EPA guidance on the early intervention in clinical high-risk states of psychoses

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Abstract

The aim of this guidance paper of the European Psychiatric Association (EPA) is to provide evidence-based recommendations on the early intervention in clinical high-risk (CHR) states of psychoses as assessed according to the EPA guidance on early detection. These recommendations were derived from the current empirical evidence and a meta-analysis on the efficacy of psychological and pharmacological interventions in CHR samples. Studies had to investigate conversion rate and/or functioning as treatment outcome in CHR patients defined by the ultra-high risk and/or basic symptom criteria. Besides analyses on treatment effects on conversion rate and functional outcome, age and intervention approach were examined as potential moderators. Based on data of 15 studies (n=1394), early intervention approaches generally produced significantly reduced conversion rates at 6- to 48-month follow-ups compared to the control conditions. However, they failed to achieve significantly greater functional improvements because both early intervention and control conditions produced similar positive effects. With regard to the intervention approach, both psychological and pharmacological interventions produced significant effects on conversion rates but not on functional outcome relative to the control conditions. Early intervention in youth samples was generally less effective than in predominantly adult samples. Six evidence-based recommendations for an early intervention in CHR samples could already be formulated although more studies to investigate the specificity of treatment effects and potential age effects in order to tailor interventions to the individual treatment needs and risk status are clearly needed.

Key words: prevention, early intervention in Europe, meta-analysis, risk, psychosis, adolescents, youth, cognitive-behavioral therapy, antipsychotics, neuro-protective

1. Introduction

Each year 38.2% of the population of the European Union, i.e., 164.8 million persons, suffer from any mental disorder (Wittchen et al., 2011). This is associated with huge societal and individual burden (Gustavsson et al., 2011; Whiteford et al., 2013). Prevention has therefore become an integral part of European and international health care policies in order to reduce the prevalence and burden of mental disorders across the lifespan (EC, 2005, 2008; Campion et al., 2012; Haro et al., 2014).

1.1. Functional disability in psychotic disorders

Schizophrenia is among the seven leading causes of years lost to disability (YLDs) in adults in Europe (Wittchen et al., 2011). This is mainly due to the fact that functional recovery rates have not changed substantially over the past 25 years, despite advances in pharmacological and psychological treatments (Jääskeläinen et al., 2013, Shivashankar et al., 2013). As a consequence, prevention of schizophrenia and psychotic disorders in general has attracted special interest (Solis, 2014).

Functional impairments are already present before (Addington et al., 2011) and often worsen until the onset of psychosis (Häfner et al., 1999). Furthermore, they are one of the main predictors of poor clinical outcome including conversion to psychosis (Granö et al., 2014). This emphasizes the need to intervene as early as possible to avoid or at least diminish these burdens and thereby to prevent transition to manifest psychosis.

1.2. Prevention in clinical high risk states of psychoses

In psychosis research, an indicated prevention approach has been adopted that targets help-seeking persons who experience early signs of the emerging psychosis but do not meet diagnostic criteria with the ultimate goal to prevent the incidence of the disorder (McGlashan & Johannesson, 1999; McGorry et al., 1998, 2002). Thus, indicated prevention faces two

challenges: (1) the accurate identification of the target population and (2) their effective treatment. For the purpose of early detection, two complementary sets of clinical high risk (CHR) criteria have been developed: the basic symptom (Huber, 1966; Schultze-Lutter, 2009) and the ultra-high risk (UHR) approach (Miller et al., 2003; Yung et al., 2005). Their evidence is systematically reviewed by and recommendations for their use are given in the accompanying European guidance on early detection (see Schultze-Lutter et al., this issue). Notably, fulfilling these criteria only indicates an increased risk for developing psychosis which is always associated with an error probability resulting in false-positive predictions (Ruhrmann et al., 2010). This has fueled ongoing debates about the risk of negative effects associated with the identification and treatment of CHR states of psychoses (e.g., stigmatization, financial loss) (e.g., Fusar-Poli et al., 2014; Nelson, 2014; ethics-chapter).

1.3. Need for treatment in clinical high risk states of psychoses

In addition to the markedly increased risk for developing psychosis (Schultze-Lutter et al., this issue), the most important argument in favor of an intervention in CHR patients is the reported distress and stigmatization caused by their mental problems already at the time of referral to an early detection and intervention service (Kline et al., 2014; Rüsch et al., 2014a,b; Stowkowy et al., 2014). This is reflected by their even higher levels of hopelessness, depressiveness, anxiety, and poor quality of life in comparison to other help-seeking patients and patients with first-episode psychosis (Bechdolf et al., 2005; Lee et al., 2011; Pruessner et al., 2011; Granö et al., 2014a,b). Accordingly, they often fulfill the diagnostic criteria for another mental disorder, in particular for depression, anxiety, and substance abuse or dependence, which require treatment (Woods et al., 2009; Hui et al., 2013; Fusar-Poli et al., 2014). Furthermore, CHR patients exhibit poor coping skills, low self-efficacy, and excessive external attributions that resemble profiles of depressive patients and might unfavorably interact with their frequent depressive mood (Schmidt et al., 2014).

In addition, CHR patients demonstrate abnormalities in neuro- and social cognition with performances that are usually intermediate between those of healthy controls and schizophrenia patients (Fusar-Poli et al., 2013; Giuliano et al., 2013; Thompson et al., 2013; Bora et al., 2014; Brent et al., 2014), and are associated with markedly impaired functional outcome and negative symptoms (Addington et al., 2009; Lin et al., 2011; Carrion et al., 2013; Olvet et al., 2013; Granö et al., 2014; Salokangas et al., 2014). Consistent with the conceptualization of psychoses as neurodevelopmental disorders, these neuro- and social-cognitive abnormalities are also accompanied and possibly reflected by various abnormalities in functional and structural imaging (Smieskova et al., 2013; Bois et al., 2014), in electrophysiological measures (Higuchi et al., 2013; Kayser et al., 2014) and neurochemistry (Leweke et al., 2012; Egerton et al., 2014; Gran et al., 2014). In summary, CHR patients are – independent of any potential risk to develop psychosis in the future – certainly in need for treatment (Ruhrmann et al. 2010).

1.4. Requirements for early intervention approaches

In accordance with this obvious need for treatment, an increasing number of interventions have been evaluated in CHR samples in recent years (Ruhrmann et al., 2012; Okuzawa et al., 2014; Stafford et al., 2014). With the primary goal to prevent conversion to psychosis, they have mainly built upon well-established interventions for adult schizophrenia patients and used conversion to psychosis as their primary outcome (McGorry et al., 2002; Morrison et al., 2004). Other more recently developed interventions have taken into account that CHR patients not only suffer from risk symptoms but also from several other mental problems and have targeted a broader array of outcomes in various settings with various intervention techniques (e.g., intensive case management, multi-family psychoeducation) (Granö et al., 2014a,b; Marvin et al., 2014). Yet most “new generation” intervention studies have an uncontrolled single-group design, therefore lack methodological rigor, and were not included in recent meta-analyses on the efficacy of

randomized controlled trials (RCTs) in CHR states (Cella & Preti, 2010; Marshall & Rathbone, 2011; Fusar-Poli et al., 2013; van der Gaag, 2013; Stafford et al., 2013; Hutton & Taylor, 2014). Current guidelines have not considered these “new generation” interventions (DGPPN, IEPA; NICE). Moreover, no sufficient evidence-based differential indication for the available interventions exists, which would require the examination of the treatment approach as a potential moderator variable in meta-analyses and/or in direct comparison in large RCTs with multiple treatment arms. In this context, age should also be studied as a potential moderator because CHR samples commonly include adolescents and young adults who differ in their social, emotional, and cognitive developmental state.

1.4. Aims

The main aim of this guidance paper on the early intervention in CHR states was therefore to evaluate the efficacy of intervention approaches in CHR patients that focus on both prevention of conversion to psychosis and improvement in functional outcome with special consideration of the potential moderating effects of age and intervention type. This served the ultimate goal to derive evidence-based recommendations on early intervention in CHR states assessed according to the recommendations provided by the EPA guidance on their early detection (see [Schultze-Lutter et al.], this issue).

2. Methods

2.1. Study selection

2.1.1. Literature search

We conducted a systematic literature search in June 2014 in PubMed (no time limit), PsycInfo (no time limit), Scopus (no time limit) that covers all journals included in Embase, and in the Cochrane Collaboration Controlled Trials Register using the following search terms and syntax: *((prevention) OR (early intervention) OR (treatment) OR (therapy)) AND ((risk) OR (prodrome)*

Tab. 1 Characteristics of studies included in the meta-analysis

Psychological interventions (PSY)									
Study	**Coun -try**	**De-sign**	**In- & exclusion criteria**	**Sample size**	**Sample characteristics**	**Inter-vention**	**Control group**	**Follow-up** (months after baseline); **Dropout-rate** (Post-therapy)	**Extracted outcome**
Morrison et al., 2004 [x], 2007 [x]; **GE 1**-	UK	RCT	Inclusion criteria: - Risk for psychosis (PANSS) Exclusion criteria: - < 16 years, > 36 years - Current or past receipt of antipsychotic medication	60 EG: 37 CG: 23	- Age (yrs.): EG: 20.6±4.9 / CG: 21.5±5.2 *(Age group: ADULT)* - Gender: (male): EG: 60% / CG: 83% - Co-morbidities: not reported	CBT + monitoring; 26 sessions, 6 months	Monitoring; monthly	6, 12, 36; EG / CG: 30% / 30%	TR (PANSS)
Addington et al., 2011 [x]; Marshall et al., 2012 [x]; **GE 1**-	CAN	RCT	Inclusion criteria - 14 to 30 years - Risk for psychosis (SIPS) Exclusion criteria - Lifetime or current axis-I psychotic disorder - Prior treatment with an antipsychotic - IQ < 70 - Past/current central nervous system disorder	51 EG: 27 CG: 24	- Age (yrs.): EG: 20.8±4.5 / CG: 21.1±3.7 *(Age group: ADULT)* - Gender (male): EG: 67% / CG 75% - Co-morbidities (EG / CG): mood disorders: 26% / 26%, alcohol abuse: 18% / 18%, cannabis abuse: 10% / 10%	CBT; max. 20 sessions (mean=12±6.2, range=1-26), 6 months	Supportive Therapy: coping with current problems, psycho-education; 20 sessions, 6 months	6, 12, 18; EG / CG: 30% / 33%,	TR (SIPS), FO (GAF & SFS)
Morrison et al., 2012,	UK	RCT	Inclusion criteria: - At-risk for psychosis (CAARMS)	288 EG: 144 CG:	- Age (yrs.): EG: 20.7±4.2 / CG: 20.8±4.5 *(Age*	CBT + Monitoring; Max. 26	Monitoring; monthly	6, 12, 18, 24; EG / CG: 33% / 31%	TR (CAARMS or reports from family

[x]; Morrison et al., 2011, 2013 [x]; **GE 1^{+}**			- 14-35 years - Help-seeking Exclusion criteria: - Current or previous receipt of antipsychotic drugs - Moderate to severe learning disability - Organic impairments - Insufficient English	144	*group: ADULT)* - Gender: (male): EG: 62% / CG: 63% - Co-morbidities (total sample, >5%): Depressive disorder: 34%, dysthymic disorder: 7%, panic disorder with agoraphobia: 6%, panic disorder without agoraphobia: 11%, social phobia: 11%, specific phobia: 11%, generalized anxiety disorder: 9%, obsessive compulsive disorder: 8%	sessions, 6 months; plus up to 4 booster-sessions in the following 6 months;			doctors), FO (GAF)
Bechdolf et al., 2012 [x]; Bechdolf et al., 2007 [x]; **GE 1^{-}**	GER	RCT	Inclusion criteria: - At least one of 10 thought or perceptional basic symptoms (ERIraos) and/or - Reduction in the GAF Score (DSM-IV) of at least 30 points within the past year and at least one of these risk factors: first-degree relative with schizophrenia /schizophrenia spectrum disorder or pre-/perinatal complications; Exclusion criteria: - APS or BLIPS - Present or past diagnosis of a psychotic disorder, bipolar disorder, organic brain	128 EG: 63 CG: 65	- Age (yrs.): EG: 25.2±5.4 / CG: 26.8±6.2 *(Age group: ADULT)* - Gender: (male): 62% / 65% - Co-morbidities: not reported	Integrated treatment: : Individual CBT, multi-family psycho-education (group), social skills training (group), cognitive remediation 25 sessions, 12 months	Supportive counselling: coping with current problems, basic psycho-education; 30 sessions, 12 months	6, 12, 18, 24; EG / CG: 19%, / 12%	TR (DSM-IV), FO (SAS II)

			disorder, substance dependence - Mental retardation - Previous treatment with antipsychotics - Acute suicidality - < 17 years, > 35 years						
Van der Gaag et al., 2012 [x]; Rietdijk et al., 2010 [x]; **GE 1++**	NL	RCT	Inclusion criteria - 14 to 35 years - At-risk for psychosis (CAARMS 2006) - SOFAS score ≤ 50 and/or a reduction by 30% for at least 1 month in the past year Exclusion criteria: - Current or previous use of antipsychotic medication with ≥ 15 mg cumulative haloperidol equivalent - Severe learning impairment - Problems due to an organic condition - Insufficient competence in Dutch; - History of psychosis	201 EG: 98 CG: 103	- Age (yrs.): EG: 22.9±5.6 / CG: 22.6±5.5 *(Age group: ADULT)* - Gender (male): EG: 50% / CG: 49% - Co-morbidities: (total sample, > 5%): Anxiety disorders: 27%, depression: 26%, personality disorders: 8%, ADHD: 7%, addiction problems: 6%;	CBT + Treatment As Usual (TAU); max. 26 sessions, weekly; 6 months; additional evidence-based treatment for axis-I and axis-II disorders;	Treatment As Usual (TAU); additional evidence-based treatment for axis-I and axis-II disorders;	6, 12, 18; EG / CG: 15% / 12%	TR (CAARMS 2006), FO (SOFAS)
McGorry et al., 2013 [x]; Yung et al. 2011 [x]; **GE 1+**	AUS	RCT	Inclusion criteria: - Age 14-30 years - Melbourne metropolitan area - Risk for psychosis (CAARMS 2006) Exclusion criteria: - History of psychotic or manic episode - Medical condition that accounts for symptoms - Neurologic, biochemical or	72 EG: 44 CG: 28	- Age (yrs.): EG: 18.0±2.7 / CG: 18.8±3.7 *(Age group: YOUTH)* - Gender (male): EG: 49% / CG: 47% - Co-morbidities: not reported	EG : CBT + Placebo; 12 months; CBT: Weekly to monthly basis; 50-60 min./session with the number of sessions not determined	Supportive therapy + placebo; 12 months;	6, 12; EG: 34% / CG: 32%	TR (CAARMS 2006), FO GAF)

			hematologic abnormalities - Serious co-existing illnesses - Lifetime antipsychotic dose of 15mg or more of haloperidol - Any previous or current use of mood-stabilizing medication - History of severe drug allergy - IQ<70 - Pregnancy or lactation - Insufficient English			in advance;			
Miklowitz et al., 2014 [x]; O'Brien et al., 2014 [x]; **GE 1^{+}**	USA	RCT	Inclusion criteria: - 12 and 25 years - Speaks and writes English - At-risk for psychosis (SIPS) Exclusion criteria: - Current schizophrenia or schizoaffective disorders - Developmental disorders - Substance use disorders - Neurological disorders	129 EG: 66 CG: 63	- Age (yrs.): EG: 17.3±4.2 / CG: 17.4±3.9 *(Age group: YOUTH)* - Gender (male): EG: 59 % / CG: 56% - Co-morbidities (EG / CG, >10%): depressive disorder (40% / 29%), anxiety disorders (42% / 50%), ADD (21% / 18%), learning disorders (11% / 7%)	Family focused treatment; 18 sessions à 60 minutes, 6 months	Enhanced care; 3 weekly psycho-educational sessions, 1 month	6; EG: 17% / CG: 25%	TR (SIPS), FO (GAF)
O'Brien et al., 2007 [x]; **GE 2^{-}**	USA	No CG	Inclusion criteria: - 12-22 years - At-risk for psychosis (SIPS) Exclusion criteria: - DSM-IV diagnosis of a schizophrenia spectrum disorder - IQ<70 - Current drug or alcohol dependence	16	- Age (yrs.): 15.7 (range: 12.5-18.5) *(Age group: YOUTH)* - Gender: (male): 50% - Comorbidities (>10%): Mood disorders: 63%, depressive	Psycho-educational multi-family group; Weekly sessions à 90 minutes, 9 months	-	9; 45% declined or dropped out	FO (GAF)

			- Current neurological disorder		disorder: 31%, depressive disorder NOS: 19%, anxiety disorder NOS: 31%, generalized anxiety disorder: 19%, ADHD: 13%, eating disorder NOS: 19% / 0%				
Hooker et al., 2014 [x]; **GE 2⁻**	USA	No CG	Inclusion criteria: - 15-35 years - At-risk for psychosis (SIPS) Exclusion criteria: - Major medical / neurological illness - Non-fluent English - MR-contraindication - IQ<70	28 EG: 14 CG: 14	- Age (yrs.): 21.9±4.2 *(Age group: ADULT)* - Gender (male): 50%	CRT; neuro- and social-cognitive computerized exercises; 1h each day, 5 days/week, 8 weeks;	-	3; 18%	FO (Global Functioning Role and Social scales)
Pharmacological studies - with antipsychotics – (MED)									
McGlashan et al., 2006 [x]; McGlashan et al., 2003 [x]; Woods et al., 2003 [x]; **GE 1⁺**	USA	RCT	Inclusion criteria: - 12-45 years - Help-seeking - At-risk for psychosis (SIPS)¨ Exclusion criteria: - Past or current psychotic disorder - Treatable psychiatric disorder that could account for the prodromal symptoms - Suicidal or homicidal - Prodromal symptoms due to drug/alcohol use	60 EG:31 CG: 29	- Age (yrs.): EG: 18.2±5.5 / CG: 17.2±4.0 *(Age group: YOUTH)* - Gender (male): EG: 68% / CG: 62% - Co-morbidities: Current substance abuse or dependence (EG: 13% / CG: 4%)	Olanzapine; 5-15 mg/d, 12 months; Additional individual and family psychosocial treatment, varied across sites;	Placebo; 12 months; Additional individual and family psychosocial treatment, varied across sites;	2, 12, 24; EG: 55% / CG: 35%	TR (SIPS), FO (GAF)
Woods et al., 2007 [x];	USA	No CG	Inclusion criteria: - 13-40 years - Treatment seeking outpatients	15	- Age (yrs.): 17.1±5.5 *(Age group: YOUTH)* - Gender (male): 53%	Aripiprazole; Initial doses were 1st	-	2; 13%	FO (GAF, SFS)

GE 2⁻			- Met diagnostic criteria for a possible prodromal syndrome (SIPS) Exclusion criteria: - Past or current DSM-IV criteria for any lifetime psychotic disorder - Psychiatric disorder which could account for the symptoms - Symptoms primarily as sequelae to drug or alcohol use - Alcohol or drug misuse or dependence in the past 3 months - Use of antipsychotic medication in the previous 3 months - Change in dosage of any antidepressant within 6 weeks, stimulant medication within 4 weeks or mood stabiliser within 4 weeks		- Co-morbidities: not reported	Week: 5 mg/d, 2nd Week: 10 mg/d 3rd week: 15 mg/d, 4th Week: 20mg/d and if needed to 30mg/d; 6 weeks			
Tsujino et al., 2013 [x]; **GE 2⁻**	JPN	No CG	Inclusion criteria: - 15-39 years - Help-seeking outpatients - At-risk for psychosis (SIPS) Exclusion criteria: - Previous diagnosis of any psychotic disorder (DSM-IV) - Symptoms fully accounted for by an Axis 1 disorder or sequelae of drug/alcohol use - Abuse of alcohol or drugs - Antipsychotic medication use	11	- Age (yrs.): 26.7±6.5 *(Age group: ADULT)* - Gender (male): 46% - Co-morbidities: not reported	Perospirone ; dosing according to a flexible schedule; psychosocial therapy available; 26 weeks	-	6; 25%	FO (GAF)

Pharmacological studies - combined with psychological interventions – (MED)									
McGorry et al. 2002 [x]**;** Phillips et al., 2007 [x]; **GE 1**[-]	AUS	RCT	Inclusion criteria: - 14-30 years - Live in the Melbourne metropolitan area - Risk for psychosis (CAARMS) Exclusion criteria: - Previous psychotic or manic episode - Previous treatment with an antipsychotic or mood stabilizing agent - Substance-induced psychotic disorder - IQ<70 - Inadequate command of English	59 EG: 31 CG: 28	- Age (yrs.): EG: 20±4/ CG: 20±3 *(Age group: ADULT)* - Gender (male): EG: 65% / CG: 50%	Risperidone (1-2 mg/d) + CBT + Needs-based intervention (NBI); 6 months; NBI on-going;	Needs-based intervention (NBI); 6 months; NBI on-going;	6, 12, 36-48; months; Drop-out rate: not reported, 41% non-adherent to Risperidone;	FO (GAF)
Ruhrmann et al., 2007 [x]; **GE 1**[-]	GER	RCT	Inclusion criteria: - Older than 18 years - Risk for psychosis (ERIraos) Exclusion criteria: - Lifetime DSM–IV diagnosis of schizophrenia spectrum disorder, brief psychotic episode (>1 week), delirium, dementia, amnestic and other cognitive disorders - Mental retardation - Mental disorders due to a general medical condition or psychotropic substances - Abuse of alcohol or drugs within the past 3 months or the past 4 weeks for cannabis - Any lifetime continuous treatment with high-potency	124 EG: 65 CG: 59	- Age (yrs.): EG: 25.1±6.6 / CG: 26.1±6.1 *(Age group: ADULT)* - Gender: (male): 48% / 60% - Co-morbidities: not reported	Needs-focused intervention + Amisulpride; 12 weeks; 50-800 mg/d, with increments of 50 mg at first step and 100 mg at further steps; dosage was increased as long as APS and BLIPS were	Needs-focused intervention; 12 weeks	3; EG: 29% / CG: 49%	FO (GAF)

			antipsychotics (> 1 week) or antipsychotics during 6 months prior to the study - Any contraindication for amisulpride - Women of childbearing risk not using contraception			present;			
McGorry et al., 2013 [x]; Yung et al. 2011 [x]; **GE 1+**	AUS	RCT	Inclusion criteria: - Age 14-30 years - Melbourne metropolitan area - Risk for psychosis (CAARMS, 2005) Exclusion criteria: - History of psychotic or manic episode - Medical condition that accounts for symptoms - Neurologic, biochemical or hematologic abnormalities - Serious co-existing illnesses - Lifetime antipsychotic dose of 15mg or more of haloperidol - Any previous or current use of mood-stabilizing medication - History of severe drug allergy - IQ<70 - Pregnancy or lactation - Insufficient English	71 EG: 43 CG: 28	- Age (yrs.): EG: 17.6 ±3.0) / CG: 18.8±3.7 *Age group: YOUTH)* - Gender (male): EG: 45% / CG: 47% - Co-morbidities: not reported	EG: CBT + Risperidone (0.5-2 mg/d); 12 months; CBT: Weekly to monthly basis; 50-60 min./session ; number of sessions not predetermined;	Supportive therapy + placebo; 12 months;	6, 12; EG 37% / CG: 32%	TR (CAARMS 2006), FO GAF)
Pharmacological studies - with nutritional supplements – (MED)									
Amminger et al., 2010 [x]; Mossaheb et al., 2013 [x];	AUT	RCT	Inclusion criteria: - At-risk for psychosis (PANSS) Exclusion Criteria: - History of previous psychotic disorder or manic episode - Substance-induced psychotic	81 EG: 41 CG:40	- Age (yrs.): EG: 16.8±2.4 / CG: 16.0±1.7 *(Age group: YOUTH)* - Gender (male): EG: 34% / CG: 33%	1.2 g/d ω-3 PUFAS; 12 weeks; 9 additional sessions of psychologic	Placebo (coconut oil); 12 weeks; psychologic al and	12; EG: 7% / 5%;	TR (PANSS), FO (GAF)

GE 1[+]			disorder - Acute suicidal or aggressive behavior - Current DSM-IV diagnosis of substance dependence (except cannabis dependence) - Neurological disorders - IQ<70 - Structural brain changes apparent on magnetic resonance imaging - Previous treatment with an antipsychotic or mood-stabilizing agent (>1 week) - ω-3 supplements within 8 weeks of being included in the trial - Laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, C-reactive protein, or bleeding parameters - Another severe intercurrent illness		- Co-morbidities: not reported	al and psychosocial interventions;	psychosocial interventions;		

Table 2 Within-group effect sizes at different follow-ups for improvements in functional outcome

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	p=0.83	**p=0.29**	**p=0.91**

Note. * < 0.05, ** < 0.01, ***< 0.001; Effect sizes are presented in a way that positive values indicate an improvement in functional outcome.
Abbreviations: CG, control group; EG, experimental group; g_w: standardized mean difference for pre-post improvements in the respective group;

Tab. 1 Characteristics of studies included in the meta-analysis

Psychological interventions (PSY)									
Study	**Coun -try**	**De-sign**	**In- & exclusion criteria**	**Sample size**	**Sample characteristics**	**Inter-vention**	**Control group**	**Follow-up** (months after baseline); **Dropout-rate** (Post-therapy)	**Extracted outcome**
Morrison et al., 2004 [x], 2007 [x]; **GE 1**-	UK	RCT	Inclusion criteria: - Risk for psychosis (PANSS) Exclusion criteria: - < 16 years, > 36 years - Current or past receipt of antipsychotic medication	60 EG: 37 CG: 23	- Age (yrs.): EG: 20.6±4.9 / CG: 21.5±5.2 *(Age group: ADULT)* - Gender: (male): EG: 60% / CG: 83% - Co-morbidities: not reported	CBT + monitoring; 26 sessions, 6 months	Monitoring; monthly	6, 12, 36; EG / CG: 30% / 30%	TR (PANSS)
Addington et al., 2011 [x]; Marshall et al., 2012 [x]; **GE 1**-	CAN	RCT	Inclusion criteria - 14 to 30 years - Risk for psychosis (SIPS) Exclusion criteria - Lifetime or current axis-I psychotic disorder - Prior treatment with an antipsychotic - IQ < 70 - Past/current central nervous system disorder	51 EG: 27 CG: 24	- Age (yrs.): EG: 20.8±4.5 / CG: 21.1±3.7 *(Age group: ADULT)* - Gender (male): EG: 67% / CG 75% - Co-morbidities (EG / CG): mood disorders: 26% / 26%, alcohol abuse: 18% / 18%, cannabis abuse: 10% / 10%	CBT; max. 20 sessions (mean=12±6.2, range=1-26), 6 months	Supportive Therapy: coping with current problems, psycho-education; 20 sessions, 6 months	6, 12, 18; EG / CG: 30% / 33%,	TR (SIPS), FO (GAF & SFS)
Morrison et al., 2012,	UK	RCT	Inclusion criteria: - At-risk for psychosis (CAARMS)	288 EG: 144 CG:	- Age (yrs.): EG: 20.7±4.2 / CG: 20.8±4.5 *(Age*	CBT + Monitoring; Max. 26	Monitoring; monthly	6, 12, 18, 24; EG / CG: 33% / 31%	TR (CAARMS or reports from family

[x]; Morrison et al., 2011, 2013 [x]; **GE 1^{+}**			- 14-35 years - Help-seeking Exclusion criteria: - Current or previous receipt of antipsychotic drugs - Moderate to severe learning disability - Organic impairments - