

Can Fluoxetine Combined with Cognitive Behavioral Therapy Reduce the Suicide and Non-Suicidal Self-Injury Incidence and Recurrence Rate in Depressed Adolescents Compared with Fluoxetine Alone? A Meta-Analysis

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Objective: The efficacy of medication and psychotherapy for adolescent depression is controversial, so we conducted a meta-analysis to evaluate the efficacy of combination therapy.

Methods: We followed the PRISMA checklist in completing the meta-analysis. Relevant literature was searched in PubMed, Web of Science and Embase, Chinese databases CNKI and WanFang Data. We included the literature on the comparison of the fluoxetine plus psychotherapy or cognitive-behavioral therapy (CBT) and each treatment alone for adolescent depression published in 1980–2021. All statistical analyses were performed using Stata software.

Results: After careful review, a total of 489 relevant articles were retrieved, and 13 studies were finally included. In comparison with the control group (fluoxetine alone), fluoxetine plus CBT achieved higher response rate ($RR=1.12$, 95% CI: 1.04, 1.21), lower incidence of adverse Reactions ($RR=0.62$, 95% CI: 0.40, 0.96), lower proportion of suicide or self-injury ($RR=0.94$, 95% CI: 0.74, 1.20), and lower one-year recurrence rate ($RR=0.27$, 95% CI: 0.16, 0.45). Before treatment, there were no significant differences in Hamilton Depression Scale score (HAMD), Children's Depression Rating Scale Revised (CDRS-R) score, and Clinical Global Impression (CGI) Severity score. After treatment, HAMD score ($SMD=-1.01$, 95% CI: -1.39, -0.63), CDRS-R score ($SMD=-0.10$, 95% CI: -0.26, -0.07), and CGI score ($SMD=-0.22$, 95% CI: -0.54, -0.10) were significantly lower in the combined treatment group than in the control group.

Conclusion: Adolescents simultaneously treated with fluoxetine and CBT had significantly reduced incidence of depressive symptoms, suicide or NSSI, adverse reactions, and one-year recurrence of symptoms, than adolescents treated with fluoxetine alone. This indicates fluoxetine plus CBT may be superior to fluoxetine alone for the clinical treatment of adolescent depression.

Keywords: adolescent depression, fluoxetine, psychotherapy, cognitive behavioral therapy, CBT, meta-analysis

Introduction

Major depressive disorder (MDD) is a common disease burden in people aged between 10 to 24 years.¹ In the United States, about 11% to 14% of adolescents between 15 and 18 years are diagnosed with depression, and 25% have sub-threshold depressive symptoms that lead to difficulties in daily functioning.² Depression in adolescents often leads to impairments in social functioning and poor academic performance. Furthermore, individuals who suffer from depression during adolescence are at an increased risk of developing depression and other psychopathology in adulthood.³ Furthermore, depressed adolescents often engage in self-harming behaviors, including smoking, substance misuse, unhealthy eating, non-suicidal self-injury (NSSI), and suicide.⁴ NSSI is a widespread problem among depressed adolescents. Studies have shown that about 48% of adolescents with depression have attempted suicide or NSSI.^{5,6}

Because of the harmful effects of depression on adolescents, there is a need to develop effective treatments to manage depression in adolescents.

The standard treatment for depression includes antidepressant medications, psychotherapy, and a combination of medication and psychotherapy. Acute phase treatment interventions for adolescent depression have demonstrated efficacy in achieving response compared to placebo or usual care.

The main pharmaceutical treatments for depression include selective serotonin reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, and tricyclic antidepressants.⁷ However, although antidepressants are an effective treatment for depression and anxiety in adolescents, they also have several side effects. Therefore the use of antidepressants in children and adolescents must be carefully monitored. The Food and Drug Administration (FDA) issued a black box warning that the use of antidepressants in people under 25 years can increase the risk of suicidal thoughts and behavior. However, there was considerable debate in academic journals and the international media. Causal relationships cannot be established with certainty until there is a vast improvement in post-marketing surveillance.⁸ Eventually, fluoxetine and escitalopram are 2 FDA-approved antidepressants for the short-term management and maintenance of MDD in young adults. Many studies have shown that antidepressants can reduce depressive symptoms, long-term administration can cause serious side effects, such as headaches, sleep disturbances, weight gain, nausea, and constipation.⁹ Psychotherapy, in the form of interpersonal psychotherapy, family therapy, and cognitive behavioral therapy (CBT), is often used in the management of depression in children and adolescents.¹⁰ Although psychotherapy was found to be an effective treatment for depression, it still has numerous limitations. Psychotherapy requires several treatment cycles, and it takes time to produce the desired results.¹¹ The long treatment duration also increases the costs for the patients. In order to overcome the limitations of psychotherapy, some studies proposed using antidepressants in combination with psychotherapy.¹² However, there are currently no comprehensive studies evaluating the therapeutic outcomes of fluoxetine combined with psychotherapy. Therefore we aimed to conduct a meta-analysis of the literature published in recent years to evaluate the therapeutic effect and safety of fluoxetine combined with psychotherapy in the management of depression in adolescents.

Materials and Methods

Search Strategy

The PubMed, Web of Science, Embase, China National Knowledge Infrastructure, and WanFang databases were searched to identify relevant research articles published in either English or Chinese up to October 2021. The keywords used for the search were “adolescent depression” AND “fluoxetine” AND “psychotherapy” OR “cognitive behavioral therapy”.

Inclusion and Exclusion Criteria

We adopted the following inclusion criteria: (1) Study design: randomized controlled trial, cohort study and clinical trial; (2) Study subjects: adolescent patients diagnosed with depression; (3) Intervention: fluoxetine plus CBT (treatment group) in relation to fluoxetine alone (control group); (4) Outcome measures: response rate, incidence of adverse reactions, one-year recurrence rate, Hamilton Depression Scale score (HAMD), Children's Depression Rating Scale-Revised score (CDRS-R), and Clinical Global Impression Severity score (CGI). Adverse effects included headache, nausea, hyperhidrosis, dizziness, lethargy and incidents of suicide or NSSI.

We excluded studies for the following reasons: (1) literature not related to adolescent depression; (2) duplicate literature: more than one report based on the same study population published, in which case only the most comprehensive publication was included in this meta-analysis; (3) literature in which relevant data were not provided, and the data and original text could not be obtained; (4) literature with poor quality, missing data; (5) case reports, systematic reviews, and animal experiments.

