with. The possible associa-
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13 260 tion between ESs and uneven dropout in the intervention and control groups was analyzed for the
14
15 261 15 studies that reported dropout by regressing the difference in dropout rates on the overall ESs
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17 262 across all outcomes. The result indicated that larger dropouts in the intervention group compared
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19 263 were generally associated with smaller ES's (Slope = -0.02), but the association did not reach statis-
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21 264 tical significance (p = 0.268).
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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)

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3												
4	Tuschen-Caffier et al.	Germany	I: 34 (22) C: 24 (24)	NRCT	Cognitive-behavioral therapy	CBT	Couples	10-12	32	IS: one item MF: one item	-	1 (4)
5	1999											
6												
7	Domar et al.	USA	I: 56 (20) C: 63 (14)	RCT	Psychological intervention	MBI	Group	10	10	D: BDI A: STAI	+	4 (10)
8	2000											
9												
10	Terzioglu	Turkey	I: 60 (60) (50 %) C: 60 (60) (50 %)	RCT	Counseling	Other	Individual	5	5	D: BDI A: STAI	+	2 (5)
11	2001											
12												
13												
14	Hosaka et al.	Japan	I: 37 (37) C: 37 (37)	NRCT	Structured intervention	MBI	Group	5	5		+	3 (6)
15	2002											
16	McNaughton-Cassill et al.	USA	I: 43 (43) (39.5 %) C: 37 (37) (48.6 %)	NRCT	Couples support	CBT	Couples	6	3	D: BDI A: BAI	-	2 (5)
17	2002											
18												
19	Emery et al.	Switzerland	I: 158 (110) (34.8 %) C: 152 (131) (42.8 %)	RCT	Pre-IVF counseling	Other	Couples	1	1	D: BDI A: STAI	-	3 (6)
20	2003											
21												
22												
23	Lee	Taiwan	I: 64 (64) C: 68(68)	RCT	Nursing crisis intervention program	MBI	Individual	7	7	D: SDS A: STAI	-	1 (4)
24	2003											
25												
26												
27												
28												
29	De Klerk et al.	The Netherlands	I: 22 (18) C: 22 (15)	RCT	Counseling	Other	Group	3	4-5	D: HADS A: HADS	+	3 (6)
30	2005											
31												
32	Schmidt et al.	Denmark	I: 13 (13) C: 435 (435)	NRCT	Stress management	Other	Group	5	6	IS: COMPI	-	1 (4)
33	2005											
34	Chan et al.	Hong Kong, China	I: 101 (69) C: 126 (115)	RCT	The Eastern body-mind intervention	MBI	Group	4	4	A: STAI	-	3 (7)
35	2006											
36												
37	Levitas et al.	Israel	I: 89 (89) C: 96 (96)	NRCT	Hypnosis	MBI	Individual	1	1		+	0 (1)
38	2006											
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4	Nilforooshan et al.	Iran	I: 30 (30)	RCT	Cognitive-	CBT	Group	6	6	D: BDI	-	2 (6)
5	2006		(50 %)		behavioral					A: BAI		
6			C: 30 (30)		counseling							
7			(50 %)									
8	Tuil et al.	The	I: 108 (102)	RCT	Internet-	Other	Individual	Infinite	2	D: BDI	-	3 (6)
9	2007	Nether-	(50 %)		based health					A: STAI		
10		lands	C: 96 (78)		record							
11			(48.7 %)									
12	Cousineau et al.	USA	I: 96 (49)	RCT	Psycho-	Other	Online	1-2	4	IS: FPI	-	4 (8)
13	2008		C: 92 (49)		educational					MF: RDAS		
14					support							
15	Faramarzi et al.	Iran	I: 42 (29)	RCT	Cognitive-	CBT	Group	10	10	D: BDI	-	3 (6)
16	2008		C: 40 (30)		behavioral					A: Cattell		
17					therapy							
18	Lancastle and Boivin	Wales,	I:28 (28)	RCT	Brief coping	Other	Individual	14	2	IS: CIQ	-	4 (8)
19	2008	UK	C: 27 (27)		intervention							
20	Noorbala et al.	Iran	I: 288 (288)	UCT	Cognitive-	CBT	Group		24	D: BDI	-	3 (8)
21	2008		(50 %)		behavioral							
22					therapy							
23	Mori	Japan	I: 85 (85)	RCT	Stress man-	Other	Individual	3	12	D: HADS	-	4 (8)
24	2009		C: 40 (40)		agement					A: HADS		
25	Panagopoulou et al.	England,	I: 50 (50)	RCT	Expressive	Other	Individual	3	1	IS: ISS	-	3 (7)
26	2009	UK	C: 98 (98)		writing in-					A: STAI		
27					tervention							
28	Haemmerli et al.	Switzer-	I: 60 (46)	RCT	Coaching	Other	Online	13	8	IS: IDS	-	3 (6)
29	2010	land	C: 64 (41)		and support					D: CES-D		
30										A: STAI		
31	Sexton et al.	USA	I: 21 (15)	RCT	Web-based	Other	Individual		2	IS: FPI	-	3 (6)
32	2010		C: 22 (16)		copying with							
33					infertility							
34	Domar et al.	USA	I: 46 (46)	RCT	Mind/body	MBI	Group	10	10		+	4 (6)
35	2011		C: 51(51)		program for							
36					infertility							
37	Hughes and Mann de	Canada	I: 21 (21)	UCT	Art therapy	Other	Group	8 (2hrs)	8	D: BDI	-	0 (2)
38	Silva									A: BAI		
39												
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4	2011											
5												
6	Chan et al.	Hong	I: 141 (141)	RCT	Integrative	MBI	Group	4 (3hrs)	4	A: STAI	+	3 (6)
7	2012	Kong, China	C: 110 (110)		body-mind- spirit inter- vention					MF: C-KMS		
8												
9												
10	Gorayeb et al.	Brazil	I: 93 (93)	RCT	Brief cogni- tive- behavioral intervention	CBT	Group	5 (2hrs)	5		+	1 (4)
11	2012		C: 95 (95)									
12												
13												
14	Koszycki et al.	Canada	I: 31 (23)	UCT	Interpersonal and support- ive therapy	Other	Individual	12 (50min)	12	IS: FPI	-	3 (7)
15	2012									D: BDI HAM-D		
16												
17	Matthiesen et al.	Denmark	I: 42 (15)	RCT	Expressive writing in- tervention	Other	Individual	3 (20min)	1	IS: COMPI	-	4 (8)
18	2012		C: 40 (16)									
19												
20	Mosalanejad et al.	Iran	I: 32 (32)	RCT	Cognitive- behavioral treatment	CBT	Group	12 (2hrs)	12	D: DASS	-	1 (4)
21	2012		C: 33 (33)							A: DASS		
22												
23	Mosalanejad et al.	Iran	I: 16 (16)	NRCT	Cognitive- behavioral therapy	CBT	Group	15 (1,5hrs)	16	D: DASS	-	2 (5)
24	2012b		C: 15 (15)							A: DASS		
25												
26	Catoire et al.	France	I: 50 (50)	UCT	Hypnosis	MBI	Individual	4	1	A: STAI	-	4 (7)
27	2013											
28	Galhardo et al.	Portugal	I: 55 (55)	NRCT	Mindful- ness-based program for infertility	MBI	Group	10 (2hrs)	10	IS: ISE	-	1 (4)
29	2013		C: 37 (37)							D: BDI A: STAI		
30												
31	Vizheh et al.	Iran	I: 86 (86)	RCT	Marital counseling	Other	Group	3 (1.5hrs)	3	MF: MSQ	+	4 (8)
32	2013		(50 %)									
33			C: 94 (86)									
34			(54.7 %)									
35												
36												
37												

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.

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- 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 Depression 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 included³⁷ and the *modified Jadad range 0-11 (total score)* included additional points for: inclusion of a control group, pre-post data, blinding of participants or researchers, use of standardized and reliable outcome measures and report of pre-post correlations.

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2 282 *Quality ratings*
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4 283 All included studies were methodologically assessed with both the original Jadad scale and the ad-
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6 284 ditional methodological criteria. The original Jadad scores ranged from 0 to 4 with a mean of 2.28
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8 285 (SD: 1.36), and the modified total quality scores ranged from 1 to 10 with a mean of 5.36 (SD:
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10 286 2.05). The main methodological issue was that only very few studies attempted to blind or mask the
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12 287 intervention conditions to either patients or researchers. The quality ratings for each criterion for
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14 288 each study and total scores are shown in Table 2.
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4 289**Table 2 Modified Jadad scores (original Jadad criteria + 6 additional criteria)**

Study	Jadad criteria							Additional criteria						Jadad	Total
	1	2	3	4	5	6	7	a	b	C	d	e	f		
	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

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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

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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.

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2 298 **Effects of psychosocial intervention**
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5 299 The results of the meta-analyses are shown in Table 3.
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8 300 *Pregnancy rates*
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10 301 A statistically significant and robust effect size (RR = 2.01) was found for the 10 studies which had
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12 302 investigated effects of psychosocial intervention on clinical pregnancy rates, with the chance of
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14 303 becoming pregnant being doubled in the intervention group. Adjusting for possible publication bias,
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16 304 the risk ratio was somewhat lower (1.57). A forest plot of the effects of psychological intervention
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18 305 on pregnancy outcomes are shown in Figure 2.
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22 306 (Insert Figure 2 near here)
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25 307 *Combined psychological outcomes*
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27 308 Combining the effect sizes of the 35 studies which had included one or more psychological out-
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29 309 comes revealed a statistically significant, robust⁵¹, medium³⁹ effect size ($g = 0.59$). The results indi-
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31 310 cated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger pub-
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33 311 lished ESs. When imputing missing ESs,⁵² the resulting adjusted pooled ES was smaller (0.31), but
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35 312 remained statistically significant. Taking gender into consideration, the ES (0.51) remained statisti-
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37 313 cally significant for women, still suggesting a robust effect. The ES was smaller for men (0.34) and
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39 314 did not reach statistical significance. A forest plot of the effects of psychological intervention on the
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41 315 combined psychological outcomes is shown in Figure 3.
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46 316 (Insert Figure 3 near here)
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49 317 *Infertility-related distress*
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51 318 Only ten studies had included infertility-related distress as an outcome. Small ESs were found for
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53 319 women and men combined (0.24) and women alone (0.37), and did not reach statistical signifi-
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55 320 cance.
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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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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	-	-

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UCT	7	215	6.0	6	=0.424	0.0	0.55	0.40 – 0.70	<0.001	90	45
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.51</i>	<i>0.36 – 0.66</i>	<i><0.05</i>	-	-
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
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.37</i>	<i>-0.19 – 0.93</i>	<i>ns</i>	-	-
MBI	9	841	57.7	8	<0.001	86.1	0.61	0.17 – 0.65	<0.001	158	55
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.42</i>	<i>0.01 – 0.84</i>	<i><0.05</i>	-	-
Other	19	1430	149.2	9	<0.001	87.9	0.50	0.18 – 0.81	=0.002	246	105
<i>Adjusted for publication bias</i>	<i>(24)^e</i>	-	-	-	-	-	<i>0.17</i>	<i>-0.20 – 0.54</i>	<i>ns</i>	-	-
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
<i>Adjusted for publication bias</i>	<i>(26)^e</i>	-	-	-	-	-	<i>0.50</i>	<i>0.25 – 0.75</i>	<i><0.05</i>	-	-
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. I² 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 × *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))

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2 334 *Depression*

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4 335 Twenty-one studies had assessed depressive symptoms. A statistically significant ES (1.00) was
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6 336 found for women and men combined. However, when adjusting for possible publication bias, the
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8 337 results changed dramatically to a small, non-significant ES of 0.31. Similar results were found for
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10 338 women alone with a statistically significant ES of 0.73 reduced to a non-significant 0.29 after ad-
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12 339 justing for possible publication bias. For men alone, the ES (0.13) did not reach statistically signifi-
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14 340 cance.

