META-ANALYSIS

Check for updates

A Meta-analytic Review: Psychological Treatment of Subthreshold Depression in Children and Adolescents

Pim Cuijpers, PhD, Blanca S. Pineda, EdD, Mei Yi Ng, PhD, John R. Weisz, PhD, Ricardo F. Muñoz, PhD, Claudio Gentili, MD, PhD, Soledad Quero, PhD, Eirini Karyotaki, PhD

Objective: Subthreshold depression has been found to be associated with considerable impairment and an increased risk of developing major depression. Although several randomized trials have examined the effects of psychological interventions for subthreshold depression in children and adolescents, no meta-analysis has integrated the results of these trials.

Method: We searched 4 bibliographic databases and included randomized trials comparing psychological interventions with control conditions in children and adolescents scoring above a cut-off of a depression questionnaire but not meeting diagnostic criteria for major depression (or persistent depressive disorder) according to a diagnostic interview. Effect sizes and incidence rates of major depression were pooled with random effects meta-analyses.

Results: A total of 12 trials with 1,576 children and adolescents met inclusion criteria. The overall effect size indicating the difference between treatment and control at post-test was $g = 0.38$ (95% CI = 0.14–0.63), which corresponds to a number-needed-to-treat (NNT) of 8.4. Heterogeneity was moderate to high ($I^2 = 61$; 95% CI = 28–79), and there was significant risk of publication bias ($p < .04$). The 2 studies in children less than 12 years of age showed nonsignificant effects ($g = 0.01$; 95% CI = –1.16 to 1.18). We found no significant effect on the incidence of major depression at follow-up (relative risk = 0.52; 95% CI = 0.25–1.08), although this may be related to low statistical power.

Conclusion: Interventions for subthreshold depression may have positive acute effects in adolescents. There is currently insufficient evidence, however, that these interventions are effective in children less than 12 years of age, or that they prevent the onset of major depression at follow-up.

Key words: subthreshold depression, psychological treatment, cognitive-behavioral therapy, meta-analysis, prevention

J Am Acad Child Adolesc Psychiatry 2021;60(9):1072–1084.

Depression in children and adolescents is a major public health challenge, with an estimated prevalence rate of 2.6%,[1] but with much higher and increasing prevalence rates during adolescence.[2] It has been estimated that almost 14% of adolescents will meet criteria for a depressive disorder before age 18 years.[3] Depression in youths has been associated with increased suicide risk,[4] functional impairment,[5,6] and several negative health outcomes in adulthood, such as poorer self-perceived general health, higher health care use, and increased work impairment due to physical health.[7] Most adults with recurrent depression had their initial depressive episode as teenagers.[8]

Much of the research in this area has focused on children and adolescents with major depression according to diagnostic criteria for such disorders as defined in the different versions of the *DSM* and *International Classification of Diseases* (*ICD*).[1,2,5,6] It has become increasingly clear, however, that a categorical approach to depression may not be optimal, and that depression can be better considered as a continuum, ranging from no depression at all to very severe at the other end, and many different states in between.[9-11] From this perspective, subthreshold depression is important. This can be defined as clinically relevant depressive symptomatology that does not meet diagnostic criteria for major depression or persistent depressive disorder (ie, dysthymia).[9-11]

Subthreshold depression is important from a clinical perspective for several reasons. First, it has been found to be a clinically relevant condition in itself. It has been shown in adults that subthreshold depression is associated with functional impairment,[12] increased economic costs,[13] help seeking,[12] and excess mortality.[14] The strength of these associations has been found to be lower than in major depression. However, the impact at a population level of excess economic costs and excess mortality have been found to be comparable to the impact of major depressive disorder, because the prevalence of subthreshold is higher than the prevalence of major depressive disorder.[13,14] The same

patterns have been established in adolescents, among whom subthreshold depression has been found to be associated with a range of adverse outcomes, such as an increased burden of disease, impaired functioning, and suicide risk.[9]

A second reason why subthreshold depression is important is its strong association with adverse long-term outcomes: adolescents with subthreshold depression have also been found to be at risk for developing other disorders, including substance-use disorders,[15] anxiety disorders, and suicidality.[10] However, 1 of the main reasons that many of the studies targeted individuals with subthreshold depression was because it significantly increases risk for developing a depressive disorder (major depression or persistent depressive disorder) in the near future, both in adults[12] and in adolescents.[10,15] Some of these studies were specifically intended to test whether reducing symptoms led to a reduction in incidence (ie, the proportion of new cases) of depressive episodes. Individuals already meeting criteria for a depressive episode would not have been appropriate for a prevention trial.

Treatment of subthreshold depression in children and adolescents is therefore important. It may not only reduce the impact that depression has on children, adolescents, and their families, but it may also prevent the onset of future depressive disorders and other adverse outcomes. In past decades, a number of randomized trials have examined the effects of psychological treatments on subthreshold depression in children and adolescents. To our knowledge, no meta-analysis has focused on these trials and integrated their results into 1 estimate of the effects. Previous reviews have summarized a number of trials in this field,[9,11] but results from a considerable number of trials are presently available, making a meta-analytic review possible.

Here, we present the results of a meta-analytic review of psychological interventions aimed at children and adolescents with subthreshold depression, and compared to control conditions in randomized trials.

METHOD

Identification and Selection of Studies

The protocol for this meta-analysis has been published at the Open Science Framework.[16]

We used an existing database of studies on the psychological treatment of depression. This database has been described in detail elsewhere,[17] and has been used in a series of earlier published meta-analyses.[18] For this database, we searched 4 major bibliographic databases (PubMed, PsycInfo, Embase, and the Cochrane Library) by combining terms (both index terms and text words) indicative of depression and psychotherapies, with filters for randomized controlled trials. The full search string for 1 database (PubMed) is given in Supplement 1 (available online), and all search strings can be found at the website of the project (www.metapsy.org). We also searched a number of bibliographical databases to identify trials in non-Western countries,[19] because the number of trials on psychological treatments in these countries is growing rapidly (the British Library for Development Studies; the Eldis; the World Health Organization (WHO) Global Index Medicus; the Latin-American and Caribbean System on Health Sciences Information (LILACS); the Indice Bibliográfico Español de Ciencias de la Salud (IBECS); the AfricaBib; the IndMed; the KoreaMed; and African Journals Online). Furthermore, we checked the references of earlier meta-analyses on psychological treatments of depression, including meta-analyses of trials in children and adolescents,[20,21] as well as a recent meta-analysis on studies on preventing the onset of depressive disorders.[22] The database is continuously updated and was developed through a comprehensive literature search from 1966 to January 1, 2020. All records were screened by 2 independent researchers (PC and EK), and all papers that could possibly meet inclusion criteria according to 1 of the researchers were retrieved as full-text. The decision to include or to exclude a study in the database was also made by the 2 independent researchers, and disagreements were resolved through discussion.

