

# Cognitive behavioural therapy improves pregnancy outcomes of in vitro fertilization-embryo transfer treatment: a systematic review and meta-analysis

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## Abstract

**Objective:** The study aim was to examine the effects of cognitive behavioural therapy (CBT) on the pregnancy outcomes of women receiving in vitro fertilization-embryo transfer (IVF-ET) treatment.

**Methods:** A literature review was performed using the databases MEDLINE, the Cochrane Database, Embase, Chinese National Knowledge Infrastructure (CNKI) and WANFANG. Eligible studies were selected according to inclusion and exclusion criteria. Relevant data were extracted and the quality of studies assessed. Odds ratios with 95% confidence intervals were pooled to statistically analyse the difference between intervention and control groups.

**Results:** Ten studies were selected for the systematic review and meta-analysis. The findings showed that CBT and cognitive-related therapy significantly improved the pregnancy rate of women undergoing IVF-ET treatment. Subgroup analysis showed that patients who received CBT, rather than complex psychological interventions, and those who received interventions delivered by professional psychologists, were more likely to become pregnant during IVF-ET treatment.

**Conclusion:** CBT and cognitive-related interventions had significant effects on the pregnancy outcomes of women receiving IVF-ET treatment. CBT treatment (rather than complex psychological interventions) provided by professional psychologists is strongly recommended.

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## Keywords

Cognitive behavioural therapy, in vitro fertilization-embryo transfer, pregnancy, systematic review, meta-analysis, psychological intervention

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## Introduction

According to the World Health Organization, approximately one-quarter of couples in developing countries are infertile.<sup>1</sup> In vitro fertilization (IVF) is one of the best therapies for infertile couples; however, the success rate is relatively low (20%). This can cause substantial financial burden and emotional difficulties such as depression and anxiety.<sup>2</sup>

To alleviate the emotional burden for infertile couples, various psychological interventions have been used in clinical practice, including cognitive behavioural therapy (CBT), self-compassion, coping strategies and mind/body interventions. Of these psychological interventions, CBT has been widely used in patients undergoing IVF-embryo transfer (ET) treatment.<sup>3</sup> CBT is a short-term, skill-focused treatment that aims to alter maladaptive emotional responses by changing the patient's behaviours and thoughts.<sup>4</sup> The aim of CBT is to change cognitions, then change emotions and behaviours. A meta-analysis of 31 prospective studies from 1978 to 2010 reported that CBT improves pretreatment stress/distress in patients undergoing assistive reproductive technology.<sup>5</sup> CBT also improves the outcomes of IVF-ET treatment. Wang and Xie enrolled 126 women scheduled to receive IVF-ET treatment and conducted a psychological intervention that included CBT before the cycle. The results suggested that the combined psychological intervention increased the pregnancy rate.<sup>6</sup>

Similarly, a prospective study in Brazil reported a positive effect of a cognitive behavioural group intervention on the pregnancy rate of women undergoing IVF-ET treatment.<sup>7</sup> However, an exploratory randomized trial in the United States reported that a psychological intervention had no significant effect on IVF outcomes.<sup>8</sup> Therefore, findings are inconsistent. Nevertheless, the relationship between CBT and the pregnancy outcomes of IVF-ET treatment deserves further exploration.

To address the inconsistent findings of previous studies, we conducted a comprehensive systematic review and meta-analysis to investigate the clinical efficacy of CBT or cognitive-related psychological interventions on pregnancy outcomes in women receiving IVF-ET treatment.

## Methods

### *Literature search*

A comprehensive literature search was conducted of the electronic databases MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, the Chinese National Knowledge Infrastructure (CNKI) and WANFANG (updated on 1 November 2020) by two independent researchers (Y Qi and JW Liu). The following keywords were used: (infertility OR in vitro fertilization OR IVF OR embryo transfer OR IVF-ET OR assisted reproduction therapy OR ART OR

intracytoplasmic sperm injections OR ICSI), AND (Cognitive OR Cognitive behavioral therapy OR CBT), AND (pregnancy OR pregnan\* OR pregnancy rate). The equivalent Chinese terms were used to search the Chinese databases. The reference lists of all studies selected for systematic review were also reviewed for possible inclusion. This study has been registered with PROSPERO (ID: 274641).

