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Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups

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ABSTRACT

Over the last decade many studies were conducted to assess the feasibility of early detection of people at risk of developing psychosis and intervention to prevent or delay a first psychotic episode. Most of these studies were small and underpowered. A meta-analysis can demonstrate the effectiveness of the efforts to prevent or postpone a first episode of psychosis.

A search conducted according the PRISMA guideline identified 10 studies reporting 12-month follow-up data on transition to psychosis, and 5 studies with follow-ups varying from 24 to 48 months. Both random and fixed effects meta-analyses were conducted.

The quality of the studies varied from poor to excellent. Overall the risk reduction at 12 months was 54% (RR = 0.463; 95% CI = 0.33–0.64) with a Number Needed to Treat (NNT) of 9 (95% CI = 6–15). Although the interventions differed, there was only mild heterogeneity and publication bias was small. All sub-analyses demonstrated effectiveness. Also 24 to 48-month follow-ups were associated with a risk reduction of 37% (RR = .635; 95% CI = 0.44–0.92) and a NNT of 12 (95% CI = 7–59). Sensitivity analysis excluding the methodologically weakest study showed that the findings were robust.

Early detection and intervention in people at ultra-high risk of developing psychosis can be successful to prevent or delay a first psychosis. Antipsychotic medication showed efficacy, but more trials are needed. Omega-3 fatty acid needs replication. Integrated psychological interventions need replication with more methodologically sound studies. The findings regarding CBT appear robust, but the 95% confidence interval is still wide.

1. Introduction

The identification of individuals at high risk of developing a psychotic disorder has long been a goal of clinicians because it is thought that early treatment of this group may prevent onset of the disorder, or at least minimize its impact. Over the last 20 years, two broad sets of criteria have been used to diagnose the Clinical High Risk (CHR) state: the Ultra High Risk (UHR) and the Basic Symptoms (BS) criteria. The UHR state requires the presence of one or more of: attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), or trait vulnerability plus a marked decline in psychosocial functioning (Genetic Risk and Deterioration Syndrome: GRD). BS are subjectively experienced disturbances of different domains including perception, thought processing, language and attention that are distinct from classical psychotic symptoms, in that they are independent of abnormal thought content, reality testing and insight into the symptoms' psychopathological nature. Reliable and valid instruments have been developed and refined to identify the UHR group (Miller et al., 2002; Yung et al., 2005) and the BS group (Schutze-Lutter et al., 2007). CHR subjects who met UHR or BS criteria or a combination of both had a transition rate of 18% after 6 months, 22% after one year, 29% after two years and 36% after three years (Fusar-Poli et al., 2012).

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The first prevention trials were small. A meta-analysis was conducted using the data from the first five randomized controlled trials (Preti and Cella, 2010). The pooled relative risk was 0.36, meaning that the risk of a first psychosis was reduced by 64%, and statistically significant. Heterogeneity was absent, meaning that differences across the primary studies could be attributed to random sample error rather than to systematic factors. The Cochrane group conducted another meta-analysis using six studies, but did not pool the data (Marshall and Rathbone, 2011). The most recent meta-analysis was based on seven studies (Fusar-Poli et al., 2013) and reported a relative risk of 0.34 (95% CI: 23–7; $p < 0.001$), indicating the interventions were successful in reducing the risk of a first psychotic episode in a statistically significant way by 66%. These outcomes were associated with a number needed to treat (NNT) of 6 indicating that 6 UHR individuals need to receive treatment for preventing one more transition to psychosis compared to treatment as usual.

Currently, a total of ten prevention trials in CHR have been conducted doubling the number of trial participants and thus strengthening the evidence-base considerably. The aim of the present study is to conduct a meta-analysis of the ten prevention trials in CHR to obtain a more precise understanding of the feasibility to prevent the transition from a high-risk status to a psychotic episode.

2. Methods

2.1. Data collection

Only randomized controlled trials were included. Any control condition was accepted.