We included randomized controlled trials in which a psychological intervention was compared with a control condition in children and adolescents up to 18 years of age with clinically relevant depressive symptoms but no major depressive disorder or persistent depressive disorder, as established with a standardized diagnostic interview such as the Schedule for Affective Disorders and Schizophrenia for children (K-SADS)[23] or the Child Assessment Schedule (CAS).[24] In these trials, a full-blown depressive disorder at baseline was an exclusion criterion. Clinically relevant depressive symptoms were defined as scoring above a standard clinical level cut-off on a depression symptom questionnaire. We included only individual, group, and guided self-help interventions. Interventions without any human interaction were not included.

Quality Assessment and Data Extraction

We assessed the validity of included studies using 4 criteria of the "Risk of Bias" assessment tool, version 1, developed by the Cochrane Collaboration.[25] This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence, the concealment of allocation to conditions, the prevention of knowledge of the allocated intervention (masking of assessors), and dealing

with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). Assessment of the validity of the included studies was conducted by 2 independent researchers, and disagreements were resolved through discussion.

We also coded the definition of subthreshold depression, the diagnostic instrument (to exclude the presence of a depressive disorder) participant characteristics (recruitment method; generic versus specific target group, such as participants with general medical disorders; mean age; proportion of girls); age group (children with a mean age up to 12 years; adolescents with a mean age between 12 and 18 years); characteristics of the psychological treatments (type of therapy; treatment format; number of sessions); and general characteristics of the studies (type of control group; publication year; country where the study was conducted).

Outcome Measures

For each comparison between a psychological treatment and a control condition, the effect size indicating the difference between the 2 groups at posttest was calculated (Hedges *g*).[26] Effect sizes were calculated by subtracting (at posttest) the average score of the psychotherapy group from the average score of the control group and dividing the result by the pooled SD. Because some studies had relatively small sample sizes, we corrected the effect size for small sample bias.[26] If means and SDs were not reported, we used the procedures of the Comprehensive Meta-Analysis software (see below) to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such as *t* value or *p* value) to calculate the effect size.

When more than 1 depression measure was used in a study, we pooled the outcomes within the study before pooling the effect sizes across the studies. However, we also conducted sensitivity analyses in which we used only 1 depression outcome measure from each study, based on an algorithm that we used in a previous meta-analysis on psychotherapies for depression.[21] Effect sizes were calculated using Comprehensive Meta-Analysis (CMA; version 3.3070).

Apart from the effect sizes, we calculated the relative risk (RR) of developing a major depressive disorder at follow-up, defined as the proportion of incident cases in the intervention condition divided by the proportion of incident cases in the control conditions. Major depressive disorder at follow-up had to be established with a diagnostic interview. We choose the time to follow-up closest to 12 months after randomization as the main outcome for incidence, because this was the time point reported by most studies. The time frame from posttreatment to follow-up assessment is shorter than the 1-year duration required to diagnose children and adolescents with persistent depressive disorder; thus, the incidence of persistent depressive disorder during follow up could not be examined as an outcome. In addition to the RR of developing a major depressive disorder, we also calculated the risk difference (RD) and the number-needed-to-treat (NNT) as 1 divided by the RD. The RD is the difference between the proportion of case patients in the treatment and control group. We also calculated the acceptability of the intervention, defined as study dropout for any reason, as well as the RR of acceptability (proportion of dropouts in the interventions divided by the proportion of dropouts in the control conditions). The RRs for incidence rates and acceptability were calculated in R (see below).

Meta-analyses

To calculate pooled mean effect sizes, we used the "meta" and "metaphor" packages in R and conducted all analyses in R studio (version 1.1.463 for Mac). Because we expected considerable heterogeneity among the studies, we used a random effects pooling model in all analyses. We used the inverse variance method for pooling effect sizes with the Hartung−Knapp adjustment for the random effects model.<<? BEGIN

NNTs were calculated using the formulae provided by Furukawa *et al.*,[27] in which the control group's event rate was set at a conservative 19% (based on the pooled response rate of 50% reduction of symptoms across trials in psychotherapy for depression).[28] As a test of homogeneity of effect sizes, we calculated the I^2 statistic and its 95% confidence interval, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity.[29]

We tested for publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure,[30] which yields an estimate of the effect size after correction for the funnel plot asymmetry. We also conducted an Egger test of the intercept to quantify the bias captured by the funnel plot and to test whether it was significant. The RRs indicating incidence and acceptability of the interventions were pooled across studies, with the Hartung and Knapp method to adjust test statistics and confidence intervals, and a value of 0.1 added for studies with a zero-cell count.

We analyzed differences between subgroups using a mixed-effects model. In this model, studies within subgroups were pooled with a random effects model, whereas

tests for differences between subgroups were conducted with a fixed effects model. Multivariate and bivariate meta-regression analyses were conducted to examine possible sources of heterogeneity, testing whether the effect size was associated with relevant characteristics of studies.

We conducted the following sensitivity analyses: (1) analyses in which we limited the analyses to studies with low risk of bias (low risk for all 4 items of the risk of bias tool); and (2) analyses in which studies outliers were excluded (outliers are studies of which the 95% confidence interval (CI) of the effect size does not overlap with the 95% CI of the pooled effect size).

RESULTS

Selection and Inclusion of Studies

After examining a total of 24,769 records (18,217 after removal of duplicates), we retrieved 2,912 full-text papers for further consideration. We excluded 2,900 of the retrieved papers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. A total of 12 randomized controlled trials (with 13 comparisons between a psychotherapy and a control group) met inclusion criteria for this meta-analysis.[31-42] Ten of these studies with 11 comparisons included adolescents (mean age 12−18 years), and 2 studies included children (mean age <12 years).

Characteristics of Included Studies

In the 12 included trials, 1,576 children and adolescents participated (859 in the intervention and 717 in the control conditions).

