

Subthreshold Depression: A Systematic Review and Network Meta-Analysis of Non-Pharmacological Interventions

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Background: Subthreshold depression (StD) is considered to be the “precursor” stage of major depressive disorder (MDD), which could cause higher risk of suicide, disease burden and functional impairment. There have been various non-pharmacological interventions for StD. However, the comparison of their effectiveness still lacks sufficient evidence. We performed a systematic review and network meta-analysis to evaluate and rank the efficacy of multiple non-pharmacological interventions targeting StD.

Methods: We conducted a thorough search across various databases including PubMed, Medline, Embase, Web of Science and PsycINFO from inception to December 2022. All included studies were randomized controlled trials (RCTs) of non-pharmacological interventions for patients with StD compared with control group (CG). Several universal scales for measuring depression severity were used as efficacy outcomes. The surface under the cumulative ranking curve (SUCRA) was used to separately rank each intervention using the “Stata 17.0” software.

Results: A total of thirty-six trials were included, involving twenty-eight interventions and 7417 participants. The research found that most non-pharmacological interventions were superior to controls for StD. In each outcome evaluation by different scales for measuring depression, psychotherapy always ranked first in terms of treatment effectiveness, especially Problem-solving Therapy (PST), Behavioral Activation Therapy (BAT), Cognitive Behavioral Therapy (CBT)/Internet-based CBT (I-CBT)/Telephone-based CBT (T-CBT). Since different groups could not be directly compared, the total optimal intervention could not be determined.

Conclusion: Here, we show that psychotherapy may be the better choice for the treatment of StD. This study provides some evidence on StD management selection for clinical workers. However, to establish its intervention effect more conclusively, the content, format and operators of psychotherapy still require extensive exploration to conduct more effective, convenient and cost-effective implementation in primary healthcare. Notably, further research is also urgently needed to find the biological and neural mechanisms of StD by examining whether psychotherapy alters neuroplasticity in patients with StD.

Keywords: subthreshold depression, non-pharmacological intervention, efficacy, comparison, network meta-analysis, systematic review

Introduction

Depression is highly prevalent and ranked third among the global burden of disease by WHO, expected to rise to being the number one ranked disease by 2030.¹ This trend poses a substantial challenge for health systems in both developed and developing countries. Whether in the DSM-IV or ICD-10 diagnostic classification system, a diagnosis of major depressive disorder (MDD) requires the time course, number of symptoms and severity to meet certain threshold requirements.

Subthreshold depression (StD) (also called subsyndromal, subclinical or minor depression) was coined by Judd et al² in 1994 and has been widely accepted by scholars. StD was regarded at a “preclinical” stage of MDD,³ referring to a depressive state with at least two or more depressive symptoms, including mood depression or loss of interest and pleasure, with a duration of at least two weeks, and accompanied by impaired social functioning. This state does not meet criteria for major depressive episodes. In addition, having a higher score than a certain cut-off in self-rated depression scales was also recognized as an alternative definition by researchers.^{4,5} StD has been a highly prevalent condition, with approximately 2.9%–9.9% incidence rate among adults in primary care, 1.4%–17.2% among adults in community settings,⁶ and 38.7% among older adults receiving home care.⁷ And during COVID-19, the proportion of the population meeting the criteria for StD was even as high as 47.8%, suggesting that the epidemic perhaps act as a stressor affecting all population.⁸ In addition, the state of StD is associated with gender, family status, economic and employment status, disability and impairment associated, health service use and comorbidity,⁵ the prevalence of StD among patients with diabetes reached 11.6% evaluated by the Patient Health Questionnaire 9-item (PHQ-9).⁹ Prevention and treatment of cardiovascular diseases also play an important role in preventing depression and other mental disorders.¹⁰

The pathophysiological features of depressive disorder are complex. The monoamine hypothesis has prevailed for the pathogenesis of depression, holding that depression is caused by the depletion of 5-HT, norepinephrine, or dopamine in the central nervous system (CNS). The other pathogenesis includes stress, neurotrophins and neurogenesis, excitatory and inhibitory neurotransmission, (epi)genetics, inflammation, the opioid system, myelination, and the gut-brain axis, among others. The neural substrate of depression refers to the abnormalities in neuronal activity and neurotransmitters associated with depression in the brain. Battaglia et al^{11,12} addressed the role of specific neuropharmacological adjuvants that act on neurochemical synaptic transmission and found that depression can be present with neurotransmitter-related abnormalities, including dysregulation of neurotransmitters such as epinephrine, norepinephrine, and dopamine. In addition, the synaptic plasticity in patients with depression may be affected by abnormal release and reuptake of neurotransmitters, changes in synaptic structure, inflammation and stress response, which in turn affects emotional regulation and cognitive function, and deficits in emotion regulation may also lead to mood disorders.¹³

Mitochondria are multifunctional organelles which produce cellular energy and play a major role in other cellular functions including homeostasis, cellular signaling, and gene expression, among others. In recent years, researchers have found that mitochondrial abnormalities may lead to disturbances in energy metabolism, which can lead to depressive symptoms. Abnormal mitochondrial function can lead to both an increase in oxidative stress, inflammation and apoptosis, as well as affecting the synthesis and regulation of neurotransmitters, which in turn can affect mood and cognitive function.^{14,15} Furthermore, Hakamata et al¹⁶ found that the blunted interleukin-6 diurnal rhythm predicts depressive symptoms, modulated by amygdala emotional hyporeactivity and gene-stressor interactions. These findings may indicate a potential mechanism underlying vulnerability to depressive disorders, suggesting their early detection, prevention, and treatment through the understanding of immune system dysregulation. To delve into the new neurobiological mechanisms behind neuropathogenesis, stimulation effects, brain responses, researchers have utilized a variety of neuroimaging techniques such as structural and functional magnetic resonance imaging (s/fMRI), electroencephalography (EEG), diffusion tensor imaging (DTI) etc., all of which provide structural, functional, and chemical brain detailed visualizations and measurements of the brain.^{17–20} The integration of these techniques enables a deeper understanding of the pathophysiology of these disorders and facilitates the development of more effective therapies.

Compared with healthy individuals, StD was associated with a higher risk of suicide, disease burden, and functional impairment.²¹ Cuijpers et al²² conducted a 6-year longitudinal study on older adults and found that 7.8% of those with StD developed MDD, the rate reached 12% after 3-year follow-up in a Dutch study.²³ Early appropriate interventions for StD that can reduce the risk of developing depression have attracted widely attention. Previous meta-analysis indicated that antidepressants did not demonstrate therapeutic advantages for StD over placebos,²⁴ and benzodiazepines were also not determined to their potential therapeutic role.²⁵ Furthermore, according to the Guidelines from the National Institute for Health and Care Excellence (NICE), people with StD should not be recommend pharmacological therapy. Consequently, non-pharmacological treatments currently become important means for StD. Scholars globally were gradually dedicated to exploring in the field. There were various types of methods applied to the treatment of StD, including psychological therapy (ie, cognitive behavioral therapy, problem-solving therapy, behavioral activation,

cognitive therapy, mindfulness therapy, etc.), physical activity therapy (ie, aerobic exercise, Chinese Tai Chi, etc.), psychosocial therapy (ie, counseling therapy) and others. In terms of treatment forms, there were not only group face-to-face treatments,^{26,27} but also self-help or professional guided treatments based on the internet, telephone, email, manual, and so on.^{28,29}

A few previous meta-analyses have evaluated the effectiveness of partial measures for StD. He et al³⁰ allocated non-pharmacological interventions among adults into one of two groups: intervention classes (physical activity, psychosocial intervention, psychotherapy and so on) and individual modalities, and showed that psychotherapy demonstrated statistically significant superiority over conventional treatment. A meta-analysis conducted by Spanish researchers assessed the effectiveness of pure or minimal support self-help interventions based on cognitive, behavioural or cognitive-behavioural treatments in older adults, had further been validated to have short-term therapeutic effects, but the long-term preventive effects were not yet clear.³¹ Moreover, Cuijpers et al³ first presented evidence showing that psychological interventions had a small to moderate but significant effect on reducing depressive symptoms in adolescents with StD. Jiang et al³² suggested that electroacupuncture or bright light therapy appeared to be the better choices in the treatment of StD.

However, perhaps there were still some differences between trials those included in patient characteristics, study interventions, outcome assessments or study designs, which make comprehensive comparability remain unclear. Therefore, we decided to conduct a new, comprehensive network meta-analysis (NMA) of non-pharmacological interventions to identify and rank the efficacy of multiple therapies for people aged over 12 years old with StD.

Methods

Protocol and Registration

The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42022355683). It was reported according to Preferred Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (PRISMA).³³

Eligibility Criteria

Studies fulfilling the following the “PICOS” inclusion criteria were included in our meta-analysis:

1. Population (P): study participants were patients aged over 12 years old with clinically considered StD, described in the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), or Research Diagnostic Criteria (RDC);
2. Intervention (I): study participants underwent non-pharmacological interventions, including psychotherapy, physical activity therapy, psychosocial therapy, and others explored;
3. Comparison (C): study participants assigned to the control group did not receive active treatment, but only no treatment, treatment as usual (TAU), enhanced TAU, or on the waiting list;
4. Outcome (O): the outcome of efficacy will refer to mean overall change on continuous depression severity scales and included study was required to report at least one of the following indicators: Scores of Depression Scale (CES-D), Beck Depression Inventory scale (BDI/BDI-II), the Patient Health Questionnaire-9 (PHQ-9), the Kessler Screening Scale for Psychological Distress (K-6), Hamilton Depression Scale (HAMD/HRSD), Quick Inventory of Depressive symptomatology (QIDS), Geriatric Depression Scale (GDS), Self-rating Depression Scale (SDS);
5. Study Design (S): published randomized controlled trials (RCTs) in English.
6. Other requirements: articles whose full text could be retrieved and with complete or obtainable data.