### ***Inclusion and exclusion criteria***

Studies were included if they met the following inclusion criteria: (1) Randomized controlled trial, case-control study or pilot study designed to explore the effect of cognitive-related therapy on pregnancy outcomes in patients receiving IVF-ET; (2) Available information on pregnancy rates in the intervention and control groups; (3) Study participants received IVF-ET, intracytoplasmic sperm injection or assisted reproductive technology; (4) Study participants received CBT or psychological interventions containing cognitive therapy before or during the IVF cycle; (5) The study was published in English or Chinese. The exclusion criteria were as follows: (1) Case reports, study protocols or reviews; (2) Studies published in languages other than English or Chinese; (3) Studies on non-human subjects. Two of the authors (YL and YS) independently assessed the eligibility of the searched articles against the inclusion and exclusion criteria. Any disagreement between the two reviewers was resolved by a third author (HZ).

### ***Data extraction and quality assessment***

Two authors (YL and YS) extracted the relevant data from the eligible studies. The following key components of the included studies were extracted: (1) General information, including first author, publication year and country of origin; (2) Case number,

mean age and mean infertility duration; (3) Characteristics of the intervention: type, duration, timing, person who delivered the intervention, control group and conclusions; (4) Pregnancy outcomes: pregnancy rates in intervention and control groups. All discrepancies between the two reviewers were resolved by a third author (HZ). The quality of eligible studies was assessed using the Cochrane Collaboration tool for risk of bias assessment.<sup>9</sup> Six items were considered in the quality assessment: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. Each item was rated as 'low risk of bias', 'high risk of bias', and 'unclear risk of bias'. A study was classed as 'A' if all six items were judged as low risk of bias, as 'C' if all six items were judged as high risk of bias and as 'B' for all other judgments. In this study, two independent authors reviewed the eligible studies and assessed the quality of studies. This systematic review and meta-analysis adhered to the PRISMA statement guideline.

### ***Statistical analysis***

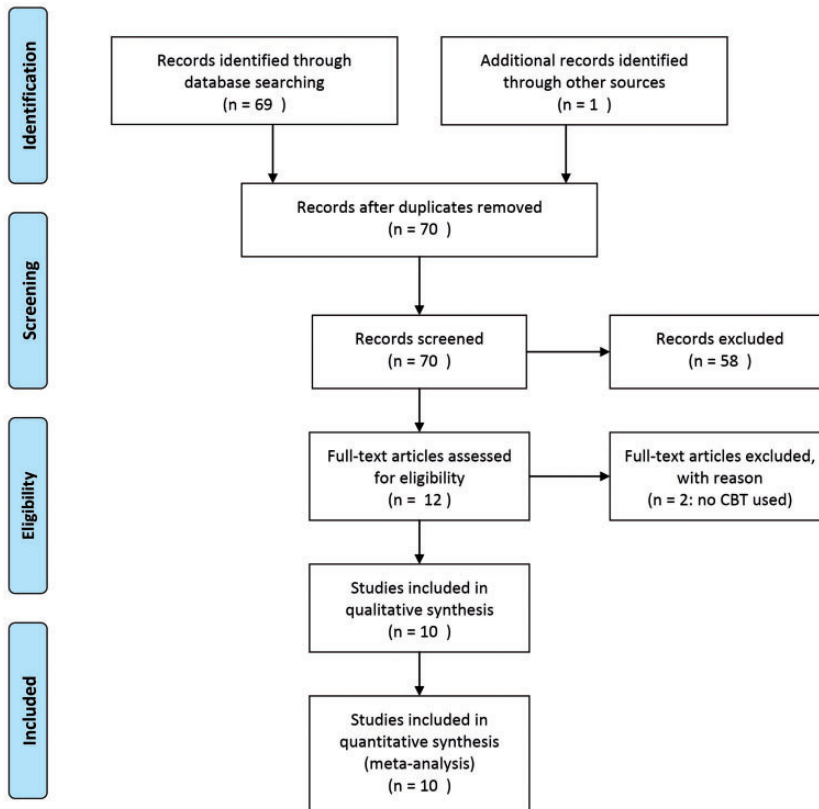
The pooled data were used to assess the effect of CBT on the pregnancy rate of patients receiving IVF-ET using odds ratios (OR) and 95% confidence intervals (95% CIs). Heterogeneity among the trials was determined using the  $I^2$  statistic, and was defined as  $100\% * (Q - df) / Q$ , where  $Q$  is Cochran's heterogeneity statistic and  $df$  is the degrees of freedom, with a fixed-effects model set at low statistical inconsistency ( $I^2 < 25\%$ ). Otherwise, we used a random-effects model, which is better adapted to clinical and statistical