A summary of key characteristics of the included studies is presented in Table 1. The instrument to measure depressive symptoms and the lower cut-off as threshold for depressive symptoms varied considerably across studies. Seven studies used the Center for Epidemiological Studies depression scale (CES-D),[43] but with different cut-offs, and 3 used the Children's Depression Inventory (CDI),[44] but also with varying cut-offs (the instruments and the cut-offs are presented in Table 1). The different versions of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) were used to exclude the presence of full-blown depressive disorders (major depression and/or persistent depressive disorder). Seven studies recruited participants through schools. Two studies were aimed at students with a general medical disorder (epilepsy and irritable bowel syndrome), and 1 study was aimed at children of depressed parents. The mean age of the students ranged from 10 to 14.4 years, and the proportion of girls ranged from 51% to 85%. Eight studies used cognitive−behavioral therapy (CBT), 3 used interpersonal psychotherapy (IPT), and 1 study used supportive therapy (supportive expressive intervention). A group format was used in 8 studies, an individual format in 2 studies, and a mixed individual and group format in 3 studies. The number of sessions ranged from 6 to 16. Eight studies used a usual care control group, 3 used a nonspecific intervention (such as school counseling), 1 study used a waitlist, and 1 study used a control group in which participants only received only a brochure about depression and treatment options. Nine studies were conducted in the United States and 3 studies in Europe.

The risk of bias in most studies was modest. Risk of bias for sequence generation was low in 8 studies and unclear in the other 4. Risk of bias for allocation to conditions was low in 1 study, unclear in 8 studies, and high in the remaining 3. Risk of bias because of blinded outcome assessment was low in 10 studies, unclear in 1 study, and high in 1 study. Bias related to intention-to-treat analyses was low in 9 studies, unclear in 2 studies, and high in 1 study. Overall, risk of bias was low (low risk of bias on 3 or 4 items) in 8 studies, and high (low risk of bias in 0−2 items) in 4 studies.

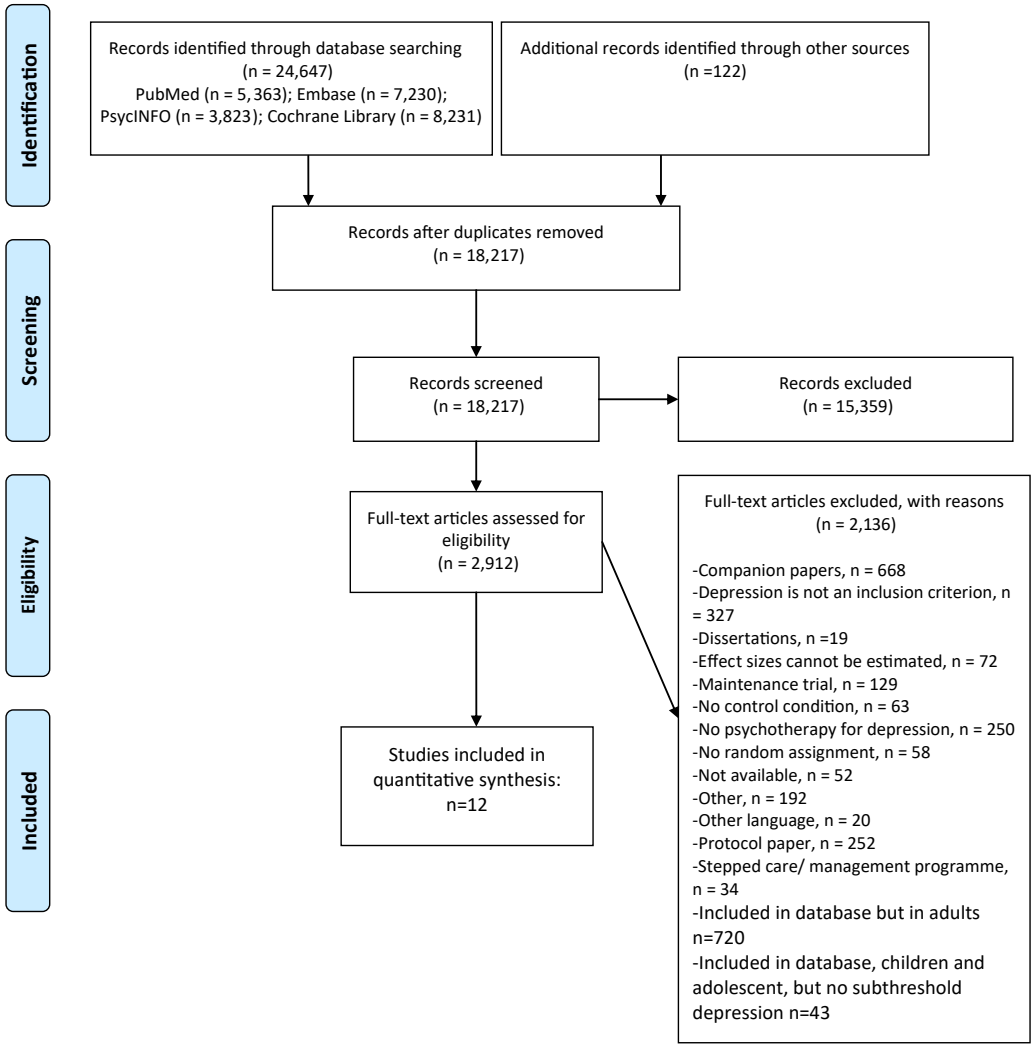
Effects of Psychological Interventions on Depressive Symptomatology

The pooled effect size indicating the difference between the psychological interventions and control conditions at posttest was $g = 0.38$ (95% CI = 0.14–0.63), indicating a significant, small- to-medium effect, which corresponds to an NNT of 8.4. Heterogeneity was moderate to high ($I^2 = 61$; 95% CI = 28–79), and the prediction interval ranged from −0.44 to 1.21. The results of these analyses are reported in Table 2. The forest plot is given in Figure 2.

We included 2 effect sizes from 1 study.[38] However, these 2 effect sizes are not independent of each other, and this may artificially reduce heterogeneity and affect the pooled effect size. Therefore, we conducted sensitivity analyses in which we included only 1 effect size from each study. In the first analysis, we included only the highest effect size, and in the second analysis, we included only the lowest effect size (Table 2). As can be seen, the effect sizes and the level of heterogeneity resulting from these analyses were comparable to those of the main analyses.