Databases and Search Strategy

We systematically searched online the following databases from inception to December 2022 for eligible English-language journal RCTs: PubMed, Medline, Embase, Web of Science, and PsycINFO. Combined with the references or studies of previous studies and systematic reviews, some additional records were manually supplemented. The following key terms were used: (“subthreshold depression” OR “subsyndromal depressive symptoms” OR “subsyndromic depression” OR “subclinical

depression” OR “Subsyndromal symptomatic depression” OR “minor depression” OR “StD” OR “SD” OR “SDS”) AND (“randomized clinical trial” OR “randomized controlled clinical trial” OR “RCT”) etc. The search strategy was applied to titles and abstracts. We exported the search results into the reference management software Endnote X9.

Data Extraction

Two researchers independently searched and screened the titles and abstracts of records. Full-text papers were retrieved to determine all potentially eligible studies that met the inclusion criteria. For studies published more than once, we included only the trial with the most complete and informative data. Any ambiguous disagreements were settled by consensus or by a discussion with a third researcher.

The following data were extracted and collected in Microsoft Excel spreadsheets using a standard data extraction form: article title, publication year, first author’s name, setting, sample size, sex distribution, mean age or age range, details of the interventions in each group, mode of intervention (i.e., in-person or digital, group or individual), duration of intervention, outcome data etc.

Assessment of the Risk of Bias in Included Studies

The risk of bias of all included RCTs was assessed by two reviewers independently using the Cochrane Risk Bias tool (By Review Manager 5.4 Software). The indicators of the tool consists of 7 items including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The judgment results were expressed as low risk of bias, high risk of bias and bias risk uncertain. Disagreements about quality assessment were resolved by discussion until a consensus was reached.

Statistical Analysis

The network meta-analysis was conducted using Stata 17.0 software program to combine direct and indirect evidence of StD. There were several measures of StD, we divided the articles into different groups based on the type of scale and then analyzed each group separately. The effect size (ES) of continuous variables was expressed as a standardized mean difference (SMD) and 95% confidence interval (95% CI). To note that, although 7 articles used the Hamilton scale, their versions were inconsistent including HAMD, HAMD-14, HAMD-17 and HRSD. To avoid bias in research choices and considering similarity of scale types, we included them in a group after discussion and used weighted mean difference (WMD) to represent the ES. We calculated whether there was a significant difference in the inconsistency model. If $P > 0.05$, we chose a consistency model; if $P < 0.05$, an inconsistency model was selected.³⁴ When there was at least one closed loop in the evidence network (refers to a comparison of multiple interventions included in the study and forming a closed loop), local inconsistency test (node-splitting method) and loop inconsistency were required. We obtained the rank of each intervention through the surface under the cumulative ranking (SUCRA), with $0 \leq \text{SUCRA} \leq 100\%$ (or represented as $0 \leq \text{SUCRA} \leq 1$), the higher the SUCRA value means the better the rank.³⁵ Performing sensitivity analyses to evaluate the stability of the results, and assessing publication bias in interventions using a funnel plot.

Results

Identification of Studies

A total of 26,876 records were initially searched, with 19,640 remained after eliminating duplicates. Their titles or abstracts were screened for this systematic review and 4515 articles remained for full-text review. We finally included 36 eligible articles in this systematic review based on the inclusion criteria. The PRISMA flowchart of detailed study selection process is shown in [Figure 1](#).

Study Characteristics

The studies were published from 2001 to 2022, and a total of 36 trials were included involving 7417 participants, with 52.22% ($n=3873$) receiving non-pharmacological interventions, in which 47.78% ($n=3544$) receiving control treatment. The characteristics of all included studies are summarized in [Table 1](#).

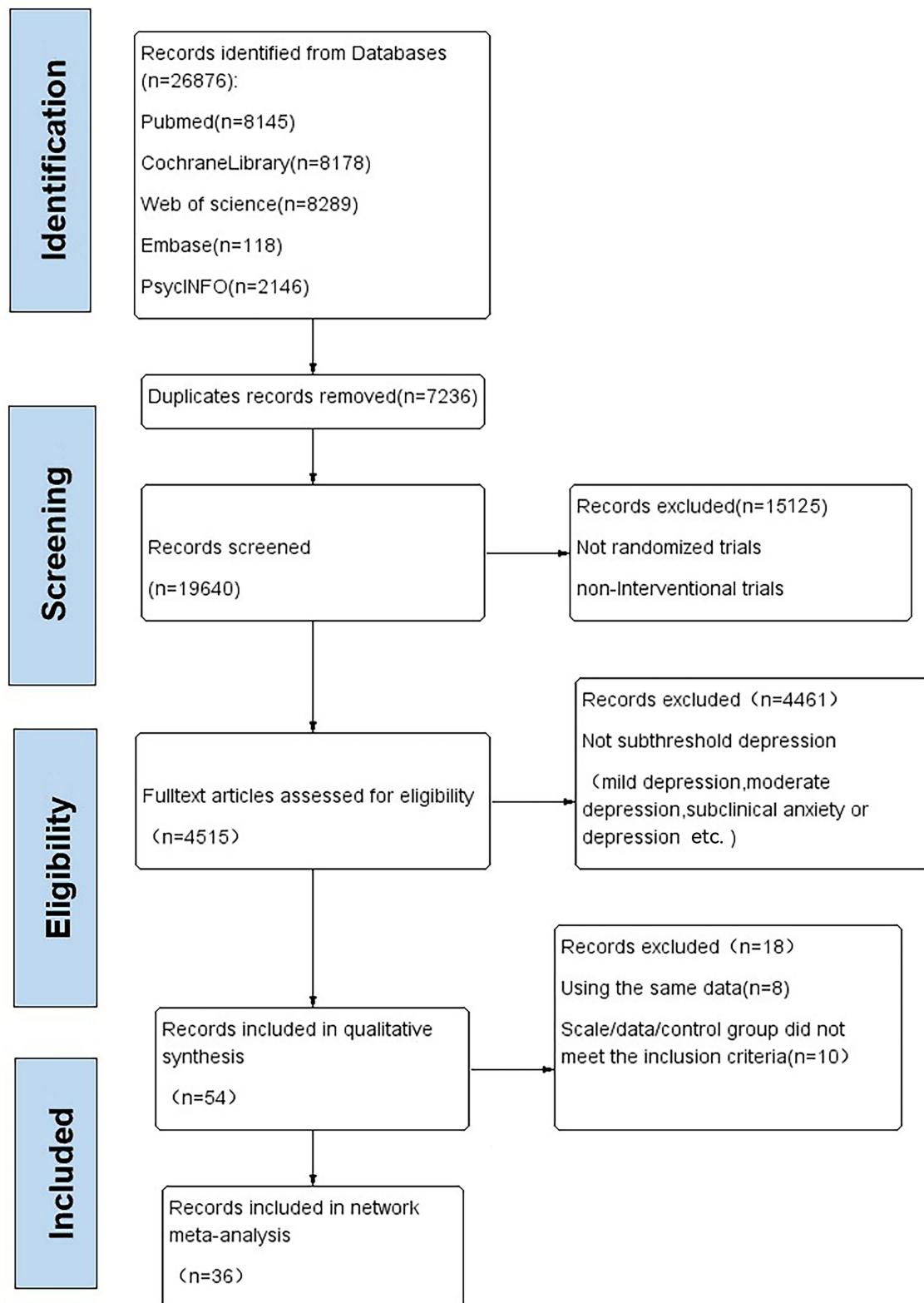


Figure 1 Flow diagram for search and selection of the included studies.

Population: The age of study participants ranged approximately from 12 to 90 years old, 65.86% of them were female (4 articles with unclear or not obtainable gender information). The included RCTs were conducted in China (n=7), ^{36–39,44,45,47} the United States (n=5), ^{27,52,58,62,65} Japan (n=5), ^{40,46,48,57,59} the Netherlands (n=5), ^{50,61,63,64,67}