We conducted literature searches following the PRISMA guideline (Liberati et al., 2009) using five databases: Ovid MEDLINE and EMBASE, both from 1996 to November 2012, PsycINFO from 1987 to November 2012, EBM Reviews — Cochrane Central Register of Controlled Trials, and EBM Reviews — Cochrane Database of Systematic Reviews, 2005 to November 2012. We also examined published reviews and meta-analyses. Within each of the databases three searches were carried out:

The first search was on “prodromal” (7201), “ultra-high risk” (1099) OR “ultra high risk” (61) OR “high clinical risk” (188) OR “clinical high risk” (417) OR “at risk mental state” (509) OR “risk of progression” (7055) OR “progression to first-episode psychosis” (9) OR “prodromally symptomatic” (28);

The second search was on “RCT” (20,968) OR "randomised controlled trial" (19,886) OR "randomized controlled trial" (560,250);

The third search was on “psychosis” (90,442)

Combining the three searches and the examination of the reviews resulted in 118 references (see Fig. 1). Removing duplicates left 70

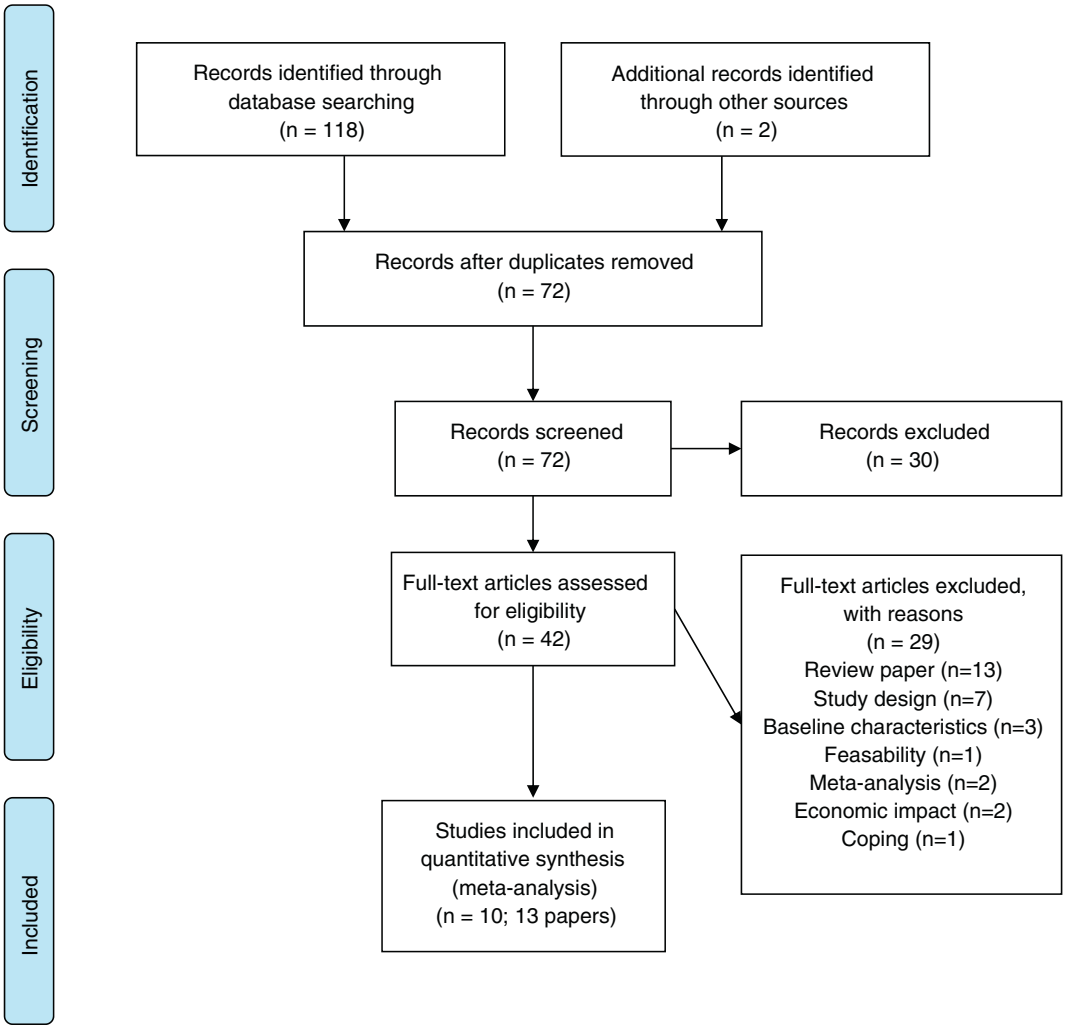

Fig. 1. Flowchart of selected studies.

papers. Two more trials were added: one paper in press by McGorry and colleagues (McGorry et al., 2013) and the recently published paper by van der Gaag and colleagues (van der Gaag et al., 2012).