One study was an outlier because the 95% CI of its effect size did not overlap with the pooled effect size.[40] Exclusion of this study resulted in a somewhat smaller effect size ($g = 0.30$; 95% CI = 0.12–0.48) and low-to-moderate heterogeneity ($I^2 = 42$; 95% CI = 0–71). Sensitivity analyses in which we included only studies with low risk of bias indicated a significant effect ($g = 0.40$; 95%

FIGURE 1 PRISMA Flow Chart on the Selection of Studies



CI = 0.05–0.75) that was comparable to the effect size found for all studies. When the effect sizes for the studies were calculated with an alternative method (only 1 depression measure for each study; in studies with multiple measures, 1 measure was selected using an algorithm), the pooled effect size was comparable to the effect size of the main analyses ($g = 0.42$; 95% CI = 0.15–0.70; $I^2 = 67$; 95% CI = 40–81; NNT = 7.5).

We found indications for potential publication bias. The Egger test of the intercept pointed at significant asymmetry of the funnel plot ($p = .04$) (Table 2). The Duvall and Tweedie trim and fill procedure indicated 3 missing studies, and after adjustment for these missing studies, the effect size dropped to $g = 0.24$ (95% CI = −0.06 to 0.54), which was no longer significant. Heterogeneity was high in these analyses ($I^2 = 71$; 95% CI = 51–82). After exclusion of the outlier, the Egger test result was no longer significant ($p > 0.1$), and the Duval and Tweedie trim and fill procedure indicated 2 missing studies, a significant adjusted effect size ($g = 0.24$; 95% CI = 0.03–0.45), and moderate heterogeneity ($I^2 = 51$; 95% CI = 11–74).

Because only 2 studies were focused on children and these had small effects, we also conducted the major analyses and subgroup analyses for studies with adolescents only. The results of these analyses are reported in Table S1 (available online). Overall, there were no main differences with the analyses of the full sample of studies.

TABLE 1 Selected Characteristics of Included Studies

Study	Cut-off	Diagnosis	Recruitment	Ethnicity	Comorbidities: excluded	Current diagnoses[a]	Mean age, y	% Women	Therapy	Frm	No. sess	Control	Country	RoB[b]
Arnarson, 2009[31]	75th−90th percentile on CDI and/or ≥75th percentile negative composite of CASQ	CAS	Schools	NR	Dysthymia, bipolar, cyclothymia, anorexia, bulimia, psychotic, substance dependence, ADHD, ODD, conduct disorder	NR	14.5	51	CBT	G	14	CAU	ICE	± ± + −
Clarke, 2001[33]	Symptoms of MDD and/or CES-D > 24	K-SADS-E	HMO, children of depressed parents	22% Non-White	No excluded comorbidites	22% Anxiety; 16% disruptive; 1% substance use disorder	14.6	64	CBT	G	15	CAU	US	+ + + +
Clarke, 1995[32]	CES-D > 24	K-SADS	Schools	93% Non-Hispanic White	No excluded comorbidites	13% Anxiety disorder	15.3	70	CBT	G	15	CAU	US	± ± ± ±
De Cuyper, 2004[34]	CDI > 11 (thinking of death was removed)	CAS	Schools	NR	No Axis-I problems	NR	10.0	75	CBT	G	16	WL	BEL	± ± + +
Gillham, 2006[35]	CDI > 7 (boys) or 9 (girls)	K-SADS-P	HMO	73% White, 9% African American, 8% Latino/Latina, 2% Asian, 7% other	No excluded comorbidites	NR	11.5	53	CBT	G	12	CAU	US	+ ± + +
Martinovic, 2006[36]	BDI > 6 or CESD > 9	K-SADS-E-R	Epilepsy patients 13−19 y	NR	Psychotic symptoms, schizophrenia, bipolar disorder, social phobia, agoraphobia, panic disorder	NR	17.4	60	CBT	I	8	CAU	SER	+ − − ±

(*continued*)

TABLE 1 Continued

Study	Cut-off	Diagnosis	Recruitment	Ethnicity	Comorbidities: excluded	Current diagnoses[a]	Mean age, y	% Women	Therapy	Frm	No. sess	Control	Country	RoB[b]
Rohde, 2014[37]	>2 Symptoms of depression on CES-D	K-SADS	Schools	6% Hispanic, 2% Asian American, 1% African American, 72% White, 1% Native American, 18% other/ mixed	No other diagnoses were excluded	NR	15.5	68	CBT	G	6	Bro-chure only	US	+ − + +
Stice, 2008 — cbt[38]	CES-D ≥20	K-SADS	Mass mailings	2% Asian, 9% African American, 46% White, 33% Hispanic, 10% other/ mixed	No other diagnoses were excluded	NR	15.6	56	CBT	G	6	CAU	US	+ − + +
Stice, 2008 — supportive[38]									SUP	G	6	CAU	US	+ − + +
Szigethy, 2007[39]	CDI ≥ 9	K-SADS-PL	Hospitals; adolescents with IBD	78.1% White, 14.6% African American, 2.4% Hispanic, 4.9% unspecified	No bipolar, psychotic disorders	15% Anxiety; 15% disruptive disorder	15.0	51	CBT	I	10	CAU	US	± ± + +
Young, 2006[41]	CES-D > 16	K-SADS-PL	Schools	93% Hispanic, 7% other	No bipolar, panic, OCD, PTSD, psychosis, ODD, conduct disorder, untreated ADHD	22% Anxiety disorder	13.5	85	IPT	M	10	SUP	US	+ ± + +

(*continued*)

TABLE 1 Continued

Study	Cut-off	Diagnosis	Recruitment	Ethnicity	Comorbidities: excluded	Current diagnoses[a]	Mean age, y	% Women	Therapy	Frm	No. sess	Control	Country	RoB[b]
Young, 2010[42]	CES-D > 16	K-SADS-PL	Schools	74% Hispanic, 39% African American	No bipolar, panic, OCD, PTSD, psychosis, ODD, conduct disorder, untreated ADHD	No disorders (>10%)	14.5	60	IPT	M	10	SUP	US	+ ± + +
Young, 2016[40]	CES-D > 16	K-SADS-PL	Schools	38.2% Hispanic, 38.2% White non-minority non-Hispanic, 19.9% African American, 4.3% Asian, 8.1% other/ mixed	bipolar, psychotic, substance abuse, conduct disorder	10% Anxiety disorder	14.0	67	IPT	M	10	SUP	US	+ ± + +

Note: ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; BEL = Belgium; CAS = Child Assessment Scale; CAU = care-as-usual; CBT = cognitive-behaviorial therapy; CDI = Child Depression Inventory; CES-D = Center for Epidemiological Studies depression scale; Fr = format; G = group format; HMO = health maintenance organization; I = individual format; IBD = inflammatory bowel disease; ICE = Iceland; Ind = individual format; IPT = interpersonal psychotherapy; K-SADS-E-R = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version Revised; K-SADS-E = SADS for School-Age Children, Epidemiological Version; K-SADS-P = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present child and parent interview; K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia for Children, Present Version; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; M = mixed format; N sess = number of sessions; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder; RoB = risk of bias; SER = Serbia; Sup = supportive therapy; Uncl = unclear; US = United States; WL = waiting list.