Data Extraction and Assessment of Methodological Quality

Two investigators performed the literature search independently. The titles, and abstracts, were reviewed carefully to identify relevant articles. Any duplicate studies were removed. The full texts were then reviewed, and irrelevant

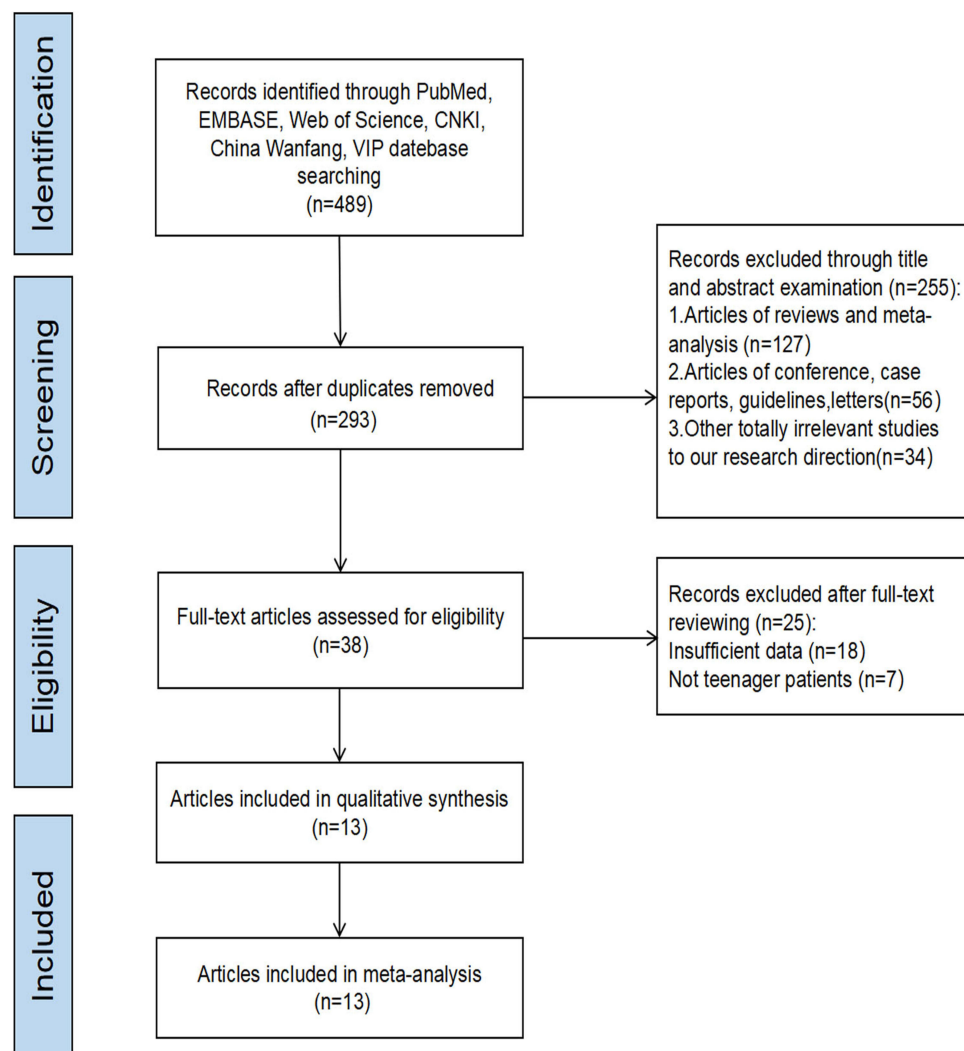


Figure 1 Flow diagram illustrating the study selection.

studies and those with insufficient data were removed. The final articles retrieved by the investigator were compared, and any disagreements were resolved through discussion. Subsequently, the 2 investigators extracted the following data from the manuscript; first author, year of publication, study design, sample size, main outcome measures, and risk estimates with the corresponding 95% confidence interval (95% CI). In the process of data extraction, any disagreements were resolved through discussion by both parties or judged by a third party. The methodological quality of the included literature was evaluated using the Jadad scoring system. The Jadad score consisted of 5 items and 3 broad categories, including randomization (2 items), blinding (2 items), and dropouts and withdrawals (1 item). Each item within each category is assigned a score of 1 if it complies and 0 if it does not comply. The final score ranges from 0 to 5 points, and a score of 3 or higher indicates good methodological quality.

Statistical Analyses

All statistical analyses were performed using the Stata software version 16 (StataCorp LLC, College Station, TX, USA). The adjusted odds ratio (OR) for each treatment outcome was extracted for the meta-analysis. If the OR was not provided, the raw data were used to calculate it. All outcome measures were expressed as standardized mean difference (SMD) and risk ratio (RR). The statistical heterogeneity between the studies was evaluated using the Q statistic and the I-square (I^2) statistic. An I^2 value below 50% and a p-value above 0.1 indicate low heterogeneity, and therefore, the fixed-effect model was used to analyze the data.

Table I Characteristics of Studies Included in the Meta-Analysis

Study	Year	Sample Time (Year.Month)	Cases Treat/ Con	Age (Years)		Disease (Months)		Sex (Male/Female)		Dose Mg (Max)	Study Design	Outcome Measures
				Treat Group	Con Group	Treat Group	Con Group	Treat Group	Con Group			
Lu ¹³	2020	2018.02–2020.01	30/30	13.2±1.4	12.8±1.3	8.1±1.2	8.4±1.2	18/12	17/13	40	RCT	①
Guo ¹⁴	2010	2005.12–2009.12	33/40	15.67±1.97	15.20±1.45	NR	NR	19/21	14/19	20	RCT	①②③
Li ¹⁵	2013	2010.05–2012.05	39/39	18.10±5.20	17.80±4.60	NR	NR	24/15	22/17	20	RCT	①③⑦
Jia ¹⁶	2015	2012.03–2014.03	32/30	14.20±4.20	14.60±4.30	8.8±5.7	9.2±6.3	12/20	8/22	60	RCT	③
Zhu ¹⁷	2009	2006.10–2008.02	23/23	15.80±1.20	16.00±1.10	NR	NR	8/15	9/14	20	RCT	③⑦
Fan ¹⁸	2021	2019.01–2020.01	35/35	15.67±2.51	15.55±2.51	12.14±1.32	12.24±1.51	23/12	23/12	40	RCT	①②③
Han ¹⁹	2019	2014.11–2016.10	50/50	15.03±1.72	15.42±1.56	25.3±5.6	28.2±7.5	21/29	24/26	20	RCT	①②③⑦
Huang ²⁰	2009	2005.12–2008.03	17/22	16.48±2.81	16.01±2.51	NR	NR	7/10	8/14	60	RCT	①②③
Liu ²¹	2015	2012.01–2013.01	45/45	16.40±3.10	16.80±4.20	3–36	3–36	24/21	25/20	20	RCT	③⑦
Shen ²²	2008	2004.03–2006.02	23/23	15.80±1.20	16.00±1.10	NR	NR	8/15	9/14	20	RCT	③⑦
Kennard ²³	2014	NR	75/69	13.50±2.7	14.20±2.4	9.63±8.61	10.83±9.43	37/38	39/30	40	RCT	②④⑤⑥⑦
March ²⁴	2004	2000.01–2003.09	107/109	14.60±1.49	14.55±1.56	12.31±2.32	9.89±3.79	47/60	50/59	40	RCT	②④⑤⑥
Goodyer ²⁵	2008	2000–2004	105/103	13.90±4.18	14.20±4.30	9.79±4.42	12.31±1.01	78/27	76/27	40	RCT	①②④⑤⑥

Note: ①: Effective rate;②: Adverse effects rate;③: HAMD scores after treatment;④: CDRS-R scores after treatment;⑤: CGI scores after treatment;⑥: incidents of suicide or self-injury;⑦: recurrence rate.