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18 341 *State anxiety*

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20 342 Twenty-five studies had included state anxiety as outcome. A statistically significant, robust medi-
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22 343 um ES (0.51) was found for women and men combined. Adjusting for possible publication bias led
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24 344 to a smaller, but statistically significant, ES (0.31). For women, the ES of 0.53 was statistically sig-
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26 345 nificant, but smaller (0.32) and non-significant when adjusting for publication bias. For men only,
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28 346 the analysis produced a small, non-significant ES of 0.32.

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32 347 *Marital function*

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34 348 Only 5 studies (N = 633) had included measures of marital function, and only very small (ES: 0.09-
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36 349 0.08) non-significant effects were found.

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39 350 **Possible moderators**

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41 351 As the Q -statistics were generally statistically significant ($p < 0.10$) and the I^2 -statistic indicated low
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43 352 to medium heterogeneity, we, when a sufficient number of studies were available for each analysis,
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45 353 explored possible sources of heterogeneity and analyzed whether the ESs for pregnancy and com-
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47 354 bined psychological outcomes varied according to between-study differences in study design and
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49 355 intervention characteristics (type and format). The results are shown in [Table 3](#).

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53 356 *Study design*

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55 357 The ESs found for pregnancy outcomes were statistically significant for both randomized controlled
56
57 358 trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.8), with the ES for NRCT

1 359 being considerably smaller (1.9) when adjusting for publication bias. The difference did not reach
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3 360 statistical significance. For psychological outcomes, statistically significant results were found for
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5 361 both RCTs ($g= 0.70$) and UCTs (0.55), but not for NRCTs (0.28). When adjusting for publication
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8 362 bias, the ES for RCTs was considerably reduced (0.26). Furthermore, between-group differences
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10 363 did not reach statistical significance.

13 364 *Intervention type*

15 365 The number of studies for each intervention type was insufficient to explore differences in pregnan-
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17 366 cy outcomes. For the combined psychological outcomes, statistically significant, and – as indicated
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19 367 by the large failsafe numbers – robust effects, were found for all three intervention categories with
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21 368 the largest ES found for CBT ($g=0.84$), followed by MBI (0.61) and other intervention types (0.50).
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23 369 The between-group differences, however, did not reach statistical significance. Furthermore, the
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25 370 results suggested the possibility of publication bias, and when adjusting for publication bias, all
26
27 371 three ESs were reduced from medium to small.

29 372 *Intervention format*

31 373 For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats.
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33 374 Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group differ-
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35 375 ence did not reach statistical significance. For the combined psychological outcomes, a statistically
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37 376 significant effect was found for Group format ($g= 0.76$) ($p < 0.001$). The ESs for intervention for-
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39 377 mats such as Individual, Couples, and Online did not reach statistical significance. The overall be-
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41 378 tween-group difference for intervention formats was statistical significant ($p < 0.001$).

43 379 *Other study characteristics*

45 380 The possible moderating influence of the continuously assessed study characteristics of mean age,
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47 381 intervention duration, number or sessions, and study quality (modified quality scores) were ana-
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49 382 lyzed with meta-regression. As seen in [Table 4](#), no significant effects were found for any of the
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51 383 moderators for either pregnancy or the combined psychological outcomes. A total of 6 studies had

384 examined effects on both pregnancy and anxiety. When examining the possible role of anxiety re-
 385 duction as a mediator of the effect on pregnancy outcome with meta-regression, a statistically sig-
 386 nificant association was found between the ESs for anxiety and pregnancy, indicating that the great-
 387 er the reduction in anxiety, the greater the likelihood of achieving pregnancy (see [Table 4](#)).

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

Dependent variable	Independent variable	K	Beta ^a	95% CI	<i>p</i>
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

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

391 Discussion

392 Primary findings

393 Our meta-analysis of the available evidence suggests that women who receive some form of psy-
 394 chological intervention are approximately twice as likely to become pregnant when compared to
 395 controls receiving standardized care or active control intervention. Although the results of the 10
 396 currently available studies taken together appeared robust, there were some indications of publica-
 397 tion bias in favor of studies with larger positive effect sizes. It should also be noted that the preci-
 398 sion of the effect size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. Fur-
 399 thermore, although the between-group difference did not reach statistical significance, when disre-
 400 garding the possibility of publication bias, NRCT's yielded greater effects (RR: 2.8 (95 % CI: 1.55
 401 – 5.06)) than RCT's (RR: 1.7 (95 % CI: 1.17 – 2.40)). Compared with other types of interventions
 402 that historically have been introduced to improve pregnancy rates in ART (improved culture media,

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2 403 new hormone stimulation regimens etc.), even an effect corresponding to the lower limit of the con-
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4 404 fidence interval is substantial. While the results could be considered surprising, the available data
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6 405 do provide any clear-cut reasons to reject this finding, which is further supported by the results of
7
8 406 the meta-regression showing that larger reductions in anxiety were associated with improved preg-
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10 407 nancy outcomes. With respect to the psychological outcomes currently reported in the literature, the
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12 408 results suggest that psychological intervention could be effective in reducing anxiety (25 studies) as
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14 409 well as depressive symptoms (21 studies) with the effects corresponding to medium and large effect
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16 410 sizes (0.5 and 1.0). As seen for pregnancy outcomes, there were indications of publication bias in
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18 411 the direction of larger positive effects, and adjusting for publication bias resulted in a considerably
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20 412 smaller, statistically non-significant, effect size for depressive symptoms. The pooled results did not
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22 413 reach statistical significance for the 10 studies which had investigated effects on infertility-related
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24 414 distress and the 5 studies which had included measures of marital function.

28 29 415 **Comparing with results of previous reviews**

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31 416 The present review included 39 studies of a total of 3401 women (3064) and men (347). The partic-
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33 417 ipants received various psychosocial interventions lasting from one week to six months, including
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35 418 cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions.
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37 419 The present review evaluates almost twice the number of studies included in the most recent previ-
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39 420 ous review,³¹ which reported mixed results of the efficacy of psychosocial intervention. Whereas
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41 421 the former review found no evidence for attenuating distress, there was promising support of psy-
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43 422 chological intervention increasing pregnancy chances for women not receiving ART.³¹ In line with
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45 423 the second review from 2005,³⁰ we found more credible results for group intervention than for other
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47 424 formats, e.g. online interventions, individual, and couples intervention.³⁰ The first review published
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49 425 in 2003 also highlighted group interventions as more effective, especially if the interventions em-
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51 426 phasized education and skills training, such as relaxation. Our results concurred with these earlier
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53 427 observations, suggesting that interventions delivered in groups may be more effective in reducing
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55 428 distress. Moreover, although the comparison did not reach statistical significance; prior to adjusting
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2 429 for publication bias, the intervention type of CBT appeared to be more effective than MBI and other
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4 430 types of interventions. Here, it should be noted that the categorization of interventions may be
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6 431 somewhat ambiguous. For example, the study by Cousineau et al. (2000)⁸³ could have been catego-
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8 432 rized as a mind-body intervention, as the authors had provided a website that directed attention to-
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10 433 wards relaxation exercises. However, as there was no reporting of whether the participants were
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12 434 engaged in weekly or daily training, we chose to interpret relaxation as an optional feature, and
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14 435 hence the study was not categorized as MBI. The possible ambiguity and considerable variability in
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16 436 interventions forced us to categorize many studies as “other”, which limits our understanding the
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18 437 possible mechanisms in psychosocial interventions. Taken together, the available data do not pro-
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20 438 vide a clear basis for understanding possible differences between effects of different intervention
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22 439 types, and the results should be interpreted with caution. The more recently conducted studies in-
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24 440 cluded in the present review have contributed by increasing the size of the available dataset consid-
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26 441 erably, and taken together, the currently available evidence suggests that offering psychosocial in-
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28 442 terventions may improve both chances of pregnancy and quality-of-life for infertile patients going
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30 443 through fertility treatment.
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36 444 **Strengths and limitations**