[a]*Only diagnoses established with a diagnostic interview and with prevalence of more than 10%, and clustered into categories of disorders.*

[b]*Risk of bias (RoB); this column indicates 4 criteria (sequence generation, allocation concealment, blinded assessment, intention-to-treat analyses) rated as high risk of bias (−), unclear (±), or low risk of bias (+).*

Subgroup Analyses

To explore potential sources of heterogeneity, we conducted a few subgroup analyses (the small number of studies did not permit more subgroup analyses). We examined whether the effect sizes of the studies in children differed from those in adolescents, whether studies with low risk of bias differed from the other studies, whether the effect sizes for CBT differed from other types of therapy (mostly IPT), and whether the effect sizes differed for care-as-usual and other control groups. The results are reported in Table 2. The only significant difference that we found was between studies in children compared to those in adolescents (p = .01). The 2 studies in children indicated an effect size of g = 0.01 (95% CI = −1.16 to 1.18), whereas it was g = 0.44 (95% CI = 0.16–0.71) in adolescents. Heterogeneity in the subgroup of studies in adolescents was not markedly lower than in the full sample of studies (I^2 was 59% compared to 61%).

Effects on Incidence and Acceptability

The effects of psychological interventions on the incidence of a major depressive disorder at follow-up are reported in Table 3. The effects pointed in the positive direction, with an RR of 0.52 (95% CI = 0.25–1.08), indicating a 48% lower chance of developing a depressive disorder in the intervention group compared to the control group, although this difference was not significant. This may be related to low power. Heterogeneity was moderate (I^2 = 57; 95% CI = 14–79), and the prediction interval ranged from 0.05 to 5.71. The RD was −0.10 (95% CI = −0.20 to −0.00), which did reach significance levels (p < .05). The corresponding NNT was 10.0.

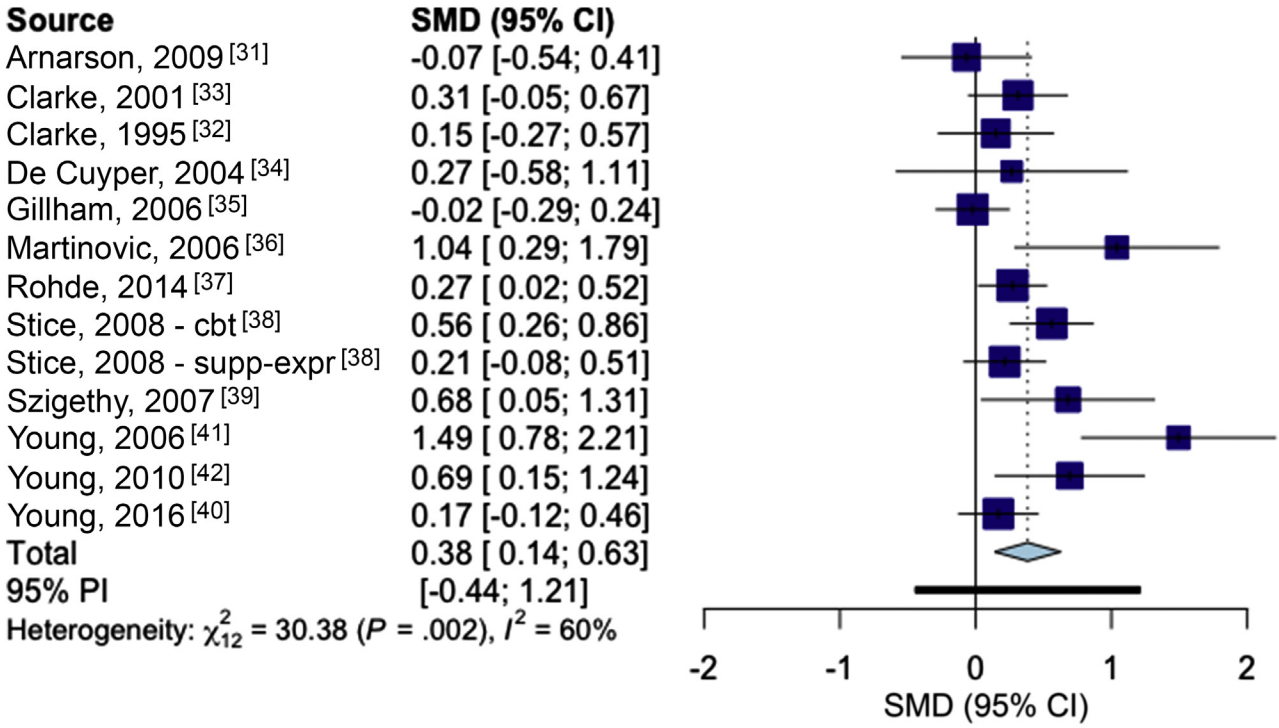
The results of the sensitivity analyses in which only 1 effect size was included for each study indicated no major influence on heterogeneity of the main outcomes (Table 3). The 7 studies with low risk of bias indicated an RR of 0.44 (95% CI = 0.18–1.05; not signficant) with moderate

TABLE 2 Effects of Psychological Interventions for Subthreshold Depression in Children and Adolescents Compared With Control Groups: Hedges g[a]