Table 1 Characteristics of Included Trials (n=36) Ordered Chronologically

Author (Year)	Country	Setting	N	Age	Female %	Inclusion Criteria	Model	Format	Course	Outcome
Ying et al, 2022 ³⁶	China	Social	329	≥18	66.4	CES-D≥16, No MDE	I-CBT	Digital/Individual	5 weeks	CES-D, PHQ-9, BDI-II
Wang et al, 2022 ³⁷	China	School	30	12–14	NM	PHQ-9≥10, No MDD	AE	In person/Group	12 weeks	PHQ-9
Sun et al, 2022 ³⁸	China	Hospital	65	≥18	43.1	CES-D≥16, 7≤HAMD≤17	BAT	In person/Individual	6 weeks	CES-D, HAMD-17
Au et al, 2022 ³⁹	China	Community	168	<70	68.5	5≤PHQ-9≤9, No MDD	T-CBT	Digital/Individual	12 weeks	BDI-II
Kageyama et al, 2021 ⁴⁰	Japan	Social	32	18–24	34.37	CES-D≥16, No MDE	VISA-PWS	Digital/Individual	5 weeks	CES-D, K-6
Sander et al, 2020 ²⁹	Germany	Hospital	295	≥18	62.4	PHQ-9≥5, No MDD	IT-CBT	Digital/Individual	6–9 weeks	PHQ-9, HAMD, QIDS
Ayudhaya et al, 2020 ⁴¹	Thailand	Hospital	82	≥60	81.3	13≤GDS≤24	BAT	In person/Group	12 weeks	GDS
López et al, 2019 ⁴²	Spain	Caregiver	173	44–64	73.4	CES-D≥16, No MDE	PST	In person/Group	5 weeks	CES-D
Basanovic et al, 2019 ⁴³	Australia	Community	202	≥45	NM	5≤PHQ-9≤14, No MDE	CBM	Digital/Individual	52 weeks	PHQ-9
Zhang et al, 2019 ⁴⁴	China	School	56	17–22	57.1	BDI-II>14, SDS>53 No MDD	MBSR	In person/Group	8 weeks	BDI-II
Zhang et al, 2018 ⁴⁵	China	School	64	16–19	64	Symptoms	MTCC	In person/Group	8 weeks	PHQ-9
Yamamoto et al, 2018 ⁴⁶	Japan	School	31	20–39	80.6	SDS≥39, Self-report No mental disorder	IPC	In person/Group	3 weeks	SDS
Wong et al, 2018 ⁴⁷	China	Clinic	231	≥20	93.1	5≤ PHQ-9≤14, No MDD	BAM	In person/Group	8 weeks	BDI-II, SDS
Takagaki et al, 2018 ⁴⁸	Japan	School	118	18–19	38.1	BDI-II ≥10, No MDE	BAT	In person/Group	5 weeks	BDI-II
Singhal et al, 2018 ⁴⁹	Australia	School	120	13–18	NM	14≤CDI≤24	CBT	In person/Group	8 weeks	CES-D
Pols et al, 2018 ⁵⁰	the Netherlands	Clinic	236	≥18	45.3	PHQ-9≥6, No MDD	STEPEED	Stepped/Individual	1 year	PHQ-9
Ebert et al, 2018 ⁵¹	Germany	Social	204	≥18	80.4	CES-D≥16, No MDD	PST+BT	Digital/Individual	7 weeks	QIDS, HRSD, CES-D
Pan et al, 2017 ⁵²	America	Social	120	≥18	78	14≤BDI-II≤28	DI, NI	In person/Individual	20 minutes	BDI-II
Lewis et al, 2017 ⁵³	Britain	Clinic	705	≥65	57.7	Self-report, No MDD	CASPER	Digital/Individual	7–8 weeks	PHQ-9
Pibernik et al, 2015 ⁵⁴	Croatia	Clinic	209	18–65	54.1	Self-report (PHQ-2) No MDD	CBT+PST PE	In person/Group	6 weeks	CES-D
Hermanns et al, 2015 ⁵⁵	Germany	Hospital	214	18–70	56.5	CES-D≥16, No MDD	CBT	In person/Group	In-Hospital	CES-D, PHQ-9
Buntrock et al, 2015 ⁵⁶	Germany	Social	406	≥18	65.2	CES-D≥16, No MDE	I-CBT	Digital/Individual	3–6 weeks	CES-D
Imamura et al, 2014 ⁵⁷	Japan	Company	762	NM	53.3	No MDD	I-CBT	Digital/Individual	6–10 weeks	BDI-II, K6
Kasckow et al, 2014 ⁵⁸	America	Clinic	23	≥50	0	CES-D>11, No MDE	PST	In person/Individual	6–8 weeks	BDI, HRSD

Morgan et al, 2012 ²⁸	Australia	Social	1326	18–78	77.6	Symptoms (PHQ-9)	E-BT	Digital/Individual	6 weeks	PHQ-9
Furukawa et al, 2012 ⁵⁹	Japan	Company	118	20–57	22	K6≥9, BDI-II≥10	T-CBT	Digital/Individual	8 weeks	BDI-II, K6
Ullmann et al, 2011 ⁶⁰	Columbia	Community	47	≥65	70.2	16≤CES-D<25	Feldenkrais	In person/Group	5 weeks	CES-D
Joling et al, 2011 ⁶¹	the Netherlands	Community	170	≥75	NM	CESD≥16, No MDD	BB-CBT	Digital/Individual	12 weeks	CES-D
Gellis et al, 2010 ⁶²	America	Healthcare agency	36	≥65	86.8	CES-D≥16, Symptoms No MDD	PST+BAT	In person/Individual	6 weeks	BDI-II, HAMD-17
Konnert et al, 2009 ²⁶	Canada	Nursing home	64	≥60	77	Depression risk (GE9) No MDD	G-CBT	In person/Group	7 weeks	CES-D, GDS
Spek et al, 2007 ⁶³	the Netherlands	Social	301	50–75	63.5	EDS≥12, No MDD	I-CBT	Digital/Individual,	8 weeks	BDI-II
Dam et al, 2007 ⁶⁴	the Netherlands	Social	110	18–65	61.8	BDI≥10, No MDD	G-CBT	In person/Group	6 weeks	BDI
Young et al, 2006 ⁶⁵	America	School	41	11–16	85.4	16≤CES-D≤39, No MDE	IPT	In person/Group	8 weeks	CES-D
Neugebauer et al, 2006 ⁶⁶	Columbia	Hospital	19	≥18	100	Symptoms (K-SADS-PL) HAMD-17 >7	T-IPC	Digital/Individual	9 weeks	HAMD-17
Willemse et al, 2004 ⁶⁷	The Netherlands	Clinic	216	18–65	66.2	Symptoms, No MDD	CBT	Digital/Individual	28 weeks	CES-D
Clarke et al, 2001 ²⁷	America	Organization	94	13–18	59.6	CES-D≥24, No MDD	G-CT	In person/Group	NM	CES-D, HAMD-14

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; PHQ-9, the 9-item Patient Health Questionnaire; BDI, Beck Depression Inventory Scale; HAMD, Hamilton Depression Scale; K-6, Kessler Screening Scale for Psychological Distress; QIDS, Quick Inventory of Depressive Symptomatology; GDS, Geriatric Depression Scale; SDS, Self-rating Depression Scale; HRSD, Hamilton Rating Scale for Depression; CDI, Children's Depression Inventory; PHQ-2, the 2-item Patient Health Questionnaire; GE9, Geriatric Depression Scale scores; K-SADS-PL, the Schedule for Affective Disorders and Schizophrenia for School-Age Children; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; CBT, Cognitive Behavioral Therapy; I-CBT, Internet-based CBT; T-CBT, Telephone-based CBT; IT-CBT, Internet- and Telephone-based CBT; BB-CBT, Bibliotherapy-based CBT; G-CBT, Group CBT; AE, Aerobic Exercise; BAT, Behavioral Activation Therapy; VISA-PWS, Video viewing Smartphone Application Intervention involving Positive Word Stimulation; PST, Problem-solving Therapy; CBM, Cognitive Bias Modification; MBSR, Modified Mindfulness-Based Stress Reduction; MTCC, Mindfulness-based Tai Chi Chuan; IPC, Interpersonal Counseling; BAM, Behavioral Activation with Mindfulness; STEPEED, a stepped-care prevention programme; BT, Behavior Therapy; DI, Directive Intervention (Psychoeducation); NI, Non-directive Intervention (Psychoeducation); CASPER, Collaborative care and active surveillance for Screen-Positive Elders; PE, Physical Exercise; BT, Behavior Therapy; E-BT, Email-based BT; Feldenkrais, a Mind-Body Intervention; IPT, Interpersonal Psychotherapy; T-IPC, Telephone-administered IPC; G-CT, Group Cognitive Therapy; NM, not mentioned.

Germany (n=4),^{29,51,55,56} Australia (n=3),^{28,43,49} Columbia (n=2),^{60,66} Thailand (n=1),⁴¹ Croatia (n=1),⁵⁴ Spain (n=1),⁴² Canada (n=1)²⁶ and Britain (n=1).⁵³ Most studies were two-arm trials (n=32), and remaining were three-arm trials (n=4). The diagnostic criteria for StD are not unified among those studies. According to the statistics, there were 25 studies combining severity rating scales with interviews (to exclude MDD or MDE) to get the diagnose of StD, 2 articles combining symptoms with interviews, 7 articles only using scales, and 2 articles single relying on symptoms.

Interventions: In total, there were 28 different non-pharmacological interventions, summarized into 7 categories, including psychotherapy (n=30), physical activity therapy (n=2), psychosocial therapy (n=3), Feldenkrais (n=1), collaboration therapy (n=2), stepped therapy (n=1) video-viewing therapy (n=1). The network plot of all interventions is shown in Figure 2.

Control group: A total of 36 RCTs utilized non-active control conditions, including waitlist (WL; n=3), treatment as usual (TAU; n=20), enhanced TAU (ETAU=10; ie, education, discussion, etc.) and TAU before WL (n=2).

Types of outcome assessment: We found that 15 studies used CES-D (n=2), 12 studies used BDI/BDI-II, 9 studies used PHQ-9, 7 studies used Hamilton Depression Scale HAMD/HRSD, 3 studies used K-6 2 studies used QIDS, 2 studies used GDS and 2 studies used SDS.

Risk of Bias Assessment

Most studies presented a low risk in the randomization process and allocation concealment. There were 11 (30.6%) studies rated as having a high risk of bias for ‘blinding of participants and personnel; this is, though, typically unavoidable in studies of psychological interventions. There were 2 studies reported a high risk of bias for ‘blinding of outcome assessment (the residents in the treating group occasionally revealed their participation in group to the raters, thus introducing potential bias among assessors), and this was rated as unclear in 13 studies (36.1%). The risk of attrition bias was low: only two studies did not address incomplete data. Three studies were rated as having a high risk of