Abbreviations: Treat, treatment; Con, control; RCT, randomized controlled trial; NR, not reported.

Conversely, the random-effect model was adopted for studies with high heterogeneity. Sensitivity analysis was performed to assess the impact of individual studies on the overall results. Funnel plots were used to assess the publication bias for outcome measures evaluated in more than 9 studies.

Results

Search results and Description of Studies

The initial literature search yielded a total of 489 articles, of which 196 were duplicated articles and were therefore removed. After screening the titles and abstracts, 255 articles were deemed irrelevant to the study, and another 25 studies were excluded after evaluating the full texts due to insufficient data. Finally, 13 studies were included in the meta-analysis.^{14–26} The literature screening process and results are illustrated in Figure 1. Further details of the included studies are shown in Table 1. Figure 2A illustrates the overall risk of bias, and Figure 2B illustrates the risk of bias for each of the 13 included studies.

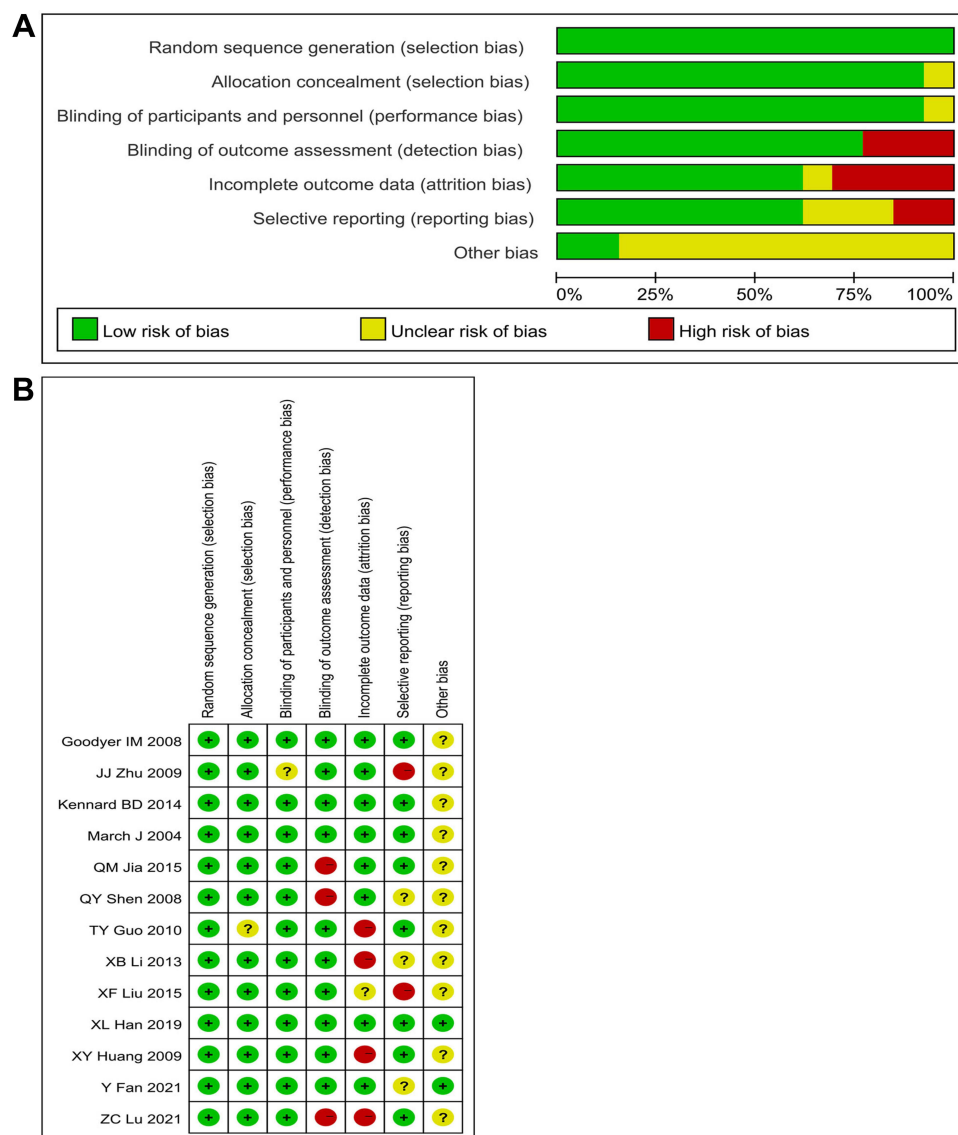


Figure 2 (A) The risk of bias graph. **(B)** The risk of bias for each of the included studies.

