Cognitive behavioural therapy for psychosis prevention

Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis

Short title: CBT for psychosis prevention.

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ABSTRACT

Background: Clinical equipoise regarding preventative treatments for psychosis has encouraged the development and evaluation of psychosocial treatments, such as cognitive behavioural therapy (CBT).

Method: A systematic review and meta-analysis was conducted, examining the evidence for the effectiveness of CBT-informed treatment for preventing psychosis in people who are not taking antipsychotic medication, when compared to usual or non-specific control treatment. Included studies had to meet basic quality criteria, such as concealed and random allocation to treatment groups.

Results: Our search produced 1940 titles, out of which we found 7 completed trials (6 published). The relative risk (RR) of developing psychosis was reduced by over 50% for those receiving CBT at every time-point (RR at 6 months 0.47 [0.27, 0.82], p=0.008 [fixed-effects only; 6 RCTs, N=800]; RR at 12 months 0.45 [0.28, 0.73], p=0.001 [6 RCTs, N=800]; RR at 18-24 months 0.41 [0.23, 0.72], p=0.002 [4 RCTs, N=452). Heterogeneity was low in every analysis and the results were largely robust to the risk of an unpublished 12-month study having unfavourable results. CBT was also associated with reduced subthreshold symptoms at 12 months, but not at 6 or 18-24 months. No effects on functioning, symptom-related distress or quality of life were observed. CBT was not associated with increased rates of clinical depression or social anxiety (2 studies).

Conclusions: CBT-informed treatment is associated with a reduced risk of transition to psychosis at 6, 12 and 18-24 months, and reduced symptoms at 12 months. Methodological limitations and recommendations for trial reporting are discussed.

Key words: Cognitive behavior therapy, at-risk mental state, prodromal psychosis, subthreshold symptoms.

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INTRODUCTION

One of the most important advances in mental healthcare over the last 20 years has been the development of reliable methods for identifying those who are at greatly increased risk of developing psychosis (Chuma & Mahadun, 2011, Fusar-Poli *et al.*, 2012a, Yung *et al.*, 1996b). The success of this approach has prompted calls for the inclusion of concepts such as 'prodromal psychosis', 'psychosis-risk syndrome' and 'attenuated psychosis syndrome' in the upcoming revision of the American Psychiatric Association's Diagnostic and Statistical Manual (Carpenter, 2009, Carpenter & van Os, 2011, Woods *et al.*, 2010). This has sparked much controversy and debate (Corcoran *et al.*, 2010, Yung *et al.*, 2010), and it seems such proposals have now been set aside. One objection was that inclusion will lead to many young people being unnecessarily treated with antipsychotic drugs (Bentall & Morrison, 2002, Fusar-Poli & Yung, 2012, Morrison *et al.*, 2010) – drugs which may be associated with a range of adverse effects, including weight-gain (McGlashan *et al.*, 2006), diabetes (Mitchell *et al.*, 2012), reduced cognitive functioning (Bowie *et al.*, 2012, Faber *et al.*, 2011) and reductions in brain tissue (Ho *et al.*, 2011, Moncrieff & Leo, 2010, Radua *et al.*, 2012, Tost *et al.*, 2010). Although off-label prescription of antipsychotics is now not uncommon (Broome *et al.*, 2005, Fusar-Poli *et al.*, 2012b, Nieman *et al.*, 2009), and although they lead to moderate improvements in symptoms for people with established psychosis (Leucht *et al.*, 2009), whether they are beneficial, acceptable or harmful to young people at risk of developing psychosis remains unclear (Bechdolf *et al.*, 2011, Marshall & Rathbone, 2011, McGlashan *et al.*, 2006, McGorry *et al.*, 2002). It was in this context that the highly favourable results of a recent trial of omega-3 fatty acids (fish oils), an inexpensive treatment with no known major adverse effects, were welcomed (Amminger *et al.*, 2010).

Clinical equipoise regarding preventative treatments for psychosis has encouraged the development and evaluation of non-pharmacological psychosocial treatments, such as cognitive behavioural therapy (CBT) (French & Morrison, 2004, French *et al.*, 2003) and family-focused interventions (O'Brien *et al.*, 2007, Schlosser *et al.*, 2011). Although a recent Cochrane review found no clear evidence of efficacy for CBT (Marshall & Rathbone, 2011) several important and relevant studies have been published since. If such interventions are effective in preventing or delaying psychosis, then this would have important implications for clinicians and policy-makers (McGorry *et al.*, 2006).

The aim of this study was to systematically review and meta-analyse the evidence for the effectiveness of CBT-informed care for preventing psychosis in people who are at risk but are not taking prophylactic antipsychotic medication, when compared to usual or non-specific control treatment. Meta-analysis can provide greater statistical power over individual studies, particularly when study heterogeneity is low. They also provide additional information concerning effect size precision and heterogeneity that are valuable in clarifying the nature of effects and lend themselves to a more comprehensive and unbiased summary of the literature than that usually attained through informal review.

Our primary hypothesis was that CBT-informed interventions would be associated with a significantly reduced rate of transition to psychosis. Secondary hypotheses were that CBT-informed interventions would be associated with improved overall symptoms, functioning and quality of life. We also examined adverse effects and acceptability, the latter indexed by the numbers leaving early for any reason.

METHODS

Search

The Cochrane Group Trials Register (CENTRAL), PubMed, EMBASE, Medline, references of two recent reviews, including a systematic Cochrane review (Marshall & Rathbone, 2011, Preti & Cella, 2010), the online clinical trials registers of the US government (clinicaltrials.gov), European Union (clinicaltrialsregister.eu), World Health Organisation (apps.who.int/trialsearch) and Current Controlled Trials Ltd (controlled-trials.com) were searched in April 2012. The CENTRAL and PubMed searches were limited to the years 2008-2012, given the recent Cochrane review completed their last search in 2009. All years up to April 2012 were searched in EMBASE, Medline and the clinical trial registries. Most of the search terms used in a recent systematic review of transition outcomes in the at-risk group were also used here, as they seemed suitably broad (Fusar-Poli *et al.*, 2012a). These were 'psychosis risk, ultra high risk, prodromal psychosis, psychosis transition… and psychosis onset'. Other terms searched for were 'psychosis prevention' and 'at-risk mental state'. The initial search was limited to the abstract, title and keywords (see PRISMA diagram, Figure 1). To ensure the work was up-to-date as possible, we searched for published reports of any initially unpublished trials on a weekly basis from April 2012 until the manuscript was accepted for publication.

Studies were included only if participants at high risk of developing psychosis were randomly allocated to receive various interventions, one of which had to include CBT but not pharmaceutical treatment, and one of which had to be treatment as usual or a non-specific control treatment (i.e., supportive therapy, monitoring, case management). Included studies had to meet basic quality criteria, such as concealed and random allocation to treatment groups.

Pre-registration of review protocol

The review protocol was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews) (Hutton, 2012).

Data extraction and outcomes

The primary outcome was transition to psychosis, as defined in each study. Secondary outcomes were reduction in overall symptoms (or when not reported, positive symptoms) and improvements in functioning (preferably Global Assessment of Functioning scores) and quality of life.

A strict intention-to-treat (ITT) analysis for dichotomous data was employed, using the total numbers randomised to each group as the denominator in each case. Those leaving early or unaccounted for were assumed to have had the unchanged outcome. Examination of the impact of changing this assumption was intended, but only if data-reporting would allow it. For secondary continuous outcomes, summary data based on a mixed-model repeated measures imputation method were used when available; if not available, it was expected the analysis would be restricted to analysing data incorporating last observation carried forward assumptions. Following Leucht et al., we extracted and analysed mean change scores when reported, and endpoint scores otherwise (Leucht *et al.*, 2009).

To reduce the impact of attrition bias, study data was only included if this incorporated end-point scores from 50% or more of those who were randomised, excluding the analysis of leaving the study early. We contacted study authors to request missing or unpublished data. All extractions were carried out by the first author, and independently confirmed by the second. Any discrepancies were resolved by discussion.

Meta-analytic calculations

For binary data, the relative risk (RR) of the unfavourable outcome together with 95% confidence intervals was calculated. The absolute risk difference (RD) and numbers needed to treat (NNT) were calculated only if the RR was significant. The NNT was calculated in two ways; (1) as the inverse of the RD, as per Leucht et al (Leucht *et al.*, 2009) and (2) as the inverse of the product of the relative risk reduction (RRR) and an 'assumed control risk' (ACR), as per Higgins et al (Higgins *et al.*, 2011b). Inclusion of the latter was a post-hoc decision, but one which acknowledges that *"Risk differences are least likely to be consistent across baseline event rates; thus, they are rarely appropriate for computing numbers needed to treat in systematic reviews."*(Higgins *et al.*, 2011b). ACRs were derived from Fusar-Poli et al (Fusar-Poli *et al.*, 2012a).

Continuous data from different outcome measures were combined to allow calculation of the standardised mean difference (SMD) (Higgins *et al.*, 2011b). This and 95% confidence intervals (CI) were calculated using Revman software, which uses the Hedges' g adjustment for small sample bias. Statistical significance was assumed if the probability of a chance result was less than 0.05, using two-tailed hypotheses throughout. The magnitude of effect which would be considered clinically significant was not pre-specified, as there is little relevant data to inform such considerations in this group. A random-effects analysis was used for both continuous and binary outcomes but a secondary analysis using fixed-effects was carried out if heterogeneity was moderate or less, as per the methodology of the NICE schizophrenia guidelines (NICE, 2009). Results from both are reported only where the estimates differ. Moderate heterogeneity was assumed if the I^2 statistic was 40% (Higgins *et al.*, 2011b, NICE, 2009). We also examined whether the primary outcome results were robust to excluding individual studies from the analysis. Calculations were performed by the first author, and independently replicated by the second. There were no discrepancies.