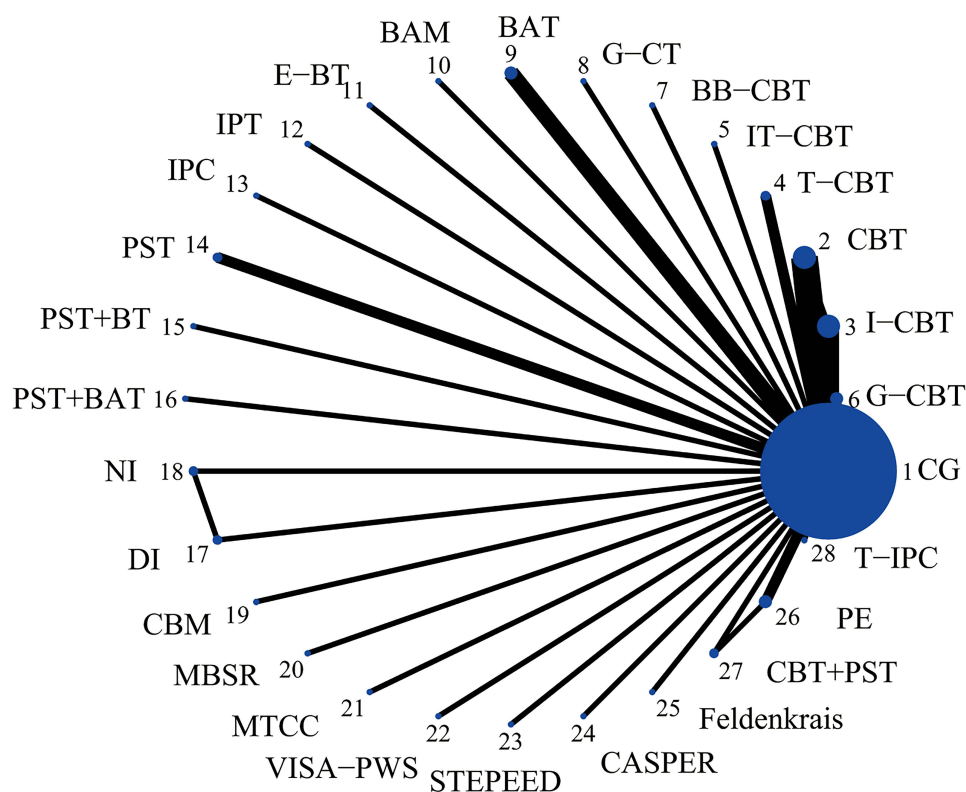


Figure 2 Evidence network map for the comparison of different non-pharmacological interventions. The numbers represent different intervention measures. The size of the blue nodes relates to the number of participants in that intervention type, and the thickness of lines between the interventions relates to the number of studies for that comparison.

selective reporting bias. None of the studies reported a high risk of bias for other biases. All studies presented a low risk in the attrition bias and reporting bias. In terms of other bias, most included studies are assessed as low risk. The results of the risk bias assessment are shown in [Figure 3](#).

Network Meta-Analysis

CES-D

A total of 15 studies reported the results of CES-D, 2 three-arm trials and 13 two-arm trials, with 14 interventions included. The evidence network plot presented two closed loops (see [Figure 4](#)). We conducted a global inconsistency test ($P=0.84$), a local inconsistency test using node-splitting method ($P>0.05$) and a loop inconsistency (95% CrI included 0), all showing no significant difference between direct and indirect comparisons. Therefore, a consistency model was selected for analysis. We found that most of the treatments show better efficacy on CES-D compared with CG alone. Interventions with significant statistical differences include: PST (MD -12.30, 95% CrI -20.89, -3.71) ($P=0.005$), I-CBT (MD -7.94, 95% CrI -13.59, -2.29) ($P=0.006$), CBT (MD -6.51, 95% CrI -10.72, -2.30) ($P=0.002$). The SUCRA of CES-D is in order from large to small: PST (90%)>I-CBT (74%)>IPT (68%)>CBT (66%)>G-CT (61%)>Feldenkrais (59%)>G-CBT (44%)>VISA-PWS (42%)>BAT (36%)>PE (26%)>BB-CBT (24%)>CG (20%) (see [Figure 4](#)).

BDI-II and BDI

There were 10 studies involving 11 interventions using BDI-II for the outcome assessment, 2 three-arm trials and 8 two-arm trials. The node cleavage method showed significant difference between direct and indirect comparisons ($P=0.04$). Thus, we chose an inconsistency model. According to statistics, PST+BAT (MD -9.04, 95% CrI -15.84, -2.24), ICBT (MD -7.04, 95% CrI -12.21, -1.87), BAT (MD -6.24 95% CrI -11.38, -1.10), CBT (MD -5.74, 95% CrI -10.91, -0.57), T-CBT (MD -5.36, 95% CrI -10.41, -0.31) had positive effects relative to the control group ($P<0.05$). In addition, the SUCRA of BDI-II is ordered sequentially: PST+BAT (92%)>I-CBT (83%)>BAT (74%)>CBT (67%)>T-CBT (63%)>BAM (51%)>G-CBT (44%)>DI (29%)>MBSR (28%)>CG (12%)>NI (%)> (8%). The network plot and ranking results are presented in [Figure 5A](#).

For BDI, 2 studies and 3 interventions were included to evaluate the outcome. The consistency model was used due to inconsistency test result showing no significant difference ($P>0.05$). From the direct evidence, when compared to CG,

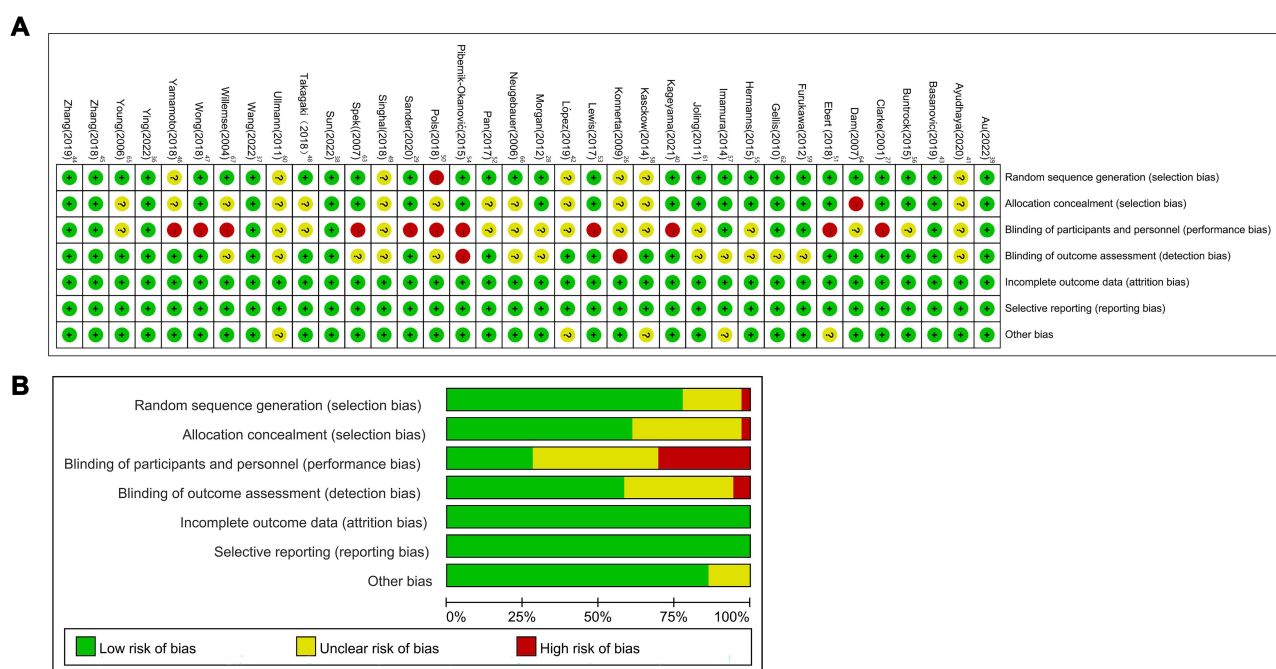


Figure 3 (A) Risk of bias summary: each risk of bias item for each included study. (B) Risk of bias graph: each risk of bias item presented as percentage.

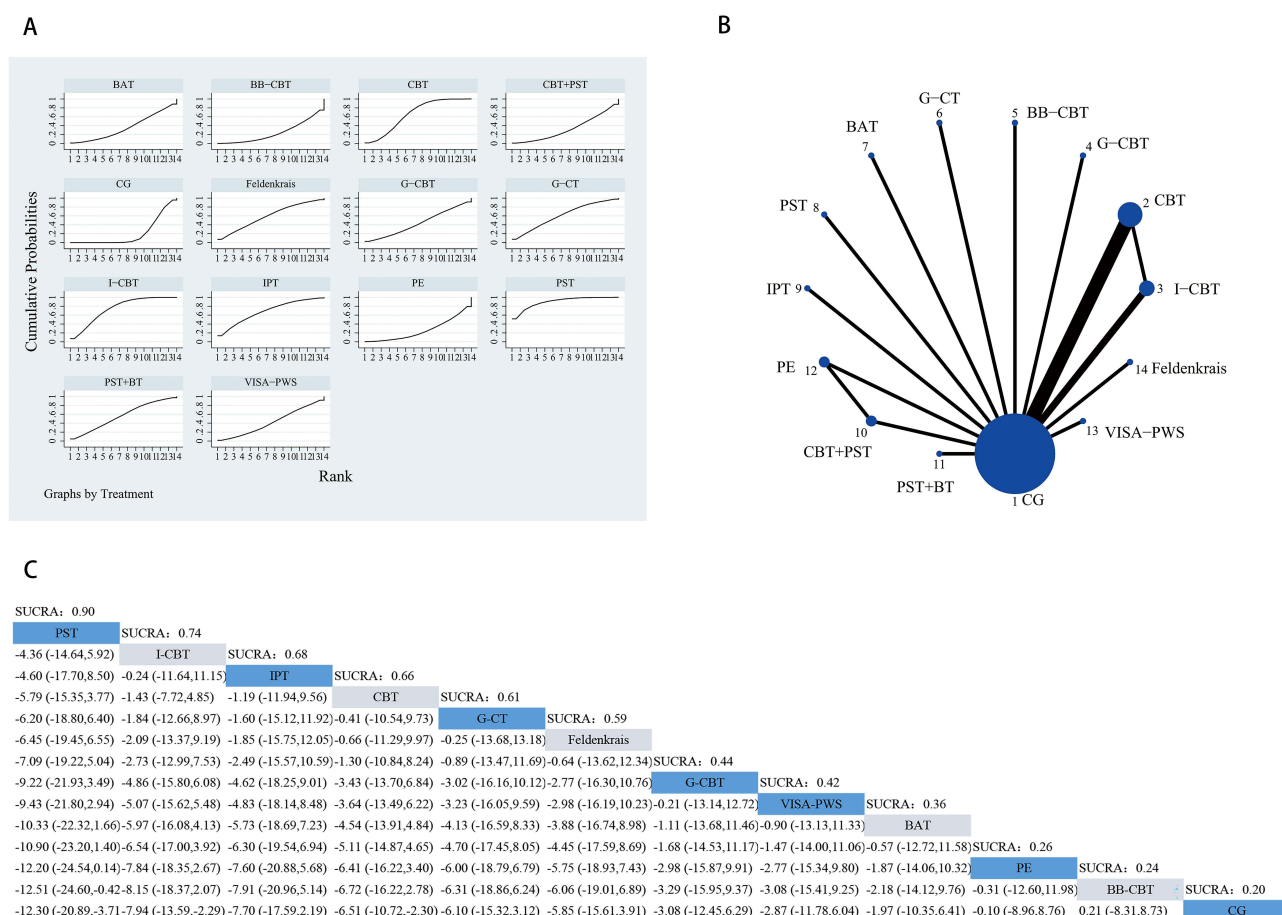


Figure 4 Results of the network meta-analysis for CES-D scores. **(A)** The SUCRA value of individual modalities. The area under the curve predicts the efficacy of various treatment measures. The larger the area under the curve is, the better the efficacy is. **(B)** Evidence network map of eligible comparisons. The numbers represent different intervention measures. The size of the blue nodes relates to the number of participants in that intervention type, and the thickness of lines between the interventions relates to the number of studies for that comparison. **(C)** Ranking of each intervention based on the SUCRA values and the league table for the relative effects of all treatments.