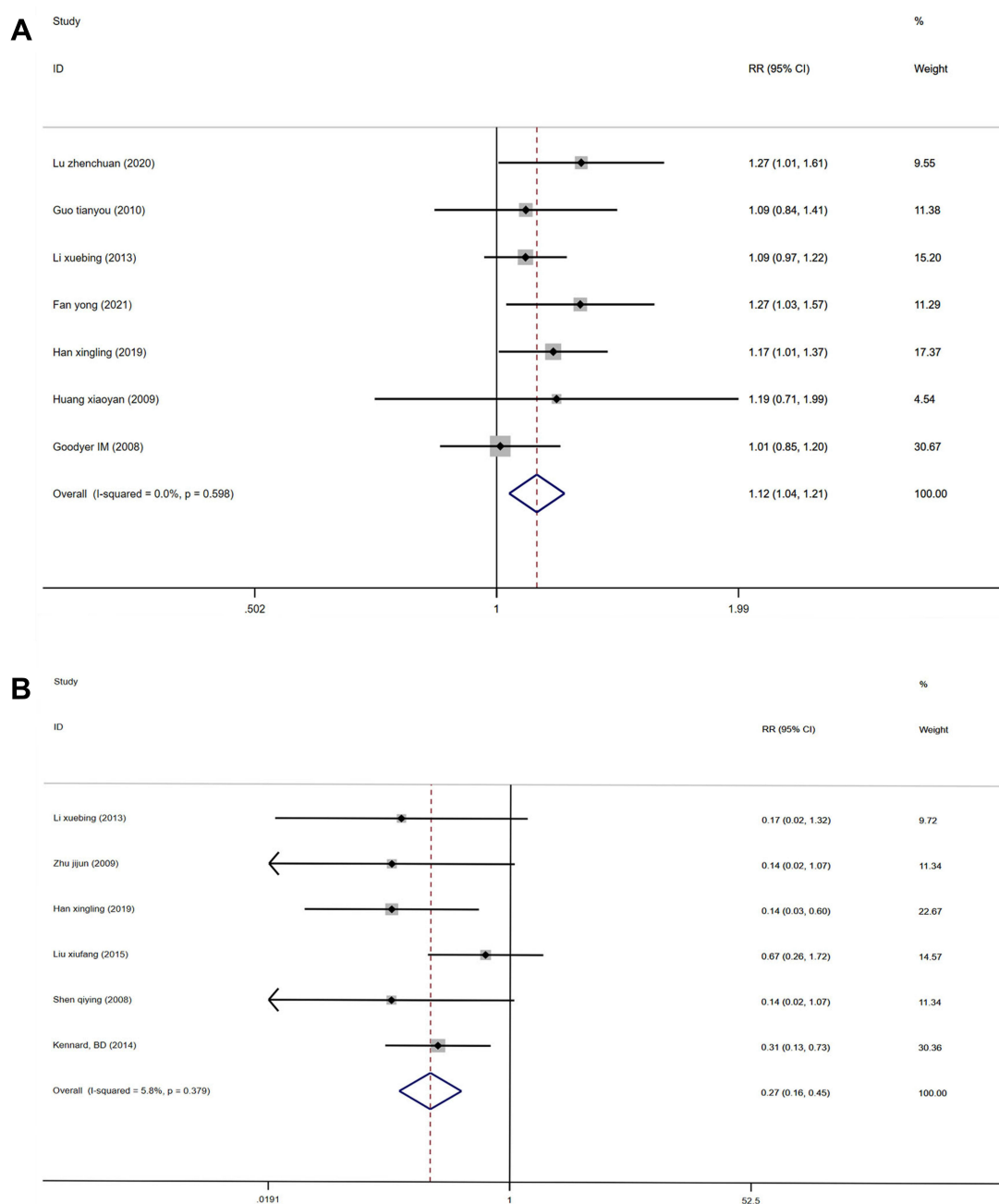


Figure 3 (A) Forest plots comparing the response rate between the treatment and control groups. **(B)** Forest plots comparing the recurrence rate between the treatment and control groups.

Response Rate and Recurrence Rate After Treatment

Seven studies compared the response rate between treatment and control group.^{13–15,18–20,25} No marked heterogeneity was found among the included studies ($I^2 = 0.0\%$, $P = 0.598$), so we used a fixed-effect model for analysis. The result showed a significantly higher response rate in the fluoxetine plus CBT group compared with the control group ($RR = 1.12$, 95% CI: 1.04, 1.21, [Figure 3A](#)).

Six included studies compared the recurrence rate between treatment and control group.^{15,17,19,21–23} The fixed-effect model was also used for analysis since the heterogeneity among these studies was low ($I^2 = 5.8\%$, $P = 0.379$). Compared

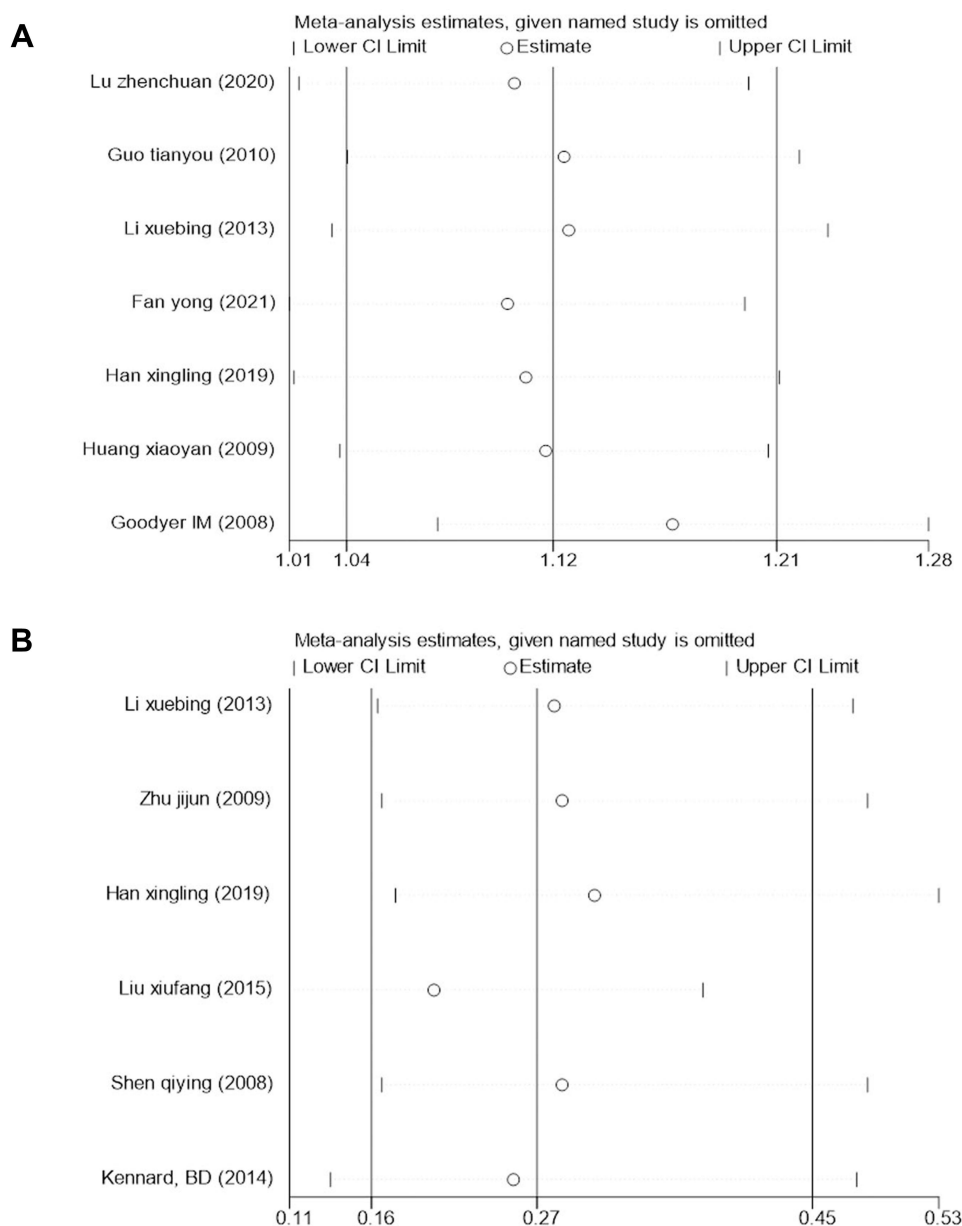


Figure 4 (A) Sensitivity analysis of response rate after treatment. **(B)** Sensitivity analysis of recurrence rate after treatment.

with the control group, the treatment group had a significantly lower one-year recurrence rate ($RR = 0.27$, 95% CI: 0.16, 0.45, [Figure 3B](#)).

The sensitivity analysis did not reveal any major changes in the pooled results indicating that the results of the response and recurrence rates were robust ([Figures 4A and B](#)).

Incidence of Adverse Reactions and Proportion of Suicide or NSSI After Treatment

Seven studies compared the incidence rate of adverse reactions between treatment and control group.^{14,18–20,23–25} Since no marked heterogeneity was found among the included studies ($I^2 = 0.0\%$, $P = 0.901$), the fixed-effect model was used to analyze the data. The incidence rate of adverse events in the fluoxetine plus CBT group was lower when compared with the control group ($RR = 0.62$, 95% CI: 0.40, 0.96, [Figure 5A](#)).

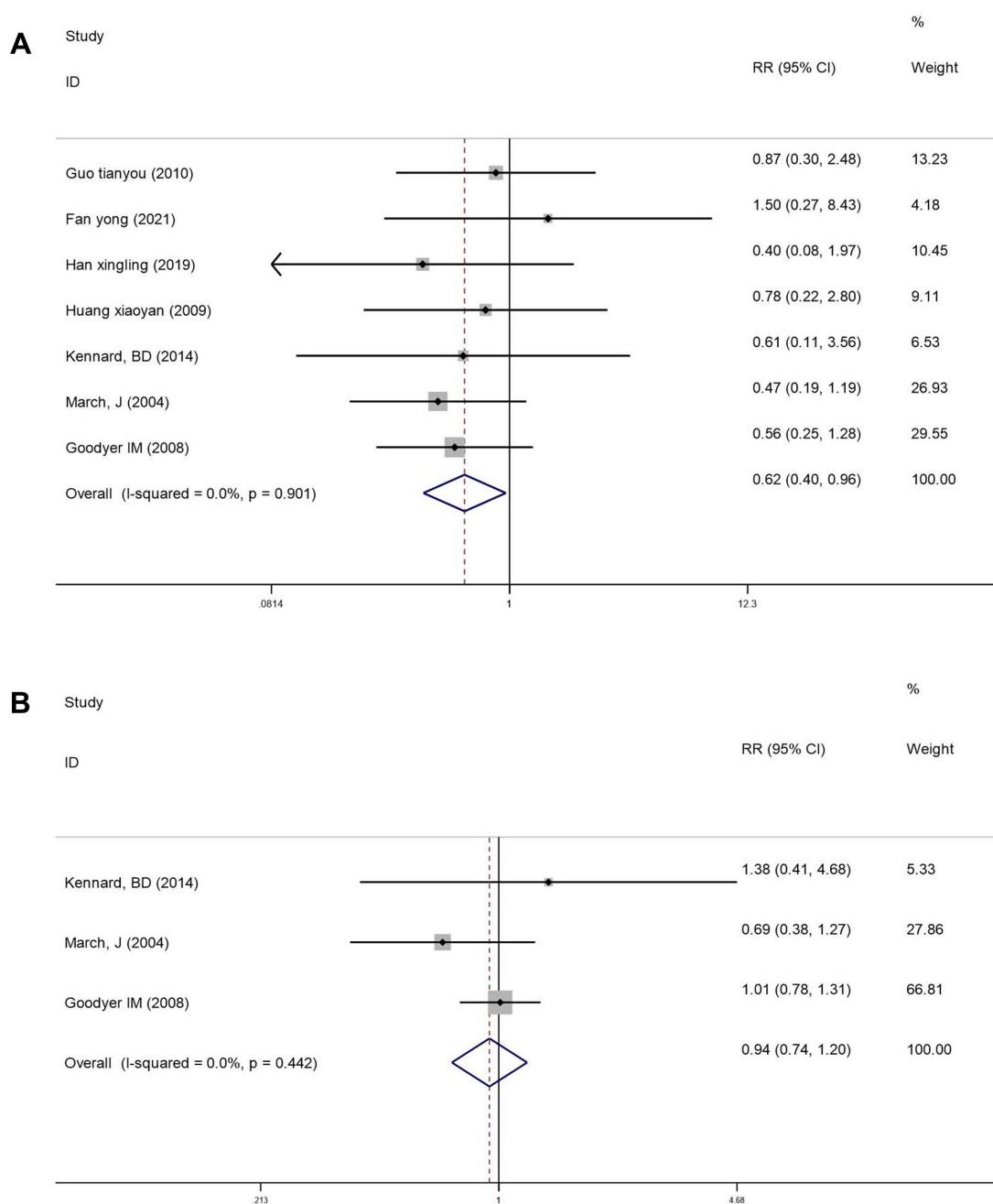


Figure 5 (A) Forest plot comparing the incidence of adverse reactions after treatment. **(B)** Forest plot comparing the proportion of suicide or NSSI after treatment.

Three of the included studies compared the proportion of suicide or NSSI between the two groups.^{23–25} The fixed-effect model was used for analysis since the heterogeneity was low ($I^2 = 0.0\%$, $P = 0.442$). The results showed that fluoxetine plus CBT resulted in a more significant reduction in the rate of suicide and NSSI when compared with the control group (RR = 0.94, 95% CI: 0.74, 1.20, **Figure 5B**).

The sensitivity analysis showed low sensitivity, confirming that the incidence of adverse reactions and suicide or NSSI results were robust (**Figures 6A and B**).

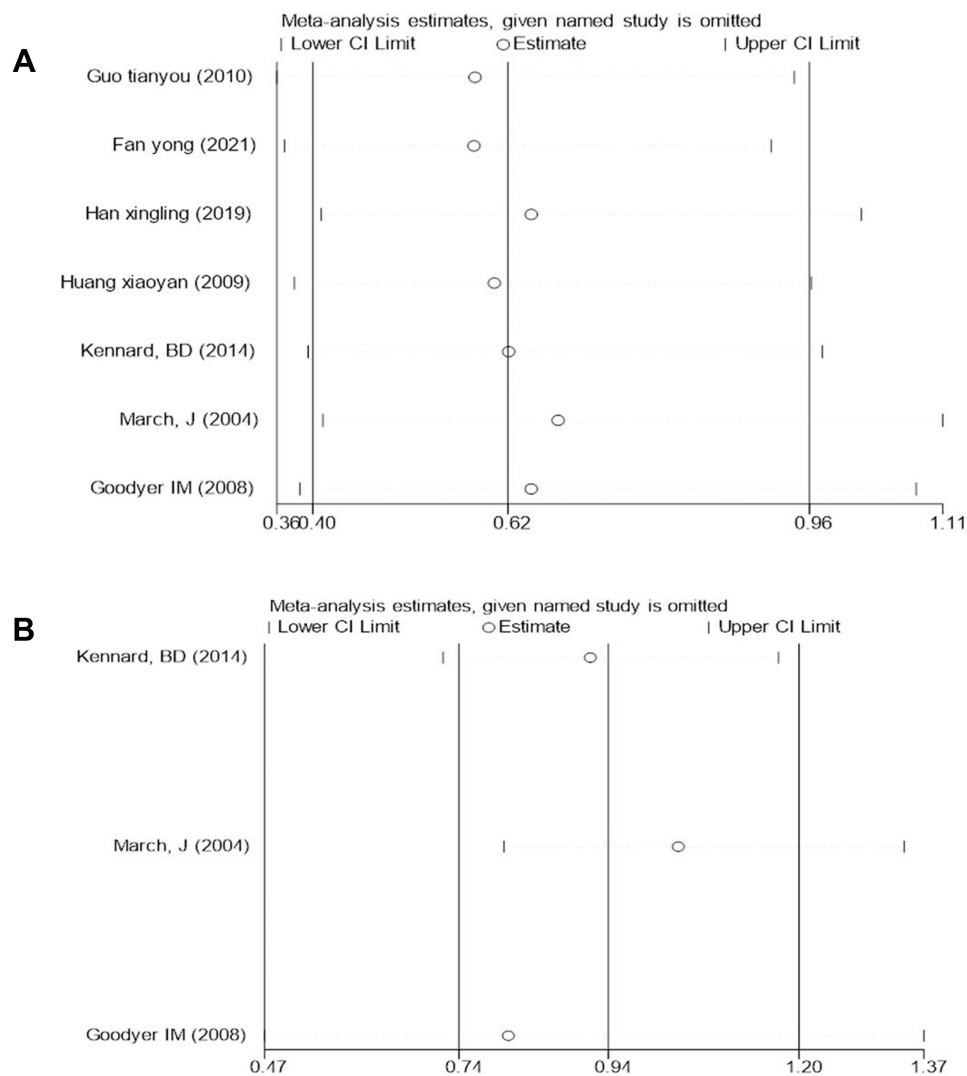


Figure 6 (A) Sensitivity analysis of incidence of adverse reactions after treatment. **(B)** Sensitivity analysis of proportion of suicide or NSSI after treatment.

HAMD Score After Treatment

Nine studies compared the HAMD score between the treatment and control groups.^{14–22} Significant heterogeneity ($I^2 = 78.5\%$, $P \leq 0.001$) was noted between the studies, and therefore, the random-effects model was used to analyze the data. The patients treated with fluoxetine plus CBT had a significantly lower HAMD score when compared with the control group (SMD = -1.01 , 95% CI: -1.39 , -0.63 , Figure 7).

The symmetrically shaped funnel plot indicates a low risk of publication bias (Figure 8). Additionally, the sensitivity analysis confirmed that the pooled effect size was still of statistical significance, and the direction of the forest plot did not change significantly before and after the removal of any literature (Figure 9).

CDRS-R Score and CGI Score After Treatment

Three studies compared the difference in CDRS-R scores between the treatment and control groups.^{23–25} Since the heterogeneity between the studies was low ($I^2 = 24.0\%$, $P = 0.268$), the fixed-effect model was used to analyze the data. The CDRS-R scores of patients treated with fluoxetine plus CBT were significantly lower when compared with the control group (SMD = -0.10 , 95% CI: -0.26 , 0.07 , Figure 10A).

Three of the included studies compared the CGI scores between the treatment and control groups.^{23–25} Since the heterogeneity between the studies was high ($I^2 = 72.1\%$, $P = 0.028$), the random-effect model was used to analyze the

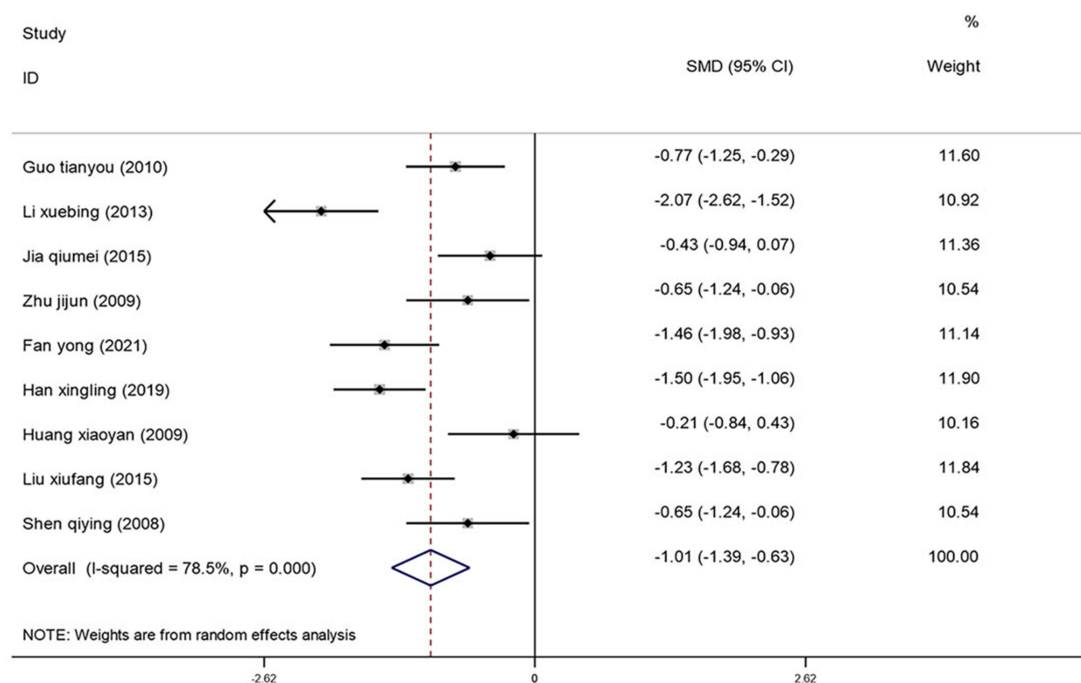


Figure 7 Forest plot comparing the HAMD score between the treatment and control groups.

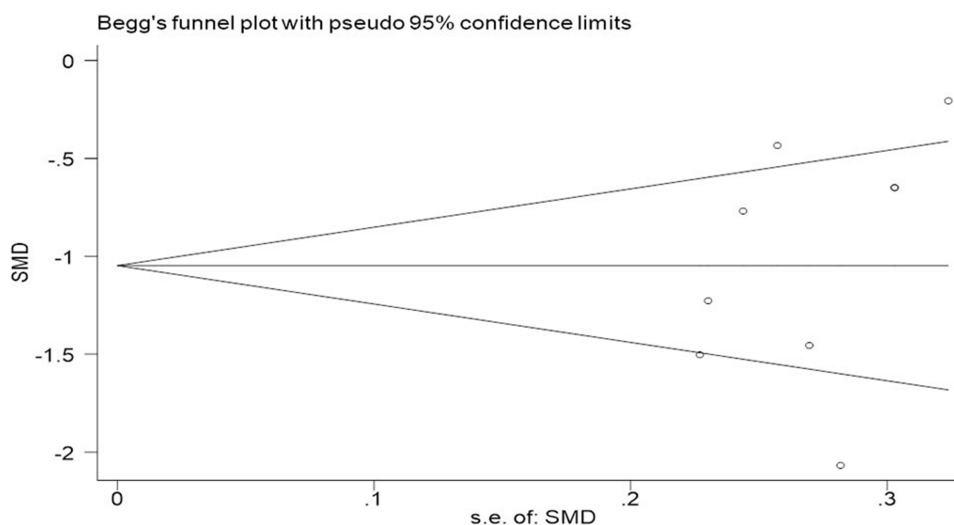


Figure 8 Funnel plot of HAMD score after treatment.

data. The treatment group had a lower CGI score when compared with the control group (SMD = -0.22, 95% CI: -0.54, 0.10, Figure 10B).

The sensitivity analysis confirmed that the results for the CDRS-R scores and CGI scores were reliable (Figures 11A and B).

Discussion

Depression in adolescents is a common debilitating condition that leads to poor quality of life and an increased risk of suicide and self-harm. Depressed adolescents are often treated with the antidepressant fluoxetine hydrochloride, a selective serotonin reuptake inhibitor (5-HT). This drug inhibits the absorption of 5-HT in the central

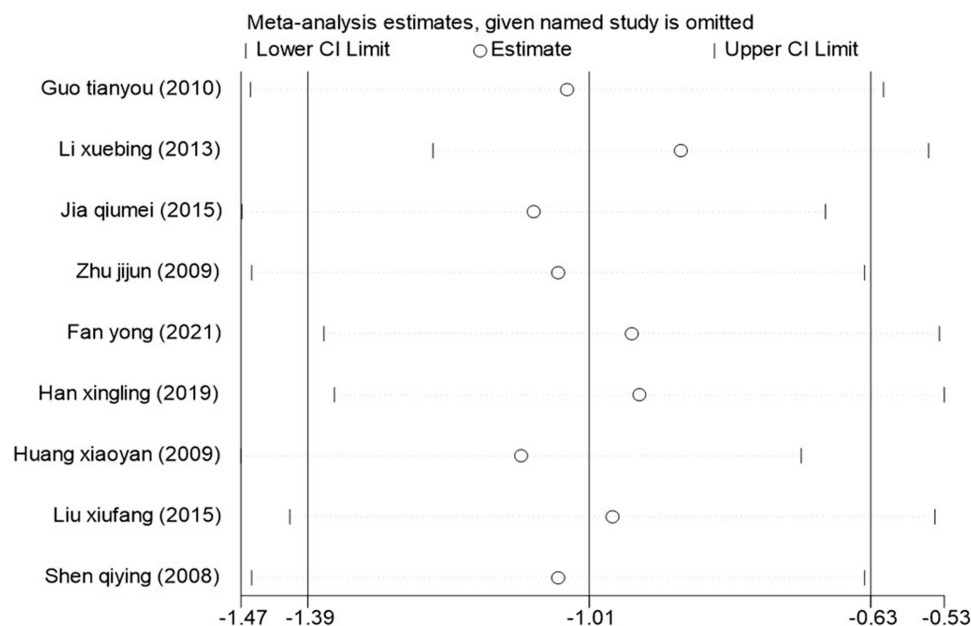


Figure 9 Sensitivity analysis for the HAMD score after treatment.

nervous system, leading to increased secretion of neurotransmitters that help reduce depressive symptoms. However, the therapeutic effect of this treatment in adolescents is limited, and the incidence of relapse and adverse effects are high.²⁶ Studies have also shown that the prolonged use of antidepressants can also increase suicidal thoughts and behavior in children and adolescents.²⁷ Therefore, more effective intervention methods are required. In order to overcome this problem, antidepressant medications are often used with psychotherapies in routine clinical practice to manage depression. Although numerous meta-analyses have shown that both psychotherapy and antidepressant are effective in reducing depressive symptoms,²⁸ to our knowledge, the comparative efficacy and safety of these interventions are still inconclusive. A network meta-analysis evaluated the treatment outcomes of 16 antidepressants, 7 psychotherapies, and 5 combination therapy regimes to manage acute depressive symptoms in children and adolescents (18 years and younger). The study also found that fluoxetine (either alone or in combination with CBT) provided the best outcomes for managing moderate-to-severe depressive disorders in children and adolescents.⁷ However, this study still lacked high-quality evidence. CBT is a structured, long, and expensive process designed to replace the patients' negative thinking with healthier, positive ideas.²⁹ The optimal timing of implementing CBT during the treatment of depressed adolescents is still not well understood. The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of CBT as a first-line treatment for depressed adolescents. However, studies have shown that for severely depressed patients, CBT does not results in better outcomes when compared with treatment using antidepressant medication alone or combined CBT with antidepressants.³⁰ Conversely, other studies have shown that combined therapy can reduce the effectiveness of antidepressive therapy and cause drug resistance in depressed adolescent patients.³¹

Therefore in this manuscript, we present the first meta-analysis comparing the treatment efficacy and adverse events of fluoxetine treatment with combined fluoxetine and CBT in the management of depression in adolescents. A total of 13 randomized controlled trials were included in this meta-analysis, and 1232 adolescents with depressive disorders were assigned to 2 or 4 controlled treatment conditions.

Our findings indicate that the combination of fluoxetine with CBT effectively reduced the incidence of depressive symptoms and adverse reactions in adolescent patients. Notably, the findings of the meta-analysis indicate that the combined therapy could improve the treatment effectiveness (RR = 1.12, 95% CI: 1.04, 1.21), lower the incidence of adverse reactions (RR = 0.62, 95% CI: 0.40, 0.96), reduce the incidence of suicide or NSSI (RR = 0.94, 95% CI: 0.74,