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38 445 Our systematic review and meta-analysis has several strengths. We conducted a comprehensive
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40 446 search and performed the review in accordance with the recommended guidelines.³⁴ In order to lim-
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42 447 it the possibility of selection bias, we encouraged authors of eligible studies to elaborate on their
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44 448 results if the data reported was insufficient, and asked authors of papers written in foreign language
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46 449 to submit their results to us in English. The included studies represented a range of different coun-
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48 450 tries, has used comparable outcome measures, and provided fairly comprehensive descriptions of
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50 451 the interventions studied. In addition, we conducted a detailed evaluation of the methodological
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52 452 quality in order to detect any issues that could possible affect the accuracy of the effect sized calcu-
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54 453 lated. While not all characteristics, in particular reproductive, could be assessed; most general
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1 454 methodological aspects were covered. We also explored heterogeneity and made adjustments for
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4 455 possible publication bias, when required.
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7 456 Some limitations of the currently available data should also be noted. First, the samples investigated
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9 457 may not have been as homogeneous as could be wished for. A small number of infertile participants
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11 458 did not receive treatment with ART, and, furthermore, it was not consistently reported what type of
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13 459 ART procedure the participants received, what phase or treatment they were in, or the causes of
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15 460 infertility. This information is clearly important when interpreting the outcomes, and unknown be-
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17 461 tween-study and within-study between-group differences, e.g. in numbers of cycles, idiopathic in-
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19 462 fertility and embryo transfer, may have influenced the results, in particular for pregnancy outcomes.
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21 463 However, such differences are likely to be less important in RCT's, where randomization is ex-
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23 464 pected to reduce their influence. Although the difference did not reach statistical significance, RCTs
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25 465 reported smaller ESs for pregnancy outcomes than NRCTs, which could be interpreted as support-
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27 466 ing the concern that infertility and treatment characteristics may have been unevenly distributed
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29 467 between psychological treatment arms, thus increasing the risk for misattribution of outcomes to
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31 468 intervention, at least for NRCTs. On the other hand, we found no statistical significant associations
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33 469 between study quality scores and either pregnancy or psychological outcomes, no statistically sig-
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35 470 nificant differences in dropout rates between intervention and control groups, and, as suggested by
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37 471 the large failsafe numbers, improvements generally appeared quite robust. A second possible limita-
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39 472 tion is the high level of heterogeneity indicated by Q and I² statistics, and the pooled effect sizes
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41 473 reported in the present review should thus be viewed as an estimate of the average expected effect
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43 474 across a wide range of different settings. A third issue is that the considerable dropout rates and lack
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45 475 of intention-to-treat analyses may have influenced the results, and it cannot be excluded that fertili-
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47 476 ty- and treatment-related factors such as non-optimal fertilization, small number of eggs, etc. may
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49 477 have demotivated some participants and made them drop out of the study, while individuals who
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51 478 progressed through the treatment phases with more satisfactory outcomes were more likely to com-
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53 479 plete the study. Fourth, the indications of publication bias found for several results suggest the pos-
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2 480 sibility of a “file drawer problem”, i.e. the existence of relevant unpublished null-findings, a com-
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4 481 mon problem when conducting systematic reviews. Finally, due to inconsistencies in the reporting
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6 482 of causes of infertility, we are unable to evaluate the possible associations between effect sizes and
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8 483 causes of infertility. Although meta-analysis remains the gold standard when evaluating the current
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10 484 evidence within a field of research, as is often the case with systematic reviews, qualitative as well
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12 485 as quantitative, the overall level of the evidence reported in our review may be challenged by publi-
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14 486 cation bias and the heterogeneity and methodological limitations of the available published studies.

17 18 487 **Clinical and practical implications**

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20 488 We found evidence for improvement in general psychological symptoms such as anxiety and de-
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22 489 pression, but not for infertility-specific distress. A possible explanation for the latter could be the
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24 490 lack of sensitivity of the infertility-related distress measures used. The questions used in these
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26 491 measures are directly concerned with thoughts and feelings about involuntarily childlessness, and
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28 492 rumination about the involuntary childlessness may persist, even when psychosocial intervention
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30 493 improves general psychological wellbeing. Of particular interest is the result of our meta-regression
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32 494 analysis of the six studies which had included both pregnancy and anxiety as outcomes showing
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34 495 that larger reductions in anxiety were associated with greater chances of pregnancy. Anxiety is a
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36 496 state of arousal, which over time is physically and mentally stressful for the individual.¹⁷ Reducing
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38 497 distress, anxiety in particular, may increase the physiological ability to cope with stress and advance
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40 498 the possibility of impregnation. We found no association between mean age and pregnancy rates
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42 499 outcomes, which may seem surprising, since age is the most important predictor of pregnancy out-
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44 500 comes of ART.^{99,100} However, our meta-regression was conducted for the mean age of the *samples*
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46 501 and the mean age across study samples showed little variation (Mean age: 32.7; SD: 2.4). The rather
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48 502 narrow age interval across study samples may explain an apparent lack of association between age
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50 503 and chance of pregnancy. Our findings also suggest that group interventions appear to be more effi-
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52 504 cacious than individual, couples, or online interventions. There could be various reasons for this.
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54 505 Firstly, group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3)

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2 506 than individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive im-
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4 507 pact of “group settings” i.e. the sense-of-community between participants, reducing the feelings of
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6 508 isolation or alienation and sharing with individuals in the same life situation etc.¹⁰¹⁻¹⁰⁴
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9 **Recommendations for future research**

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11 510 Despite the overall positive effects of psychosocial interventions found in the literature, our results
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13 511 suggest a need for further studies with more rigorous methodology, including more strict reporting
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15 512 of causes of infertility, the types of ART used, and which phases of treatment participants are in.
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17 513 Also, most of the studies were conducted in high-income countries, it is therefore important to note
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19 514 that the assertions made here cannot be generalized to low-income and developing countries. There
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21 515 is thus a need for research in low-income or developing countries as well. Another aspect pertaining
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23 516 to generalizability is the challenge of comparing volunteering infertile participants in psychosocial
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25 517 efficacy studies with the general population of infertile individuals. The response rates in this area
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27 518 are moderate, and it seems important in future studies to explore and compare characteristics of not
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29 519 only dropouts and completers, but also of non-responders and responders. Furthermore, it would be
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31 520 of importance to develop clinically meaningful categories of distress with the purpose of improving
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33 521 interventions targeted to the various types and levels of distress experienced by the participants.
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35 522 Psychological well-being/distress fluctuates over time during fertility treatment and a stepped care
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37 523 approach could be potentially valuable in this population.¹⁰⁵ It is also possible that interventions
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39 524 aimed at relieving distress conducted at different phases in treatment may obtain different psycho-
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41 525 logical outcome results. This calls for improved reporting and comparability of the timing of the
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43 526 psychosocial interventions and greater precision and comparability of the timing of outcome as-
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45 527 sessments. Also needed are studies testing specific hypotheses concerning possible moderating and
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47 528 mediating mechanisms of the effects of interventions on distress and pregnancy outcomes. For ex-
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49 529 ample, which psychosocial factors do we need to target to optimize effects on distress and pregnan-
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51 530 cy rates, and which biomarkers affected by psychosocial interventions, e.g. oxidative stress, in-
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53 531 flammatory processes, can best explain the observed effects. This could assist in developing a more
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2 532 solid evidence base providing better guidance for patients, health professionals, and policy makers
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4 533 about “what works for whom” in infertile patients.
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8 534 **Conclusions**

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10 535 In conclusion, the present meta-analysis of 39 studies suggests that psychosocial intervention, in
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12 536 particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety
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15 537 and depressive symptoms and for improving pregnancy outcomes of ART. Moreover, there is some
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17 538 preliminary evidence to suggest that reduction in anxiety achieved through psychological interven-
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19 539 tion may improve the chance of pregnancy. Despite the robust overall effect found, the considerable
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21 540 heterogeneity of the available studies with respect to methodological quality, intervention type and
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23 541 format still warrants caution as to the conclusions which can be drawn.
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43
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45
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47
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49
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8 557 Data sharing: No additional data available

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11 558 **What is already known on this topic**

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14 559 Previous reviews have been inconclusive concerning the efficacy of psychosocial interventions for
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16 560 reducing distress and improving clinical pregnancy chances.

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19 561 **What this study adds**

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22 562 Synthesizing the currently available evidence suggests that psychosocial interventions could pro-
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24 563 vide clinically meaningful benefits for infertile women and men. Psychosocial intervention leads to
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26 564 reductions in anxiety and depressive symptoms, and larger reductions in anxiety appear to be asso-
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28 565 ciated with increased fertility rates for women in treatment for infertility.

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32 566 **Legends to figures**

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35 567 Figure 1. PRISMA flowchart of selection of studies

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38 568 Figure 2. Effects of psychosocial intervention on pregnancy rates

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41 569 Figure 3. Effects of psychosocial intervention on combined psychological outcomes

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For peer review only

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

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5 Abstract

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

9 **Design:** Systematic review and meta-analysis.

10 **Data sources** PsycINFO, PubMed, Embase, CINAHL, Web of Science and The Cochrane Library
11 between 1978 and April 2014.

12 **Study selection** Studies were considered eligible if they evaluated the effect of any psychosocial
13 intervention on clinical pregnancy and/or distress in infertile participants, used a quantitative ap-
14 proach, and were published in English.

15 **Data extraction** Study characteristics and results were extracted and the methodological quality
16 assessed. Effect sizes (Hedges g) were pooled using a random effect model. Heterogeneity was as-
17 sessed using the Q statistic and I^2 , and publication bias evaluated using Eggers' method. Possible
18 moderators and mediators were explored with meta-ANOVAs and meta-regression.

19 **Results** We identified 39 eligible studies (total $N = 2746$ men and women) assessing the effects of
20 psychological treatment on pregnancy rates and/or adverse psychological outcomes, including de-
21 pressive symptoms, anxiety, infertility stress, and marital function. Statistically significant and ro-
22 bust overall effects of psychosocial intervention were found for both clinical pregnancy ($RR = 2.01$;
23 $CI: 1.48-2.73$; $p < 0.001$) and combined psychological outcomes (Hedges $g = 0.59$; $CI: 0.38-0.80$;
24 $p = 0.001$). The pooled effect sizes (ES) for psychological outcomes were generally larger for wom-
25 en ($g: 0.51-0.73$) than men ($0.13-0.34$), but the difference only reached statistical significance for
26 depressive symptoms ($p = 0.004$). Meta-regression indicated that larger reductions in anxiety were
27 associated with greater improvement in pregnancy rates (Slope: 0.19 ; $p = 0.004$). **No clear-cut differ-**
28 **ences were found between effects of cognitive behavioral therapy (CBT) ($g = 0.84$), mind-body in-**
29 **terventions (0.61), and other intervention types (0.50).**

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

33 **Strengths and limitations of this study**

- 34 • A major strength of this study is the extensive search of various databases from 1978 to
35 April 2014, as well as a comprehensive methodological assessment
- 36 • Further analyses were performed to account for publication bias, yielding conservative ef-
37 fect sizes and thus strengthening the robustness of the estimates
- 38 • Heterogeneity **and indications of publication bias were** observed for several of the outcomes
- 39 • Substantial variation of the methodological quality **and missing information on fertility and**
40 **ART treatment** may limit the interpretability of the outcomes

41 Introduction

42 Fecundity has become a growing problem for many couples trying to conceive a child and although
43 not all couples choose to seek medical assistance, more than 10% of the childbearing population has
44 resorted to assisted reproductive technology (ART) to conceive.¹⁻⁵ Being involuntarily childless and
45 going through various ART procedures imposes considerable stress on the couple, and childlessness
46 is often perceived as a life crisis where the emotional strain equals that found for traumatic
47 events.^{2,6-10} Although infertile couples may be considered mentally healthy in general,¹¹ several
48 studies indicate that coping with infertility is associated with periodically heightened levels of psy-
49 chological symptoms of distress, depression and anxiety.^{12,13} Feelings of loss, grief, anger, and sad-
50 ness are not uncommon, and women often report bodily disparagement, lack of femininity, shame,
51 and self-blame.^{2,14} There is some evidence to suggest that dysregulation in the uterus microenvi-
52 ronment may influence the ability to conceive, e.g. oxidative stress and inflammation,^{15,16} which
53 may be promoted by psychological distress.^{17,18} Such findings have lead several studies to investi-
54 gate possible links between mental state and pregnancy outcome.^{10,19-24} Although the results have
55 been mixed, reviews of the literature have generally reached the conclusion that psychosocial fac-
56 tors such as depressive symptoms, anxiety, distress, and certain coping strategies are linked to re-
57 duced chances of pregnancy.^{12,25,26} Two recently published meta-analyses, however, report conflict-
58 ing results.^{27,28} Whereas one meta-analysis supported the conclusion that emotional distress may be
59 critical to the success of fertility treatment outcome,²⁷ the other did not find sufficient support for