CBT (MD -6.10 , 95% CrI -9.45 , -2.75) ($P < 0.05$) had positive effects, whereas PST (MD -2.30 , 95% CrI -6.74 , 2.14) ($P > 0.05$) did not. The forest plot and ranking results are presented in Figure 5B.

PHQ-9

To evaluate the PHQ-9 outcome, 9 studies and 10 interventions were included. From the network plot of Figure 6, we found that I-CBT (MD -3.90 , 95% CrI -4.51 , -3.29), AE (MD -3.07 , 95% CrI -3.98 , -2.16), MTCC (MD -2.50 , 95% CrI -3.60 , -1.40), CBT (MD -2.20 , 95% CrI -2.79 , -1.61), IT-CBT (MD -1.62 , 95% CrI -2.46 , -0.78), CASPER (MD -1.50 , 95% CrI -2.13 , -0.87), CBM (MD -1.14 , 95% CrI -2.11 , -0.17), EBT (MD -0.80 , 95% CrI -1.26 , -0.34) had better effects ($P < 0.05$) compared to the CG, however STEPEED (MD -0.43 , 95% CrI -1.45 , 0.59) ($P > 0.05$) did not. The SUCRA of PHQ-9 is as followed: I-CBT (99%) > AE (87%) > MTCC (74%) > CBT (68%) > IT-CBT (50%) > CASPER (47%) > CBM (35%) > EBT (23%) > STEPEED (14%) > CG (2%) (see Figure 6).

HAMD/HRSD

A total of 7 RCTs assessed depression severity for StD in this group, including 3 using HAMD-17, 2 using HAMD-14, 1 using HAMD and 2 using HRSD. There was no loop structure (see Figure 7) and consistency model was selected ($P > 0.05$). Among 7 interventions, BAT (SMD -0.95 , 95% CrI -1.46 , -0.43) and IT-CBT (SMD -0.35 , 95% CrI -0.58 , -0.12) showed better effectiveness compared to CG ($P < 0.05$). No statistical difference was observed in groups of PST + BAT, T-IPC, G-CT and PST + BT. As ranking results and forest plot showed in Figure 7, BAT was the intervention with the highest ranking, with SUCRA 91%.

K6, GDS, SDS, QIDS

There were 3 trials for outcome evaluation with K-6 and using inconsistency model ($P < 0.05$), 2 trials each with GDS, SDS and QIDS, all using consistency model ($P > 0.05$). In the K6 group, T-CBT (MD -3.1, 95% CrI -4.85, -1.35) showed great effectiveness compared to CG and has the highest ranking (SUCRA, 95%). In the GDS group, BAT (MD -3.06, 95% CrI -4.25, -1.87) and G-CBT (MD -3.01, 95% CrI -4.18, -1.84) showed better effectiveness and BAT was the intervention with the highest ranking (SUCRA, 77%), G-CBT the next-highest ranking (SUCRA, 73%). We found no significant difference both in SDS and QIDS group. The ranking results are summarized in Figure 8A and forest map in Figure 8B.

Publication Bias and Sensitivity Analysis

When the effect size of each indicator was taken as the abscissa and the standard error as the ordinate-corrected funnel plot (see Figure 9). Each dot represented a direct comparison of different interventions, and the number of points of the same color represented the number of pairwise comparisons in the study. The results showed that all studies were basically distributed on both sides of the midline in the middle, the left and right distribution was roughly symmetrical, suggesting publication bias risk low. There was a few studies deviated far from the regression line, suggesting that there may be small sample studies. Sensitivity analysis was performed by sequentially omitting one study and our studies showed stable.

Discussion

In this network meta-analysis, we compared the effectiveness of 28 non-pharmacological interventions in changing the severity of depression applied 9 kinds of scale. Our study showed evidence that most non-pharmacological treatments for patients with StD had advantages over the control treatment. Furthermore, we found that PST was the best therapy to