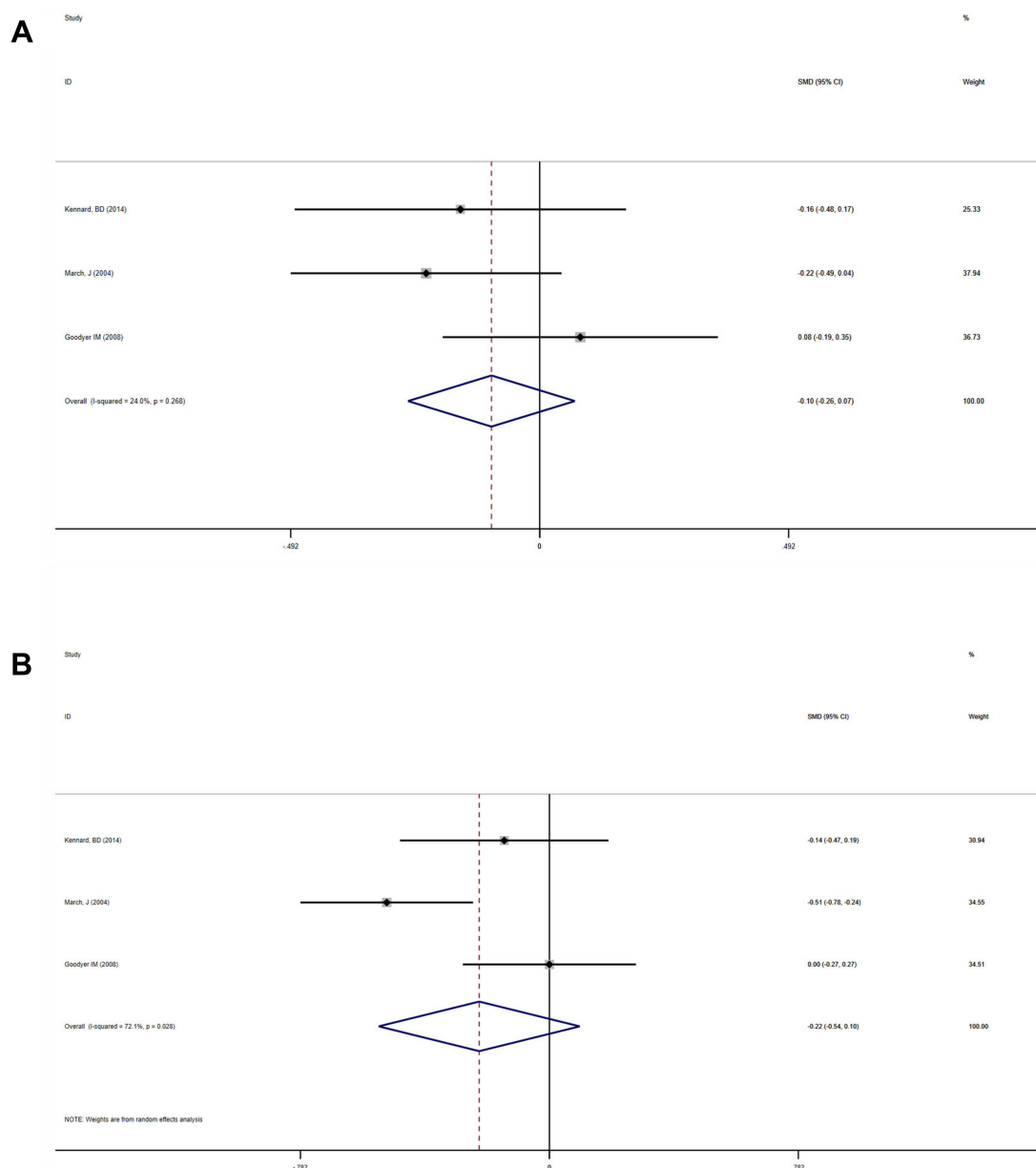


Figure 10 (A) Forest plot comparing the CDRS-R score between the treatment and control groups. **(B)** Forest plot comparing the CGI score between the treatment and control groups.

1.20), and reduce the one-year recurrence rate ($RR = 0.27$, 95% CI: 0.16, 0.45). The study also found that fluoxetine could reduce the HAMD score, CDRS-R score, and CGI score in depressed adolescents. However, fluoxetine combined with psychotherapy was more effective.

This study has some limitations that have to be acknowledged. It is important to note that the follow-up period of the included studies was short. Therefore, more longitudinal studies are required to evaluate the long-term benefits of combined therapy. Furthermore, only a few studies reported the incidence rate of suicide or self-harm, leading to insufficient analysis and weakening the credibility of the results. Significant heterogeneity was also reported for the CGI and HAMD indicators. The heterogeneity was attributed to the psychotherapy technique and the professional background of the psychologists. Other factors, such as the wide range of outcome measures used

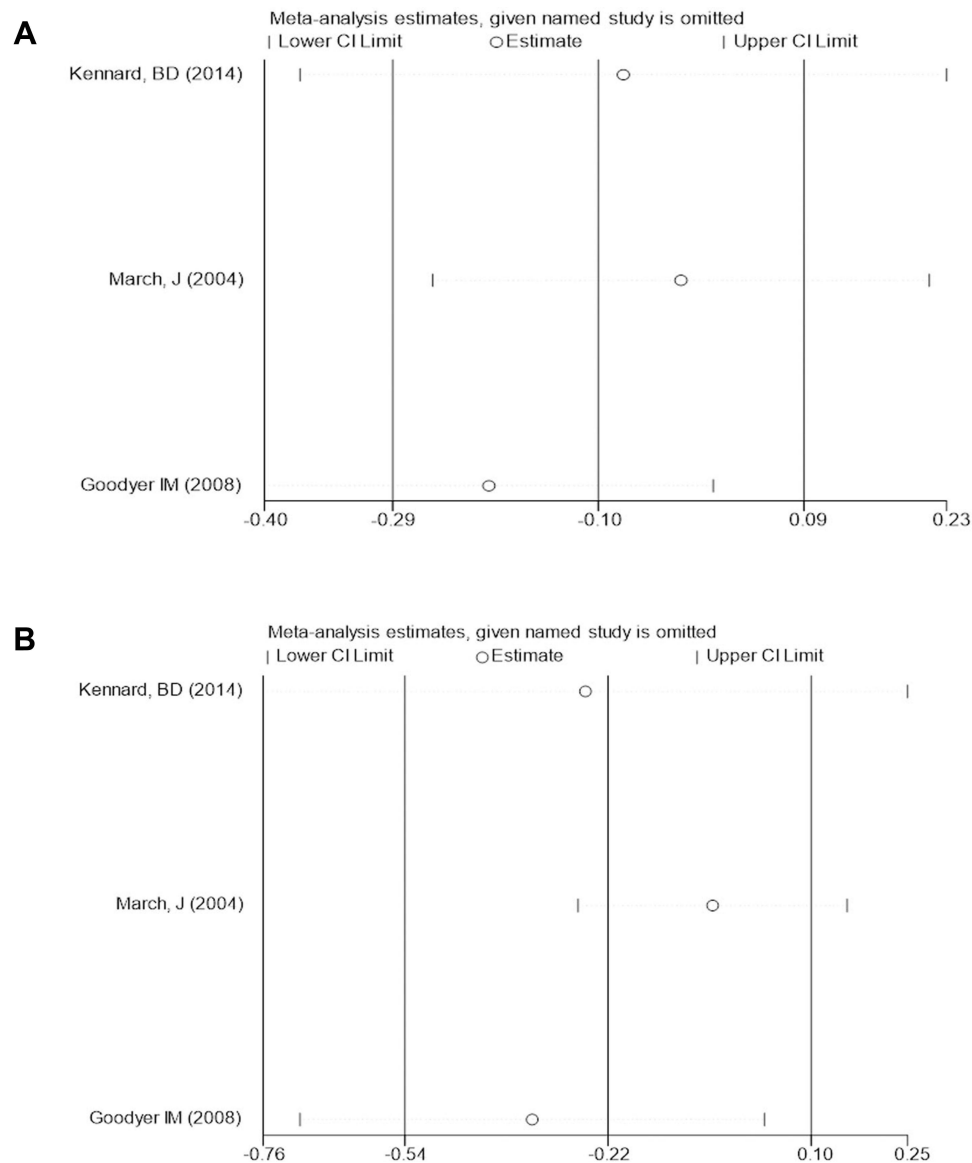


Figure 11 (A) Sensitivity analysis of CDRS-R score after treatment. **(B)** Sensitivity analysis of CGI score after treatment.

to evaluate the severity of depressive symptoms and the difficulty of diagnosing depression, may also have contributed to heterogeneity between studies.

Conclusion

Compared with fluoxetine therapy alone, the combination of fluoxetine with CBT improved the treatment efficacy and safety for depression in adolescents. Most importantly, the combined therapy reduced the risk of suicide or self-injury and the relapse rate in depressed adolescents. However, the quality of this meta-analysis is limited by the small number of published randomized controlled trials, the short-term follow-up, and the heterogeneity in the evaluation of psychotherapy effects. Therefore more high-quality longitudinal studies are recommended to confirm the findings of this meta-analysis.

Data Sharing Statement

All datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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