2.2. Data extraction

Seventy-two papers were screened on titles; 30 were removed because they addressed other topics. 42 full-text papers were assessed and 29 were removed from further analysis (See Fig. 1). 13 papers reported on 10 studies.

Three studies intervened with antipsychotic medication: an older Australian study (McGorry et al., 2002; Phillips et al., 2007) a recent Australian study (Yung et al., 2011; McGorry et al., 2013) and the American PRIME study (McGlashan et al., 2006). One study compared omega-3 fatty acids with placebo (Amminger et al., 2010).

Two studies evaluated integrated psychological therapies (Nordentoft et al., 2006; Bechdolf et al., 2012) and five studies evaluated CBT (Morrison et al., 2004, 2007, 2012; Addington et al., 2011; van der Gaag et al., 2012; McGorry et al., 2013).

In all, ten randomized prevention trials reported effects on transition rates from CHR status to a first episode of psychosis at 12 months follow-up (see Table 1). The study by McGorry and colleagues contributes more than once to the evidence table, because they conducted a trial with three arms and one control group was compared with two active interventions, one antipsychotic medication + CBT, and another placebo + CBT (McGorry et al., 2013). Thus, the ten studies contributed data on eleven contrasts.

2.3. Quality assessment

The quality of the studies was assessed with the Clinical Trials Assessment Measure (CTAM) (Tarrier and Wykes, 2004; Wykes et al., 2008). This instrument has been developed to assess the quality of clinical trials of psychosocial interventions and is based on the CONSORT statement. Two clinical trial specialists (SC and ABPS), who were neither involved in this meta-analysis nor in any of the reviewed studies, independently assessed the quality of the ten studies.

2.4. Data analysis

The outcomes across the trials were synthesized using Comprehensive Meta-Analysis version 2.2 (www.meta-analysis.com/) and Stata version 11 (StataCorp, 2011). The pooled relative risk, RR, was based on the random effects model of DerSimonian and Laird (DerSimonian and Laird, 1986; DerSimonian and Kacker, 2007).

Heterogeneity is a concern in meta-analysis as it may introduce the problem of 'comparing apples with oranges'. Heterogeneity was tested with a χ^2 test. We also report the I^2 statistic. When $I^2 = 0\%$, 25%, 50% or 75%, then no, low, moderate or high heterogeneity must be assumed (Higgins et al., 2003). As the I^2 statistic is known to be imprecise, reporting its 95% confidence interval is recommended (Ioannidis et al., 2007). The 95% confidence interval was calculated using the non-central χ^2-based approach within the Heterogi module in Stata (Orsini et al., 2005). Splitting the meta-analytical data file into subgroups of studies that used the same type of intervention and then reporting outcomes further investigated heterogeneity. It is worth noting that a fixed effects meta-analysis employing the Mantel–Haenszel method is recommended only when there is no marked heterogeneity across the primary studies (Hedges and Olkin, 1985; Cooper and Hedges, 1994). Because of the diversity of interventions we calculated Tau-square. If Tau-square equals zero, than the random and fixed effects meta-analysis have similar results.

Meta-analysis may be subject to publication bias. We conducted Begg & Mazumdar's rank correlation test to quantify the bias captured by the funnel plot and to test whether it was statistically significant (Begg and Mazumdar, 1994). Publication bias was further evaluated using Duval and Tweedie's trim and fill procedure, which yields an adjusted estimate of the pooled effect size after the publication bias has been taken into account (Duval and Tweedie, 2000a, 2000b). The third way to examine publication bias was to use the Fail/Safe N analysis, which indicates the number of missed studies that would turn the results to a clinically less important $RR \geq 0.80$ and $RR \geq 0.90$.

3. Results

3.1. Characteristics of the included studies

Table 1 presents a comparison of the 11 contrasts included in this meta-analysis. Dropout rates, age and sex are presented by condition.

Table 1
Description of the interventions, patient characteristics, location, and transition criteria.