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3 60 this hypothesis.²⁸ The different conclusions could be due to between-study methodological differ-
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5 61 ences, e.g. in the chosen measures of distress and definitions of pregnancy (e.g. serum positive test,
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7 62 clinical pregnancy, or live birth).
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10 63 Nonetheless, the evidence indicating a considerable psychosocial burden associated with infertility
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12 64 and its treatment has inspired several researchers to explore the effect of various psychosocial inter-
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14 65 ventions in reducing distress, improving quality-of-life, and thereby, possibly, optimize the chances
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16 66 of pregnancy. So far, three meta-analyses have reviewed effects of psychological interventions on
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18 67 mental health and pregnancy outcome. Again, the results have been mixed. The first meta-analysis,
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20 68 published in 2003, concluded that psychological intervention appeared to have a beneficial effect on
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22 69 negative emotions,²⁹ particularly anxiety. An effect of counseling was also found for infertility-
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24 70 related distress, whereas no clear effect was seen on pregnancy rates. Although the original system-
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26 71 atic review identified 25 independent studies, the final meta-analysis only included 8–10 studies
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28 72 selected on the basis of their methodological quality. The second meta-analysis published in 2005
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30 73 focused on differences in effects related to intervention format, e.g. individual/couple vs. group
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32 74 setting.³⁰ Overall, the results suggested that both individual/couple and group interventions were
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34 75 effective in reducing emotional distress as well as increasing the conception rate. In contrast to the
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36 76 two first meta-analyses, which had investigated both controlled and uncontrolled studies, the third
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38 77 meta-analysis from 2009, which only included controlled studies,³¹ found no evidence for an effect
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40 78 of psychological interventions on emotional distress. An effect, however, was found for pregnancy
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42 79 rates, but only for infertile couples not in ART.
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49 80 Taken together, while showing promising results, the findings of existing quantitative systematic
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51 81 reviews, the most recent published in 2009, are mixed. The literature within this field is expanding,
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53 82 and studies of new psychosocial intervention approaches building on existing knowledge and target-
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55 83 ing specific problems of infertile patients, e.g. mind/body interventions, web-based treatments, and
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57 84 online psycho-education programs, have since been published. Furthermore, the more recently pub-
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3 85 lished studies have generally used randomized controlled trial designs, a notable strength reducing
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5 86 the risk of bias and making the studies more easily comparable.³² An updated review and meta-
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7 87 analysis is needed to determine to which degree psychosocial interventions may reduce infertility
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10 88 related distress related to improvement of pregnancy chances during fertility treatment.

11 12 13 14 89 **Methods**

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16 90 The present study was conducted in accordance with the preferred reporting items for systematic
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18 91 reviews and meta-analysis (PRISMA) recommendations.^{33,34} An *a priori* designed study protocol
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21 92 guided the literature search, study selection, and data synthesis.

22 23 24 93 **Search strategy and criteria**

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26 94 A comprehensive and systematic search of the literature published between 1978 (first baby born
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28 95 after in vitro fertilization) and April 2014 was conducted, using a sensitive search strategy recom-
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30 96 mended for reviews by Higgins and Green.³⁵ When conducting the searches, we combined key-
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32 97 words representing the two primary concepts, infertility and psychosocial treatment: (i) “infertil*”,
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34 98 “childlessness”, “IVF”, “ICSI”, “fertility treatment/problems” “assisted reproduction” and (ii) “psy-
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36 99 chological/psychosocial intervention”, “social support”, “couples therapy”, “psycho-education”,
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39 100 “internet-based intervention” and “behavioral therapy” (for a full search history, see appendix 1).
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41 101 We identified relevant records by electronic searches in general medical and psychological data-
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43 102 bases: PubMed, PsycINFO, The Cochrane Library, Embase, CINAHL, and Web of Science. Fur-
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45 103 thermore, we cross-examined reference lists of the retrieved papers and reviews for additional rele-
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47 104 vant studies. We did not pursue the grey literature or trial registries, and limited our search to in-
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49 105 clude only peer-reviewed articles published in English.

50 51 52 53 106 **Study selection**

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55 107 Studies were considered eligible if they 1) reported data on infertile participants 2) presented data
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57 108 on a psychosocial intervention or a supportive program 3) included both baseline and post-
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3 109 intervention measures of stress, distress or pregnancy outcome 4) used a quantitative research ap-
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5 110 proach. In general terms, infertility refers to not being able to conceive for more than one year
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7 111 without contraception (WHO, 2002). Despite this standard definition, a recent review has found
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9 112 considerable between-study variation in definitions.³⁶ Furthermore, infertility can be graded in rela-
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11 113 tion to clinical diagnosis and duration. The present meta-analysis reviews studies using several dif-
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13 114 ferent definitions of the term “infertile”, and includes all studies of patients diagnosed with different
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15 115 types of infertility and in different types and stages of ART treatments, e.g. intrauterine insemina-
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17 116 tion (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). “Psychosocial
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19 117 interventions or supportive programs” were defined as all interventions with a psychosocial aim that
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21 118 did not include the prescription of medication had a primary physical focus, e.g. acupuncture or
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23 119 massage therapy. However, studies using “psychophysiological” approaches, e.g. relaxation, guided
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25 120 imagery or meditation exercises as part of a psychosocial program, were included. The interven-
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27 121 tions could be delivered in individual-, group-, couples-, or internet-based format. We included both
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29 122 controlled and uncontrolled trial studies, but chose to exclude expert opinion, magazines, commen-
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31 123 taries, case reports, editorials, newspaper articles, newsletters, and books chapters. Neither did we
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33 124 include abstracts-only, doctoral theses, or conference presentations. Our primary outcome was
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35 125 pregnancy rate, defined as *clinical pregnancy*. This clinical definition implies a visualization of at
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37 126 least one gestational sack and fetal heartbeat in approximately the 5th week after fertilization. Sec-
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39 127 ondary outcome measures were psychological ratings of depressive symptoms, anxiety, generalized
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41 128 stress, specific infertility stress, and interpersonal functioning assessed through self-reported ques-
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43 129 tionnaires.

50 **Data extraction and quality assessment**

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52 131 All full-text articles were read by two independent review authors (IFV, NGS) and the data extract-
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54 132 ed according to predefined criteria. Disagreements were discussed with a third author (YF) and re-
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56 133 solved by consensus. If information on any outcome was missing or if clarifications were needed,
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3 134 authors were contacted for further information. Each study was assessed for methodological quality
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5 135 using the Jadad criteria,³⁷ a commonly used tool to evaluate methodological quality, e.g. use and
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7 136 adequate description of randomization- and blinding procedures, and description of drop-out rates
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10 137 (score range: 0-5). In addition to the 0-5 points possible on the original Jadad scale, one additional
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12 138 point was given for each of the following: (a) *was a control group included*; in order to
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14 139 acknowledge whether the intervention group was compared with another group, although randomi-
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16 140 zation was not used, (b) *were both pre- and post-data presented*; as including both pre- and post-
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18 141 intervention data will provide more accurate results. (c) *Was any form of blinding or masking of*
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20 142 *conditions to patients, or (d) blinding of researchers attempted*; acknowledging if the study had
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22 143 attempted to masking the active condition, (e) *was a standardized and reliable outcome measure*
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24 144 *used*; a criterion increasing the validity and comparability of the outcomes, and (f) *were pre-post*
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26 145 *correlations provided*; which could provide better estimates of the effect size. The modified scale
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28 146 yielded a total quality score ranging from 0-11. With respect to the modified quality score, the mean
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30 147 score difference between Rater 1 and 2 (means (SD): 5.2 (1.8) and 5.6 (2.0)) did not reach statistical
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32 148 significance ($t(77) = 1.1$; $p = 0.28$), and the inter-rater score correlation was $r = 0.83$ ($p < 0.001$).
33
34 149 Kappa statistic was not used, as this assumes the nominal data and no natural ordering of ratings.
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36 150 Quality ratings were not used as weights when calculating aggregated effect sizes (ES) as this is
37
38 151 generally discouraged due to the risk of introducing additional bias.³⁸ Instead, associations between
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40 152 ESs and study quality indicators were explored with meta-ANOVAs (design) and meta-regression
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42 153 (modified quality-score). In cases where we were unable to retrieve articles from the authorized
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44 154 databases, authors were contacted between 1-3 times in order to amend the data collected.
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155 **Calculating effect sizes**

156 The effect sizes (ESs) used were the risk ratio (RR) for pregnancy and Hedges g for psychological
157 outcomes. Hedges' g is a variation of Cohen's d which enables correction of potential bias due to
158 small sample size.^{39,40} A positive Hedges' g indicates result in the expected direction, e.g. a reduc-
159 tion in distress in the intervention group compared to controls. A $RR > 1.0$ indicates a greater pro-
160 portion of pregnancies in the intervention group. RRs were based on pregnancy rates and total N in
161 the intervention and control groups ($k=10$) (k = number of studies). When possible, Hedges' g was
162 calculated on the basis of reported means and SDs at pre and post-intervention or means and SDs of
163 change scores. This was possible for 50 of 61 effect sizes. When required and available, the report-
164 ed pre-post correlations were used in the calculation. This was the case for 5 ES's. When unavaila-
165 ble, the pre-post correlation was set to 0.50. When SDs were unavailable, two approaches were
166 used. For STAI state anxiety scores, the average pre- and post SDs (10.9 and 10.8) for the studies
167 which reported the SD was used, as the SDs appeared to be highly comparable across the remaining
168 studies. For other measures, ESs were estimated either on the basis of sample size and either p -
169 value or Eta square. In one study reporting only medians,⁴¹ the means and SDs were estimated fol-
170 lowing a previously suggested approach.⁴²

171 **Heterogeneity**

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

179 **Analytical strategy**

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

190 Prior to the search, statistical power analyses were conducted as previously recommended.⁴⁶ Based
191 on the findings of the earlier meta-analysis,³¹ we expected to find a RR of 1.4 for pregnancy rates
192 and an average sample size of $N=76$. We expected to be able to detect a similar small ES (Hedges g
193 = 0.28 or RR = 1.4) with an alpha of 5% and a statistical power of 80%, with a total of only 9 stud-
194 ies, using a random-effects model. Based on these results, we considered it worthwhile to conduct
195 the meta-analysis. The calculations were conducted using Comprehensive Meta-Analysis, Version 2
196 (www.meta-analysis.com), IBM SPSS-20, and various formulas in Microsoft Excel.

197 **Publication bias**

198 The possibility of publication bias, a widespread problem when conducting meta-analyses, was
199 evaluated with funnel plots,⁴⁷ Egger's method, and by calculating fail-safe numbers.^{48,49} A funnel
200 plot is a graphic illustration of study ESs in relation to study size or precision. Egger's test provides
201 a statistic for the skewness of results.⁵⁰ Calculation of fail-safe numbers is aimed at achieving an
202 indication of the number of unpublished studies with null-findings that would reduce the result to
203 statistical non-significance ($p > 0.05$). It has been suggested that a reasonable level is achieved if the

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3 204 fail-safe number exceeds $5K+10$ ($K = N$ studies in the meta-analysis).⁵¹ If the results were sugges-
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5 205 tive of publication bias, an adjusted ES was calculated using Duval and Tweedie's trim and fill
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7 206 method,⁵² which imputes ESs of missing studies and recalculates the ES accordingly.

11 207 **Results**

14 208 **Study selection**

17 209 In a first screening, duplicates were identified, and titles and abstracts reviewed. A total of 157 stud-
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19 210 ies were found potentially relevant and reviewed independently by two raters. Four articles could
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21 211 not be retrieved due to "no access" policy from the university, and the authors did not respond to
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23 212 our enquiries.⁵³⁻⁵⁶ Initially, the raters were uncertain or disagreed on 13 (8.3%) articles (inter-rater
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25 213 agreement: 0.78; $p < 0.001$ (Kappa statistic)) indicating "substantial agreement."⁵⁷ After negotiation,
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27 214 5 of these were included, resulting in 41 potentially eligible articles. One additional study was ex-
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29 215 cluded due to the combination of psychological intervention with a psychoactive drug, and one
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31 216 study had insufficient statistical data and the authors did not respond to our enquiry. We thus in-
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33 217 cluded a total of 39 studies in the present review. On three occasions authors provided unpublished
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35 218 additional data.⁵⁸⁻⁶⁰ Figure 1 shows a flow chart of the study selection process.

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40 219 (Insert Figure 1 near here)

43 220 **Study characteristics**

45 221 **The study characteristics are summarized in Table 1.** Based on outcome, 29 of the studies were aimed at
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47 222 reducing negative emotional distress,^{41,58-85} with the targeted outcomes being infertility-related distress
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49 223 ($k=10$), depression ($k=21$), anxiety ($k=25$), and marital function ($k=5$). Five studies focused solely on the
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51 224 outcome of pregnancy,⁸⁶⁻⁹⁰ and 5 studies had included distress as well as pregnancy as outcome.^{78,91-94} **Twen-**
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53 225 **ty-one studies were randomized controlled trials (RCTs),^{58,61,65-72,74,75,83,85,89-95} and ten studies were non-**
54
55 226 **randomized controlled studies (NRCTs),^{41,59,60,76,79,80,86-88,96} with most control groups receiving standardized**
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57 227 **care or being waiting-list controls.** Only three studies had included an active/attention control condition, e.g.

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3 228 non-emotional writing or receiving an information booklet.^{70,71,74} One study offered gift certificates to the
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5 229 control group participants if they responded to the follow-up questionnaires.⁸⁹ Relatively few studies were
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7 230 uncontrolled (UCT) (k= 8).^{62-64,73,77,81,82,84} The reporting of the participants' medical treatment status was
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9 231 inconsistent. Five studies did not provide information on treatment status (whether or not in current ART
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11 232 treatment), 3 studies reported that some, but not how many, of the participants were in treatment, and 31
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13 233 studies reported that their participants were currently in ART treatment, although not what kind of treatment
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15 234 e.g. IUI, IVF/ICSI, or treatment cycle. The cause of infertility was also inconsistently reported, and some
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17 235 participants may still have been under evaluation during the study period. Twenty-five studies had included
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19 236 only women, while the remaining 14 studies had included both women and men. The included studies had
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21 237 reported data for a total of 3401 participants (3064 women and 347 men). The mean age and mean duration
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23 238 of infertility for intervention group participants was (32.7 yrs. SD 2.2) and (4.6 yrs. SD 2.1) and for control
24
25 239 group participants (32.6 yrs. SD=1.7) and (5.1 yrs. SD=3.0). The specific intervention strategies mostly em-
26
27 240 ployed were cognitive behavioral therapy (k=8) and mind/body intervention (k=12). The remaining studies
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29 241 had used a variety of interventions, including stress management, hypnosis, art therapy, expressive writing
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31 242 intervention, crisis intervention, and various types of counseling. Some studies had included more than one
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33 243 approach, e.g. cognitive behavioral approaches supplemented with mind-body techniques such as relaxation.
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35 244 To be categorized as mind/body intervention, a study had to use such strategies as the general approach over
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37 245 the course of intervention. Thus, if studies had mainly used cognitive behavioral therapy strategies and only
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39 246 incorporated other approaches, e.g., relaxation exercises, in one or two sessions, they were categorized as
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41 247 cognitive behavioral therapy interventions. The number of sessions ranged from 1 to 24, lasting approxi-
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43 248 mately from 20 minutes to 3 hours and the duration of psychosocial intervention ranged from 1 week to 28
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45 249 months.

250 *Attrition*

251 A total of 15 studies reported the number of participants at baseline and then again at follow-up, and
252 as seen in Table 1, dropout varied across studies. Although the dropout rates in the intervention
253 groups were somewhat higher (Mean: 30.5% (SD: 20.2)) than in controls (24.9% (24.8)), the differ-
254 ence did not reach statistical significance (t(28):0.68, p=0.50). Furthermore, only four studies ex-

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3 255 plicitly stated that the analysis was based on an intention-to-treat (ITT) approach.^{70,72,83,92} Two addi-
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5 256 tional studies used methods comparable to ITT, e.g. carrying last (baseline) observations forward or
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7 257 use of multilevel linear modeling.^{69,97} Four studies stated that there were no differences between
8
9 258 completers and dropouts without specifying this further,^{41,64,81,85} and the remaining studies failed to
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11 259 report whether there were dropouts or how such missing data were dealt with. The possible associa-
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13 260 tion between ESs and uneven dropout in the intervention and control groups was analyzed for the
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15 261 15 studies that reported dropout by regressing the difference in dropout rates on the overall ESs
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17 262 across all outcomes. The result indicated that larger dropouts in the intervention group compared
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19 263 were generally associated with smaller ES's (Slope = -0.02), but the association did not reach statis-
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21 264 tical significance (p = 0.268).
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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)

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4	Tuschen-Caffier et al.	Germany	I: 34 (22) C: 24 (24)	NRCT	Cognitive-behavioral therapy	CBT	Couples	10-12	32	IS: one item MF: one item	-	1 (4)
5	1999											
6												
7	Domar et al.	USA	I: 56 (20) C: 63 (14)	RCT	Psychological intervention	MBI	Group	10	10	D: BDI A: STAI	+	4 (10)
8	2000											
9												
10	Terzioglu	Turkey	I: 60 (60) (50 %) C: 60 (60) (50 %)	RCT	Counseling	Other	Individual	5	5	D: BDI A: STAI	+	2 (5)
11	2001											
12												
13												
14	Hosaka et al.	Japan	I: 37 (37) C: 37 (37)	NRCT	Structured intervention	MBI	Group	5	5		+	3 (6)
15	2002											
16	McNaughton-Cassill et al.	USA	I: 43 (43) (39.5 %) C: 37 (37) (48.6 %)	NRCT	Couples support	CBT	Couples	6	3	D: BDI A: BAI	-	2 (5)
17	2002											
18												
19	Emery et al.	Switzerland	I: 158 (110) (34.8 %) C: 152 (131) (42.8 %)	RCT	Pre-IVF counseling	Other	Couples	1	1	D: BDI A: STAI	-	3 (6)
20	2003											
21												
22												
23	Lee	Taiwan	I: 64 (64) C: 68(68)	RCT	Nursing crisis intervention program	MBI	Individual	7	7	D: SDS A: STAI	-	1 (4)
24	2003											
25												
26												
27												
28												
29	De Klerk et al.	The Netherlands	I: 22 (18) C: 22 (15)	RCT	Counseling	Other	Group	3	4-5	D: HADS A: HADS	+	3 (6)
30	2005											
31												
32	Schmidt et al.	Denmark	I: 13 (13) C: 435 (435)	NRCT	Stress management	Other	Group	5	6	IS: COMPI	-	1 (4)
33	2005											
34	Chan et al.	Hong Kong, China	I: 101 (69) C: 126 (115)	RCT	The Eastern body-mind intervention	MBI	Group	4	4	A: STAI	-	3 (7)
35	2006											
36												
37	Levitas et al.	Israel	I: 89 (89) C: 96 (96)	NRCT	Hypnosis	MBI	Individual	1	1		+	0 (1)
38	2006											
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4	Nilforooshan et al.	Iran	I: 30 (30)	RCT	Cognitive-behavioral counseling	CBT	Group	6	6	D: BDI	-	2 (6)
5	2006		(50 %)							A: BAI		
6			C: 30 (30)									
7			(50 %)									
8	Tuil et al.	The Netherlands	I: 108 (102)	RCT	Internet-based health record	Other	Individual	Infinite	2	D: BDI	-	3 (6)
9	2007		(50 %)							A: STAI		
10			C: 96 (78)									
11			(48.7 %)									
12	Cousineau et al.	USA	I: 96 (49)	RCT	Psycho-educational support	Other	Online	1-2	4	IS: FPI	-	4 (8)
13	2008		C: 92 (49)							MF: RDAS		
14												
15	Faramarzi et al.	Iran	I: 42 (29)	RCT	Cognitive-behavioral therapy	CBT	Group	10	10	D: BDI	-	3 (6)
16	2008		C: 40 (30)							A: Cattell		
17												
18	Lancastle and Boivin	Wales, UK	I:28 (28)	RCT	Brief coping intervention	Other	Individual	14	2	IS: CIQ	-	4 (8)
19	2008		C: 27 (27)									
20	Noorbala et al.	Iran	I: 288 (288)	UCT	Cognitive-behavioral therapy	CBT	Group		24	D: BDI	-	3 (8)
21	2008		(50 %)									
22												
23	Mori	Japan	I: 85 (85)	RCT	Stress management	Other	Individual	3	12	D: HADS	-	4 (8)
24	2009		C: 40 (40)							A: HADS		
25	Panagopoulou et al.	England, UK	I: 50 (50)	RCT	Expressive writing intervention	Other	Individual	3	1	IS: ISS	-	3 (7)
26	2009		C: 98 (98)							A: STAI		
27												
28	Haemmerli et al.	Switzerland	I: 60 (46)	RCT	Coaching and support	Other	Online	13	8	IS: IDS	-	3 (6)
29	2010		C: 64 (41)							D: CES-D		
30										A: STAI		
31	Sexton et al.	USA	I: 21 (15)	RCT	Web-based coping with infertility	Other	Individual		2	IS: FPI	-	3 (6)
32	2010		C: 22 (16)									
33												
34	Domar et al.	USA	I: 46 (46)	RCT	Mind/body program for infertility	MBI	Group	10	10		+	4 (6)
35	2011		C: 51(51)									
36												
37	Hughes and Mann de Silva	Canada	I: 21 (21)	UCT	Art therapy	Other	Group	8 (2hrs)	8	D: BDI	-	0 (2)
38										A: BAI		
39												
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4	2011											
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6	Chan et al.	Hong	I: 141 (141)	RCT	Integrative	MBI	Group	4 (3hrs)	4	A: STAI	+	3 (6)
7	2012	Kong,	C: 110 (110)		body-mind-					MF: C-KMS		
8		China			spirit inter-							
9					vention							
10	Gorayeb et al.	Brazil	I: 93 (93)	RCT	Brief cogni-	CBT	Group	5 (2hrs)	5		+	1 (4)
11	2012		C: 95 (95)		tive-							
12					behavioral							
13					intervention							
14	Koszycki et al.	Canada	I: 31 (23)	UCT	Interpersonal	Other	Individual	12 (50min)	12	IS: FPI	-	3 (7)
15	2012				and support-					D: BDI		
16					ive therapy					HAM-D		
17	Matthiesen et al.	Denmark	I: 42 (15)	RCT	Expressive	Other	Individual	3 (20min)	1	IS: COMPI	-	4 (8)
18	2012		C: 40 (16)		writing in-							
19					tervention							
20	Mosalanejad et al.	Iran	I: 32 (32)	RCT	Cognitive-	CBT	Group	12 (2hrs)	12	D: DASS	-	1 (4)
21	2012		C: 33 (33)		behavioral					A: DASS		
22					treatment							
23	Mosalanejad et al.	Iran	I: 16 (16)	NRCT	Cognitive-	CBT	Group	15 (1,5hrs)	16	D: DASS	-	2 (5)
24	2012b		C: 15 (15)		behavioral					A: DASS		
25					therapy							
26	Catoire et al.	France	I: 50 (50)	UCT	Hypnosis	MBI	Individual	4	1	A: STAI	-	4 (7)
27	2013											
28	Galhardo et al.	Portugal	I: 55 (55)	NRCT	Mindful-	MBI	Group	10 (2hrs)	10	IS: ISE	-	1 (4)
29	2013		C: 37 (37)		ness-based					D: BDI		
30					program for					A: STAI		
31					infertility							
32	Vizheh et al.	Iran	I: 86 (86)	RCT	Marital	Other	Group	3 (1.5hrs)	3	MF: MSQ	+	4 (8)
33	2013		(50 %)		counseling							
34			C: 94 (86)									
35			(54.7 %)									

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.

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- 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 Depression 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 included³⁷ and the *modified Jadad range 0-11 (total score)* included additional points for: inclusion of a control group, pre-post data, blinding of participants or researchers, use of standardized and reliable outcome measures and report of pre-post correlations.

For peer review only

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2 282 *Quality ratings*
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4 283 All included studies were methodologically assessed with both the original Jadad scale and the ad-
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6 284 ditional methodological criteria. The original Jadad scores ranged from 0 to 4 with a mean of 2.28
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8 285 (SD: 1.36), and the modified total quality scores ranged from 1 to 10 with a mean of 5.36 (SD:
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10 286 2.05). The main methodological issue was that only very few studies attempted to blind or mask the
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12 287 intervention conditions to either patients or researchers. The quality ratings for each criterion for
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14 288 each study and total scores are shown in [Table 2](#).
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49289 **Table 1 Modified Jadad scores (original Jadad criteria + 6 additional criteria)**

Study	Jadad criteria							Additional criteria						Jadad	Total
	1	2	3	4	5	6	7	a	b	C	d	e	f		
	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

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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

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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.

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2 298 **Effects of psychosocial intervention**
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5 299 The results of the meta-analyses are shown in [Table 3](#).
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8 300 *Pregnancy rates*
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10 301 A statistically significant and robust effect size (RR = 2.01) was found for the 10 studies which had
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12 302 investigated effects of psychosocial intervention on clinical pregnancy rates, with the chance of
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14 303 becoming pregnant being doubled in the intervention group. Adjusting for possible publication bias,
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16 304 the risk ratio was somewhat lower (1.57). **A forest plot of the effects of psychological intervention**
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18 305 **on pregnancy outcomes are shown in Figure 2.**
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22 306 (Insert Figure 2 near here)
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25 307 *Combined psychological outcomes*
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27 308 Combining the effect sizes of the 35 studies which had included one or more psychological out-
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29 309 comes revealed a statistically significant, robust⁵¹, medium³⁹ effect size ($g = 0.59$). The results indi-
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31 310 cated possible publication bias (skewed funnel plot, Egger's test ($p < 0.05$)) in favor of larger pub-
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33 311 lished ESs. When imputing missing ESs,⁵² the resulting adjusted pooled ES was smaller (0.31), but
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35 312 remained statistically significant. Taking gender into consideration, the ES (0.51) remained statisti-
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37 313 cally significant for women, still suggesting a robust effect. The ES was smaller for men (0.34) and
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39 314 did not reach statistical significance. **A forest plot of the effects of psychological intervention on the**
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41 315 **combined psychological outcomes is shown in Figure 3.**
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46 316 (Insert Figure 3 near here)
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49 317 *Infertility-related distress*
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51 318 Only ten studies had included infertility-related distress as an outcome. Small ESs were found for
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53 319 women and men combined (0.24) and women alone (0.37), and did not reach statistical signifi-
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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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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
<i>Adjusted for publication bias</i>	(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	-	-

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UCT	7	215	6.0	6	=0.424	0.0	0.55	0.40 – 0.70	<0.001	90	45
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.51</i>	<i>0.36 – 0.66</i>	<i><0.05</i>	-	-
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
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.37</i>	<i>-0.19 – 0.93</i>	<i>ns</i>	-	-
MBI	9	841	57.7	8	<0.001	86.1	0.61	0.17 – 0.65	<0.001	158	55
<i>Adjusted for publication bias</i>	<i>(10)^e</i>	-	-	-	-	-	<i>0.42</i>	<i>0.01 – 0.84</i>	<i><0.05</i>	-	-
Other	19	1430	149.2	9	<0.001	87.9	0.50	0.18 – 0.81	=0.002	246	105
<i>Adjusted for publication bias</i>	<i>(24)^e</i>	-	-	-	-	-	<i>0.17</i>	<i>-0.20 – 0.54</i>	<i>ns</i>	-	-
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
<i>Adjusted for publication bias</i>	<i>(26)^e</i>	-	-	-	-	-	<i>0.50</i>	<i>0.25 – 0.75</i>	<i><0.05</i>	-	-
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. I² 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 × *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))

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2 334 *Depression*

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4 335 Twenty-one studies had assessed depressive symptoms. A statistically significant ES (1.00) was
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6 336 found for women and men combined. However, when adjusting for possible publication bias, the
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8 337 results changed dramatically to a small, non-significant ES of 0.31. Similar results were found for
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10 338 women alone with a statistically significant ES of 0.73 reduced to a non-significant 0.29 after ad-
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12 339 justing for possible publication bias. For men alone, the ES (0.13) did not reach statistically signifi-
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14 340 cance.

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18 341 *State anxiety*

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20 342 Twenty-five studies had included state anxiety as outcome. A statistically significant, robust medi-
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22 343 um ES (0.51) was found for women and men combined. Adjusting for possible publication bias led
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24 344 to a smaller, but statistically significant, ES (0.31). For women, the ES of 0.53 was statistically sig-
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26 345 nificant, but smaller (0.32) and non-significant when adjusting for publication bias. For men only,
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28 346 the analysis produced a small, non-significant ES of 0.32.

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32 347 *Marital function*

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34 348 Only 5 studies (N = 633) had included measures of marital function, and only very small (ES: 0.09-
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36 349 0.08) non-significant effects were found.

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39 350 **Possible moderators**

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41 351 As the Q -statistics were generally statistically significant ($p < 0.10$) and the I^2 -statistic indicated low
42
43 352 to medium heterogeneity, we, when a sufficient number of studies were available for each analysis,
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45 353 explored possible sources of heterogeneity and analyzed whether the ESs for pregnancy and com-
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47 354 bined psychological outcomes varied according to between-study differences in study design and
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49 355 intervention characteristics (type and format). The results are shown in [Table 3](#).

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53 356 *Study design*

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55 357 The ESs found for pregnancy outcomes were statistically significant for both randomized controlled
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57 358 trials (RCT) (RR=1.7) and non-randomized controlled studies (NRCT) (2.8), with the ES for NRCT

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2 359 being considerably smaller (1.9) when adjusting for publication bias. The difference did not reach
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4 360 statistical significance. For psychological outcomes, statistically significant results were found for
5
6 361 both RCTs ($g= 0.70$) and UCTs (0.55), but not for NRCTs (0.28). When adjusting for publication
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8 362 bias, the ES for RCTs was considerably reduced (0.26). Furthermore, between-group differences
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10 363 did not reach statistical significance.

13 364 *Intervention type*

15 365 The number of studies for each intervention type was insufficient to explore differences in pregnan-
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17 366 cy outcomes. For the combined psychological outcomes, statistically significant, and – as indicated
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19 367 by the large failsafe numbers – robust effects, were found for all three intervention categories with
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21 368 the largest ES found for CBT ($g=0.84$), followed by MBI (0.61) and other intervention types (0.50).
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23 369 The between-group differences, however, did not reach statistical significance. Furthermore, the
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25 370 results suggested the possibility of publication bias, and when adjusting for publication bias, all
26
27 371 three ESs were reduced from medium to small.

30 372 *Intervention format*

32 373 For pregnancy outcomes, the number of studies was sufficient for Group and Individual formats.
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34 374 Both formats yielded statistical significant ES's (RR: 2.03 and 1.65), but the between-group differ-
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36 375 ence did not reach statistical significance. For the combined psychological outcomes, a statistically
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38 376 significant effect was found for Group format ($g= 0.76$) ($p < 0.001$). The ESs for intervention for-
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40 377 mats such as Individual, Couples, and Online did not reach statistical significance. The overall be-
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42 378 tween-group difference for intervention formats was statistical significant ($p < 0.001$).