Risk of bias

Risk of bias was assessed with the Cochrane Collaboration Risk of Bias tool (version 5.1.0) (Higgins *et al.*, 2011b). This involves categorising studies as having a low, high or unclear risk of bias in the areas of selection and allocation of participants, intervention concealment, attrition and reporting (Higgins *et al.*, 2011a). The results of this assessment were used to inform intepretation of reported effect sizes and overall conclusions.

RESULTS

Study selection

The process of selecting studies is detailed in Figure 1. The initial search produced 1940 papers and conference abstracts. The vast majority of these were clearly irrelevant (e.g., involved different clinical population such as dementia or established psychosis, or were brain imaging studies, antipsychotic trials or correlational studies). Overall, 48 were possibly relevant. Screening of abstracts reduced this to 14. The full-text publications or reports for each of these were traced. A further 6 were then excluded as they did meet inclusion criteria (see Figure 1). A total of 8 studies were relevant, 2 of which could not be included because they were ongoing (Bechdolf *et al.*, 2011) or have yet to be published (Stain, 2012 – see Table 1). Trial publication details are given in Table 1.

Study characteristics and treatment

Trial characteristics and baseline demographics for all studies are given in Table 2.

The CBT provided was based on published treatment manuals. Four trials (Addington *et al.*, 2011, Morrison *et al.*, 2012a, Morrison *et al.*, 2004, Rietdijk *et al.*, 2010) were based on one approach

(French & Morrison, 2004). The remaining two trials (Bechdolf *et al.*, 2012, McGorry *et al.*, 2012) were each based on one of two other published manuals (Bechdolf *et al.*, 2010, Yung *et al.*, 2004). All approaches involved time-limited and structured sessions, formulation, self-monitoring, collaboration, homework between sessions, use of cognitive and behavioural experiments and other strategies to address unhelpful appraisals and improve coping, a focus on patient goals and work on addressing a range of difficulties as prioritised by the patient.

Risk of bias

Selection bias refers to the risk of researchers being able to influence, or have knowledge of, allocation of participants to treatment (Higgins *et al.*, 2011a). Such bias has been found to inflate effect size estimates by around 30-40% (Schulz *et al.*, 1995). A particular strength of the included trials was that randomisation and allocation procedures were clearly described and adequate in most cases, meaning such bias was generally low. However, although well-described and involving adequate concealment, the randomisation procedure in Morrison 2004 produced significantly unequal sample sizes, meaning the risk of selection bias was unclear.

Detection bias refers to the risk that those completing outcome assessments know who received which treatment (Higgins *et al.*, 2011a). This is more of a problem when the assessments depend on the subjective judgement of the assessor (e.g., diagnosis), and less of a problem when they are more objective (e.g., death, unemployment). The risk of bias in this domain was unclear in 2 out of 6 trials because they did not report whether or not there were blind-breaks (Addington *et al.*, 2011, Yung *et al.*, 2011), and high in one study because they did not report attempts to use blinding (Bechdolf *et al.*, 2012) and described their study as open-label in their published protocol. The other 3 studies did report some blind-breaks (Morrison *et al.*, 2012a, Morrison *et al.*, 2004, van der Gaag *et al.*, 2012), however we assessed risk of bias as low for at least the assessment of transition because each trial introduced new blinded raters to either take over or validate the assessments, while one trial also validated their assessments by comparing them to an external measure with some ecological validity - prescription of antipsychotic medication by an independent psychiatrist (Morrison *et al.*, 2004). Incidence of unblinding was also relatively low (5-22%) in two studies (Morrison *et al.*, 2012a, van der Gaag *et al.*, 2012), although precise figures were not reported for the third (Morrison *et al.*, 2004).

Performance bias refers to the risk of participants or clinical personnel being aware of treatment allocation (Higgins *et al.*, 2011a), as this may result in a change in behaviour designed to please the experimentor. A high risk of such bias is unavoidable in therapy trials, particularly when assessments rely on participant self-report, and indeed there is evidence from two included trials that at least some participants are able to conceal psychotic symptoms if motivated to do so (Morrison *et al.*, 2004, van der Gaag *et al.*, 2012).

There was a high risk of bias from selective reporting by Bechdolf 2012, in that no continuous symptom endpoint or change data were reported in either the main (Bechdolf *et al.*, 2012) or a secondary publication (Bechdolf *et al.*, 2007), despite this being identified a priori as a secondary outcome (see Table 1 for details of online trial protocol). The first author has advised there were no group differences with respect to symptoms, but these analyses were not reported in the main publication because peer-reviewers argued the figures would be distorted by the premature exit of those who developed psychosis.

A number of outcomes from Morrison 2012 (Morrison *et al.*, 2012a) (quality of life at all assessment points, and all outcomes at 24-months) were at high risk of attrition bias due to large amounts of missing data (>50%) over and above planned drop-out (Xia *et al.*, 2009). This was also true for all 36-

month outcomes from Morrison 2004 (Morrison *et al.*, 2007, Morrison *et al.*, 2004). In the other studies, attrition bias was either low for the primary analysis of transition rates, or unclear (McGorry *et al.*, 2012). Risk of attrition bias inevitably increases as drop-out increases, which in turn is normally a function of trial duration. Thus the longer-term outcomes are more suspect in this domain than shorter-term outcomes.

Outcomes

Primary outcome (see Figures 2-4)

Transition at 6-months: All 6 trials contributed to this outcome, providing data from 800 participants. The difference in transition rates observed in the random-effects analysis (RR 0.52 [0.27, 1.02], p=0.06) just failed to meet the criterion for statistical significance, meaning the odds of such a difference arising by chance alone were 1:17 instead of the requisite 1:20. Results achieved statistical significance (p=0.03) if we excluded equivocal data from (Yung *et al.*, 2011).

Since heterogeneity was low (13%), a fixed-effects analysis was also conducted, as per our protocol. In this analysis the effect size was comparable if not slightly larger (RR 0.47 [0.27, 0.82]) but highly statistically significant (p=0.008), meaning the odds of the observed differences arising by chance alone were 1:125. These odds fell to 1:17 (p=0.06) if we removed CBT favourable results from the large van der Gaag et al trial (van der Gaag *et al.*, 2012).

Based on an observed absolute risk reduction of -0.05 [-0.08, -0.01], the number needed to treat for all 6 studies combined was 20 (13, 100). However the control group transition rate of 9% (4% in CBT; 6% overall) was lower than other meta-analytical estimates, where 18% were found to make transition over 6 months (Fusar-Poli *et al.*, 2012a). The NNT estimate derived from the product of the Fusar-Poli et al transition rate and our observed fixed effect RRR was considerably smaller at 10 (8, 31).

The control group transition rate increased to 12% (5% in CBT; 9% overall) if we excluded both a study of early prodromal psychosis (i.e., where fewer would be expected to develop psychosis) (Bechdolf *et al.*, 2012), and a study where 29 potential participants were excluded because they developed or disclosed established psychosis between baseline assessments, before they were randomised (Morrison *et al.*, 2012a).

Sensitivity analyses: The magnitude and precision of the effect favouring CBT was reduced if we excluded the Bechdolf 2012 study (random effects: RR 0.58 [0.31, 1.07], p=0.08; fixed effects: RR 0.55 [0.31, 0.99], p=0.05, RD-NNT 25 [13, ∞], ACR-NNT 12 [8, 556]), which differed from the other trials in respect of non-masked assessments, additional psychosocial interventions received by the CBT group (cognitive remediation, family psychoeducation) and population studied (early prodromal). Since this study was described as CBT in both the trial protocol and in a previous publication (Bechdolf *et al.*, 2007), and since they reported the numbers developing a first episode of psychosis, we deemed inclusion to be valid. The effect size was also slightly smaller and less precise if we assumed the 7 participants in 2 RCTs (Morrison *et al.*, 2004, van der Gaag *et al.*, 2012) assessed as having concealed their pre-randomisation transition to psychosis (e.g., as evidenced by past antipsychotic use or self-report) were in fact new transitions (random effects: RR 0.64 [0.37, 1.11], p=0.11; fixed effects: RR 0.56 [0.34, 0.94], p=0.03, RD-NNT 25 [13, 100], ACR-NNT 13 [8, 93]).

Transition at 12-months: All 6 trials also contributed data to this outcome. A random-effects analysis found CBT was associated with a significantly reduced risk of transition (RR 0.45 [0.28, 0.73], p=0.001, RD -0.09 [-0.14, -0.04]), with a numbers needed to treat of between 11 (7, 25), using the

inverse of the observed RD, and 8 (6, 17) using the observed RRR and an assumed control risk of 22% (Fusar-Poli *et al.*, 2012a). No heterogeneity was observed, however the fixed-effects analysis produced a slightly better relative risk estimate (RR 0.40 [0.25, 0.64], p=0.0001) and a slightly reduced estimate of the absolute risk reduction (RD -0.08 [-0.12, -0.04]). The results were robust to a leave one-out analysis, suggesting they were not driven by one trial alone.

Overall, just over 13% of the control-group participants included in this analysis developed psychosis (5% in the CBT group; 9% overall), which is clearly lower than the 22% reported elsewhere (Fusar-Poli *et al.*, 2012a). Removing data from the 2 trials where baseline transition risk may have been reduced by trial design issues (Bechdolf *et al.*, 2012, Morrison *et al.*, 2012a) resulted in a comparable control group transition rate of 18% (7% in CBT; 12% overall). The pooled data from the remaining 4 trials remained favourable to CBT, if not slightly more so.