Intervention	Author	Year	Duration interv.	Experimental condition				Control condition				Country	Transit. criterion
				Intervention	Dropout %	Age mean (SD)	Male Sex %	Intervention	Dropout %	Age mean (SD)	Male Sex (%)		
Anti-psychotic medication	McGorry et al.	2002	6 m.	1–2 mg/day Risperidone + CBT + NBI	54%	20 (3.6)	58%	NBI	0%	20 (3.6)	58%	AU	CAARMS
	McGlashan et al.	2006	12 m.	5–15 mg/day Olanzapine	55%	17 (4.0)	62%	Placebo	35%	18 (5.5)	68%	USA	SIPS
	McGorry et al.	2013	12 m.	0.5–2 mg/day Risperidone + CBT	37%	18 (3.0)	35%	Placebo + ST	32%	19 (3.7)	46%	AU	CAARMS
Omega-3 fatty acid	Amminger et al.	2010	2 m.	1.2 g/day omega-3 fatty acid	7%	17 (2.4)	34%	Placebo	5%	16 (1.7)	33%	AUS	CAARMS
Integrated psychological intervention	Nordentoft et al.	2006	24 m.	ACT + SST + MFP	12%	25 (5.6)	74%	CMHT	19%	25 (3.9)	59%	DK	ICD-10
	Bechdolf et al.	2012	12 m.	CBT + SST + CR + MFP	19%	25 (5.4)	62%	ST	12%	27 (6.2)	65%	GER	EIPS
Cognitive behavioral therapy	Morrison et al.	2004	6 m.	CBT	30%	21 (4.9)	60%	Monitoring	30%	22 (5.2)	83%	UK	CAARMS
	Addington et al.	2011	6 m.	CBT	41%	21 (4.5)	62%	ST	38%	21 (4.5)	75%	CAN	SIPS
	McGorry et al.	2013	12 m.	Placebo + CBT	34%	18 (2.7)	39%	Placebo + ST	32%	19 (3.7)	46%	AU	CAARMS
	Morrison et al.	2012	6 m.	CBT	34%	21 (4.2)	62%	Monitoring	35%	21 (4.5)	63%	UK	CAARMS
	van der Gaag et al.	2012	6 m.	CBT + TAU	15%	23 (5.6)	50%	TAU	12%	23 (5.5)	49%	NL	CAARMS

CBT = Cognitive behavioral therapy; NBI = Needs Based Intervention; ST = Supportive Therapy; ACT = Assertive Community Treatment; SST = Social skills training; MFP = Multi-family psycho-education; CMHT = Community Mental Health Team; CR = Cognitive remediation; TAU = standard treatment for non-psychotic disorder; AU = Australia; USA = United States of America; AUS = Austria; DK = Denmark; Ger = Germany; UK = United Kingdom; Can = Canada; NL = Netherlands; CAARMS = Comprehensive Assessment of At Risk Mental State; SIPS = Structured Interview for Prodromal Symptoms; ICD-10 = International Classification of Diseases, version 10; EIPS = early Initial Prodromal State; * = inferior study quality.

3.2. Quality of the included studies

Table 2 describes the methodological quality of the primary studies. This measure has an arbitrary cut-off score of 65. Three studies are of poor quality. We conducted a meta-regression analysis of the different quality subscales on the effect-size, defined as log(RR). We found no evidence that higher quality was associated with a lower effect-size (b = 0.020; SEb = 0.014; z = 1.425; p = 0.154). The sub-scales also showed a non-significant association. The number of trials may have been too small to conduct a meaningful meta-regression analysis. The Nordentoft study was considered the weakest of the selected studies. It recruited schizotypal patients (slightly different from UHR subjects), used no CAARMS or SIPS assessments, was not blinded and used no protocol on the use of antipsychotic medication. Hence, a sensitivity analysis will be performed excluding this study.

3.3. Overall analysis at 12 months

Fig. 2 presents the results of all studies combined in a forest plot. Table 3 shows that the pooled risk ratio (RR) at the 12 month follow-up was 0.46, indicating that the risk to make an unfavorable transition from a prodromal stage to first episode psychosis was reduced, on average, by 54%, which is statistically significant (95% confidence interval: 0.33–0.64; z = −4.62; p < 0.001). The pooled RR that was obtained under the fixed effects model was exactly the same. The pooled risk difference (RD) was 0.117 (95% CI = 0.07–0.17), implying a NNT of 9 (95% CI = 6–15).