variations.<sup>7</sup> Subgroup analysis of population, intervention type, timing and person who delivered the intervention was performed. In addition, the population for each study was determined based on the country in which the study was conducted. Egger's linear regression test and Begg's funnel plot were used to assess potential publication bias. A  $p$  value  $<0.05$  was considered statistically significant. All analyses were performed using STATA (StataCorp LP, release 12.0, College Station, TX, USA).

## Results

### Study selection and general study characteristics

As shown in Figure 1, the literature review identified 70 studies for further consideration, 58 of which were excluded after reviewing the title and abstracts. This left 12 studies for full-text review. Two of these studies were excluded because they did not use CBT or cognitive-related therapy. A final total of 10 studies<sup>6,8,10-17</sup> were



**Figure 1.** Flow diagram of selection of eligible studies in the systematic review and meta-analysis. CBT, cognitive behavioural therapy.

eligible for qualitative and quantitative analysis.

The general characteristics of the eligible studies are shown in Table 1. The studies were conducted in four countries; seven studies had Chinese participants and three studies had White participants. In total, data for 744 women in the intervention group and 776 women in the control group were quantitatively analysed. Seven studies focused on CBT and three studies<sup>8,15,17</sup> examined complex interventions that included CBT. Three studies<sup>6–8</sup> used CBT before the cycle, whereas the remaining studies used the intervention during the cycle. Finally, two studies trained study participants to self-deliver the intervention and eight studies hired professional psychologists to deliver the CBT intervention.

The quality assessment results are shown in Table 2. Most items were classified as unclear risk of bias, but a low risk of bias was observed for the items selection bias, attrition bias and reporting bias. Overall, the quality of all included studies was classified as B.

### Results of meta-analysis

To explore the clinical efficacy of cognitive-related therapy on the pregnancy rate of patients receiving IVF-ET, we performed a meta-analysis of 10 studies with 1520 participants. The overall results showed that the pregnancy rate was significantly higher in the intervention group than in the control group (OR = 2.00, 95% CIs: 1.35–2.96,  $p=0.001$ ; Figure 2). However, there was substantial heterogeneity among the studies ( $I^2=59.0\%$ ,  $p=0.009$ ; Figure 2). Therefore, subgroup analysis was conducted to investigate the potential bias contributing to the heterogeneity.

The subgroup analysis examined four potential confounding factors in the eligible studies. First, the effect of race was