45 379 *Other study characteristics*

47 380 The possible moderating influence of the continuously assessed study characteristics of mean age,
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49 381 intervention duration, number or sessions, and study quality (modified quality scores) were ana-
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51 382 lyzed with meta-regression. As seen in [Table 4](#), no significant effects were found for any of the
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53 383 moderators for either pregnancy or the combined psychological outcomes. A total of 6 studies had
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384 examined effects on both pregnancy and anxiety. When examining the possible role of anxiety re-
 385 duction as a mediator of the effect on pregnancy outcome with meta-regression, a statistically sig-
 386 nificant association was found between the ESs for anxiety and pregnancy, indicating that the great-
 387 er the reduction in anxiety, the greater the likelihood of achieving pregnancy (see [Table 4](#)).

388 **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

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

391 Discussion

392 Primary findings

393 Our meta-analysis of the available evidence suggests that women who receive some form of psy-
 394 chological intervention are approximately twice as likely to become pregnant when compared to
 395 controls receiving standardized care or active control intervention. Although the results of the 10
 396 currently available studies taken together appeared robust, there were some indications of publica-
 397 tion bias in favor of studies with larger positive effect sizes. It should also be noted that the preci-
 398 sion of the effect size estimate is limited, with possible RR's ranging from approx. 1.5 to 2.7. **Fur-**
 399 **thermore, although the between-group difference did not reach statistical significance, when disre-**
 400 **garding the possibility of publication bias, NRCT's yielded greater effects (RR: 2.8 (95 % CI: 1.55**
 401 **– 5.06)) than RCT's (RR: 1.7 (95 % CI: 1.17 – 2.40)).** Compared with other types of interventions
 402 that historically have been introduced to improve pregnancy rates in ART (improved culture media,

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2 403 new hormone stimulation regimens etc.), even an effect corresponding to the lower limit of the con-
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4 404 fidence interval is substantial. While the results could be considered surprising, the available data
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6 405 do provide any clear-cut reasons to reject this finding, which is further supported by the results of
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8 406 the meta-regression showing that larger reductions in anxiety were associated with improved preg-
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10 407 nancy outcomes. With respect to the psychological outcomes currently reported in the literature, the
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12 408 results suggest that psychological intervention could be effective in reducing anxiety (25 studies) as
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14 409 well as depressive symptoms (21 studies) with the effects corresponding to medium and large effect
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16 410 sizes (0.5 and 1.0). As seen for pregnancy outcomes, there were indications of publication bias in
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18 411 the direction of larger positive effects, and adjusting for publication bias resulted in a considerably
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20 412 smaller, statistically non-significant, effect size for depressive symptoms. The pooled results did not
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22 413 reach statistical significance for the 10 studies which had investigated effects on infertility-related
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24 414 distress and the 5 studies which had included measures of marital function.

28 29 415 **Comparing with results of previous reviews**

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31 416 The present review included 39 studies of a total of 3401 women (3064) and men (347). The partic-
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33 417 ipants received various psychosocial interventions lasting from one week to six months, including
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35 418 cognitive behavioral therapy, emotional disclosure, psycho-education, and mind/body interventions.
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37 419 The present review evaluates almost twice the number of studies included in the most recent previ-
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39 420 ous review,³¹ which reported mixed results of the efficacy of psychosocial intervention. Whereas
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41 421 the former review found no evidence for attenuating distress, there was promising support of psy-
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43 422 chological intervention increasing pregnancy chances for women not receiving ART.³¹ In line with
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45 423 the second review from 2005,³⁰ we found more credible results for group intervention than for other
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47 424 formats, e.g. online interventions, individual, and couples intervention.³⁰ The first review published
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49 425 in 2003 also highlighted group interventions as more effective, especially if the interventions em-
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51 426 phasized education and skills training, such as relaxation. Our results concurred with these earlier
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53 427 observations, suggesting that interventions delivered in groups may be more effective in reducing
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55 428 distress. **Moreover, although the comparison did not reach statistical significance; prior to adjusting**

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2 429 for publication bias, the intervention type of CBT appeared to be more effective than MBI and other
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4 430 types of interventions. Here, it should be noted that the categorization of interventions may be
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6 431 somewhat ambiguous. For example, the study by Cousineau et al. (2000)⁸³ could have been catego-
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8 432 rized as a mind-body intervention, as the authors had provided a website that directed attention to-
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10 433 wards relaxation exercises. However, as there was no reporting of whether the participants were
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12 434 engaged in weekly or daily training, we chose to interpret relaxation as an optional feature, and
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14 435 hence the study was not categorized as MBI. The possible ambiguity and considerable variability in
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16 436 interventions forced us to categorize many studies as “other”, which limits our understanding the
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18 437 possible mechanisms in psychosocial interventions. Taken together, the available data do not pro-
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20 438 vide a clear basis for understanding possible differences between effects of different intervention
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22 439 types, and the results should be interpreted with caution. The more recently conducted studies in-
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24 440 cluded in the present review have contributed by increasing the size of the available dataset consid-
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26 441 erably, and taken together, the currently available evidence suggests that offering psychosocial in-
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28 442 terventions may improve both chances of pregnancy and quality-of-life for infertile patients going
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30 443 through fertility treatment.
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36 444 **Strengths and limitations**

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38 445 Our systematic review and meta-analysis has several strengths. We conducted a comprehensive
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40 446 search and performed the review in accordance with the recommended guidelines.³⁴ In order to lim-
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42 447 it the possibility of selection bias, we encouraged authors of eligible studies to elaborate on their
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44 448 results if the data reported was insufficient, and asked authors of papers written in foreign language
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46 449 to submit their results to us in English. The included studies represented a range of different coun-
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48 450 tries, has used comparable outcome measures, and provided fairly comprehensive descriptions of
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50 451 the interventions studied. In addition, we conducted a detailed evaluation of the methodological
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52 452 quality in order to detect any issues that could possible affect the accuracy of the effect sized calcu-
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54 453 lated. While not all characteristics, in particular reproductive, could be assessed; most general
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1 454 **methodological aspects were covered.** We also explored heterogeneity and made adjustments for
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4 455 possible publication bias, when required.

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7 456 Some limitations of the currently available data should also be noted. First, the samples investigated
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9 457 may not have been as homogeneous as could be wished for. **A small number of infertile participants**
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11 458 **did not receive treatment with ART, and, furthermore, it was not consistently reported what type of**
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13 459 **ART procedure the participants received, what phase or treatment they were in, or the causes of**
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15 460 **infertility. This information is clearly important when interpreting the outcomes, and unknown be-**
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17 461 **tween-study and within-study between-group differences, e.g. in numbers of cycles, idiopathic in-**
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19 462 **fertility and embryo transfer, may have influenced the results, in particular for pregnancy outcomes.**
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21 463 **However, such differences are likely to be less important in RCT's, where randomization is ex-**
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23 464 **pected to reduce their influence. Although the difference did not reach statistical significance, RCTs**
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25 465 **reported smaller ESs for pregnancy outcomes than NRCTs, which could be interpreted as support-**
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27 466 **ing the concern that infertility and treatment characteristics may have been unevenly distributed**
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29 467 **between psychological treatment arms, thus increasing the risk for misattribution of outcomes to**
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31 468 **intervention, at least for NRCTs. On the other hand, we found no statistical significant associations**
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33 469 **between study quality scores and either pregnancy or psychological outcomes, no statistically sig-**
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35 470 **nificant differences in dropout rates between intervention and control groups, and, as suggested by**
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37 471 **the large failsafe numbers, improvements generally appeared quite robust. A second possible limita-**
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39 472 **tion is the high level of heterogeneity indicated by Q and I² statistics, and the pooled effect sizes**
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41 473 **reported in the present review should thus be viewed as an estimate of the average expected effect**
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43 474 **across a wide range of different settings. A third issue is that the considerable dropout rates and lack**
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45 475 **of intention-to-treat analyses may have influenced the results, and it cannot be excluded that fertili-**
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47 476 **ty- and treatment-related factors such as non-optimal fertilization, small number of eggs, etc. may**
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49 477 **have demotivated some participants and made them drop out of the study, while individuals who**
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51 478 **progressed through the treatment phases with more satisfactory outcomes were more likely to com-**
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53 479 **plete the study.** Fourth, the indications of publication bias found for several results suggest the pos-
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2 480 sibility of a “file drawer problem”, i.e. the existence of relevant unpublished null-findings, a com-
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4 481 mon problem when conducting systematic reviews. Finally, due to inconsistencies in the reporting
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6 482 of causes of infertility, we are unable to evaluate the possible associations between effect sizes and
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8 483 causes of infertility. Although meta-analysis remains the gold standard when evaluating the current
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10 484 evidence within a field of research, as is often the case with systematic reviews, qualitative as well
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12 485 as quantitative, the overall level of the evidence reported in our review may be challenged by publi-
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14 486 cation bias and the heterogeneity and methodological limitations of the available published studies.

17 18 487 **Clinical and practical implications**

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20 488 We found evidence for improvement in general psychological symptoms such as anxiety and de-
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22 489 pression, but not for infertility-specific distress. A possible explanation for the latter could be the
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24 490 lack of sensitivity of the infertility-related distress measures used. The questions used in these
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26 491 measures are directly concerned with thoughts and feelings about involuntarily childlessness, and
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28 492 rumination about the involuntary childlessness may persist, even when psychosocial intervention
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30 493 improves general psychological wellbeing. Of particular interest is the result of our meta-regression
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32 494 analysis of the six studies which had included both pregnancy and anxiety as outcomes showing
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34 495 that larger reductions in anxiety were associated with greater chances of pregnancy. Anxiety is a
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36 496 state of arousal, which over time is physically and mentally stressful for the individual.¹⁷ Reducing
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38 497 distress, anxiety in particular, may increase the physiological ability to cope with stress and advance
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40 498 the possibility of impregnation. We found no association between mean age and pregnancy rates
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42 499 outcomes, which may seem surprising, since age is the most important predictor of pregnancy out-
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44 500 comes of ART.^{99,100} However, our meta-regression was conducted for the mean age of the *samples*
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46 501 and the mean age across study samples showed little variation (Mean age: 32.7; SD: 2.4). The rather
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48 502 narrow age interval across study samples may explain an apparent lack of association between age
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50 503 and chance of pregnancy. Our findings also suggest that group interventions appear to be more effi-
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52 504 cacious than individual, couples, or online interventions. There could be various reasons for this.
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54 505 Firstly, group interventions had longer duration (mean: 9.5 weeks) and involved more sessions (8.3)

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2 506 than individual interventions (mean: 5.3 and 4.4) and secondly, there is evidence of a positive im-
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4 507 pact of “group settings” i.e. the sense-of-community between participants, reducing the feelings of
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6 508 isolation or alienation and sharing with individuals in the same life situation etc.¹⁰¹⁻¹⁰⁴
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9 509 **Recommendations for future research**