Sensitivity analyses: The magnitude and precision of effect favouring CBT was slightly reduced if we excluded the Bechdolf (2011) study, according to both random and fixed effects analyses (RR 0.48 [0.30, 0.79], p=0.001, RD -0.07 [-0.13, -0.02], RD-NNT 14 [8, 50], ACR-NNT 9 [6, 22]). Reclassifying 7 pre-randomisation transitions in 2 RCTs as post-randomisation transitions was also associated with a slight reduction in effect size magnitude in both the random (RR 0.53 [0.34, 0.82], p=0.005, RD -0.08 [-0.13, -0.03], RD-NNT 13 [8, 33], ACR-NNT 10 [7, 25]) and fixed effects analyses (RR 0.47 [0.30, 0.72], p=0.0005, RD -0.08 [-0.12, -0.03], RD NNT 13 [8, 33], ACR NNT 9 [6, 16]).

Transition at 18-24 months: Four trials provided usable data from 452 participants. A random-effects analysis found CBT was associated with a reduced likelihood of transition (RR 0.41 [0.23, 0.72], p=0.002, RD -0.12 [-0.18, -0.06]). The NNT was 8 (6, 14) when derived from the observed RD, and 6 (5, 11) when derived from the observed RRR and an assumed control risk of 27-29% (Fusar-Poli *et al.*, 2012a). Heterogeneity remained absent (0%), but the fixed effect analysis produced slightly more favourable results (RR 0.36 [0.21, 0.63], p= 0.0004, RD -0.12 [-0.18, -0.06]), although the NNT estimates were unaffected. Although Morrison 2012 reported equivocal 24-month data, over 50% of this was missing even after accounting for planned drop-out, therefore this was not included in the analysis. The results were also robust to a leave one-out analysis.

Approximately 18% of control-group participants in these 4 trials converted to psychosis by 18-24 months (6% in CBT; 12% overall), whereas Fusar-Poli and colleagues reported rates of 27% (18 months) and 29% (24 months). Excluding the Bechdolf (2011) study was associated with marginally increased transition rates in the control group (19%), the CBT group (8%) and overall (14%).

Sensitivity analyses

Excluding the Bechdolf study was also associated with a marginal reduction in magnitude of effect favouring CBT (random-effects: RR 0.46 [0.28, 0.75], p=0.01, RD -0.11 [-0.17, -0.05]; fixed-effects: 0.44 [0.27, 0.72], p=0.007, RD -0.11 [-0.17, -0.05]) with NNTs ranging from 6 (5, 12; based on RRR of 0.56 and ACR of 29%) to 9 (6, 20; based on RD of -0.11). Re-classifying 5 pre-randomisation transitions in van der Gaag et al (2012) as post-randomisation transitions had a slight effect on the fixed effect analysis only (RR 0.42 [0.27, 0.64], p=0.0008, RD -0.11 [-0.16, -0.06]), with NNT estimates ranging from 6 (5, 10; based on RRR of 0.58 and ACR of 29%) to 9 (6, 17; based on RD of -0.11).

Eighteen-month data from McGorry et al (2012) suffered from 47% missing data (McGorry, Yuen and Yung, personal communication) while transition at this time-point was defined pragmatically as receipt of (a) help from a State psychiatric hospital and (b) a diagnosis of psychotic illness (McGorry, Yuen and Yung, personal communication), as inferred from medical records (McGorry *et al.*, 2012). Excluding this potentially less reliable data was associated with an increase in the magnitude of the

CBT-favourable effect size in the random-effects analysis (RR 0.30 [0.12, 0.72], p=0.02, RD -0.13 [-0.18, -0.07]), with the most favourable NNT estimate now being 5 (4, 12; based on RRR of 0.70 and ACR of 29%) and the least favourable now being 8 (6, 14; based on fixed-effects RD of -0.12).

Although these results are promising, the reporting of transition rates and numbers leaving early did not allow the impact of changing assumptions about the outcome of those who left early to be easily assessed. For example, it was often not clear from the study reports whether the numbers lost to follow-up or numbers failing to complete assessments included those who made transition before that particular assessment point. Thus the figures reported above may not be robust to changing assumptions about the outcome of those leaving early.

Test of robustness of findings to unpublished study: One obvious concern is that the completed 12-month study remains unpublished because of disappointing findings. In order to test how the overall results would be affected by this risk, we entered either equivocal or even highly unfavourable data for this trial into the meta-analysis, using information in the published protocol. In each case we made several reasonable but conservative assumptons, which were: (1) the researchers recruited to target (N=78); (2) each group had an N of 39; (3) the transition rate in the control group was the same as the combined control-arm transition rate of all the other studies (i.e., 6 months: 9%; 12 months: 13%).

These tests suggested that, at 6 months, the overall RR for the favourable fixed effect analysis would be slightly smaller if we assume an equivocal result (RR 0.52 [0.31, 0.87], p=0.01), meaning the relative risk of transition would be reduced by 48% rather than 53%. Although the absolute risk reduction would only be slightly smaller (RD -0.04 [-0.08, -0.01]) the RD-derived NNT would increase from 20 to 25 (13, 100). The ACR-derived NNT, based on an 18% transition rate (Fusar-Poli *et al.*, 2012a) and an RRR of 0.48, would increase to 12 (8, 51). If, compared to the control group, twice as many people in the CBT-group developed psychosis by 6 months then the pooled effect size would be smaller and of borderline statistical significance (RR 0.62 [0.38, 1.00], p=0.05, RD -0.03 [-0.07, -0.00]).

At 12 months, the overall RR would be slightly smaller for the favourable random-effects analysis if we assume an equivocal result (RR 0.51 [0.32, 0.80], p=0.004; RD -0.08 [-0.13, -0.03]), leading to an RD-derived NNT of 13 (8, 33) and an ACR-derived NNT of 10 (7, 23; based on 22% transition rate and an RRR of 0.49). If we assume twice as many people receiving CBT made transition than those receiving the control treatment, then the magnitude of the effect size estimate would remain largely unaffected (RR 0.54 [0.27, 1.06], RD -0.07 [-0.14, -0.01]), but statistical significance would decline to trend level (p=0.07). Of course this would not render CBT ineffective; rather it would suggest a need to investigate what was causing the now considerable 49% heterogeneity (NICE, 2009).

Importantly, the Stain study researchers have advised that (a) there were few transitions in their study (b) that they recruited ~57 participants instead of the target 78 (Stain, personal communication, 2012) and (c) the reasons for non-publication do not relate to null findings. Unfortunately group comparison data were not provided.

Secondary outcomes (Figures 5 and 6)

Symptoms

Data from 4 trials (Figure 5) did not suggest a difference in overall symptom severity between groups at 6 months (Hedges' g -0.07 [-0.25, 0.12], p=0.48) and data from 2 trials did not suggest a difference

in symptom-related distress (g -0.16 [-0.53, 0.22], p=0.15), although there was notable heterogeneity (68%) in this analysis.

At 12 months, available data from 5 trials suggested CBT was associated with a small effect on symptoms (Hedges' g -0.25 [-0.46, -0.03], p=0.02). If we used endpoint instead of mean change data for the Yung (2011) study, then the effect was smaller and achieved statistical significance only when a fixed-effects analysis was used (g -0.20 [-0.39, -0.02], p=0.03). Data from 2 trials did not reveal a significant difference in symptom-related distress (g -0.17 [-0.39, 0.05], p=0.14).

Small benefits in symptom severity at 18-24 months in the two trials reporting usable data (Addington *et al.*, 2011, van der Gaag *et al.*, 2012) did not achieve statistical significance, regardless of whether we used frequency (g -0.26 [-0.57, 0.04], p=0.09) or intensity data (g -0.17 [-0.47, 0.14], p=0.28) from van der Gaag (2012). No difference in symptom-related distress was found in the one trial reporting usable 18-month data (van der Gaag *et al.*, 2012). CBT-favourable 18-24 month severity and distress data from Morrison 2012 suffered from >50% attrition and were therefore excluded.

Functioning

Three trials reported usable 6-month data on the Global Assessment of Functioning (GAF) scale (Figure 6), while one reported usable data on the Social Functioning Assessment Scale (SOFAS). No difference was observed (g -0.03 [-0.31, 0.25], p=0.84; negative sign = CBT worse). At 12-months, no difference was again observed in a combined analysis of GAF, SOFAS or Social Adjustment Scale II data from 5 trials (g. 0.03 [-0.21, 0.27], p=0.78). GAF results from Morrison 2004 suffered from >50% missing data. Two trials reported usable GAF data at 18 months, but no difference was detected (g 0.09 [-0.21, 0.39], p=0.56). Twenty-four month GAF data from Morrison 2012 was not usable due to missing data.

Quality of life

Data from two trials did not reveal group differences in relation to quality of life at 6 months (g -0.09 [-0.35, 0.18], p=0.52), or at 12 months (g 0.00 [-0.28, 0.28], p=0.99). No group differences were observed at 18 months in the one trial reporting usable data at this time-point (g 0.11 [-0.22, 0.44], p=0.51) (van der Gaag *et al.*, 2012). Morrison (2012) reported equivocal results at 6, 12 and 24 months, but over 50% of the data was missing at each time point, and therefore was not included in the analysis.