	N_{comp}	g	95% CI	I^2	95% CI	Prediction interval	NNT	p^b
All comparisons	13	0.38	0.14 to 0.63	61	28 to 79	−0.44 to 1.21	8.4	
One effect size per study (only highest)	12	0.40	0.14 to 0.67	64	32 to 80	−0.47 to 1.28	7.9	
One effect size per study (only lowest)	12	0.37	0.10 to 0.64	59	23 to 78	−0.51 to 1.25	8.6	
Outlier excluded[c]	12	0.30	0.12 to 0.48	42	0 to 71	−0.27 to 0.87	10.9	
Only low risk of bias	8	0.40	0.05 to 0.75	69	35 to 85	−0.62 to 1.42	7.9	
Adjusted for publication bias	16	0.24	−0.06 to 0.54	71	51 to 82	−0.91 to 1.39	13.9	
Alternative effect size calculation	13	0.42	0.15 to 0.70	67	40 to 81	−0.52 to 1.37	7.5	
Only adolescents (studies in children excluded)	11	0.44	0.16 to 0.71	59	20 to 79	−0.45 to 1.32	7.1	
Subgroup Analyses								
Age group								
Adolescents	11	0.44	0.16 to 0.71	59	20 to 79	−0.45 to 1.32	7.1	0.01
Children	2	0.01	−1.16 to 1.18	0			368.0	
Risk of bias								
Low	8	0.40	0.05 to 0.75	69	35 to 85	−0.62 to 1.42	7.9	0.88
Other	5	0.36	−0.18 to 0.90	50	0 to 82	−0.90 to 1.62	8.9	
Type								
CBT	9	0.30	0.06 to 0.55	51	0 to 77	−0.37 to 0.98	10.9	0.38
Other	4	0.58	−0.36 to 1.51	78	41 to 92	−2.05 to 3.21	5.2	
Control group								
Care as usual	8	0.30	0.02 to 0.58	57	5 to 80	−0.47 to 1.07	10.9	0.38
Other control	5	0.53	−0.12 to 1.18	70	24 to 88	−1.11 to 2.17	5.8	

Note: *CBT = cognitive-behavioral therapy; N_{comp} = number of comparisons; NNT = number-needed-to-treat.*
[a]*According to random effects model.*
[b]*This p value indicates difference between subgroups*
[c]*Refers to the outlier in Table 2, Young* et al.[41]

FIGURE 2 Forest Plot of Standardized Mean Difference (SMDs) for Psychotherapy Versus Control Groups in Children and Adolescents With Subthreshold Depression



heterogeneity (I^2 = 50; 95% CI = 0–79), and an RD of −0.10 (−0.18 to −0.02; $p < .05$), corresponding with an NNT of 10.2. There were again indications of publication bias. The Egger test of the intercept was significant ($p < .01$), and after adjustment for publication bias, the RR was found to be a nonsignificant 0.96 (95% CI = 0.39–2.39; I^2 = 67; 95% CI = 44–81; RD = −0.06; 95% CI = −0.17 to 0.05; NNT = 15.6). Because all studies on incidence were conducted among adolescents, no sensitivity analyses excluding studies in children were conducted.

The follow-up periods after randomization in these studies ranged from 6 to 18 months. The majority of studies (n = 7) examined incidence at 6 to 9 months' follow-up. Sensitivity analyses with only these studies also did not point at significant effects of the interventions on incidence of depressive disorders (RR = 0.45; 95% CI = 0.14–1.43; I^2 = 53; 95% CI = 0–80; RD = −0.11; 95% CI = −0.24 to 0.02; NNT = 8.9).

The main analyses on the acceptability of the interventions compared to the control conditions did not point to a significant difference between treatment and control conditions. The sensitivity analyses also did not indicate a difference for acceptability.

DISCUSSION

This is the first meta-analysis of randomized trials on the effects of psychological interventions for subthreshold depression in children and adolescents. We found that these interventions had a small to moderate but significant effect on reducing depressive symptoms in youths with subthreshold depression compared to care-as-usual and other control groups. However, this effect was found only in adolescents, whereas for children, only 2 studies were found, and these indicated an effect of almost zero. This makes it impossible to draw any conclusions about the effects in children. No significant effect was found on the incidence of depressive disorders at follow-up, but that may very well be related to the small number of studies and low statistical power. We also found considerable risk of publication bias, and the outcomes should be considered with caution.

The relatively small effects of the interventions on subthreshold depression are in line with the effects found in interventions in adults.[12] In adults, it was found that the effects of psychological interventions for subthreshold are considerably smaller than in interventions for established depressive disorders. This is not surprising, because depression is relatively

TABLE 3 Effects of Psychological Interventions for Subthreshold Depression in Children and Adolescents on Incidence of Major Depression at Follow-up and Acceptability

	N_{comp}	RR	95% CI	I^2	95% CI	Prediction interval	RD	95% CI	NNT
Incidence									
All studies	10	0.52	0.25 to 1.08	57	14 to 79	0.05 to 5.71	−0.10[a]	−0.20 to −0.00	10.0
One effect size per study (only highest)	9	0.49	0.21 to 1.17	61	19 to 81	0.04 to 6.97	−0.10	−0.22 to 0.01	9.6
One effect size per study (only lowest)	9	0.49	0.21 to 1.14	62	21 to 82	0.04 to 6.69	−0.11	−0.22 to 0.01	9.4
Only low risk of bias	7	0.44	0.18 to 1.05	50	0 to 79	0.04 to 4.39	−0.10[a]	−0.18 to −0.02	10.2
Adjusted for publication bias	15	0.96	0.39 to 2.39	67	44 to 81	0.03 to 33.48	−0.06[b]	−0.17 to 0.05	15.6
Only 6−9 mo follow up	7	0.45	0.14 to 1.43	53	0 to 80	0.02 to 11.55	−0.11	−0.24 to 0.02	8.9
Acceptability									
All studies	12	1.52	0.75 to 3.06	0	0 to 54	0.12 to 19.24	0.02	−0.02 to 0.07	45.9
One effect size per study (only highest)	9	0.49	0.21 to 1.17	61	19 to 81	0.04 to 6.97	−0.10	−0.22 to 0.05	9.4
One effect size per study (only lowest)	9	0.49	0.21 to 1.14	62	21 to 82	0.04 to 6.69	−0.10	−0.22 to 0.01	9.6
Only low risk of bias	7	1.00	0.21 to 4.68	0	0 to 65	0.02 to 56.26	−0.01	−0.05 to 0.04	147.0
Adjusted for publication bias	13	1.62	0.64 to 4.13	5	0 to 59	0.05 to 53.10	−0.01	−0.06 to 0.04	119.0

Note: N_{comp} = number of comparisons; NNT = number-needed-to-treat; RD = risk difference; RR = relative risk.
[a]RD was significant ($p < .05$).
[b]Two imputed studies.

mild at the start of the interventions, and the possibilities for improvement are more limited in subthreshold depression than in depressive disorders. The situation in adolescents is, however, somewhat different. Although the effects of interventions in subthreshold depression are small to moderate ($g = 0.44$), a recent meta-analysis found that the effects of interventions for adolescents scoring above thresholds for depression were not much higher ($g = 0.55$).[21] This suggests that the effects of interventions in subthreshold are not much smaller than those in more severely depressed adolescents. However, we did find considerable indications for publication bias in the present study. After adjustment for this bias, the effects found for the psychological interventions were no longer significant. This suggests that the effects may be smaller than the main analyses indicate.

