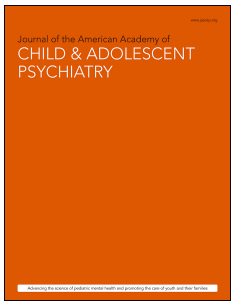

Psychological Treatment of Subthreshold Depression in Children and Adolescents: A Meta-analytic Review

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

RH = Subthreshold Depression in Youth

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Editorial
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Abstract

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 four 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 1576 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 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<0.04). The two studies in children below 12 years of age showed non-significant effects (g=0.01; 95% CI: -1.16~1.18). We found no significant effect on the incidence of major depression at follow-up (RR=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 below 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

Introduction

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.[3] Depression in youth 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 utilization 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, which does not meet diagnostic criteria for major depression or persistent depressive disorder (i.e., 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, where 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] But one of the main reasons 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 (that is, 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 of these trials into one 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.

In this paper, 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 four major bibliographical 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 one 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)'s 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, 1st 2020). All records were screened by two independent researchers (PC and EK) and all papers that could possibly meet inclusion criteria according to one of the researchers were retrieved as full-text. The decision to include or exclude a study in the database was also done by the two 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 only included 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 four 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 two independent researchers, and disagreements were solved 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); 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 two groups at post-test was calculated (Hedges' g).[26] Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the control group and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes we corrected the effect size for small sample bias.[26] If means and standard deviations 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 one 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 one 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 (version 3.3070; CMA).

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 post-treatment to follow-up assessment is shorter than the one-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 Numbers-needed-to-be-treated (NNTs) as 1 divided by the RD. The RD is the difference between the proportion of cases in the treatment and control group. We also calculated the acceptability of the intervention, defined as study drop-out for any reason, as well as the RR of acceptability (proportion of drop-outs in the interventions divided by the proportion of drop-outs 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 ‘metafor’ 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 employed 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.

NNTs were calculated using the formulae provided by Furukawa,[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 Egger's 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 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, while 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 is associated with relevant characteristics of studies.

We conducted sensitivity analyses: (1) in which we limited the analyses to studies with low risk of bias (low risk for all four items of the risk of bias tool); (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 PRISMA flowchart 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 eleven comparisons included adolescents (mean age 12 to 18 years) and two included children (mean age below 12).

Characteristics of Included Studies

In the 12 included trials, 1576 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 one was aimed at children of depressed parents. The mean age ranged from 10 to 14.4 years, and the proportion of girls ranged from 51% to 85%. Most studies (8) used cognitive-behavioral therapy (CBT), 3 used interpersonal psychotherapy (IPT) and one supportive expressive intervention. A group format was used in 8 studies, an individual format in 2 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, three used a non-specific intervention (such as school counselling), one a waitlist and one a control group in which participants only received a brochure about depression and treatment options. Nine studies were conducted in the United States and 3 in Europe.

The risk of bias in most studies was modest. Risk of bias for sequence generation was low in eight studies and unclear in the other 4. Risk of bias for allocation to conditions was low in one study, unclear in 8 and high in the remaining 3 studies. Risk of bias because of blinded outcome assessment was low in 10 studies, unclear in one study and high in one study. Bias related to intention to treat analyses was low in 9 studies, unclear in two studies and high in one 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 to 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 post-test 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 two effect sizes from one study.[38] However, these two effect sizes are not independent from each other and this may artificially reduce heterogeneity and affect the pooled effect size. Therefore, we conducted sensitivity analyses in which we included only one 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% CI: 0.05~0.75) which was comparable to the effect size found for all studies. When the effect sizes for the studies were calculated with an alternative method (only one depression measure for each study; in studies with multiple measures, one 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. Egger's test of the intercept pointed at significant asymmetry of the funnel plot (p=0.04; Table 2). Duvall and Tweedie's 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: -0.06~0.54), which was no longer significant. Heterogeneity was high in these analyses (I^2=71; 95% CI: 51~82). After exclusion of the outlier, Egger's test was no longer significant (p>0.1), and Duval and Tweedie's trim and fill procedure indicated two 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 two 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.

Subgroup analyses

In order 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 we found was between studies in children compared to those in adolescents (p=0.01). The two studies in children indicated an effect size of g=0.01 (95% CI: -1.16~1.18), while 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 is reported in Table 3. The effects pointed in the positive direction

with an RR of 0.52 (95% CI: 0.25~1.08), indicating 48% lower chance of developing a depressive disorder in the intervention group compared to the control group, but 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~-0.00), which did reach significance levels (p<0.05). The corresponding NNT was 10.0.