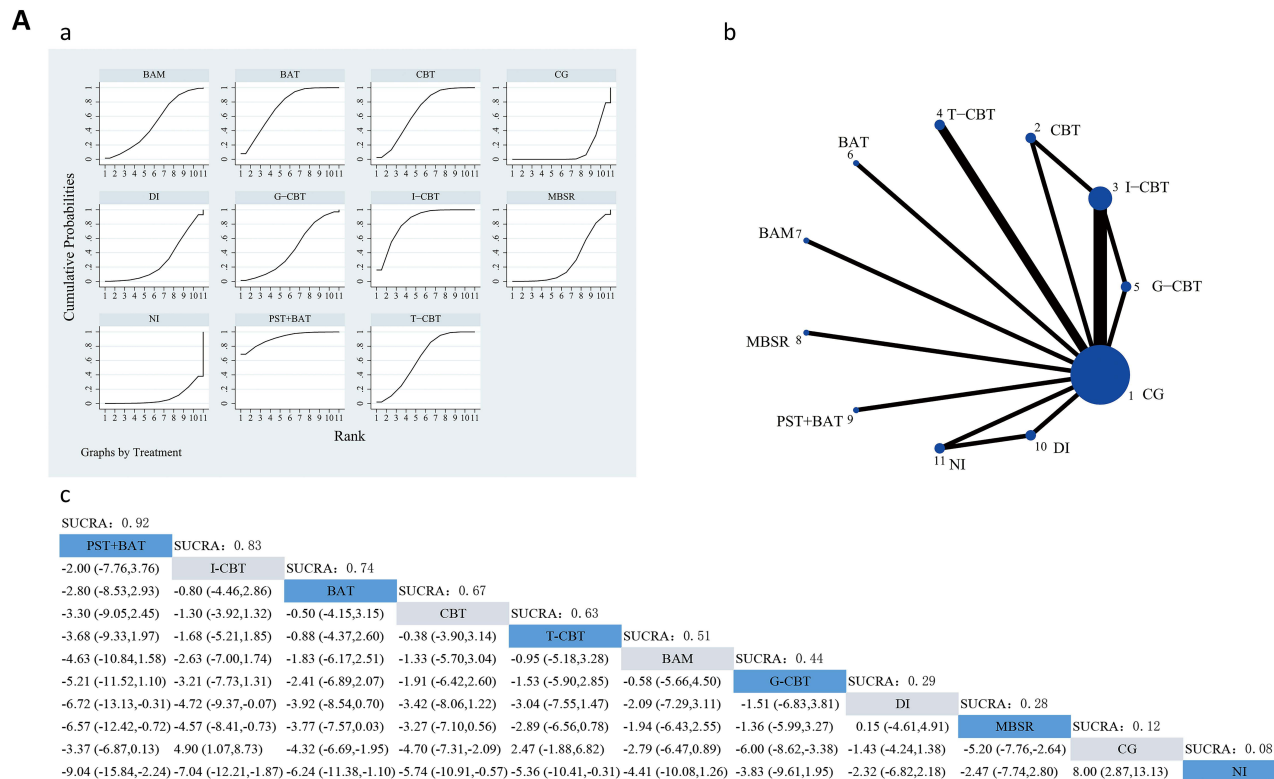


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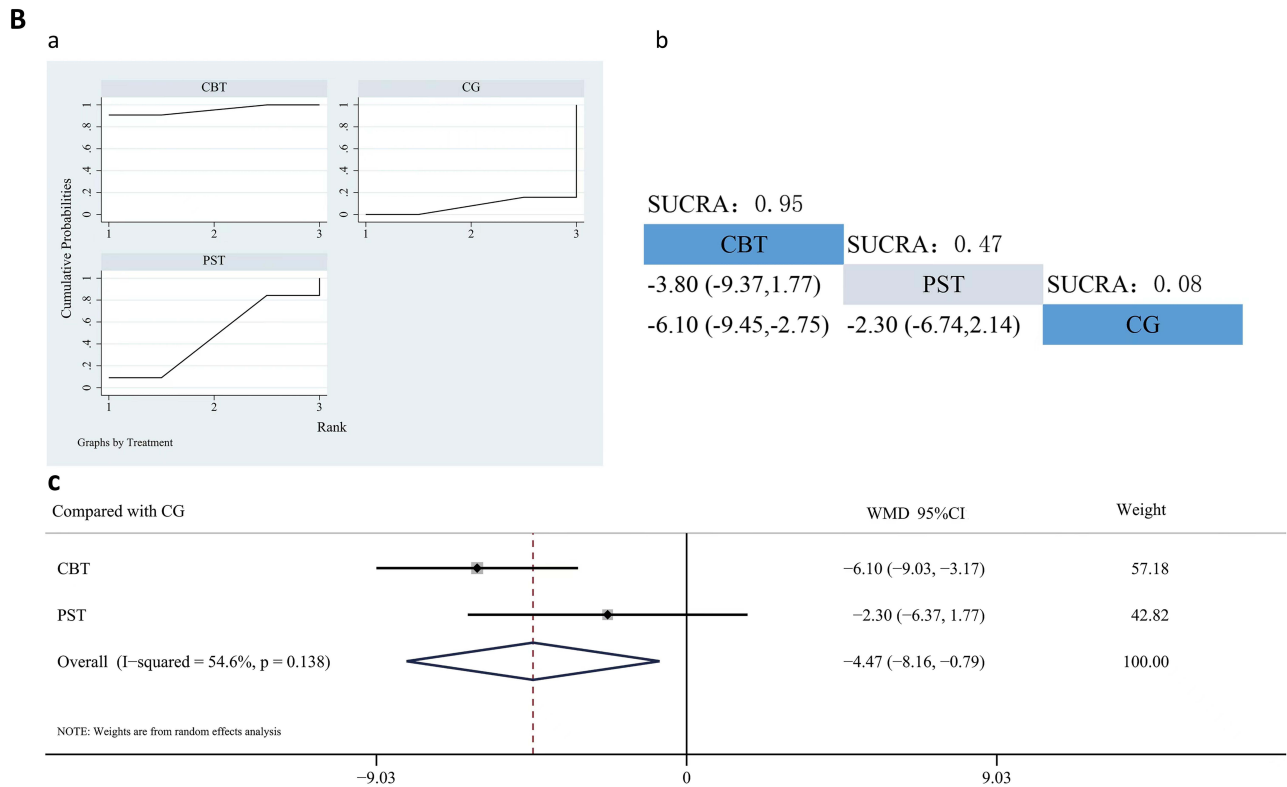
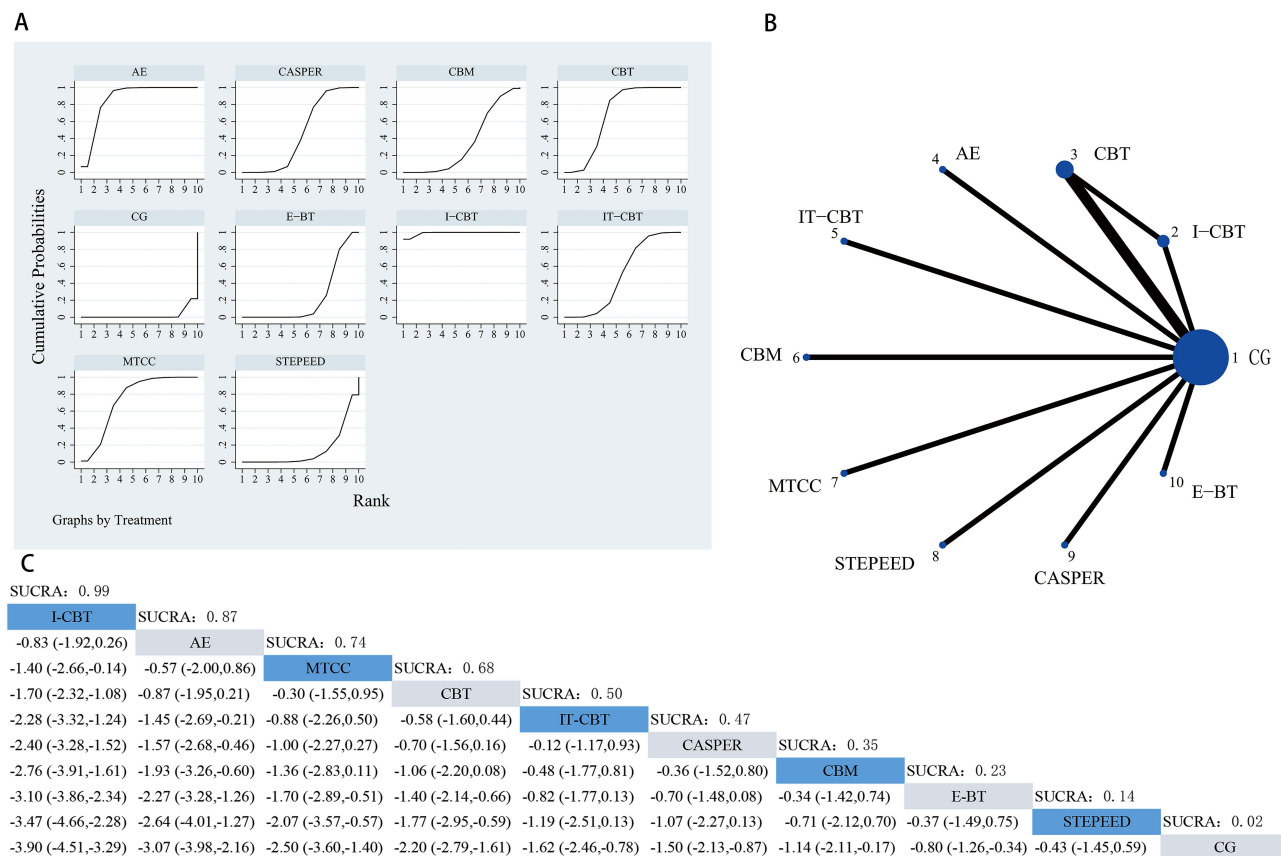


Figure 5 Results of the network meta-analysis for BDI-II/BDI scores. **(A)** Results of the network meta-analysis for BDI-II scores. **(a)** The SUCRA value of individual modalities. The area under the curve predicts the efficacy of various treatment measures. The larger the area under the curve is, the better the efficacy is. **(b)** Evidence network map of eligible comparisons. The numbers represent different intervention measures. The size of the blue nodes relates to the number of participants in that intervention type, and the thickness of lines between the interventions relates to the number of studies for that comparison. **(c)** Ranking of each intervention based on the SUCRA values and the league table for the relative effects of all treatments. **(B)** Results of the network meta-analysis for BDI scores. **(a)** The SUCRA value of individual modalities. The area under the curve predicts the efficacy of various treatment measures. The larger the area under the curve is, the better the efficacy is. **(b)** Ranking of each intervention based on the SUCRA values and the league table for the relative effects of all treatments. **(c)** Forest plot of the network meta-analysis compared with control group. **(A)** > **(D)**; **(B)** > **(E)**; **(C)** > **(F)**.

improve outcome on the CES-D, similarly PST+BAT on the BDI-II, CBT on the BDI, I-CBT on the PHQ-9, BAT on the HAMD/HRSD and GDS, and T-CBT on the K-6.

It's not difficult to notice that the most effective interventions in each group are all classified as psychotherapy. Based on the above evidence findings, we speculated that psychotherapy especially may have the best efficacy for StD, which is consistent with a previous network meta-analysis showing that psychotherapy especially CBT, may be the most effective intervention for StD.³⁰ They compared all included interventions together, the effect size was expressed as SMD because of the consistency of the scales, so there were differences in statistical methods between us. The effectiveness of psychotherapy in depression has been extensively validated in previous studies among adults, the elderly.^{68,69} In addition, Cuijpers et al³ found that interventions for StD may have positive acute effects in adolescents. Their team also reported that the types of therapy that have been examined best in primary care settings are CBT, BAT, IPT and PST.⁷⁰ This has also been mostly validated in our research showing that PST, BAT, CBT, I-CBT, and T-CBT performing better effectiveness for StD.

Kasckow et al⁵⁸ conducted a pilot study suggesting that a six-to-eight session version of PST may produce improvements in mental health functioning in primary care veterans with StD, which the sessions of PST focused on seven steps: (1) defining the problem; (2) setting a realistic goal; (3) "brainstorming" on potential solutions; (4) considering the advantages and disadvantages of each solution; (5) choosing the best solution; (6) developing an action plan; and (7) reviewing progress. Similar courses have also been implemented in other studies, PST seems well suited for medically ill the elderly given its collaborative and problem-centered approach to daily living with stressful chronic



medical conditions.⁶² However, the intervention effects were preserved until 1-year but not until 8-year follow-up, may indicating its difficult to achieve long-term prevention and necessary to conduct systematic booster sessions.⁴²

BAT is derived from the behavioral model, which was practiced to play an important role in reducing depressive symptoms and increasing behavioral activation for stroke individuals with StD.³⁸ For patients with cognitive and communication impairments, BAT may be an option to consider, which mainly facilitates activities much simpler or even more cost-effective.⁴¹

CBT, as an widely used individual intervention, had been demonstrated the superiority in treating mental problems. It was described that CBT could modify dysfunctional thoughts, core beliefs and information processing biases, which are preconditions and risk factors for depression.⁷¹ According to our study, I-CBT was the second highest intervention on both the CES-D and BDI-II, others also reported its greater reductions on all the outcomes compared to the WL group at post-intervention.⁷² I-CBT is an online intervention with many advantages, including overcoming some limitations of face-to-face cognitive-behavioral therapy,⁷³ being conducted anytime and anywhere, having relatively lower costs, providing privacy protection,⁷² helping patients avoid the stigma incurred by seeing a therapist.⁷⁴ Compared to I-CBT, T-CBT is also a remote CBT but needs to be administered by trained psychotherapists rather than self-help. Digital-based interventions are probably more easily disseminated on a large scale, implying that they save a lot of medical resources and costs.