Adverse effects

Limited data on adverse effects were available from 5 studies, most of which could not be combined for meta-analysis. Bechdolf (2012) reported that no participants were withdrawn for deteriorating mood or suicidal ideation (Bechdolf *et al.*, 2012) while analysis of reasons for drop-out in Addington (2011) suggested 1 person receiving supportive therapy discontinued after 3 months due to subjective fears of worsening paranoia and referential thinking (Addington *et al.*, 2011).

McGorry 2012 reported adverse effects at 6 months, however data was missing from almost 50% of participants and 12-month data was available for only 33% of those randomised(McGorry *et al.*, 2012). At 6-months, no significant differences were observed between CBT plus placebo (N=44) and supportive therapy plus placebo (N=28) with respect to significant weight-gain (2 vs 1, for the CBT and control groups respectively), fatigue (14 vs 8), depression (11 vs 5), concentration problems (7 vs 2), orthostatic dizziness (3 vs 3), or the psychic (18 vs 11), neurologic (4 vs 2), autonomic (13 vs 8)

or ‘other’ (11 vs 6) Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Subscales (Lingjaerde *et al.*, 1987) (all p>0.05).

No differences in numbers with clinical levels of social anxiety (6 months: RR 0.93 [0.67, 1.30], p=0.67; 12 months: 1.05 [0.73, 1.51], p=0.80) or depression (6 months: RR, 0.94 [0.74, 1.19, p=0.58; 12 months: RR 0.88 [0.67, 1.15], p=0.35) were observed in the two trials reporting this data. One trial reported 18-month data, and no significant differences were found (van der Gaag *et al.*, 2012). Morrison 2012’s 24-month figures were uninterpretable due to missing data.

Leaving the study early for any reason (Figure 7)

No differences in numbers leaving early for any reason were observed at 6 months (4 RCTs, RR 1.08 [0.82, 1.41], p=0.59), 12 months (6 RCTs, RR 0.99 [0.80, 1.23], p=0.96), 18-24 months (4 RCTs, RR 0.95 [0.79, 1.15], p=0.62) or 36 months (1 RCT, 0.96 [0.60, 1.52], p=0.85).

DISCUSSION

The results of this meta-analysis are encouraging, and suggest that prevention or delay of the onset of psychosis is achievable with a psychosocial treatment alone. CBT was associated with a signficantly reduced rate of conversion to first-episode psychosis at 6, 12 and 18-24 months after treatment, compared with those receiving either monitoring or non-specific supportive therapy. The 6-month estimate was somewhat less robust, perhaps because of limited statistical power to detect differences in a relatively low-frequency event.

At every time-point, the relative risk of transition was reduced by over 50% for those receiving CBT. Overall between 8 and 11 need to receive CBT instead of, or in addition to, non-specific support for one person to avoid transition over the longer term (12 to 18-24 months). Such figures compare favourably to other preventative treatments in medicine. According to a recent comparison of psychiatric and general medical treatments, around 27 (25, 33) patients with heart disease need to take statins to prevent one major cardiac event, while around 16 (13, 25) need to take ACE-inhibitors for one to avoid death from chronic heart failure (Leucht *et al.*, 2012).

However, the NNT estimates do not just reflect treatment efficacy. They are also very much influenced by the positive predictive value (PPV) of the high-risk criteria. If the PPV of the criteria is low (i.e., few people classified as at-risk actually make transition), then the NNT will be higher regardless of the efficacy of a treatment. Likewise, once methods of predicting risk of transition improve, fewer people who are unlikely to make transition anyway will need to receive prophylactic treatment, and the NNT will be lower. In this context, relative risk estimates are a much better index of treatment-attributable benefits than are NNTs.

Interestingly the rate of transition in the control conditions of 9-18% is considerably lower than the 18-29% reported in a recent meta-analysis (Fusar-Poli *et al.*, 2012a). Although transition rates were somewhat higher (12-19%) after excluding 2 studies where baseline transition risk was potentially diluted by trial design features, there is still a clear difference between these data-sets. This might suggest risk of transition can be substantially reduced by trial participation, where people have greater access to relatively inexpensive supportive approaches such as regular monitoring, sign-posting and support. Although Fusar-Poli and colleagues reported a transition rate of 33% in those receiving standard psychiatric care and case management (Fusar-Poli *et al.*, 2012a), perhaps the relatively persistent and accessible attention offered by trial researchers and therapists reduces the risk of crises and unmet psychosocial need? Alternatively, the low transition rate may suggest fewer participants in the CBT trials included here were genuinely ‘at-risk’, and that the PPV of the high-risk

criteria needs improving (Morrison *et al.*, 2012a). The potential implications of this uncertainty for inclusion of an attenuated psychosis syndrome in DSM-V have been outlined elsewhere (Morrison *et al.*, 2012a).

The results from the secondary analyses are harder to interpret. Although there was some evidence that CBT had a small effect on symptoms at 12 months (-0.25), the differences observed at other time points were not statistically significant. The 12-month effects are comparable to the nonsignificant effect sizes of between -0.12 (-0.62, 0.38; PANSS total) and -0.26 (-0.76, 0.25; SOPS total) reported in a double-blind 1-year trial of olanzapine vs placebo for prodromal patients (McGlashan *et al.*, 2006). However, the significant effect size for weight gain in that study was 1.18 (0.63, 1.72), many participants left early, and the results have yet to be replicated. Although the 12-month CBT effect size is much smaller than the large effect size of -0.88 (-1.34, -0.44; PANSS total) reported in a double-blind study of omega-3 fatty acids vs placebo (Amminger *et al.*, 2010), this study also awaits replication.

Also on the negative side, the secondary analysis suggests CBT has yet to demonstrate effectiveness in improving functioning in this group, at any time-point. This is an important finding, and suggests existing CBT packages should be modified to target functioning specifically. An approach based on a specific cognitive model of low functioning (Beck *et al.*, 2013, Grant & Beck, 2009) has recently shown promise in chronic established psychosis (Grant *et al.*, 2012) and could perhaps be adapted for the at-risk group. Other psychosocial treatments, such as family-focused interventions, may also have an important role to play here (O'Brien *et al.*, 2007, Schlosser *et al.*, 2011). Similar results were found for quality of life, although there was only limited data on this outcome.

However one problem with the CBT trials is that there seems to be no consensus on the best way to analyse and report continuous outcome data. Some authors excluded data from those who made transition (van der Gaag *et al.*, 2012), some made transition an exit criterion for the trial but carried forward the last observation of those who converted (Bechdolf *et al.*, 2007), while some kept everyone in the trial and did not exclude any data from any time-points (Morrison *et al.*, 2012a, Morrison *et al.*, 2004). This latter approach seems most sensible to us, as it allows direct assessment of the real-world impact of CBT, minimises the use of crude imputation strategies, and helps to preserve the benefits of randomisation that exclusions inevitably remove (Hamer & Simpson, 2009, Schulz & Grimes, 2002). Of course if more in the control treatment develop psychosis and then receive antipsychotics, then this may mask any beneficial effects of CBT at endpoint. However exposure to these drugs may also be associated with more adverse effects (McGlashan *et al.*, 2006) – effects which, if measured, should greatly inform the cost-benefit analysis. It should also be remembered that transition itself is an adverse event. If all trials retained all participants and their data in the analysis, then we would be able to provide young people with much more accurate information about what is likely to happen to them if they decide CBT is not for them.

Limitations

One possible concern is that the limited number of trials with usable outcome data (N=6) precludes the use of meta-analysis. However meta-analyses have been applied successfully to numerous other commonly used treatments for psychosis, many of which have a comparable number of studies and participants. For example, there are now more data on the long-term benefits of CBT for psychosis prevention than there are for the long-term benefits in established psychosis, compared to placebo, of drugs such as chlorpromazine (Adams *et al.*, 2007), haloperidol (Joy *et al.*, 2006), olanzapine, quetiapine and aripiprazole (Leucht *et al.*, 2009). Historically only 3-5 short-term trials have been required by the US Food and Drug Administration to license a new antipsychotic [e.g., (Dubitsky *et al.*, 2002)], and the median number of studies in a typical Cochrane review is, across medicine, six

(Mallett & Clarke, 2002). According to some experts only 2 studies are required for meta-analysis *"because all other synthesis techniques are less transparent and/or are less likely to be valid."* (Valentine *et al.*, 2010) .

Sources of heterogeneity were not investigated, but this was generally low or absent. The trials were similar enough to combine in a meaningful way and subgroup analyses would not be informative at this stage. Such considerations should not be an obstacle to answering the simple question of whether CBT is benefical or not. The control conditions varied somewhat, in that some trials compared CBT-informed interventions to basic monitoring, while others used a supportive therapy control. Arguably the latter provide a more definitive assessment of the importance of specific CBT strategies, such as normalising and behavioural experiments (French & Morrison, 2004, Morrison & Barratt, 2010). Future meta-analyses will have greater power to conduct separate comparisons, looking at CBT versus usual treatment and CBT versus a control condition.

The limited number of trials also means it would be uninformative at this stage to conduct tests for publication bias. Fail-safe N analyses are not recommended (Higgins *et al.*, 2011b), and at least 10 trials are thought to be sufficient to ensure adequate power for funnel-plot tests (Ioannidis & Trikalinos, 2007). Meta-analytical assessment of treatment efficacy should not depend on having adequate power for such tests. Such a rule would be remarkably conservative and preclude meta-analyses of almost all individual treatments for psychosis as well as treatments for many other conditions. Publication bias has now been thoroughly investigated in meta-analyses of psychosocial treatments for psychosis, including meta-analyses of CBT, and this has not been found to be a major threat to the integrity of the main findings (Niemeyer *et al.*, 2012). We have shown that our primary outcome results are reasonably robust to the (low) risk of the one unpublished completed study having highly unfavourable results.