The results of the sensitivity analyses in which only one 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 a RR of 0.44 (95% CI: 0.18~1.05; n.s.) with moderate heterogeneity (I^2=50; 95% CI: 0~79), and a RD of -0.10 (-0.18~-0.02; p<0.05), corresponding with a NNT of 10.2. There were again indications of publication bias. Egger's test of the intercept was significant (p<0.01) and after adjustment for publication bias, the RR was found to be a non-significant 0.96 (95% CI: 0.39~2.39; I^2=67; 95% CI: 44~81; RD=-0.06; 95% CI: -0.17~0.05; 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:-0.24~0.02; 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 youth with subthreshold depression compared to care-as-usual and other

control groups. However, this effect was only found in adolescents, while for children only two 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 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 for 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 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 not significant anymore. 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 two 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 this 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—development of effective alternatives to current treatments for children. Such studies, however, require large sample sizes and considerable resources and may be hard to get funded.

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 does 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. And 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 minorities, 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 below 12 years of age or that they prevent the onset of major depression at follow-up.

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Table 1. Selected Characteristics of Included Studies

Study	Cut-off	Diagnosis	Recruit-ment	Ethnicity	Comorbidities: excluded	Current diagnoses [a)]	M age	% wo-men	The-rapy	Frm	N sess	Control	Coun-try	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% Caucasian, 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 years	NR	psychotic symptoms, schizophrenia, bipolar disorder, social phobia, agoraphobia, panic disorder	NR	17.4	60	cbt	I	8	cau	SER	+ – – ±
Rohde, 2014[37]	>2 symptoms of depression on CES-D	K-SADS	Schools	6% Hispanics, 2% Asian Americans, 1%	No other diagnoses were excluded	NR	15.5	68	cbt	G	6	Bro-chure-only	US	+ – + +

				African Americans, 72% Caucasians, 1% Native American, 18% other /mixed										
Stice, 2008 – cbt[38]	CES-D ≥20	K-SADS	Mass mailings	2% Asians, 9% African	No other diagnoses were excluded	NR	15.6	56	cbt	G	6	cau	US	+ – + +
Stice, 2008 – supportive[38]				Americans, 46% Caucasians, 33% Hispanics, 10% other /mixed					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	+ ± + +
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 (more than 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; 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; 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 age = mean age; 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) RoB (risk of bias); 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 (+).

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

Note: CBT = cognitive-behavioral therapy; N_{comp} = number of comparisons; NNT: numbers-needed-to-be-treated.
[a] According to the random effects model.
[b] This *p* indicates the difference between subgroups
[c] Young *et al*., 2006.

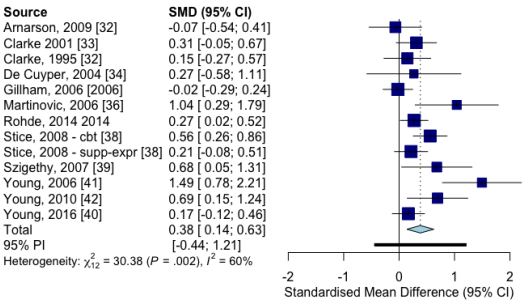
Table 3. Effects of Psychological Interventions for Subthreshold Depression in Children and Adolescents on Incidence of Major Depression at Follow-Up and Acceptability

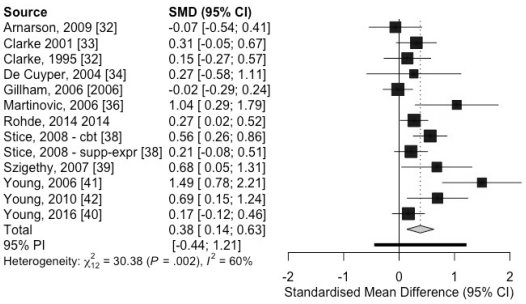
	N_{comp}	*RR*	*95% CI*	I^2	*95% CI*	*Prediction interval*	*RD*	*95% CI*	*NNT*
Incidence									
All studies	10	0.52	0.25~1.08	57	14~79	0.05~5.71	-0.10 [a)]	-0.20~-0.00	10.0
One effect size per study (only highest)	9	0.49	0.21~1.17	61	19~81	0.04~6.97	-0.10	-0.22~0.01	9.6
One effect size per study (only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