We found too few studies in younger children to say anything about the effects of interventions in this age group. The 2 studies that we found, however, had an effect size of almost zero, which is not promising for future studies. It could indicate that the effects in younger children are smaller than in adolescents. In a previous, large meta-analysis of studies on psychotherapies across age groups, we also found that the effects of therapies in children were considerably smaller than in adults, but also smaller than the effects found in adolescents.[21] However, in that larger meta-analysis, the effects in children were still significant, which is not the case in the current study. Unfortunately, the small number of studies rules out any conclusion as to whether therapies are effective in children.

However, it is clear that more research is needed before any firm conclusions can be drawn. Such research is very important, because effective treatment of subthreshold depression in younger children may prevent worse problems in adolescents and potentially in later life. This underscores the need for more tests of currently available treatments for depressive symptoms in this age group. If those tests should continue to show little evidence of benefit, that would suggest a pressing need for innovation—namely, development of effective alternatives to current treatments for children. Such studies, however, require large sample sizes and considerable resources, and funding may be difficult.

We found no significant effect of interventions for subthreshold depression on the incidence of depressive disorders at follow-up. The overall outcomes indicated a 48% reduction in incidence across studies, and some studies did indeed yield significant effects. However, the aggregate data do not provide evidence for significant preventive effects of these interventions as a whole on incidence. It may be possible that these findings are related to lack of statistical power.

This study has several strengths but also limitations. One strength is that this is the first time that all studies on interventions for subthreshold depression in children and

adolescents have been integrated within a meta-analysis. Another strength is the relatively high quality of the included studies, and the fact that a considerable number of them also reported incidence rates of depressive disorders at follow-up. There are also some limitations, however. One is that the number of studies was relatively small. We also found strong indications of publication bias, making it unclear whether the findings of this meta-analysis fairly represent the full body of research done on this topic. In addition, although the quality of the included studies was relatively good, there were also several studies with considerable risk of bias, which is still problematic, given the small number of included studies. Several of the studies also included considerable numbers of participants from ethnic minority groups, but because of the heterogeneity of the samples and the small number of studies, it was not possible to examine this in more detail.

Despite these limitations, we can conclude that interventions for subthreshold depression may have positive acute effects in adolescents. However, there is currently insufficient evidence that these interventions are effective in children less than 12 years of age, or that they prevent the onset of major depression at follow-up.

Accepted February 8, 2021.

Drs. Cuijpers and Karyotaki are with Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands. Drs. Pineda and Muñoz are with the Institute for International Internet Interventions for Health (i4Health), Palo Alto University, California. Dr. Ng is with Florida International University, Miami. Dr. Weisz is with Harvard University, Cambridge, Massachusetts. Dr. Gentili is with the University of Padova, Italy. Dr. Quero is with Universitat Jaume I, Castellón, Spain, and CIBER of Physiopathology of Obesity and Nutrition (CIBEROBN), Madrid, Spain.

The authors have reported no funding for this work.

The protocol for this paper was published at the Open Science Framework: Cuijpers P. Psychological treatment of subthreshold depression in children and adolescents: A meta-analytic review. 2020, May 23. Retrieved from osf.io/c7hty.

Dr. Cuijpers served as the statistical expert for this research.

Author Contributions
Conceptualization: Cuijpers, Pineda, Ng, Weisz, Muñoz, Gentili, Quero, Karyotaki
Formal analysis: Cuijpers
Investigation: Pineda, Ng, Muñoz, Gentili, Quero, Karyotaki
Methodology: Cuijpers, Pineda, Muñoz, Karyotaki
Supervision: Weisz
Validation: Cuijpers, Ng, Muñoz, Gentili, Quero, Karyotaki
Writing — original draft: Cuijpers
Writing — review and editing: Cuijpers, Pineda, Ng, Weisz, Muñoz, Gentili, Quero, Karyotaki

Disclosure: Dr. Cuijpers has reported support for unrelated grants from the European Commission, the Netherlands Organisation for Health Research and Development (ZonMw), and for being Chair of the Mental Health Priority Area of the Wellcome Trust in London, United Kingdom. He has received royalties for books and for occasional workshops and invited addresses. Dr. Ng has reported support from an unrelated fellowship funded through the National Institute of Mental Health (NIMH). Dr. Weisz has reported support from unrelated grants from the Institute of Education Science, US Department of Education, the Norlien Foundation, the Templeton Foundation, the United Health Group, and NIMH. He has received royalties for books and payments for invited addresses and workshops. Dr. Muñoz has reported support from unrelated grants from the National Institutes of Health (NIH) and for being Co-Chair of the Community Engagement Alliance (CEAL) project of the NIH. He has received royalties from books and payments for invited addresses. Dr. Gentili has reported support for unrelated grants from the European Commission (as local coordinator of the FET POTION Project H2020 and from the Italian Ministry of Education, University and Research (MIUR) as PI of the Progetti di Ricerca di Interesse Nazionale project TRAINED. Dr. Quero has reported unrelated support by Centro de Investigación Biomédica en Red - Fisiopatología de la Obesidad y Nutrición (CIBEROBN), an initiative of El Instituto de Salud Carlos III (ISCIII CB06 03/0052). Dr. Karyotaki has reported unrelated grant support by the Netherlands Organization for Health Research and Development (NWO; project number 019.182SG.001). Dr. Pineda has reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Pim Cuijpers, PhD, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 7-9, 1081 BT Amsterdam, The Netherlands; e-mail: p.cuijpers@vu.nl