Although different interventions were used, the meta-analysis shows that the hypothesis of homogeneity cannot be rejected (χ^2 = 15.843; df = 10; p = 0.104), suggesting that differences in the RRs across studies can be attributed to sample error. The lack of systemic differences was further supported by the I^2 of 0% (indicating low heterogeneity), but this statistic is associated with a wide 95% confidence interval (95% CI = 0–60), thus rendering it insensitive to violations of the homogeneity assumption. Heterogeneity examined by τ^2 was 0.002 (SE = 0.003). The sensitivity analysis excluding the Nordentoft study resulted in a pooled risk ratio of 0.48, indicating a reduction to 52% (95% confidence interval: 0.35–0.68; z = 4.19; p < 0.001). Thus, excluding the weakest study hardly affected the results.

3.4. Publication bias

Although Begg and Mazumbar's test did not suggest asymmetry of the funnel plot (Kendall's Tau with continuity correction: t = 0.327; z = 1.40; p = 0.16, 2-tailed), we found some indications for publication bias, because Duvall and Tweedie's trim and fill procedure showed that the effect size changed from RR = 0.46 (95% CI = 0.34–0.65) to RR = 0.51 (95% CI = 0.37–0.70) after adjustment for publication bias (number of filled studies was three). The Fail/Safe number is an estimate of the number of studies without effect (RR = 1) that are needed to render the pooled effect into a clinically less important one. To bring down the observed RR = 0.46 to a clinically less important RR = 0.80 would require a scenario in which we missed 27 studies each with RR = 1.00. Likewise, RR = 0.90 would have been obtained if 70 studies were missed. The likelihood that we have missed so many studies with null findings is small and this suggests that the risk of publication bias is also small.

3.5. Analyses by type of intervention

Table 3 presents the primary studies included in the meta-analysis. The results of the meta-analytical outcomes by type of intervention are as follows:

1) Combining the three trials examining antipsychotic medication gives a pooled RR of 0.55, which is statistically significant (p = 0.029). The NNT = 7 (95% CI = 4–77). This subset of trials is not associated with statistically significant heterogeneity (I^2 = 0%; 95% CI = 0–90; and τ^2 = 0.00).
2) Within the psychological interventions the subset of CBT-based interventions is associated with a pooled RR of 0.52 (95% CI = 0–79), which is homogenous (I^2 = 0%; 95% CI = 0–79; and τ^2 = 0.00) and has a NNT of 13 (95% CI = 7–71).

3.6. Longer-term outcomes

Fig. 3 presents the results of the five studies with longer-term (24–48 months) follow-up combined in a forest plot. The data show that the effect of the interventions persisted: the risk of becoming psychotic was still reduced by 36%. This effect is statistically significant (RR = 0.635; 95% CI = 0.44–0.92; z = −2.405; p = 0.016) and there is no heterogeneity (I^2 = 0% and τ^2 = 0.00). These outcomes did not alter after employing Duval and Tweedie's fill and trim procedure. The pooled RD was 0.084 (95% CI = 0.02–0.15), p =0.014. The NNT was estimated at 12 (95% CI = 6–50). The Fail/Safe number for RR ≥ 0.80 is 6 missed studies and for RR ≥ 0.90 is 17 missed studies, again indicating that the risk of publication bias is small.

The sensitivity analysis without the Nordentoft study resulted in comparable results (RR = 0.648; 95% CI = 0.40–1.05; z = −1751; p = 0.080), but no longer reaching statistical significance.

3.7. Secondary analyses

The studies used different secondary outcomes, including six studies that evaluated social functioning with either the Global Assessment of

Table 2
Quality ratings of the studies using CTAM.

Study	Selection and size	Randomization allocation	Blinded assessments	Control group	Correct analyses	Protocol/fidelity	Sum score
McGorry et al. (2002)	7	10	26	16	15	6	80
McGlashan et al. (2006)	7	10	13	16	11	6	63*
McGorry et al. (2013)	7	16	16	16	15	11	81
Amminger et al. (2010)	7	16	16	16	15	11	81
Nordentoft et al. (2006)	7	16	16	6	11	6	62*
Bechdolf et al. (2012)	7	13	6	6	15	6	53*
Morrison et al. (2004)	2	16	26	6	11	6	67
Addington et al. (2011)	2	13	29	16	5	11	76
Morrison et al. (2012)	7	16	32	6	15	11	87
van der Gaag et al. (2012)	7	16	32	6	15	11	87

Selection and size (0–10): 2 points = convenience sample or 5 points = geographic cohort; +5 points = greater than 27. Randomization (0–16): 10 points = randomized; +3 points = randomization process described; +3 points = independent from trial research team. Assessments (0–32): 10 points = independent assessors; +6 is standardized measurements; +10 points = blind for allocation; +3 points for description of procedures for rater blinding; +3 points = rater blinding verified. Control group (0–16): 6 points = waiting list; +10 points control groups controls non-specific effects. Correct analyses (015): 5 points = appropriate design; + 6 points intention-to-treat; +4 points = attrition less than 15%. Protocol/fidelity (0–11): 3 points = treatment adequately described; +3 points manualized; +5 points = treatment fidelity assessment.