examined by dividing the studies according to whether the population was Asian or White. The pooled pregnancy rates for Asian and White populations were higher for participants who received cognitive-related therapy (Asian [seven studies with 1116 patients]: OR = 2.41, 95% CIs: 1.36–4.28,  $p=0.003$ ; White [three studies with 404 patients]: OR = 1.55, 95% CIs: 1.02–2.36,  $p=0.04$ ; Figure 3a). Then, the intervention timing was assessed according to whether the intervention had been administered before or during the cycle, and similar results were obtained (before cycle [three studies with 480 patients]: OR = 1.70, 95% CIs: 1.14–2.53,  $p=0.009$ ; after cycle [seven studies with 1040 patients]: OR = 2.91, 95% CIs: 1.26–4.18,  $p=0.007$ ; Figure 3b). Importantly, we found a significant difference between the two groups in delivery person and intervention. Specifically, patients who received cognitive-related therapy delivered by psychologists tended to have a higher pregnancy rate than those who received a self-delivered intervention (psychologist [eight studies with 1191 patients]: OR = 2.42, 95% CIs: 1.51–3.88,  $p<0.001$ ; self-delivery [two studies with 329 patients]: OR = 1.10, 95% CIs: 0.66–1.84; Figure 3c). We categorized the study interventions into CBT and cognitive-related complex therapies. Patients who received CBT had a higher pregnancy rate than those who psychological interventions containing cognitive therapy (CBT [seven studies with 867 patients]: OR = 2.41, 95% CIs: 1.40–4.17,  $p=0.002$ ; complex therapy [three studies with 653 patients]: OR = 1.43, 95% CIs: 0.92–2.22; Figure 3d).

To explore the potential publication bias among studies, Begg's test and Egger's test were performed. As shown in Figure 4, no significant publication bias was observed (Begg's test:  $z=2.15$ ; Egger's test:  $t=2.62$ ; Figure 4).

**Table 1.** General characteristics of included studies.

| Author (year)          | Country of origin | Case number |               | Infertility time (years; mean $\pm$ SD) | Intervention     | Timing  | Delivery person                              | Control group | Conclusions   |  |   |
|------------------------|-------------------|-------------|---------------|---|------------------|---|--|---------------|---------------|--|---|
|                        |                   | CBT group   | Control group |   |                  |   |  |               |               |  |   |
| Gorayeb (2012)         | Brazil            | 93          | 95            | 32.04 $\pm$ 3.94                        | 32.42 $\pm$ 3.72 | 2   | CBT: 5 sessions, 2 h/session, for 5 weeks    | Before cycle  | Psychologist  | No treatment                                     | Group psychological intervention before IVF and ICSI increased the rate of success of these procedures.   |
| Domar (2015)           | United States     | 89          | 77            | 34.67 $\pm$ 4.26                        | 35.03 $\pm$ 4.18 | CBT: 2.22 $\pm$ 2.42;<br>CON: 2.30 $\pm$ 2.60 | Cognitive coping and relaxation intervention | Before cycle  | Self-delivery | No treatment                                     | Use of the cognitive coping and relaxation intervention did not significantly improve pregnancy rate.   |
| Czamanski-Cohen (2016) | Israel            | 25          | 25            | 29.00 $\pm$ 4.10                        | 29.00 $\pm$ 3.80 | NA  | CBT: 6 sessions, 0.5 h/session, for 6 weeks  | During cycle  | Psychologist  | 6-week CBI protocol after the IVF cycle was over | No differences in pregnancy rates were observed between the CBI and control groups.   |
| Ke (2015)              | China             | 30          | 30            | 30.09 $\pm$ 2.82                        | 29.12 $\pm$ 3.72 | CBT: 4.09 $\pm$ 0.89;<br>CON: 5.12 $\pm$ 1.72 | CBT: 8 sessions, 1.5 h/session, for 8 weeks  | During cycle  | Psychologist  | No treatment                                     | Cognitive behavioural intervention for women during the IVF-ET cycle can effectively improve pregnancy rate and produces the best therapeutic effect. |
| Cao (2016)             | China             | 80          | 80            | 32.2 $\pm$ 2.4                          | 33.10 $\pm$ 2.3  | CBT: 2.7 $\pm$ 0.6;<br>CON: 3.1 $\pm$ 0.5     | CBT  | During cycle  | Psychologist  | No treatment                                     | CBT intervention improves clinical pregnancy rate in patients undergoing IVF-ET.  |
| Mei (2014)             | China             | 60          | 60            | 33.5 $\pm$ 3.1                          | 33.2 $\pm$ 3.3   | NA  | CBT  | During cycle  | Psychologist  | No treatment                                     | CBT and nursing intervention during IVF-ET improves pregnancy rate.   |
| Sun (2018)             | China             | 45          | 45            | 31.92 $\pm$ 5.53                        | 32.17 $\pm$ 5.61 | NA  |  |               | Psychologist  | No treatment                                     |   |