https://doi.org/10.1016/j.jaac.2020.11.024

REFERENCES

1. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56:345-365.
2. Hankin BL, Young JF, Abela JRZ, *et al*. Depression from childhood into late adolescence: influence of gender, development, genetic susceptibility, and peer stress. J Abnorm Psychol. 2015;124:803-816.
3. Merikangas KR, He J, Burstein M, *et al*. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49:980-989.
4. Shaffer D, Pfeffer CR, Bernet W, Arnold V, Beitchman J, Benson RS. Practice parameter for the assessment and treatment of children and adolescents with suicidal behavior. J Am Acad Child Adolesc Psychiatry. 2001;40:24S-51S.
5. Birmaher B, Arbelaez C, Brent D. Course and outcome of child and adolescent major depressive disorder. Child Adolesc Psychiatr Clin N Am. 2002;11:619-638.
6. Kovacs M. Presentation and course of major depressive disorder during childhood and later years of the life span. J Am Acad Child Adolesc Psychiatry. 1996;35:705-715.
7. Keenan-Miller D, Hammen CL, Brennan PA. Health outcomes related to early adolescent depression. J Adolesc Health. 2007;41:256-262.
8. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry. 1998;55:56-64.
9. Balázs J, Miklósi M, Keresztény A, *et al*. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. J Child Psychol Psychiatry. 2013;54:670-677.
10. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch Gen Psychiatry. 2005;62:66-72.
11. Wesselhoeft R, Sørensen MJ, Heiervang ER, Bilenberg N. Subthreshold depression in children and adolescents—a systematic review. J Affect Dis. 2013;151:7-22.
12. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. Acta Psychiatr Scand. 2004;109:325-331.
13. Cuijpers P, Smit F, Oostenbrink J, de Graaf R, ten Have M, Beekman A. Economic costs of minor depression: a population-based study. Acta Psychiatr Scand. 2007;115:229-236.
14. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression? A meta-analysis of studies that measured both. Br J Psychiatry. 2013;202:22-27.
15. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. J Am Acad Child Adolesc Psychiatry. 1999;38:56-63.
16. Cuijpers P. Psychological treatment of subthreshold depression in children and adolescents: a meta-analytic review. Available at: osf.io/c7hty. Accessed May 23, 2020.

17. Cuijpers P, Karyotaki E. A meta-analytic database of randomised trials on psychotherapies for depression 2020. https://doi.org/10.17605/OSF.IO/825C6. Accessed March 15, 2020.
18. Cuijpers P. Four decades of outcome research on psychotherapies for adult depression: can overview of a series of meta-analyses. Can Psychol. 2017;58:7-19.
19. Cuijpers P, Karyotaki E, Reijnders M, Purgato M, Barbui C. Psychotherapies for depression in low- and middle-income countries: a meta-analysis. World Psychiatry. 2018;17:90-101.
20. Eckshtain D, Kuppens S, Ugueto A, *et al*. Meta-analysis: 13-year follow-up of psychotherapy effects on youth depression. J AmAcad Child Adolesc Psychiatry. 2020;59:45-63.
21. Cuijpers P, Karyotaki E, Eckshtain D, *et al*. Psychotherapy for depression across different age groups: a systematic review and meta-analysis. JAMA Psychiatry. 2020:e200164.
22. Cuijpers P, Pineda BS, Quero S, *et al*. Psychological interventions to prevent the onset of depressive disorders: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2021;83:101955.
23. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36: 980-988.
24. Hodges K, Kline J, Stern L, Cytryn L, McKnew D. The development of a child assessment interview for research and clinical use. J Abnorm Child Psychol. 1982;10:173-189.
25. Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
26. Hedges LV, Olkin I. Statistical Methods for Meta-analysis. Orlando, FL: Academic Press; 1985.
27. Furukawa TA, Cipriani A, Barbui C, *et al*. Imputing response rates from means and standard deviations in meta-analyses. Psychopharmacology. 2005;20:49-52.
28. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J Affect Dis. 2014;159:118-126.
29. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.
30. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56:455-463.
31. Arnarson EÖ, Craighead WE. Prevention of depression among Icelandic adolescents. Behav Res Ther. 2009;47:577-585.
32. Clarke GN, Hawkins W, Murphy M, *et al*. Targeted prevention of unipolar depressive disorder in an at-risk sample of high school adolescents: a randomized trial of a group cognitive intervention. J Am Acad Child Adolesc Psychiatry. 1995;34: 312-321.
33. Clarke GN, Hornbrook M, Lynch F, *et al*. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. Arch Gen Psychiatry. 2001;58:1127-1134.
34. De Cuyper S, Timbremont B, Braet C, De Backer V, Wullaert T. Treating depressive symptoms in schoolchildren. Eur Child Adol Psychiatry. 2004;13:105-114.
35. Gillham JE, Hamilton J, Freres DR, Patton K, Gallop R. Preventing depression among early adolescents in the primary care setting: a randomized controlled study of the Penn Resiliency Program. J Abnorm Child Psychol. 2006;34:195-211.
36. Martinović Ž, Simonović P, Djokić R. Preventing depression in adolescents with epilepsy. Epileps Behav. 2006;9:619-624.
37. Rohde P, Stice E, Shaw H, Briere FN. Indicated cognitive behavioral group depression prevention compared to bibliotherapy and brochure control: acute effects of an effectiveness trial with adolescents. J Consult Clin Psychol. 2014;82:65-74.
38. Stice E, Rohde P, Seeley JR, Gau JM. Brief cognitive-behavioral depression prevention program for high-risk adolescents outperforms two alternative interventions: a randomized efficacy trial. J Consult Clin Psychol. 2008;76:595-606.
39. Szigethy E, Kenney E, Carpenter J, *et al*. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. J Am Acad Child Adolesc Psychiatry. 2007;46:1290-1298.
40. Young JF, Benas JS, Schueler CM, Gallop R, Gillham JE, Mufson L. A randomized depression prevention trial comparing interpersonal psychotherapy: adolescent skills training to group counseling in schools. Prev Sci. 2016;17:314-324.
41. Young JF, Mufson L, Davies M. Efficacy of interpersonal psychotherapy-adolescent skills training: an indicated preventive intervention for depression. J Child Psychol Psychiatry. 2006;47:1254-1262.
42. Young JF, Mufson L, Gallop R. Preventing depression: a randomized trial of interpersonal psychotherapy-adolescent skills training. Depress Anxiety. 2010;27: 426-433.
43. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Measure. 1977;1:385-401.
44. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull. 1985; 21:995-1124.