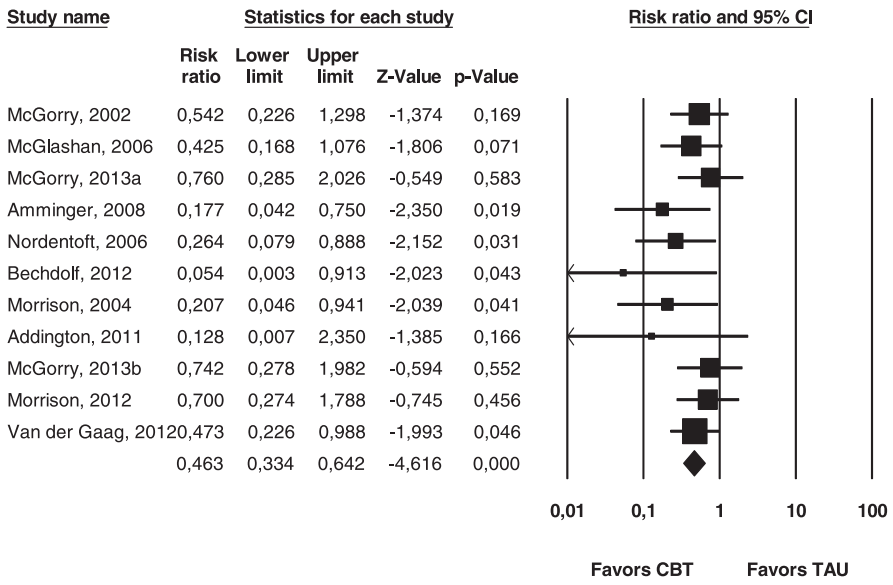

Fig. 2. Forest plot of risk ratio's for the transition to psychosis within 12 months.

Functioning (GAF) or the Social and Occupational Functioning Assessment Scale (SOFAS). Fig. 4 shows social functioning at 12 months: there is a non-significant difference favoring the experimental condition.

4. Discussion

4.1. Main findings

This meta-analysis brings together the evidence that preventive interventions in people at ultra high risk of developing a first episode of psychosis are effective. The risk of onset of disorder is reduced by 54% to 52% (1 study excluded) after 12 months, and by 37% to 35% (1 study excluded) in the longer-term (between 2 and 4 years). This suggest that preventive effects are slightly diminished over 2–4 years, but still successful in reducing the risk of developing a first psychosis. These favorable outcomes are also reflected in small NNTs of 9 at 12 months follow-up and a NNT of 12 after longer-term follow-ups. In comparison, the risk reduction in the prevention of depressive disorders is 22% with an NNT of 22 (Cuijpers et al., 2008). Although the interventions are relatively diverse, there is no statistically significant heterogeneity. This is consistent with previous systematic reviews (Preti and Cella, 2010; Fusar-Poli et al., 2013).

The diminished effects over time also indicate that the interventions are not likely to give immunity against future psychosis. However, the compromised social functioning, high distress levels and many comorbid disorders in the 'at risk group' still justify early intervention. It is important to note that those who do not transition to psychosis are not healthy "false-positives", but are help-seeking individuals suffering from a range of mental and social role functioning problems, and are carrying a poor prognosis for a range of adverse sequela (Yung et al., 2010). Hence early intervention is not only justified by the prevention of imminent psychosis, as it addresses present psychopathology and poor social functioning, as evidenced by the changes in the GAF and SOFAS scores.

4.1.1. Pharmacological interventions

Treating seven people to prevent one psychotic episode is a concern in pharmacological treatment as side effects might occur in most treated persons. As in preventive medicine, the benefits and side-effects must be balanced. For example, statins are prescribed to those with high cholesterol to prevent cardiovascular incidents. In this situation, over one hundred people need to be treated in order to prevent one adverse incident. Antipsychotic medication is effective in reducing the rate of transition to psychosis by 45%, but antipsychotics are associated with high attrition rates, e.g. 54.8% in the McGlashan et al. (2006) and McGorry et al. (2002) studies, and 37.2% in the McGorry et al. (2013) study. In addition, McGlashan and colleagues reported an 8.8 kg weight gain. The conclusion of the recent study by McGorry and colleagues was that antipsychotic medication should not be offered as a first line treatment in CHR patients. After all, the data on antipsychotic medication in CHR patients are based on small trials and more evidence is needed to demonstrate efficacy and safety.