Recommendations for future trial design

Although these are promising results, firmer conclusions about the benefits and costs of CBT-informed treatment for this group are limited by methodological problems such as small sample sizes, difficulties maintaining the single-blind, selective reporting of outcomes and inconsistent assessment or reporting of potential adverse effects. However these issues are certainly not unique to these trials (Leucht *et al.*, 2008, Miyar & Adams, 2012, Perlis *et al.*, 2010, Schulz *et al.*, 1995, Thornley & Adams, 1998) nor do they vitiate the main findings.

One particular strength of the trials included here is that they suffer from relatively low rates of missing data, and clearly reported their randomisation and treatment allocation procedures. Most trials also published their trial protocol in advance of their main publication, thus reducing scope for bias, which is also a strength of our systematic review (Bushe, 2011). All except one (McGorry *et al.*, 2012) were health service or government-funded, and the researchers generally had few financial conflicts of interest. Inclusion criteria were also not overly restrictive, thus increasing generalisability.

One particular limitation was the non-thorough and inconsistent assessment and reporting of adverse effects. Researchers should consider developing a standard protocol for assessing adverse effects in trials for the at-risk group. This may include reporting the number of people in each condition experiencing a pre-defined degree of deterioration in mood, functioning or quality of life, as well as serious adverse events (e.g., strong suicidal intent, suicide attempts, violence). This is important given preliminary evidence suggesting there may be a high prevalence of suicide risk factors in the at-risk population (Hutton *et al.*, 2011, Zimbron *et al.*, 2012). Two recent trials of CBT for established psychosis provide examples of good practice for reporting harms (Klingberg *et al.*,

2012, Klingberg *et al.*, 2010) and CONSORT provide a sensible set of recommendations (Ioannidis *et al.*, 2004).

Conclusion and clinical implications

Provision of CBT was associated with a reduced risk of transition to psychosis at 6, 12 and 18-24 months, although the 6-month benefit was less robust. The results challenge the clinical equipoise which has so far characterised the field. Based on these findings, we recommend that young people seeking help for an at-risk mental state should now be offered a package of care which includes at least 6 months of structured CBT based on one of the manuals used in these trials, and delivered by an appropriately qualified and experienced professional. These young people should be advised that engaging with CBT could halve their risk of developing psychosis over an 18-24 month period, although they are unlikely to gain additional benefits in relation to functioning or quality of life. They should also be advised that the available evidence suggests CBT is unlikely to lead to increased depression or social anxiety, but that data on adverse effects is generally very limited. This recommendation should not be taken to imply that other treatments should not also be offered to this group, if proven effective. We are advocates of treatment choice (Morrison *et al.*, 2012b) which, to be meaningful, requires several effective treatments to choose from.

Declaration of interest

There was no financial funding for this work. Both authors are employed by the NHS in England and the first author is a member of Professor Tony Morrison's (Chief Investigator in two of the key trials reviewed above) research unit. Both authors report no financial conflicts of interest.

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Figure 1 PRISMA flowchart detailing study selection

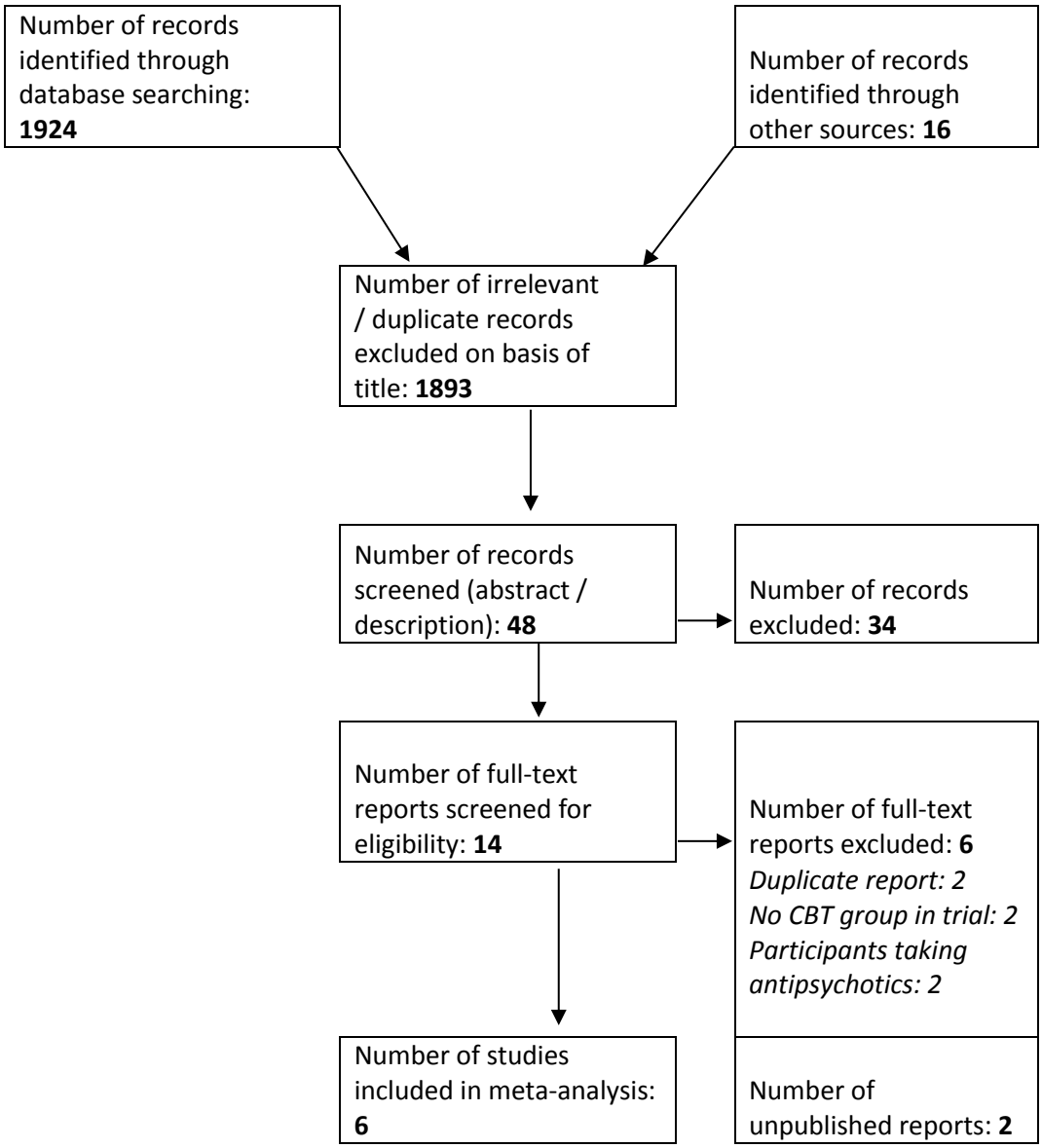
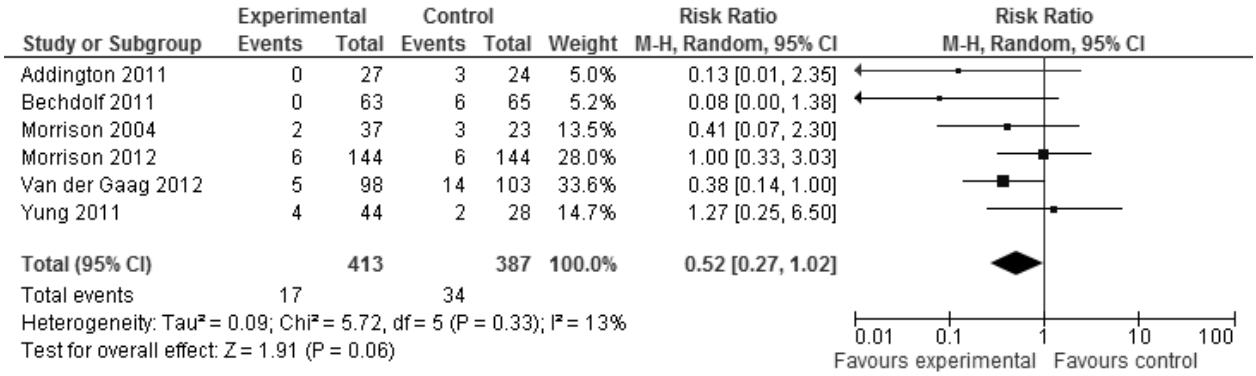


Figure 2 Transition at 6-months



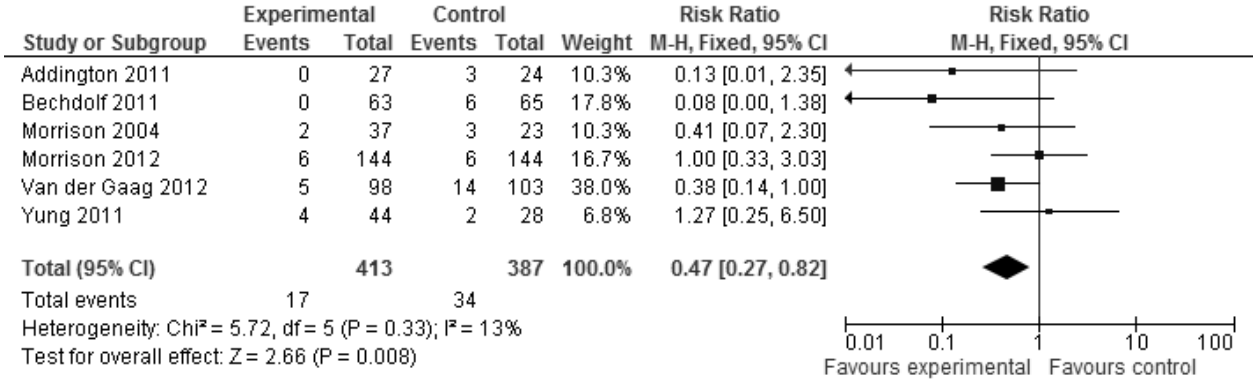
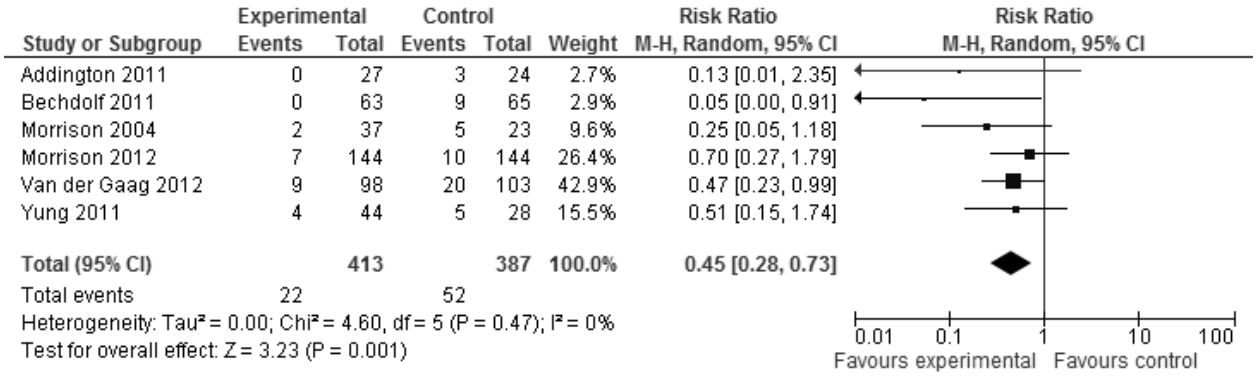


Figure 3 Transition at 12-months



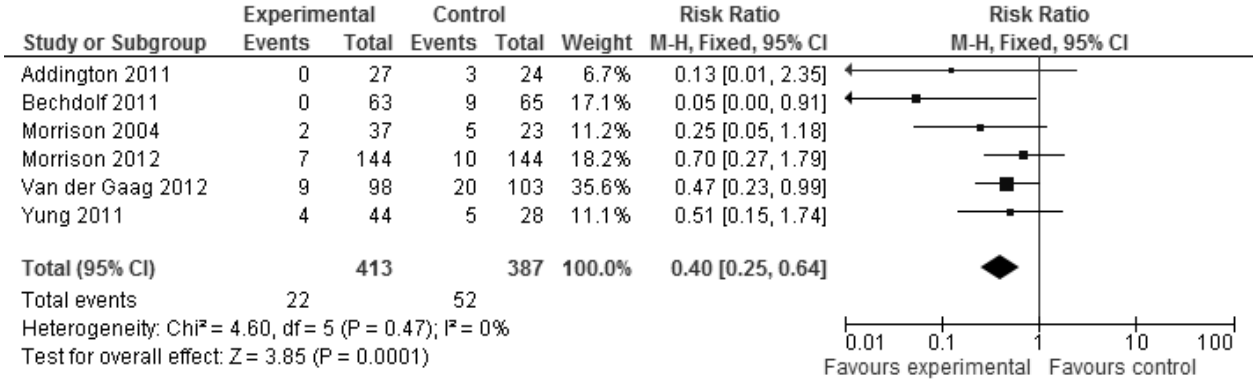


Figure 4 Transition at 18-24 months

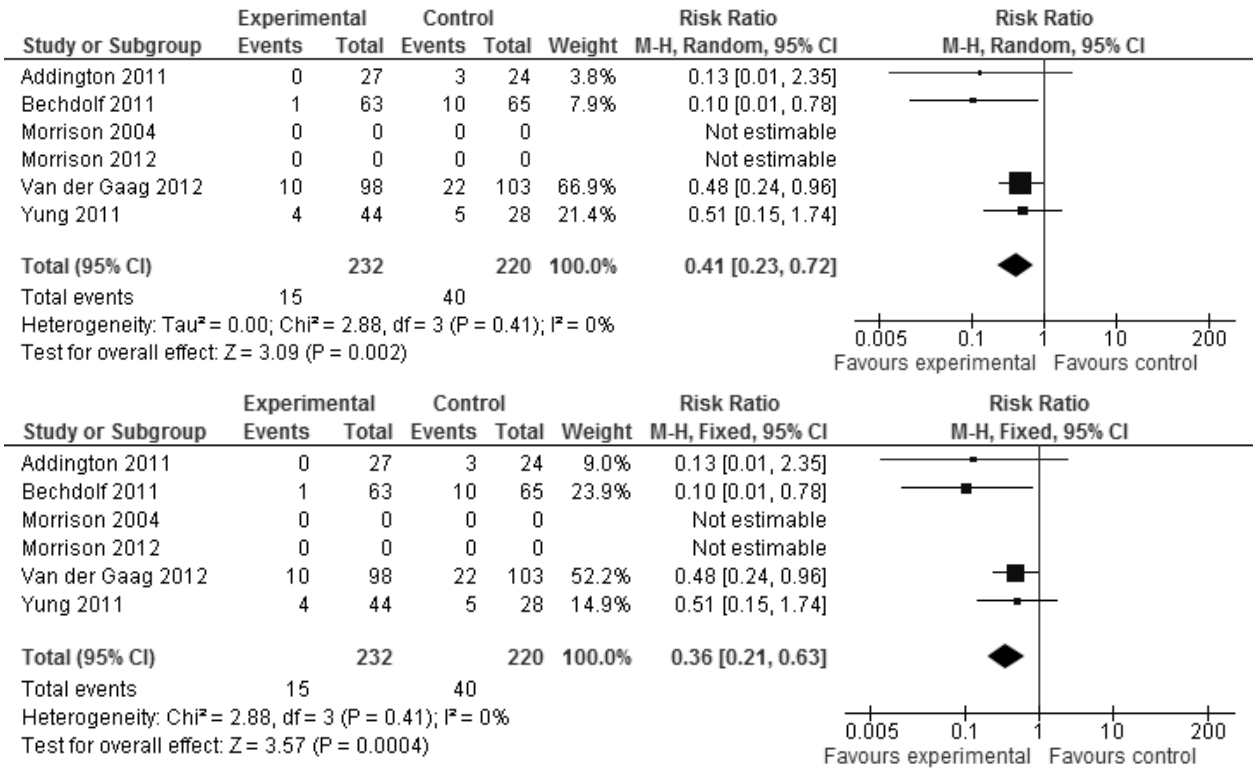
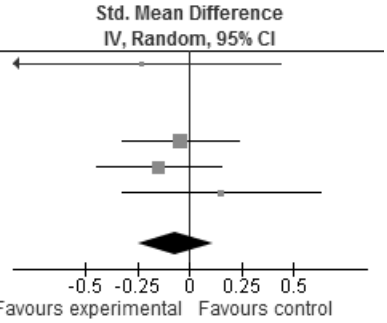


Figure 5 Symptoms at 6, 12 and 18-24 months

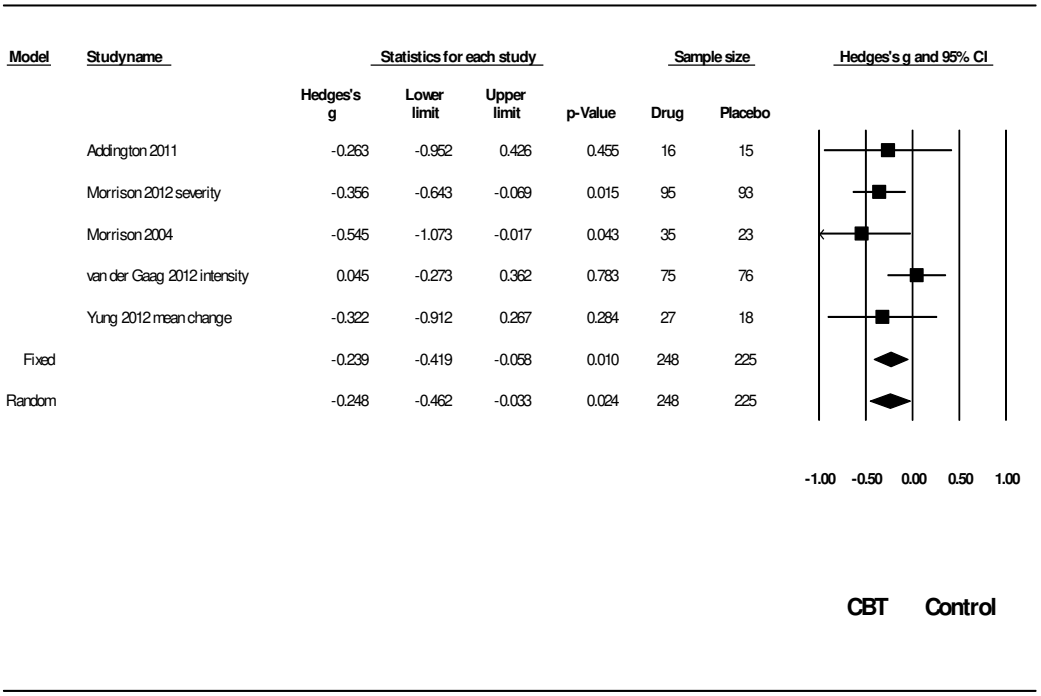
(a) **6 months**

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	6.4	5.2	19	7.6	4.9	16	7.4%	-0.23 [-0.90, 0.44]
Bechdolf 2011	0	0	0	0	0	0		Not estimable
Morrison 2004	0	0	0	0	0	0		Not estimable
Morrison 2012	17.89	16.5	97	18.69	19.34	99	41.9%	-0.04 [-0.32, 0.24]
Van der Gaag 2012	7.9	4.3	80	8.5	3.9	90	36.1%	-0.15 [-0.45, 0.16]
Yung 2011	12.4	8.8	44	11.1	7.6	28	14.6%	0.15 [-0.32, 0.63]
Total (95% CI)			**240**			**233**	**100.0%**	**-0.07 [-0.25, 0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)



(b) **12 months**



(c) **18-24 months**

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	4.6	4.6	15	4.5	4.1	13	16.7%	0.02 [-0.72, 0.76]
Bechdolf 2011	0	0	0	0	0	0		Not estimable
Morrison 2004	0	0	0	0	0	0		Not estimable
Morrison 2012	0	0	0	0	0	0		Not estimable
Van der Gaag 2012	4.1	4.2	71	4.9	3.5	69	83.3%	-0.21 [-0.54, 0.13]
Yung 2011	0	0	0	0	0	0		Not estimable
Total (95% CI)			**86**			**82**	**100.0%**	**-0.17 [-0.47, 0.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)

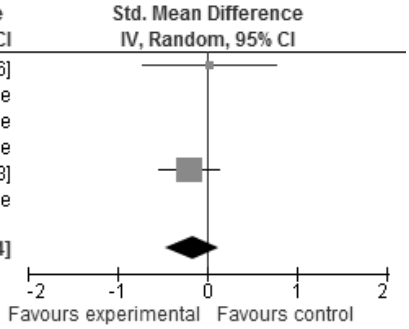
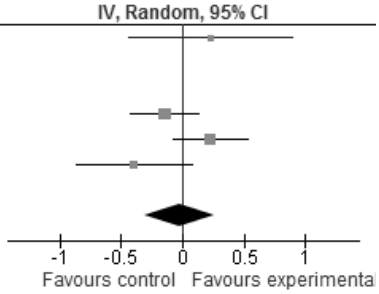


Figure 6 Functioning at 6, 12 and 18-24 months

(a) 6 months

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	64.2	14.4	19	61.3	9.9	16	13.3%	0.23 [-0.44, 0.89]
Bechdolf 2011	0	0	0	0	0	0		Not estimable
Morrison 2004	0	0	0	0	0	0		Not estimable
Morrison 2012	59.3	16.21	97	61.61	15.04	98	33.8%	-0.15 [-0.43, 0.13]
Van der Gaag 2012	53.8	9.7	80	51.5	10.6	90	32.2%	0.22 [-0.08, 0.53]
Yung 2011	5.5	5.9	44	7.8	5.5	28	20.7%	-0.40 [-0.87, 0.08]
Total (95% CI)			**240**			**232**	**100.0%**	**-0.03 [-0.31, 0.25]**

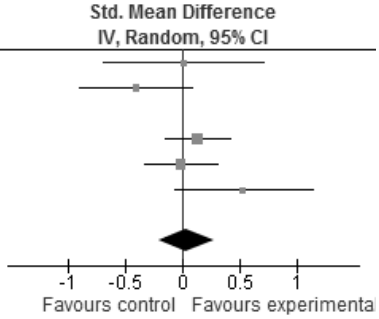
Heterogeneity: Tau² = 0.04; Chi² = 6.20, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 0.20 (P = 0.84)



(b) 12 months

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	62.7	12.3	16	62.6	10.2	15	9.7%	0.01 [-0.70, 0.71]
Bechdolf 2011	-3.3	0.945	29	-2.9	0.999	38	17.1%	-0.41 [-0.89, 0.08]
Morrison 2004	0	0	0	0	0	0		Not estimable
Morrison 2012	60.74	16.69	95	58.59	16.23	94	32.0%	0.13 [-0.16, 0.42]
Van der Gaag 2012	56.8	11.8	75	57	13.3	76	28.7%	-0.02 [-0.33, 0.30]
Yung 2011	13.1	10.5	26	7	12.5	19	12.5%	0.53 [-0.08, 1.13]
Total (95% CI)			**241**			**242**	**100.0%**	**0.03 [-0.21, 0.27]**

Heterogeneity: Tau² = 0.03; Chi² = 6.20, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 0.28 (P = 0.78)



(c) 18-24 months

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington 2011	60.2	17.9	15	63.4	11	13	16.6%	-0.21 [-0.95, 0.54]
Bechdolf 2011	0	0	0	0	0	0		Not estimable
Morrison 2004	0	0	0	0	0	0		Not estimable
Morrison 2012	0	0	0	0	0	0		Not estimable
Van der Gaag 2012	61.6	12.8	71	59.6	13.7	69	83.4%	0.15 [-0.18, 0.48]
Yung 2011	0	0	0	0	0	0		Not estimable
Total (95% CI)			**86**			**82**	**100.0%**	**0.09 [-0.21, 0.39]**

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

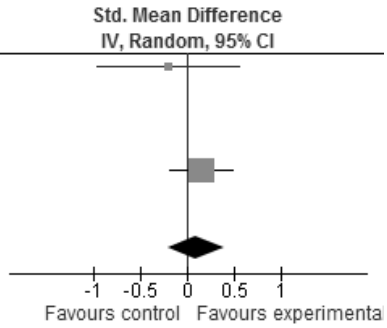
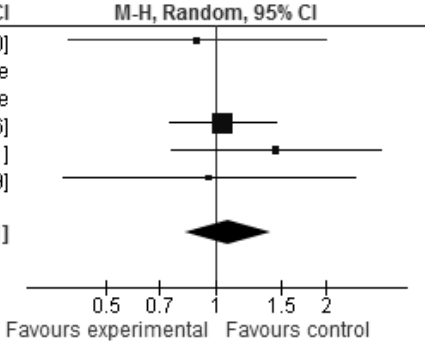


Figure 7 Leaving the study early (any reason)

(a) 6 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Addington 2011	8	27	8	24	11.0%	0.89 [0.39, 2.00]
Bechdolf 2011	0	0	0	0		Not estimable
Morrison 2004	0	0	0	0		Not estimable
Morrison 2012	47	144	45	144	63.7%	1.04 [0.75, 1.46]
Van der Gaag 2012	18	98	13	103	16.7%	1.46 [0.75, 2.81]
Yung 2011	9	44	6	28	8.6%	0.95 [0.38, 2.39]
Total (95% CI)		**313**		**299**	**100.0%**	**1.08 [0.82, 1.41]**
Total events	82		72			

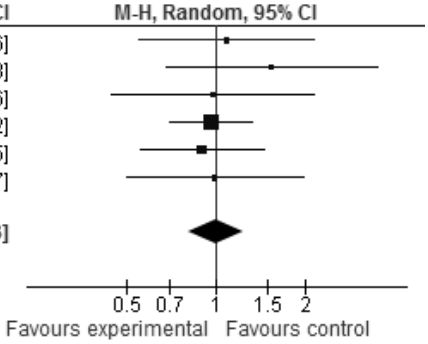
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



(b) 12 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Addington 2011	11	27	9	24	9.8%	1.09 [0.55, 2.16]
Bechdolf 2011	12	63	8	65	6.8%	1.55 [0.68, 3.53]
Morrison 2004	11	37	7	23	7.4%	0.98 [0.44, 2.16]
Morrison 2012	49	144	51	144	46.3%	0.96 [0.70, 1.32]
Van der Gaag 2012	23	98	27	103	19.9%	0.90 [0.55, 1.45]
Yung 2011	14	44	9	28	9.7%	0.99 [0.50, 1.97]
Total (95% CI)		**413**		**387**	**100.0%**	**0.99 [0.80, 1.23]**
Total events	120		111			

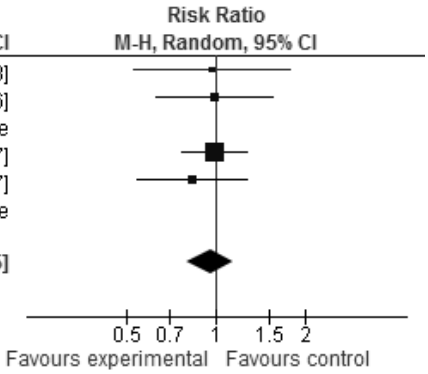
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 5 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



(c) 18-24 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Addington 2011	12	27	11	24	9.3%	0.97 [0.53, 1.78]
Bechdolf 2011	23	63	24	65	16.4%	0.99 [0.63, 1.56]
Morrison 2004	0	0	0	0		Not estimable
Morrison 2012	51	85	48	79	55.3%	0.99 [0.77, 1.27]
Van der Gaag 2012	27	98	34	103	19.0%	0.83 [0.55, 1.27]
Yung 2011	0	0	0	0		Not estimable
Total (95% CI)		**273**		**271**	**100.0%**	**0.95 [0.79, 1.15]**
Total events	113		117			

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)



(d) 36 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Morrison 2004	20	37	13	23	100.0%	0.96 [0.60, 1.52]
Total (95% CI)		**37**		**23**	**100.0%**	**0.96 [0.60, 1.52]**
Total events	20		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)

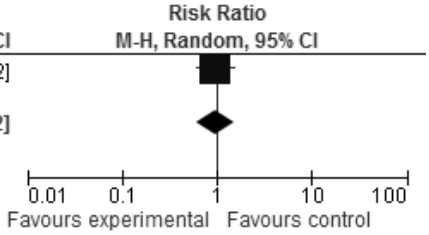


Table 1 Trial details

Trial	Year of completion	Was trial protocol registered in public domain?	Reference(s) for primary publication(s)	Reference for peer-reviewed pre-results protocol
Included in meta-analysis				-
Addington	2011	Yes[1]	(Addington *et al.*, 2011)	-
Bechdolf	2011	Yes[2]	(Bechdolf *et al.*, 2012, Bechdolf *et al.*, 2007)	-
Morrison	2004	No	(Morrison *et al.*, 2004)	(Morrison *et al.*, 2002)
Morrison	2012	Yes[3]	(Morrison *et al.*, 2012a)	(Morrison *et al.*, 2011)
Yung	2011	Yes[4]	(McGorry *et al.*, 2012, Yung *et al.*, 2011)	(Phillips *et al.*, 2009)
Van der Gaag	2011	Yes[5]	(van der Gaag, 2012, van der Gaag *et al.*, 2012)	(Rietdijk *et al.*, 2010)
Not included in meta-analysis				
Bechdolf	Ongoing	Yes[6]	Not complete	(Bechdolf *et al.*, 2011)
Stain	2012	Yes[7]	Not published or available	-

[1] http://clinicaltrials.gov/ct2/show/study/NCT00260273

[2] http://clinicaltrials.gov/ct2/show/NCT00204087

[3] http://www.controlled-trials.com/ISRCTN56283883

[4] http://www.anzctr.org.au/trial_view.aspx?ID=322

[5] http://www.controlled-trials.com/ISRCTN21353122

[6] http://www.controlled-trials.com/isrctn/pf/02658871

[7] http://www.anzctr.org.au/ACTRN12606000101583.aspx

Table 2 Trial characteristics and baseline demographics

							Baseline demographics			
Trial	**Treatments**	**Number randomised**	**Maximum duration of treatment, months (no. therapy sessions)**	**Primary criterion used to determine at-risk mental state**	**Primary criterion used to determine transition to psychosis**	**Number of centres, location (country)**	**Age, mean (SD)**	**Number female (%)**	**Baseline symptom severity, measure used, mean score (SD)**	**Follow-up data available (months after baseline)**
Included in meta-analysis										
Addington 2011 (Addington *et al.*, 2011)	CBT	27	6 (20)	COPS, SIPS (Miller *et al.*, 2003a, Miller *et al.*, 2003b)	POPS (McGlashan *et al.*, 2003)	1, Toronto, (Canada)	20.8 (4.5)	9 (33)	SOPS positive, 10.8 (4.1)	6, 12, 18
	Supportive therapy	24	6 (20)				21.1 (3.7)	6 (25)	SOPS positive, 12.3 (5)	
Bechdolf 2012 (Bechdolf *et al.*, 2012)	IPI (includes CBT)	63	12 (25)	ERIraos (Haefner *et al.*, 2011)	PANSS[5]	4, Cologne, Borne, Dusseldorf, Munich, (Germany)	25.2 (5.4)	24 (38)	PANSS positive, 9.4 (2.9)	12, 24
	Supportive counselling	65	12 (30)				26.8 (6.2)	23 (35)	PANSS positive, 9.2 (2.1)	
Morrison 2004 (Morrison *et al.*, 2004)	CBT plus monitoring	37	6 (26)	PACE (Yung *et al.*, 1996a)	PANSS[5]	1, Manchester (United Kingdom)	20.6 (4.9) [1]	14 (38)	PANSS total, 61.2 (12.2)	6, 12, 36[2]

							Baseline demographics			
Trial	**Treatments**	**Number randomised**	**Maximum duration of treatment, months (no. therapy sessions)**	**Primary criterion used to determine at-risk mental state**	**Primary criterion used to determine transition to psychosis**	**Number of centres, location (country)**	**Age, mean (SD)**	**Number female (%)**	**Baseline symptom severity, measure used, mean score (SD)**	**Follow-up data available (months after baseline)**
	Monitoring	23	n/a				21.5 (5.2) [1]	4 (17)	PANSS total, 57.5 (7.6)	
Morrison 2012 (Morrison *et al.*, 2012a)	CBT plus monitoring	144	6 (26)	CAARMS (Yung *et al.*, 2005)	CAARMS (Yung *et al.*, 2005)	5, Manchester, Birmingham, Glasgow, Cambridge, Norfolk (United Kingdom)	20.7 (4.2)	55 (38)	CAARMS severity total, 38.7 (16.8)	6, 12, 24
	Monitoring	144	n/a				20.8 (4.5)	53 (37)	CAARMS severity total, 38.2 (17.8)	
McGorry 2012 (McGorry *et al.*, 2012, Yung *et al.*, 2011) [4]	CBT plus risperidone	43	12 (NS)[3]	CAARMS (Yung *et al.*, 2005)	CAARMS (Yung *et al.*, 2005)	1, Melbourne (Australia)	NS	NS	BPRS total, 28.1 (9.2)	6, 12, 18
	CBT plus placebo	44	12 (NS)[3]				NS	NS	BPRS total, 29.1 (9.0)	

							Baseline demographics			
Trial	**Treatments**	**Number randomised**	**Maximum duration of treatment, months (no. therapy sessions)**	**Primary criterion used to determine at-risk mental state**	**Primary criterion used to determine transition to psychosis**	**Number of centres, location (country)**	**Age, mean (SD)**	**Number female (%)**	**Baseline symptom severity, measure used, mean score (SD)**	**Follow-up data available (months after baseline)**
	Supportive therapy plus placebo	28	12 (NS)[3]				NS	NS	BPRS total, 26.8 (9.3)	
Van der Gaag, (Rietdijk *et al.*, 2010, van der Gaag, 2012, van der Gaag *et al.*, 2012)	CBT plus monitoring	98	6 (26)	CAARMS (Yung *et al.*, 2005)	CAARMS (Yung *et al.*, 2005)	2, The Hague, Friesland (Netherlands)	22.9 (5.6)	49 (50)	CAARMS positive, 10.2 (3)	6, 12, 18
	Monitoring	103	n/a				22.6 (5.5)	53 (51.5)	CAARMS positive, 10.3 (2.5)	
Not included in meta-analysis										

							Baseline demographics			
Trial	**Treatments**	**Number randomised**	**Maximum duration of treatment, months (no. therapy sessions)**	**Primary criterion used to determine at-risk mental state**	**Primary criterion used to determine transition to psychosis**	**Number of centres, location (country)**	**Age, mean (SD)**	**Number female (%)**	**Baseline symptom severity, measure used, mean score (SD)**	**Follow-up data available (months after baseline)**
Bechdolf, ongoing (Bechdolf *et al.*, 2011)	Aripipiprazole and CM	NS (as at Nov 2010, 156 randomised. Target N=240)	12 (20)	EPOS (Klosterkotter *et al.*, 2005)	SOPS / POPS (McGlashan *et al.*, 2003)	9, Cologne, Bonn, Aachen, Dusseldorf, Bochum, Hamburg, Gottingen, Munchen, Berlin (Germany)	NS	NS	SIPS / PANSS	6, 12
	Placebo and CM	NS (as at Nov 2010, 156 randomised. Target N=240)	12 (20)							
	CBT	NS (as at Nov 2010, 156 randomised. Target N=240)	12 (30)							
Stain, unpublished	CBT	NS (planned total N = 78)	6 (NS)	CAARMS (Yung *et al.*, 2005)	CAARMS (Yung *et al.*, 2005)	2, Newcastle, Orange (Australia)	NS	NS	NS	6, 12

							Baseline demographics			
Trial	**Treatments**	**Number randomised**	**Maximum duration of treatment, months (no. therapy sessions)**	**Primary criterion used to determine at-risk mental state**	**Primary criterion used to determine transition to psychosis**	**Number of centres, location (country)**	**Age, mean (SD)**	**Number female (%)**	**Baseline symptom severity, measure used, mean score (SD)**	**Follow-up data available (months after baseline)**
	NDRL	NS (planned total N = 78)	6 (NS)							

Note: CBT, Cognitive Behavioural Therapy; IPI, Integrated Psychological Intervention; COPS, Criteria of Prodromal States; SIPS, Structured Interview for Prodromal Symptoms; SOPS, Scale of Prodromal Symptoms; POPS, Presence of Psychotic Symptoms; PANSS, Positive and Negative Syndrome Scale; PACE, Personal Assessment and Crisis Evaluation; CAARMS, Comprehensive Assessment of At Risk Mental State; BPRS, Brief Psychiatric Rating Scale; EPOS, European Prediction of Psychosis study; CM, Clinical Management; NDRL, Non-Directive Reflective Listening; NS, Not Supplied. [1] Median (range); [2] 36-month data not reported here as attrition >50%; [3] CBT was "offered weekly to fortnightly, depending on clinical need" and supportive therapy was "offered weekly to monthly, depending on clinical need" (Yung *et al.*, 2011); [4] Data from an additional non-randomly allocated 'monitoring' group, consisting of those who declined to enter the formal trial, was also presented but is not included here; [5]PANSS transition defined as a score of 4 or more on items measuring hallucinations and delusions and / or 5 or more on item measuring conceptual disorganisation, with a frequency of at least several times a week, and duration of more than 1 week.