Over the recent years, neuroimaging studies have identified structural and functional brain changes in patients with depression, including volume reductions in cortical and subcortical structures,^{75,76} reduced gray matter volume throughout the brain, enlarged lateral ventricles, and white matter microstructural differences.^{75,77,78} Synaptic activity plays an important role in the network pathways that emerge from cognitive, emotional, and behavioral functions. Fries et al

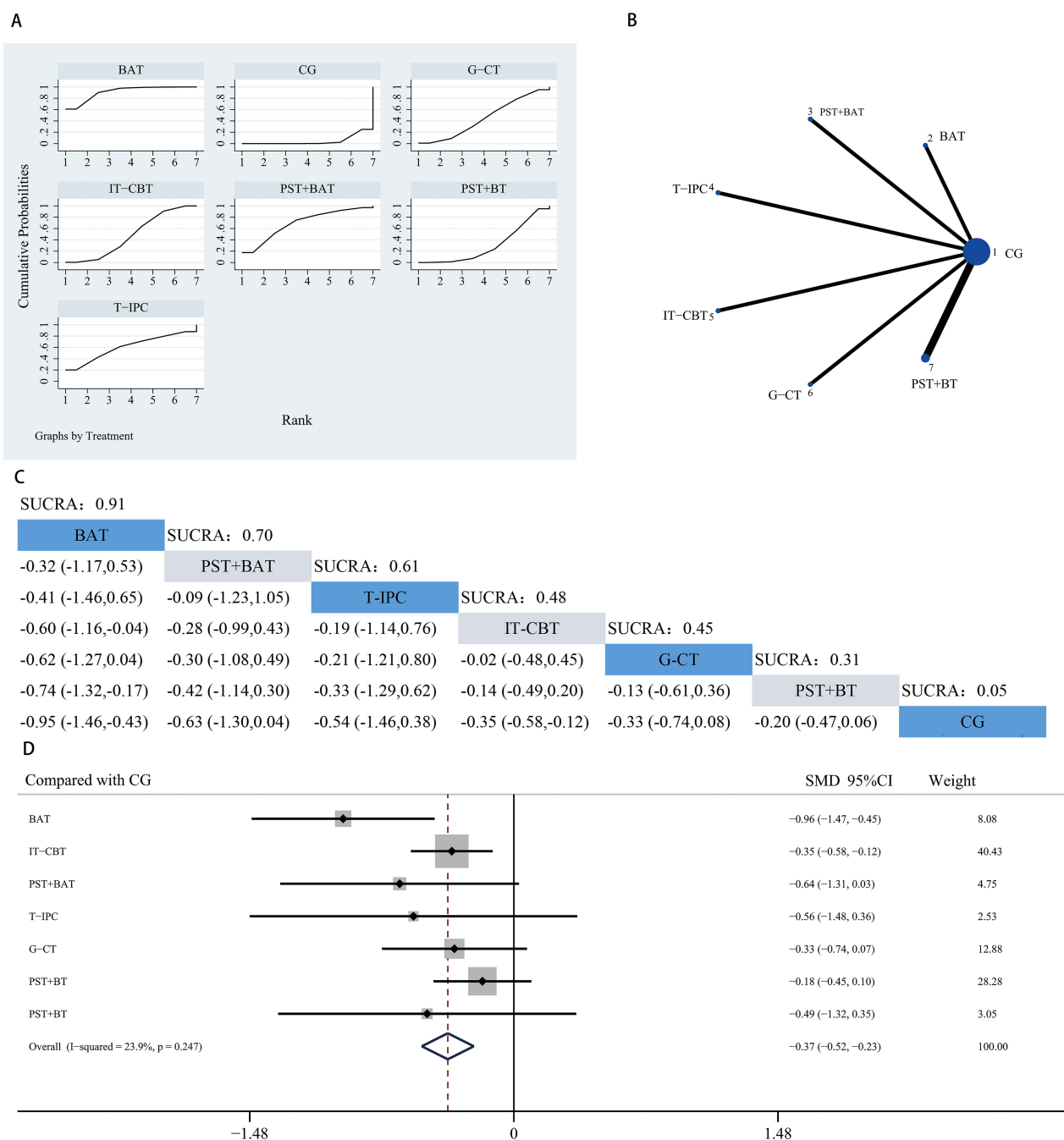


Figure 7 Results of the network meta-analysis for HAMD/HRSD scores. **(A)** The SUCRA value of individual modalities. The area under the curve predicts the efficacy of various treatment measures. The larger the area under the curve is, the better the efficacy is. **(B)** Evidence network map of eligible comparisons. The numbers represent different intervention measures. The size of the blue nodes relates to the number of participants in that intervention type, and the thickness of lines between the interventions relates to the number of studies for that comparison. **(C)** Ranking of each intervention based on the SUCRA values and the league table for the relative effects of all treatments. **(D)** Forest plot of the network meta-analysis compared with control group.

summarize relatively comprehensively the six major hypotheses for the pathogenesis of depression, elucidating how signaling pathways and molecular systems interact in depression and how each pathway or system relates to synaptic transmission.⁷⁹

There has been a gradual increase in the emphasis on neuroplasticity. It refers to the ability of the nervous system to change its own loops, such as changes in the morphologic structure and functional activity of the central nervous system and peripheral nervous system, i.e., which can readily change the process of information processing.

Impaired structural and functional plasticity of neurons in brain regions related to the control of emotions, could in turn affects the clinical manifestations of depression. Based on this, some researchers have proposed the precise modulation of neuroplasticity pathways as a new strategy for antidepressant treatment. Well-designed computerized cognitive training a resulting in activation of the medial prefrontal cortex (mPFC) and improve neural dysfunction in a serious behavioral deficit in schizophrenia.⁸⁰ The process of synaptic plasticity as LTP-like hippocampal-dependent memory is maintained by fine-tuning mechanisms that control the balance of excitatory and inhibitory neurotransmission.⁸¹ Chung et al⁸² investigated whether cognitive control training (CCT) persistently alters hippocampal neural circuit function. They show that 1) CCT facilitated learning of novel tasks in a new environment for several weeks relative to unconditioned control mice and control mice that avoided the same location when interference was reduced. 2) CCT rapidly altered the function of the entorhinal olfactory cortex-dentate gyrus synaptic circuits resulting in excitatory-inhibitory subcircuitry alterations that persisted for months. 3) CCT increased inhibition by attenuating the dentate response to inputs from the medial entorhinal cortex and, by de-inhibition, by augmenting the response to strong inputs, suggesting an enhanced overall signal-to-noise ratio. These neurobiological perspectives support the neuroplasticity hypothesis that CCT consistently optimizes information processing in neural circuits in addition to storing item-event associations.