(continued)

**Table 1.** Continued.

| Author (year) | Country of origin | Case number |               | Age (years; mean $\pm$ SD) |               | Infertility time (years; mean $\pm$ SD) | Intervention                               | Timing       | Delivery person | Control group | Conclusions   |
|---------------|-------------------|-------------|---------------|----------------------------|---------------|---|--|--------------|-----------------|---------------|---|
|               |                   | CBT group   | Control group | CBT group                  | Control group |   |  |              |                 |               |   |
| Li (2012)     | China             | 35          | 128           | NA                         | NA            | NA                                      | CBT + nursing intervention                 | During cycle | Self-delivery   | No treatment  | CBT combined with nursing intervention improves fertilization rate and pregnancy rate.  |
| Sang (2011)   | China             | 202         | 195           | 29.5                       | 4.9           | 4.9                                     | Psychological interventions, including CBT | During cycle | Psychologist    | No treatment  | CBT has no significant effect on the pregnancy rate of patients undergoing IVF-ET.  |
| Wang (2004)   | China             | 85          | 41            | 25–42                      | NA            | NA                                      | CBT  | Before cycle | Psychologist    | No treatment  | During the IVF-ET procedure, psychological intervention has a positive effect on patients, including improving the degree of satisfaction and trust, but has no effect on pregnancy rate. |
|               |                   |             |               |                            |               |   |  |              |                 |               | Psychological intervention in patients with ultrasound embryo transfer helps to improve the clinical pregnancy rate.  |

CBT, cognitive behavioural therapy; NA, not available; SD, standard deviation; IVF-ET, in vitro fertilization-embryo transfer; CON, control group; ICSI, intracytoplasmic sperm injection; CBI, cognitive behavioural intervention.



**Table 2.** Results of quality assessment of eligible studies.

| Author (year)          | Selection bias             |                        | Performance bias                       |                                | Attrition bias          |                     | Reporting bias       |   | Risk of bias classification |
|------------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|---------------------|----------------------|---|-----------------------------|
|                        | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other source of bias |   |                             |
| Gorayeb (2012)         | low                        | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Domar (2015)           | low                        | low                    | unclear                                | low                            | unclear                 | low                 | unclear              | B |                             |
| Czamanski-Cohen (2016) | low                        | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Ke (2015)              | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Cao (2016)             | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Mei (2014)             | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Sun (2018)             | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Li (2012)              | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Sang (2011)            | low                        | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |
| Wang (2004)            | unclear                    | unclear                | unclear                                | unclear                        | low                     | low                 | unclear              | B |                             |

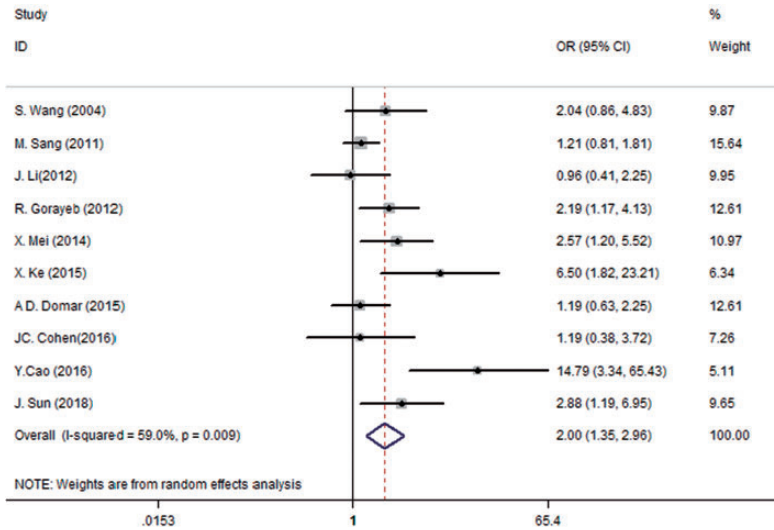
## Discussion

The results of this systematic review and meta-analysis indicated that CBT can significantly improve pregnancy outcomes in women receiving IVF-ET treatment. The subgroup analysis also suggested that CBT, not complex psychological interventions, had a significant effect on pregnancy rate. CBT delivered by professional psychologists significantly improved pregnancy rates, whereas self-delivered interventions failed to show a significant effect on pregnancy outcomes.

