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**Psychological treatments for depression in pre-adolescent children (12 years and younger):  
systematic review and meta-analysis of randomised controlled trials.**

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**Abstract (250 words)**

**Objective:** To evaluate the efficacy of psychological treatments for depression in pre-adolescent children, a disorder affecting 1-2% of children in this age-range.

**Design:** Systematic review of studies of psychological interventions to treat depressive disorder in pre-adolescent children (aged up to 12 years old). The primary outcome was level of depressive symptoms.

**Data Sources:** Studies were found using Medline, PsycINFO, EMBASE and Web of Knowledge databases and selected on several criteria.

**Eligibility criteria for selecting studies:** Only randomised controlled trials were included. Where individual studies covered a broader age range (usually including adolescents up to age 18 years), authors of those studies were contacted and requested to provide individual patient level data for those aged 12 years and younger.

**Results:** 2822 abstracts were reviewed, and from these 124 full text articles were reviewed, yielding 7 studies for which we were able to access appropriate data for this review. 5 of these studies evaluated cognitive behaviour therapy (CBT). Combined results from these studies suggest that there is a lack of evidence that CBT is better than no treatment (Standard Mean Difference -0.342 (95% Confidence Interval -0.961, 0.278), although the number of participants included in the trials was relatively small. The evidence for efficacy of family therapy and psychodynamic therapy is even more limited.

**Conclusion:** The very limited number of participants in randomised controlled trials means that there is inconclusive evidence for the psychological treatment of depression in children aged 12 years and under. Given the prevalence and significant impact of this disorder, there is an urgent need to establish the effectiveness or otherwise of psychological intervention.

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## **Introduction**

Depression is common, affecting 1 in 5 people over the course of a lifetime. It is an important cause of morbidity and mortality worldwide, and its impact on global health is increasing, with it set to become the 2<sup>nd</sup> largest cause of morbidity of any disease by 2020 [1].

The prevalence of depressive disorders rises across adolescence to reach adult levels by the mid-teens [2].

However, it is an often overlooked fact that depression is also common in the years prior to adolescence, affecting 1-2% of school age children, and that those affected in these younger years are at significantly increased risk of psychiatric disorder in adult life [3]. The origins of many cases of adult depression and other psychiatric disorders lie in the early years of life [4, 5], and those with pubertal onset have higher rates of severe outcomes, such as attempted suicide. Evidence also suggests that those with early onset depression are likely to develop additional co-morbid psychiatric conditions, including conduct disorder, anxiety disorder and substance abuse [6]. As well as affecting lifelong development and risk of future health problems, depression in children is associated with adverse current functioning which potentially impacts on peer relationships, school performance and relationships with parents.

Despite the prevalence and impact of this condition in early life, and an improved focus on identifying young people with depression in schools, almost no evidence exists to guide treatment intervention for this group of young people [7]. Whereas in adolescence there are a significant number of RCTs of both pharmacological and psychological interventions [7, 8, 9], literature in younger children (12 and under) is starkly lacking. It is possible that antidepressant medication may have a different level of efficacy in younger children and medication is also less likely to be acceptable to families of younger children. The limited reports of psychological treatment suggest that treatment approaches commonly used in adulthood and adolescence, such as cognitive behavioural therapy, may also be less effective or acceptable for younger children [10].

As no previous systematic reviews exist that address the treatment of depression in this population we undertook a review to assess the efficacy of psychological treatments for preadolescent children (aged 12 years and younger) diagnosed with major depressive disorder. This was undertaken using all available (published and unpublished) randomised controlled trials.

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## **Methods**

### **Eligibility criteria**

Studies were eligible if they fulfilled the following criteria:

- **Population:**

Children aged 12 or below with a diagnosis of Depression achieved through validated clinical assessment. Both Depressive Disorder and Dysthymia were included. Although any age cut-off is somewhat arbitrary and no age corresponds exactly to adolescence, young people aged 13 and older are consistently recognised as adolescents in studies of depression treatments and in the wider scientific literature, and 12 and under was selected as our age group to consider pre-adolescents specifically.

When an individual study included subjects aged 12 or below within a larger sample with individuals over 12 years old, we contacted the authors to obtain the data regarding those individuals relevant to our review (see PRISMA flowchart [Figure 1] for details).