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11 510 Despite the overall positive effects of psychosocial interventions found in the literature, our results
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13 511 suggest a need for further studies with more rigorous methodology, including more strict reporting
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15 512 of causes of infertility, the types of ART used, and which phases of treatment participants are in.
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17 513 Also, most of the studies were conducted in high-income countries, it is therefore important to note
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19 514 that the assertions made here cannot be generalized to low-income and developing countries. There
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21 515 is thus a need for research in low-income or developing countries as well. Another aspect pertaining
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23 516 to generalizability is the challenge of comparing volunteering infertile participants in psychosocial
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25 517 efficacy studies with the general population of infertile individuals. The response rates in this area
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27 518 are moderate, and it seems important in future studies to explore and compare characteristics of not
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29 519 only dropouts and completers, but also of non-responders and responders. Furthermore, it would be
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31 520 of importance to develop clinically meaningful categories of distress with the purpose of improving
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33 521 interventions targeted to the various types and levels of distress experienced by the participants.
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35 522 Psychological well-being/distress fluctuates over time during fertility treatment and a stepped care
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37 523 approach could be potentially valuable in this population.¹⁰⁵ It is also possible that interventions
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39 524 aimed at relieving distress conducted at different phases in treatment may obtain different psycho-
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41 525 logical outcome results. This calls for improved reporting and comparability of the timing of the
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43 526 psychosocial interventions and greater precision and comparability of the timing of outcome as-
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45 527 sessments. Also needed are studies testing specific hypotheses concerning possible moderating and
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47 528 mediating mechanisms of the effects of interventions on distress and pregnancy outcomes. For ex-
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49 529 ample, which psychosocial factors do we need to target to optimize effects on distress and pregnan-
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51 530 cy rates, and which biomarkers affected by psychosocial interventions, e.g. oxidative stress, in-
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53 531 flammatory processes, can best explain the observed effects. This could assist in developing a more
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2 532 solid evidence base providing better guidance for patients, health professionals, and policy makers
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4 533 about “what works for whom” in infertile patients.
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8 534 **Conclusions**

9
10 535 In conclusion, the present meta-analysis of 39 studies suggests that psychosocial intervention, in
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12 536 particular CBT and MBI interventions, are beneficial for reducing distress in the form of anxiety
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14 537 and depressive symptoms and for improving pregnancy outcomes of ART. Moreover, there is some
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16 538 preliminary evidence to suggest that reduction in anxiety achieved through psychological interven-
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18 539 tion may improve the chance of pregnancy. Despite the robust overall effect found, the considerable
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20 540 heterogeneity of the available studies with respect to methodological quality, intervention type and
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22 541 format still warrants caution as to the conclusions which can be drawn.
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37
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41

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43
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45
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47
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49
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7 557 Data sharing: No additional data available

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11 558 **What is already known on this topic**

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14 559 Previous reviews have been inconclusive concerning the efficacy of psychosocial interventions for
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16 560 reducing distress and improving clinical pregnancy chances.

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19 561 **What this study adds**

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22 562 Synthesizing the currently available evidence suggests that psychosocial interventions could pro-
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24 563 vide clinically meaningful benefits for infertile women and men. Psychosocial intervention leads to
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26 564 reductions in anxiety and depressive symptoms, and larger reductions in anxiety appear to be asso-
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28 565 ciated with increased fertility rates for women in treatment for infertility.

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32 566 Figure 1. PRISMA flowchart of selection of studies

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35 567 Figure 2. Effects of psychosocial intervention on pregnancy rates

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38 568 Figure 3. Effects of psychosocial intervention on combined psychological outcomes

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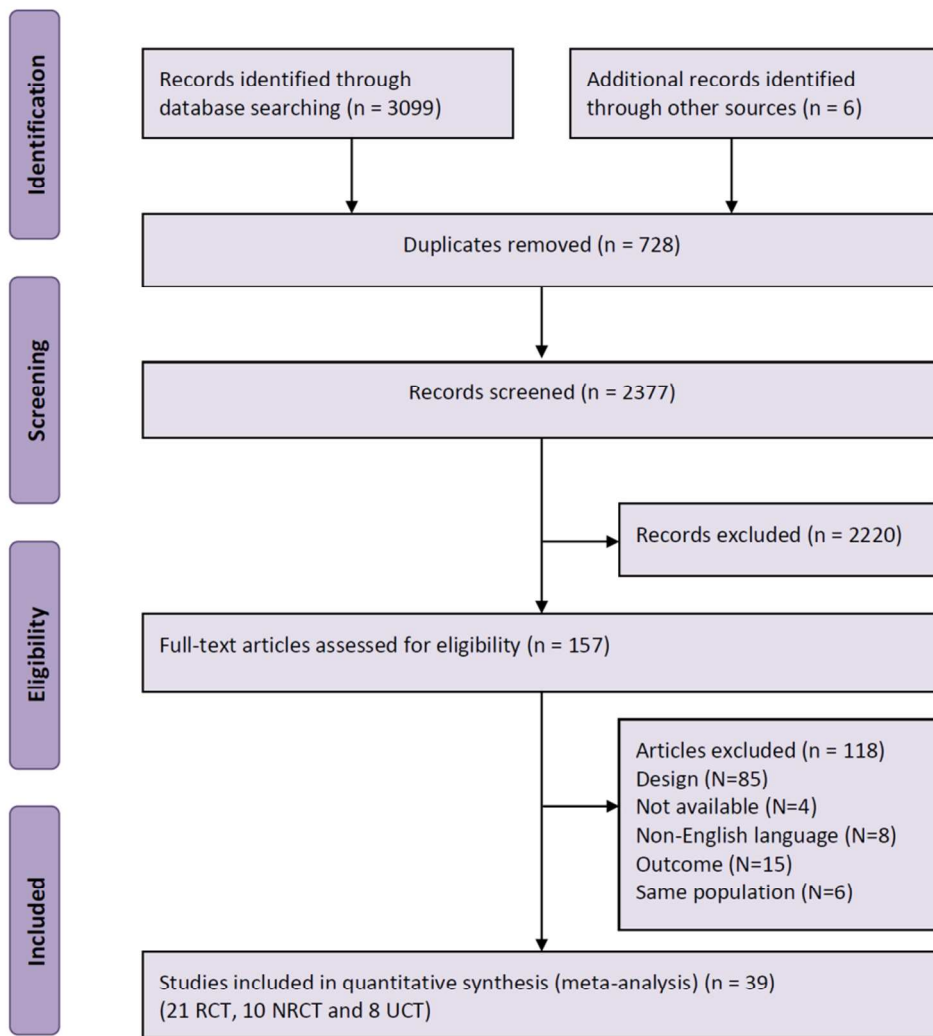


Figure 1. PRISMA flowchart of selection of studies
90x98mm (300 x 300 DPI)



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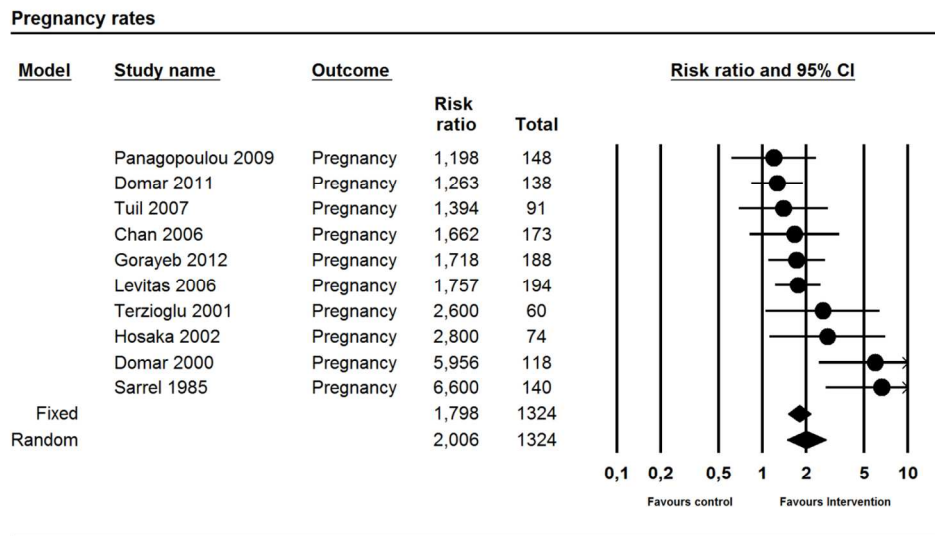


Figure 2. Effects of psychosocial intervention on pregnancy rates
154x90mm (300 x 300 DPI)

review only

Combined psychological outcomes

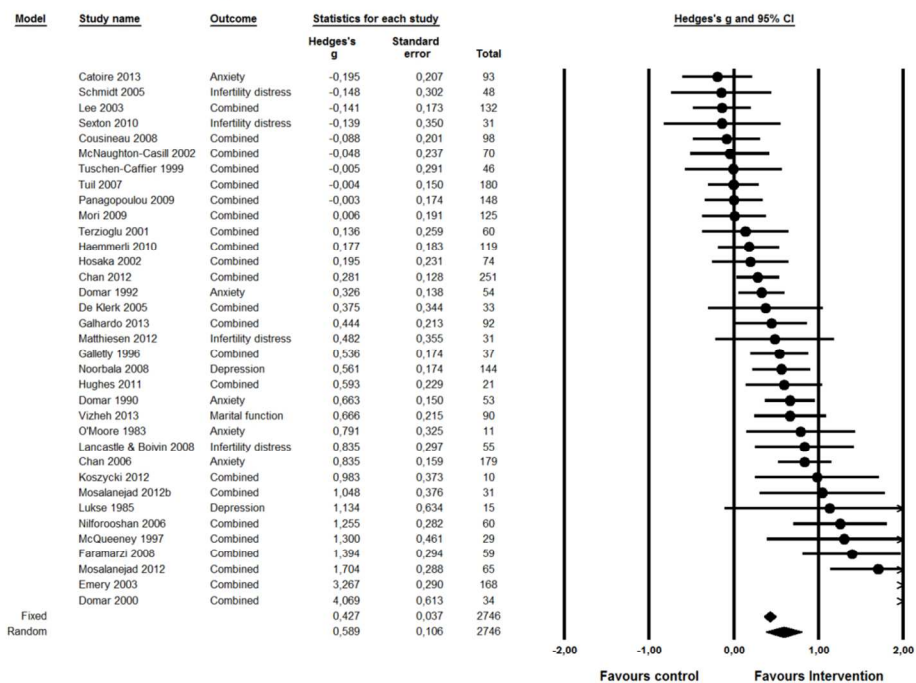


Figure 3. Effects of psychosocial intervention on combined psychological outcomes 112x90mm (300 x 300 DPI)

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-behavior* therapy"	13.914	1259	3706	32.160	13.056	2358

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

Total of all searches

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

- Additional records identified n=6



PRISMA 2009 Checklist

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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

Page 1 of 2

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.

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