Research on the effect of psychological interventions on the emotional burden in patients receiving IVF-ET treatment are inconsistent. A recent systematic review of 20 randomized controlled trials reported that there was good evidence that complex interventions (including CBT and mind/body interventions) can improve stress and anxiety among both women and men in infertile couples receiving IVF treatment.<sup>18</sup> However, this review failed to quantitatively analyse pregnancy rates owing to substantial heterogeneity in psychosocial interventions among studies. There is no consensus on whether psychological burden is a cause or consequence of infertility; stress affects the hypothalamic-pituitary-ovarian axis, which in turn leads to anovulation.<sup>19</sup> Socio-psycho-behavioural factors also affect semen quality in male patients.<sup>20</sup> Taken together, the evidence indicates that CBT and cognitive-related therapies alleviate emotional burdens, such as stress/distress and anxiety, thus improving pregnancy outcomes in women undergoing IVF-ET treatment.

It is interesting that complex interventions failed to improve pregnancy outcomes in the present study. Three studies using complex interventions, including CBT, were reviewed. In an exploratory randomized trial in the United States, a combined cognitive coping and relaxation





**Figure 2.** Pooled results of the effect of cognitive behavioural therapy on pregnancy outcomes of in vitro fertilization-embryo transfer treatment. OR, odds ratio; CI, confidence interval.

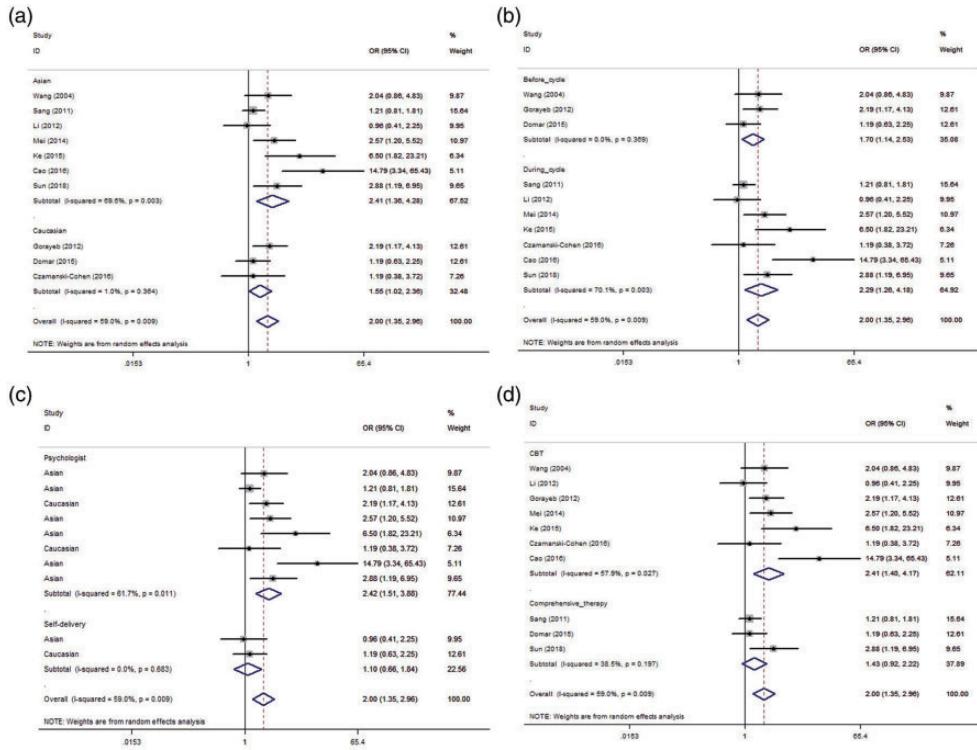
intervention was used.<sup>8</sup> Sun<sup>15</sup> combined CBT with psychological nursing before the cycle, and another study used a complex intervention that included CBT, venting therapy and group support.<sup>17</sup> There was substantial heterogeneity among the studies reviewed here, which may explain the negative results from the pooled data. Because of the small number of studies, we could not conduct detailed subgroup analysis of the complex psychological interventions. Therefore, we recommend the use of CBT, rather than complex interventions, to improve pregnancy rates in women receiving IVF-ET treatment.