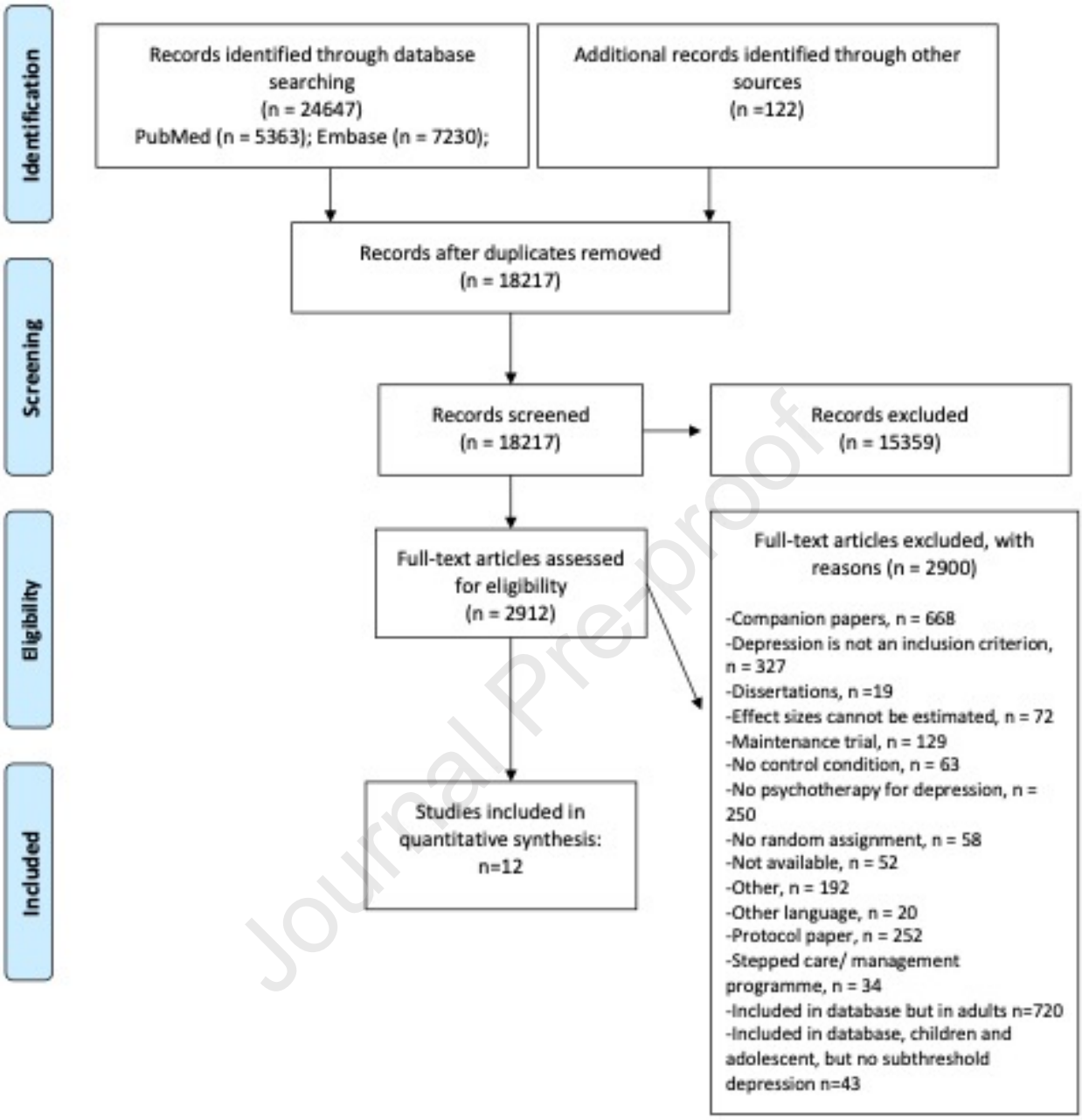
Note: N_{comp} = number of comparisons; NNT = numbers-needed-to-be-treated; RD = risk difference; RR = relative risk.
[a)] The RD was significant ($p < .05$)
[b)] 2 imputed studies

Figure 1. PRISMA Flowchart on the Selection of Studies

Figure 2. Forest Plot







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