Omega-3 was promising in preventing a first episode of psychosis in CHR patients, but this impression is based on a small study and requires replication. Replication will be conducted in two large trials: the NEURAPRO-E trial (Australian and New Zealand Clinical Trials number ACTRN12608000475347) (McGorry and Amminger, 2013) and the NAPLS-2 trial that is now running in the United States and Canada (Cadenhead, 2013).

4.1.2. Cognitive behavioral therapy

Five studies used CBT as an intervention. The three CBT studies that were recently conducted have more statistical power and used better scientific methods than the previous ones (see Table 2). Now it appears that CBT intervention is effective, but the NNT of 13 is somewhat higher than seen in the prevention trials that did not rely on CBT — perhaps owing to the lower transition rates observed in recent studies.

4.2. Strengths and limitations

The strength of this meta-analysis is that ten trials were included encompassing 1112 high-risk patients allowing for the evaluation of effects at 12 months and longer-term follow-up. Nevertheless, more long-term studies are needed to strengthen the evidence-base and to shed light on the question whether onset of psychosis was prevented or merely delayed.

Another limitation is the small number of studies with pharmacological and integrated psychosocial interventions. Our meta-analytic results regarding these sub-sets must be interpreted with caution.

Table 3
Primary studies included in the meta-analysis: risk by condition, relative risk (RR), 95% confidence interval of RR, and p-value (Intention-to-Treat).

Studies included in the meta-analysis: risk by condition (12 months follow-up)										
Intervention	Author	Year	Follow-up period	Experimental condition		Control condition		RR	95% CI	p-Value
				Event rate	Event %	Event rate	Event %			
Anti-psychotic medication	McGorry et al.	2002	12 months	6/31	19%	10/28	36%	.542	0.22–1.30	p = .169
	McGlashan et al.	2006	12 months	5/31	16%	11/29	38%	.425	0.16–1.08	p = .071
	McGorry et al.	2013	12 months	7/43	16%	6/28	21%	.760	0.28–2.03	p = .583
Omega-3 fatty acid	Amminger et al.	2010	12 months	2/41	5%	11/40	28%	.177	0.04–0.75	p = .019
Integrated psychological interv.	Nordentoft et al.	2006	12 months	3/42	7%	10/37	27%	.264	0.08–0.89	p = .031
	Bechdolf et al.	2012	12 months	0/63	0%	9/65	14%	.054	0.00–0.91	p = .043
Cognitive behavioral therapy	Morrison et al.	2004	12 months	2/37	2%	6/23	26%	.207	0.05–0.94	p = .041
	Addington et al.	2011	12 months	0/27	0%	3/24	13%	.128	0.01–2.40	p = .166
	McGorry et al.	2013	12 months	7/44	16%	6/28	21%	.742	0.28–1.98	p = .552
	Morrison et al.	2012	12 months	7/144	5%	10/144	7%	.700	0.27–1.79	p = .456
	Van der Gaag et al.	2012	12 months	9/98	9%	20/103	19%	.473	0.23–1.00	p = .046
Studies included in the meta-analysis: risk by condition (medium-term follow-up: 24–48 months)										
	Author	Year	Follow-up period	Experimental condition		Control condition		RR	95% CI	p-Value
				Event rate	Event %	Event rate	Event %			
	McGorry et al.	2002/2007	36–48 months	10/31	32%	12/28	43%	.753	0.39–1.47	p = .403
	Nordentoft et al.	2006	24 months	9/42	21%	14/37	38%	.566	0.28–1.15	p = .117
	Bechdolf et al.	2012	24 months	1/63	2%	10/65	15%	.103	0.01–0.78	p = .028
	Morrison et al.	2004/2007	36 months	7/37	19%	7/23	30%	.622	0.25–1.54	p = .305
	Morrison et al.	2012	24 months	10/144	7%	13/144	9%	.769	0.35–1.70	p = .516

RR = Risk ratio; 95% CI = 95% confidence interval.