Our pooled results suggest that CBT should be delivered by professional psychologists to improve pregnancy outcomes of IVF-ET. In this systematic review, two studies educated infertile couples to self-deliver the CBT, which obviously increased the risk of bias in the IVF-ET treatment outcome assessment.<sup>8,16</sup> Nurses should be aware of their responsibility to support infertile couples and provide the required

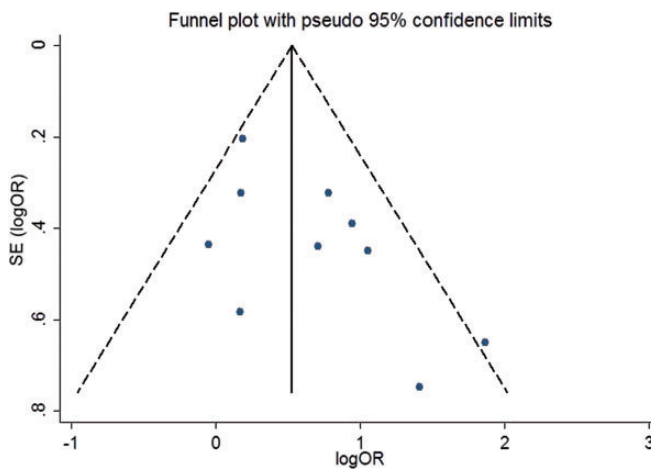
psychological suggestions, to assist professional psychologists during and after the cycle.

We also analysed the effects of potential confounding factors, including race and timing of the intervention, on the pooled results. There were no significant differences in terms of race, indicating that CBT interventions may have similar positive effects on pregnancy outcomes of IVF-ET treatment in Asian and White populations. However, considering the limited number of relevant studies, there is a need for clinical trials on other populations. The timing of interventions did not affect the pregnancy rate after CBT interventions, which suggests that CBT is effective throughout the IVF-ET treatment cycle.

There are several study limitations. First, only 10 studies were included in the systematic review and meta-analysis, and substantial heterogeneity and publication bias among studies were observed; this makes it difficult to draw firm conclusions about the effect of the interventions on pregnancy



**Figure 3.** Pooled results of subgroup analysis of the effect of cognitive behavioural therapy on pregnancy outcomes of in vitro fertilization-embryo transfer treatment. (a) race; (b) timing of intervention; (c) person who delivered the intervention; (d) intervention type. OR, odds ratio; CI, confidence interval.



**Figure 4.** Funnel plot of Begg's test of publication bias among studies. SE, standard error; OR, odds ratio.

outcomes. Additionally, intervention type and delivery person made a substantial contribution to the heterogeneity. However, we were unable to explore the reasons for this in any detail owing to the small number of studies. Importantly, CBT was also reported to improve emotional state in infertile couples. Analysis of the pooled results indicated substantial lack of consensus across the relevant studies. Another limitation was that we reviewed only studies written in English or Chinese.

In conclusion, this review and meta-analysis indicated that CBT and cognitive-related interventions had significant effects on the pregnancy outcomes of women receiving IVF-ET treatment. Moreover, CBT treatment (rather than complex psychological interventions) provided by professional psychologists is strongly recommended during clinical practice throughout the IVF-ET treatment cycle. A large-scale, well-designed and multicentre clinical trial is needed to confirm our findings.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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