A

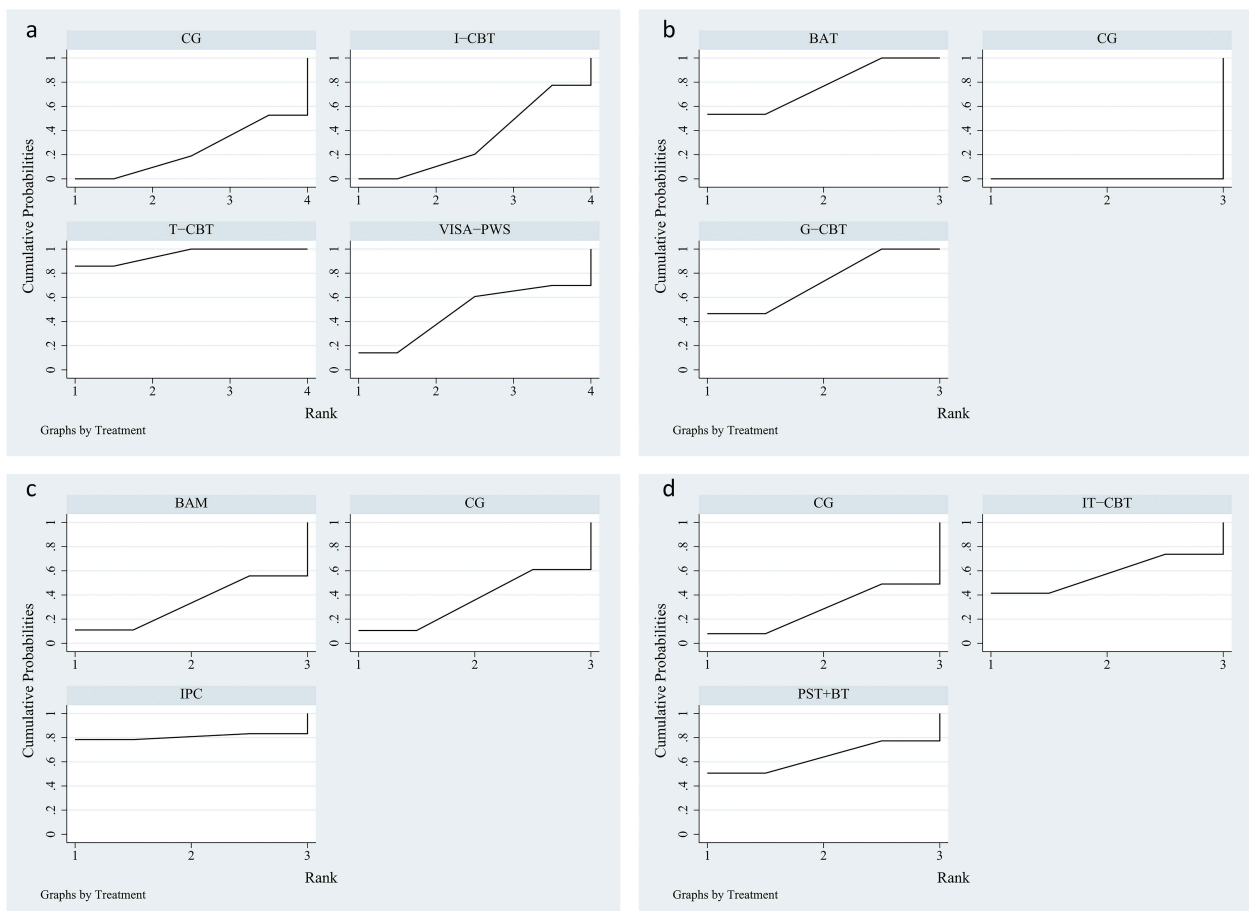


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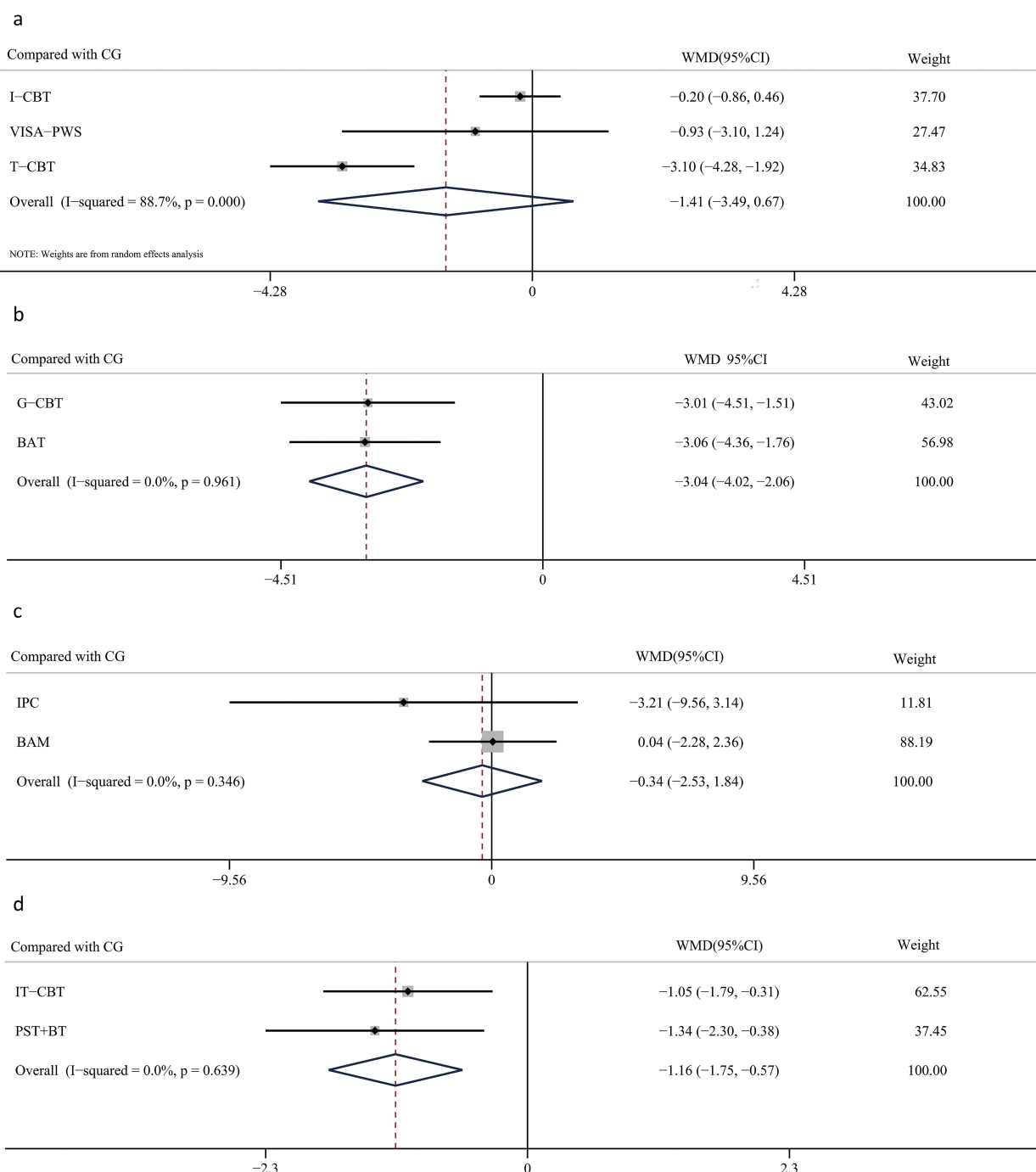
B

Figure 8 Results of the network meta-analysis for GDS/K6/SDS/QIDS scores. **(A)** Results (SCURA values) of the network meta-analysis for GDS/K6/SDS/QIDS scores. SCURA values of individual modalities based on different scales: **(a)** K6, **(b)** GDS, **(c)** SDS, **(d)** QIDS. The area under the curve predicts the efficacy of various treatment measures. The larger the area under the curve is, the better the efficacy is. **(B)** Results (forest plot) of the network meta-analysis for GDS/K6/SDS/QIDS scores. Forest plots of the network meta-analysis compared with control group for different scales: **(a)** K6, **(b)** GDS, **(c)** SDS, **(d)** QIDS. The black horizontal lines represent the confidence interval (CI) of each study. The blue hollow diamond represents the result of the entire study.

However, the effect of physical activity therapy, psychosocial therapy, stepped therapy and others explored did not show the best therapeutic effects. We are mainly considering that the proportion of articles included is small and the statistical power may be insufficient due to the limited sample size. Whether non-psychotherapy has a unique benefit for treatment of StD requires further research.

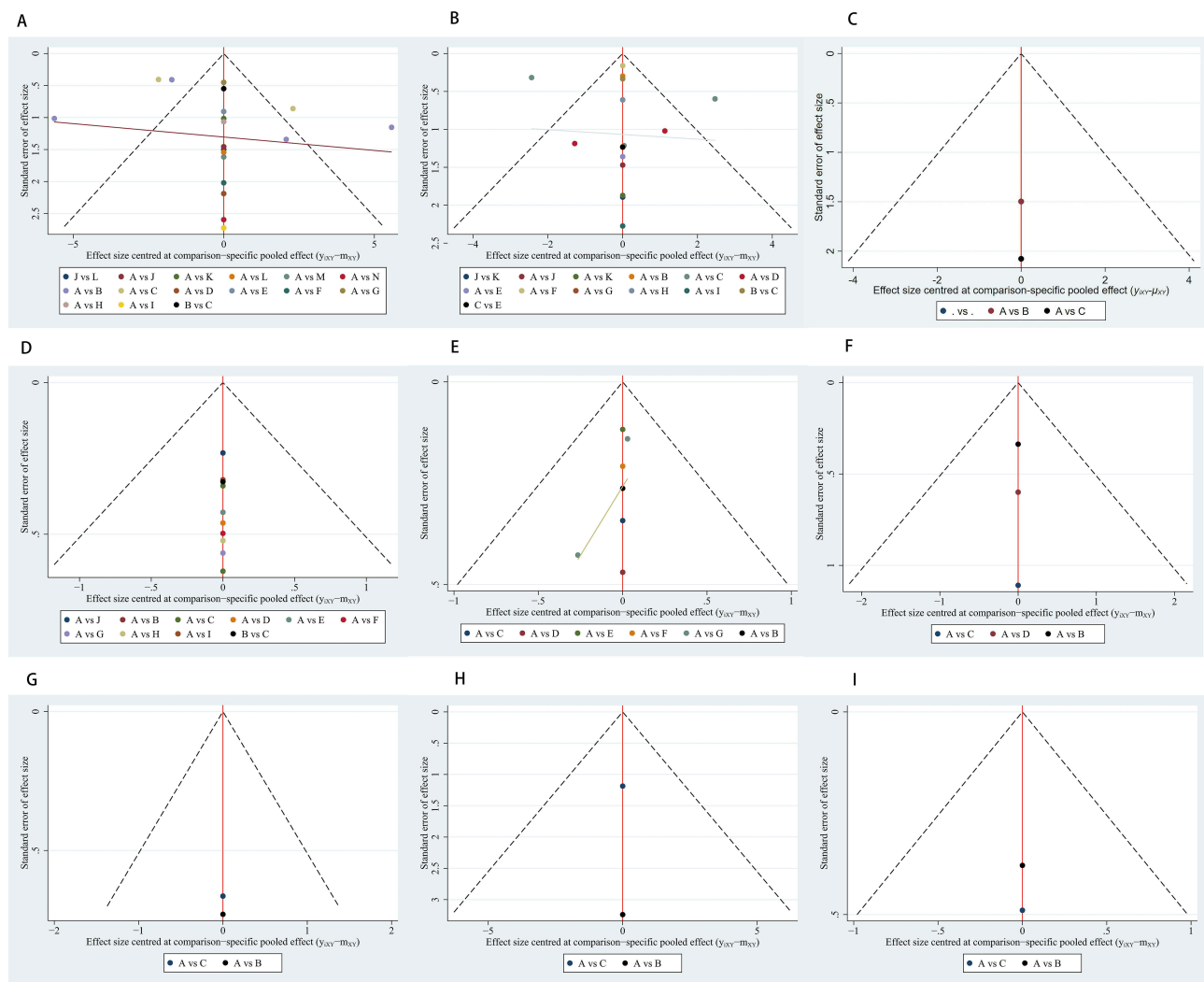


Figure 9 Funnel plots for effect size and standard error of the included studies. Funnel plots for assessing publication bias in the network meta-analysis for different scales: (A) CES-D, (B) BDI-II, (C) BDI, (D) PHQ-9, (E) HAM-D/HRSD, (F) K6, (G) GDS, (H) SDS, (I) QIDS.

Limitations

Admittedly, there were some limitations in this network meta-analysis. (1) Many RCTs use inconsistent scales, which limited the comprehensive evaluation of the efficacy of all non-pharmacological interventions included. (2) The studies applying non-psychotherapy interventions are relatively insufficient, more multi-center and high-quality RCTs are needed in the future. (3) Most articles we included were of short-term duration and long-term effects that needed further study. (4) The study languages were limited to English, which may have led to language bias and miss other treatments with national characteristics.

Conclusion

The network meta-analysis showed that psychotherapy may be the most effective intervention for StD compared to other interventions, especially PST, BAT, CBT, Digital-based CBT. This study provides some evidence on StD management selection for clinical workers. However, to establish its intervention effect more conclusively, the content, format and operators of psychotherapy still require extensive exploration to conduct more effective, convenient, and cost-effective implementation in primary healthcare. Considering the limitations of this study, notably, further research is also urgently needed to find the biological and neural mechanisms of StD by examining whether psychotherapy alters neuroplasticity in patients with StD.

Data Sharing Statement

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a substantial contribution to the report conception, study design, acquisition of data, execution, analysis and interpretation of data; took part in drafting and revising the article critically; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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