4.3. Conclusions and recommendations

Although the effects are encouraging, more research is needed. Trials with anti-psychotic medication may focus on prescription of low doses of the second-generation antipsychotics associated with low metabolic impact and possibly improved adherence rates and fewer side effects. Anti-psychotic medication can also be offered as a second line intervention after failed or partial treatment response in CBT.

The number of false-positive cases may be reduced further. This can be done by enrichment strategies such as screening (Rietdijk et al., 2012), or alternatively by not only targeting subclinical symptoms, but also biomarkers and endophenotypes such that a better job is done at identifying those people most at risk.

The finding that effects wane over time for both pharmacological and psychosocial interventions might point to the need for more elaborate interventions or booster sessions to preserve the results.

The focus on transition to psychosis must be broadened with the clinical staging idea (McGorry and Van Os, 2013). The UHR group who does not transition is still not functioning well and is suffering from anxiety or depression and limitations in social role functioning. This requires that a broader set of outcome measures must be used in a next generation of prevention studies in psychosis. After all, the UHR group is not only psychosis-prone, but more general psychopathology-prone and at risk for compromised social functioning (Yung et al., 2010).

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Contributors
Mark van der Gaag managed the literature searches and wrote the first draft of the paper. Filip Smit and Pim Cuijpers did the analyses and wrote the first draft of the paper. All authors have contributed to the final version and have approved the final manuscript.

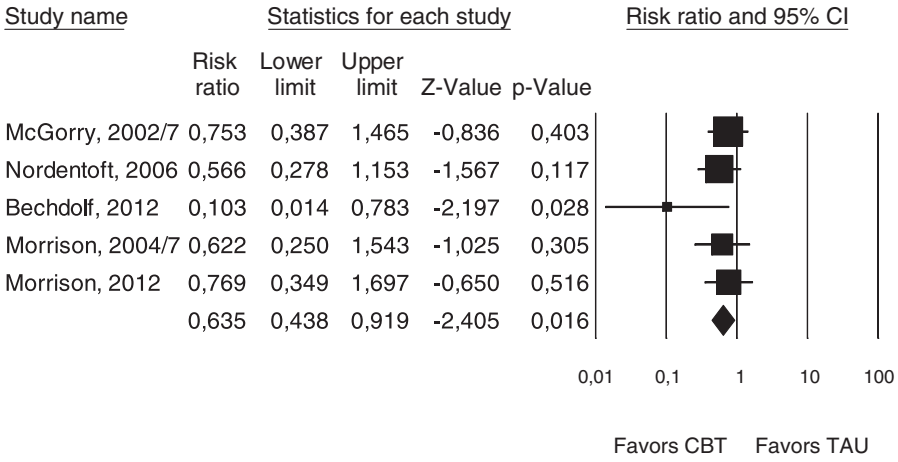

Fig. 3. Forest plot of risk ratio's for the transition to psychosis: 24 to 48 month follow-up.

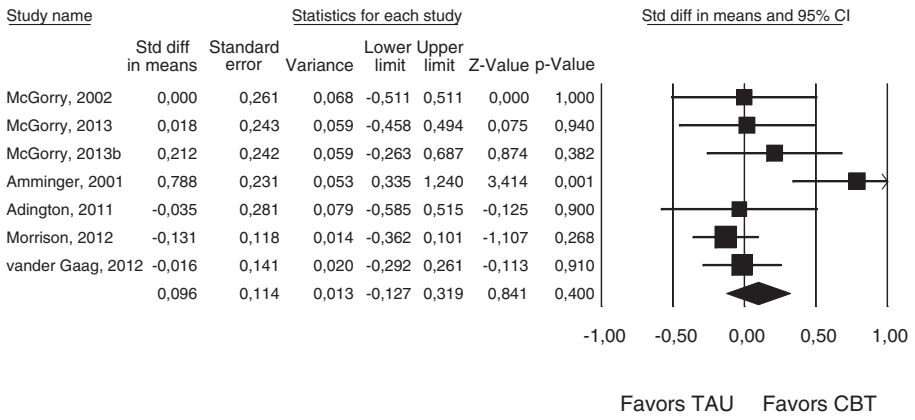

Fig. 4. Forest plot Social Functioning (GAF and SOFAS): 12 month follow-up.

Conflict of interest

The authors disclose no conflicting interests and this meta-analysis was accomplished without funding.

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