- **Interventions:**

Any psychological treatment including, but not limited to, family intervention, cognitive behavioural therapy (including face to face or computer-based format), Behavioural Therapy, Interpersonal Therapy or Psychodynamic Therapy. If there was a pharmacological intervention in addition to the psychological intervention, we included the study in the review if there was a direct comparison between a group receiving a psychological treatment and a group either with no psychological intervention or a comparison one, provided the groups did not also differ in terms of pharmacological treatment prescribed.

- **Study design:**

Only randomised controlled trials were included. When there were different publications for the same study, we included the one that presented the latest results and most relevant outcome measures to our review. Outcome measures were defined as follows in the next section.

- **Outcomes:**

- 1) Change to “no-diagnosis status” for depressive disorder;
- 2) Change in depressive symptoms (change in the score of a validated symptom questionnaire).

### **Information sources and search**

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We developed a systematic literature search strategy to identify all relevant randomised controlled trials which evaluated psychological interventions in children aged 12 or below, who had major depressive disorder.

We searched the following databases: Embase, Medline, Psycinfo, Web of Knowledge (which included Web of Science, BIOSIS Citation Index, Current Contents Connect, Derwent Innovations Index, CABI: CAB Abstracts, Chinese Science Citation Database, Data Citation Index, Journal Citation Report), for all studies up until the search date of 1<sup>st</sup> October 2014.

With advice from a registered librarian, we searched using the following keywords, covering intervention, population and study design: [psychotherapy OR psychological treatment OR “particular intervention”] AND [depression OR depressive disorder] AND [child OR adolescent] AND [random OR clinical trial]. We did not set any limits in terms of language. We included both published and unpublished studies (including dissertations). We searched for additional trials in published systematic reviews and meta-analyses. The detailed search strategies for each database are listed in the appendices.

### **Study selection**

Two authors (MAF and RS) independently performed the search. Duplicates were searched for and excluded, obtaining a final sample of references to be screened. References were initially screened by the title, then by abstract and finally after reading full text if indicated. When the reviewers did not agree about the inclusion or exclusion of a certain paper, discussion with a third author (PGR) took place to achieve consensus.

### **Data collection process and data items**

We designed a data extraction sheet, and two of the authors (MAF and RS) independently assessed each of the studies included in the final sample (see table 1 for included study details).

We included relevant information about the study (intervention, sample size, age, diagnosis criteria used, randomization method). We also performed a Jadad quality assessment [11] for each of the studies. We considered the score for blinding as positive if the assessor was blind (given the nature of individual psychological intervention it is not usually possible to have a double-blind design).

Three studies [12, 13, 14] reported results specifically and only for the age group of interest, but in most other studies it was not possible to identify the results specifically for the population of interest (aged 12 and under) from the publications. In these cases we contacted the lead author and/or funder (in the case of the NIH-funded

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studies [15, 16]) in an attempt to obtain summary or individual data for those in our selected age group. We were able to obtain this data for an additional four studies [15, 16, 17, 18]. .

### **Assessment of risk of bias of individual studies**

Quality assessment of the papers was performed using the extracted data and adapted Jadad score.

### **Statistical analysis**

One of the studies [17] included only two individuals aged 12 or below and both were in the same arm of the trial, so no further analysis was possible. Data from all the remaining studies was analysed for participants aged 12 and under.

Most studies assessed cognitive behavioural therapy (CBT). For these studies we performed a meta-analysis, using Stata SE12 (Statacorp). We extracted relevant outcome measures (mean and SD) for both intervention and control group, and the sample size for each group, and computed a pooled Standardised Mean Difference using a random effects model. Two other trials were not included in the meta-analysis. One trial [18] did not assess CBT, instead comparing two other forms of therapy (psychodynamic and family therapy). The other [13] assessed a different form of psychological intervention with a much younger age group (aged 3-7 years). The results of these two studies are described separately.

### **Results**

We obtained a total of 4296 references. When duplicates were excluded, the number went down to 2823 (see PRISMA diagram Figure 1). Following exclusion by title and abstract, we obtained a total of 124 full text articles. From these, 102 articles were excluded because they did not fulfil criteria, or they overlapped with, and did not add to, already identified articles. The main reasons for exclusion were including children of the wrong age, inadequate assessment of depressive disorder or lack of randomised design. This left a total of 22 studies which potentially fulfilled criteria. We were able to extract or obtain relevant data from 7 of these studies. (This included all the larger samples of children aged 12 and under. We contacted the authors of any studies where it appeared that all, or a proportion of, participants were aged 12 and under. In 8 cases participants aged 12 and under were either not included or were a small number and no age-specific data could be shared. In the remaining 7 cases we did not receive any reply from the authors when contacted. From the details provided in the study results, a small number of subjects were aged 12 or under.

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### **Study characteristics**

The final sample of seven studies were published between 1987 and 2012, and included a total number of 219 children aged 12 or below. One study included younger preschool children [13]. Two studies [12, 14] only included participants of preadolescent age (7-11 and 9 to 12), and the four remaining studies had a wider age range from which we included data on those aged 12 or below. Four of the studies were conducted in the USA, one in Australia and two in Europe (United Kingdom, Finland and Greece).

### **Types of interventions**

These included Cognitive Behaviour Therapy (5/7 studies) (see Table 1), in individual and group format, family therapy (1/7), psychodynamic psychotherapy (1/7), and Parent-Child Interaction Therapy Emotion Development (PCIT-ED) (1/7).

In most studies the control group was treatment as usual, but individual studies also used a Developmental Education and Parenting Intervention (DEPI) and Attention placebo. One of the studies [18] assessed two potentially active treatments, and did not have another control group.

### **Diagnosis and severity assessment tools**

In four of the studies, the Children's Depression Rating Scale (CDRS) was used as a baseline measure. K-SADS was used in one, and other instruments were used in the other studies (see table 1 for details).

The most common tool used for severity of depression, and monitoring change in depression, was the CDI (used in three studies). The other studies used the BDI, the RADS and the AWBS. For other details, see table 1.

### **Efficacy of different treatments –details in tables 1&2**

The three different interventions assessed were CBT, family therapy and focused individual psychodynamic psychotherapy.

#### **1. CBT:**

Five of the seven studies evaluated CBT, with varying approaches, including individual therapy, computerized therapy and group CBT.

#### **i. Stark**

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This small study (28 participants) had three arms: two treatment groups (self-control treatment (n=9) and behavioural problem solving (n=10)) and a waiting list group (n=9). Both intervention groups showed improvement when compared to waiting list. Follow up analysis (after 8 weeks of finishing treatment) showed maintained improvement. As both treatment groups showed similar effects, and were both based on CBT principles, we combined the two intervention groups (SC and PS) for the purposes of the meta-analysis, using the *ad hoc* calculated shared mean and SD (see table for detailed values).

#### ii. Liddle

This study also had three arms and used a group intervention. There was a single intervention arm (social competence training), and two control conditions: attention placebo (drama programme in group format) and “no-treatment”. There was no clear benefit from the intervention, and improvement in depression scores were found in all three groups. For the meta-analysis, we included the data regarding the no-treatment arm, to allow comparability with other included studies (all other studies had no intervention/waiting list).

#### iii. Stallard

This UK based study compared computerized CBT with a waiting list control. The age range was across adolescence and only two participants of this study were aged 12 or below. They were both in the intervention arm, and both made improvement. Overall the findings for the intervention were positive towards cCBT, with an improvement in depression scores, however no conclusions can be drawn for pre-adolescent children (n=2).

#### iv. Treatment of Resistant Depression in Adolescents (TORDIA)

This multicentre study examined children and young people with treatment-resistant depression, comparing different management strategies. There were four arms: continuing an SSRI drug with or without addition of CBT, and switching drug to Venlafaxine (VEN) with or without the addition of CBT. We obtained the study dataset (total n= 334), but only 6 subjects were aged 12 or under: three received CBT (2 VEN and 1 SSRI), and three did not receive CBT (2 VEN and 1 SSRI). The data for these subjects were included in the meta-analysis. For the overall study, the findings showed that adding CBT to switching medication provided a higher clinical response than only switching medication. It is worth noting that all four treatment groups received family psychoeducation.

#### v. Treatment of Adolescent Depression Study (TADS)

This multicentre study assessed the efficacy of two different treatments for depression, CBT and fluoxetine (alone and combined), resulting in a four arm study: CBT plus either fluoxetine or placebo and no psychological



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treatment plus either fluoxetine or placebo. From a full sample of 493 subjects, 48 were aged 12 years or less.

We extracted the data for those participants and included them in the meta-analysis. See table 1 for further details. Results from the age 12 and under subsample showed no statistical differences in the effectiveness of CBT vs NON CBT (see table 2 for results).

Results from the study overall (i.e. including all participants up to 18) showed that the combination of fluoxetine and CBT led to the most favourable outcomes, followed by Fluoxetine, CBT and non-intervention.

## 2. Family therapy/interventions:

### vi. Luby

This study used a novel intervention for preschool children aged 3 to 7 years (Parent-Child Interaction Therapy Emotion Development; PCIT-ED) as the intervention arm, and compared it to a control intervention (Developmental Education and Parenting Intervention), in a relatively small trial. Depressive symptoms improved in the PCIT-ED group, as well as maternal depressive symptoms. The authors of this study acknowledge the need for additional research to more fully evaluate this intervention.

### vii. Trowell

This multicentre study (UK, Greece, Finland) compared two different interventions: family therapy and focused individual psychodynamic psychotherapy. The authors allowed us access to the entire dataset (n=83), and we extracted the data for those aged 12 or below (n=49). The study lacked a no-treatment control intervention, so the comparison was between family therapy and individual psychodynamic psychotherapy. In the subsample aged 12 and below we were able to access scores for depression symptoms both pre- and post-treatment. These are not included in the meta-analysis as there was no CBT arm for comparison with other studies. Findings from the overall study showed good recovery rates for both interventions, which were sustained over time (the recovery rate for the family therapy arm at end of treatment was 75.7% and at follow up was 81.1%). It is not clear whether assessors were blind to intervention group.

## 3. Focused individual psychodynamic psychotherapy:

The single trial including this intervention is the one described in the section above undertaken by Trowell and colleagues [18]. Recovery rates were similarly high and sustained.

## **Quality assessment**

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We used an adapted version of the Jadad score, described above, allowing a point for blinding of the assessors rather than double-blinding. Four studies [13,15,16,17] had the highest adapted Jadad score (5/5), followed by Stark [12], with 4/5. The study of Trowell [18] scored 3/5 (no blinding of assessor reported) and Liddle [14] scored 1/5, as no description of either blinding or method of randomization was reported.

### **Meta analysis**

Data from the studies comparing CBT versus waiting-list/no-treatment were pooled together using STATA.

The test of heterogeneity was positive, so a random effects model was used (see Figure 2). The pooled Standard Mean Difference was -0.342 (95% Confidence Interval -0.961, 0.278;  $p=0.280$ ), indicating no clear evidence of effect for CBT for Depression in children aged 12 years and under. However, this is based on studies of CBT including a total of 101 participants, a relatively small number. We subsequently re-ran the analysis excluding the findings from the TORDIA trial as this was of a group with treatment resistant depression. This did not substantially change the findings [SMD -0.453 (-1.075, 0.169;  $p=0.153$ )]. We conducted a funnel plot, however the very small number of studies included makes this difficult to interpret meaningfully.

### **Discussion**

The key finding of this systematic review is that the evidence on which treatment of depression in children aged 12 and under is based is extremely limited and it is inconclusive when it comes to establishing the most effective forms of treatment. This is due to a lack of research studies investigating depression in this age group, and not necessarily reflective of ineffectiveness of psychological treatments. This is important as depression is common, even in this younger age group, and is associated with significant distress and impairment both currently and into adolescence and adult life. Cognitive behaviour therapy is the most widely studied therapy for this age range, but even for this therapy, the number of participants in trials is relatively small, and there is thus no clear evidence for the treatment being effective. For other psychological treatments the evidence base is even weaker. This does not mean that psychological therapy should be abandoned for this group of young people with depression, as it probably represents the most appropriate form of intervention. However it does suggest that caution should be applied when plans are made with young people and their families in formulating treatment approaches, acknowledging the uncertainties about what may work.

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This review has a number of methodological strengths and limitations. First, an extensive and systematic search was conducted including a range of relevant databases, without any language restriction. Authors were contacted, and considerable efforts were made to retrieve all available studies. We were able to include data specific to this age range from most of the key trials in the field, even where they included a much wider age range (as most do). We were also able to obtain original individual patient data from four key studies, including the two funded by the US National Institute for Health Research. In addition, we were able to combine the results of the CBT studies in a meta-analysis, to provide a combined estimate of treatment effect.

Despite these strengths, we were limited by the relatively small number of studies, and the small numbers of participants of appropriate age in the majority of them. There was also considerable heterogeneity between the studies, which limits the confidence with which we can draw conclusions from the findings of the meta-analysis. This considerably limits the robustness with which one can draw conclusions about the effectiveness or otherwise of the various psychological treatments.

The most important implication of this study is that there is insufficient evidence to allow us to confidently assess the efficacy of psychological intervention for children aged 12 years and under with depression. Further research, with larger numbers of participants is absolutely necessary. For a disorder that affects 1-2% of this age group, which is often disabling and recurrent, this is a lamentable state of affairs. Depression in this age group is under-recognised and poorly understood, and a very small minority of children with depression actually get access to specialist services. As a result of this systematic review, we now know that, even when children aged 12 and under do access these services, the treatments they receive are based on a small and inadequate body of research. This malady requires urgent remedy.

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### **Contribution and guarantor**

The original idea for this review was devised by PGR and MAF. MAF and RS conducted the searches and appraised the papers with support from PGR and EW. MAF wrote the first draft of the manuscript and all authors contributed to, and critically revised subsequent manuscripts. MAF and PGR will act as guarantors for the work.

### **Transparency Statement**

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

### **Conflict of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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### **What this paper adds**

1. What is already known on this subject

Depression is common in pre-adolescent children, affecting 1-2% of this age group

Psychological therapies are the treatment of choice as there is limited evidence for effectiveness of medication

2. What this paper adds

There is very limited research on this question with only small numbers of children included in clinical trials of psychological treatments. There thus remains uncertainty as to the most effective form of psychological intervention for depression in children aged 12 years and under.

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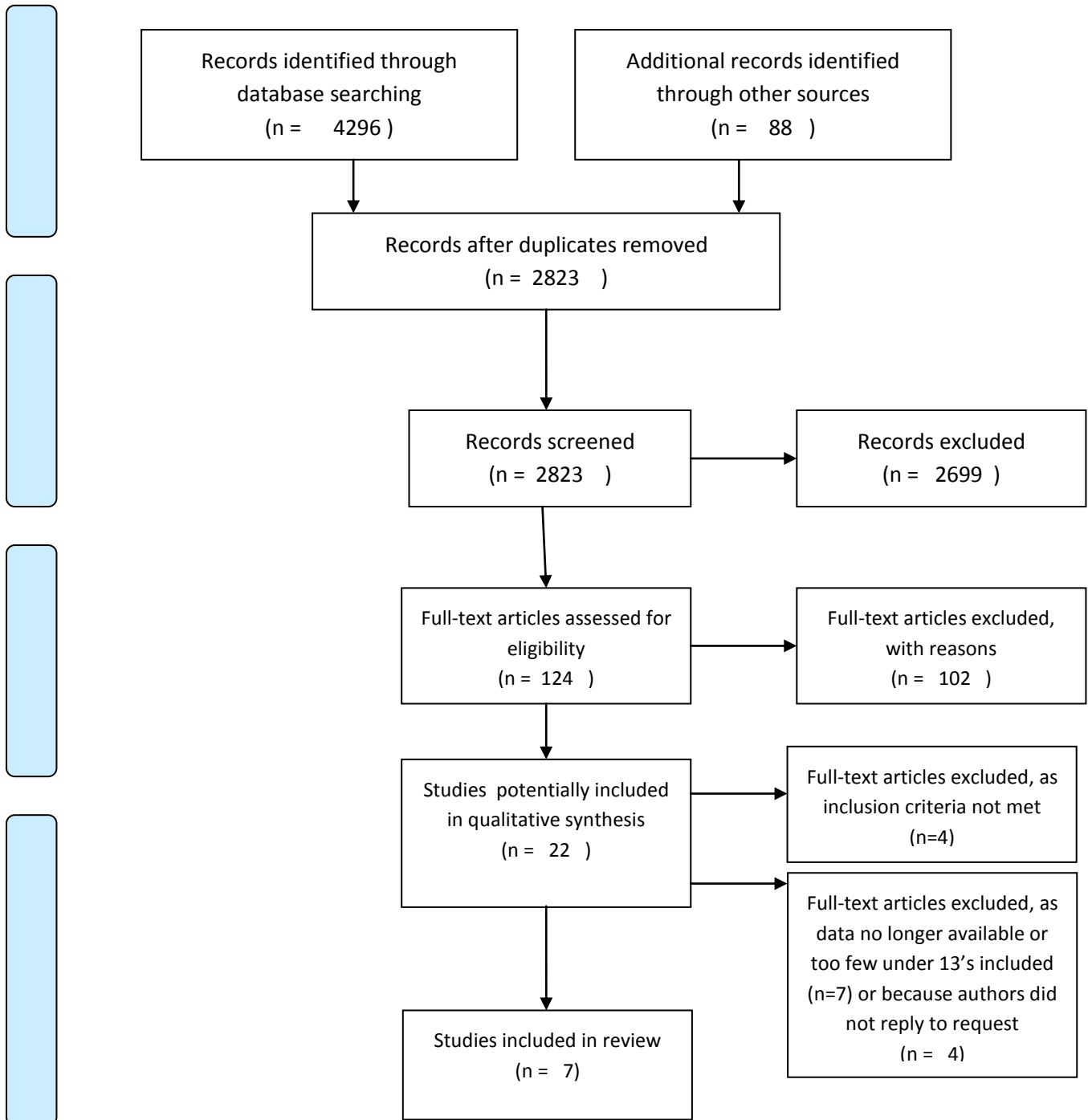
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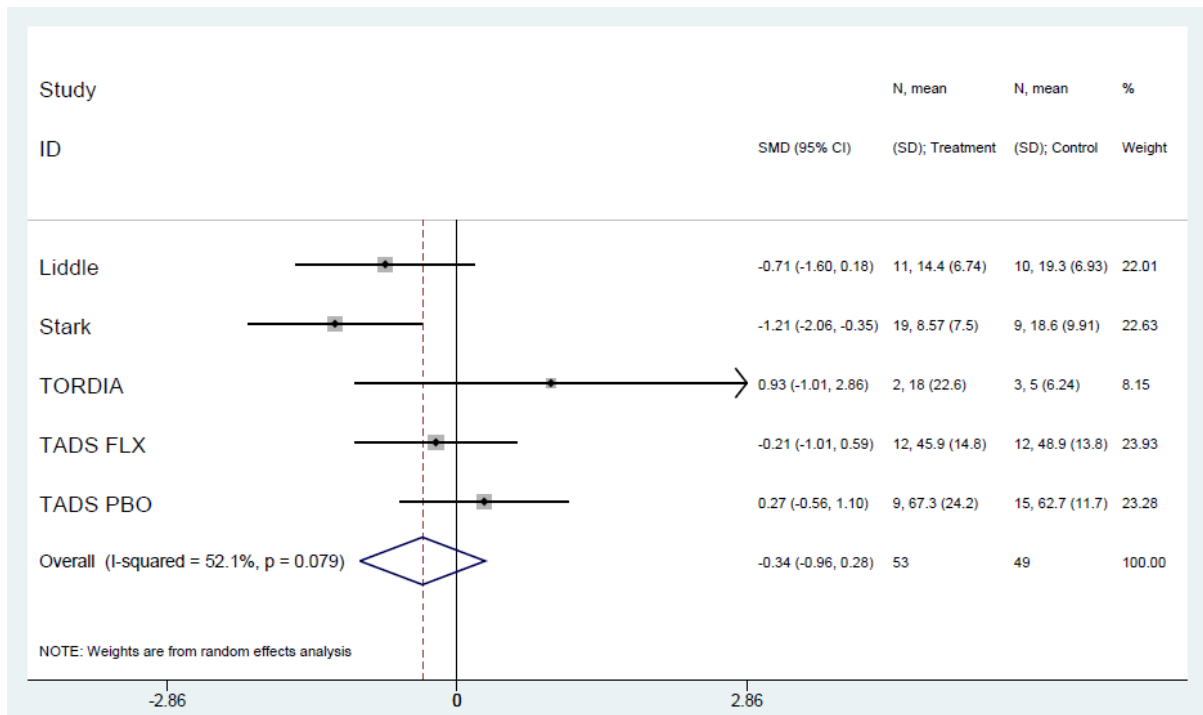
**Figure 1. PRISMA diagram – flow chart of studies**





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Figure 2. Random effects met-analysis of studies of CBT versus no treatment or waiting list control.



Heterogeneity chi-squared = 8.35 (d.f. = 4) p = 0.079

I-squared (variation in SMD attributable to heterogeneity) = 52.1%

Estimate of between-study variance Tau-squared = 0.2498

Test of SMD=0 : z= 1.08 p = 0.280

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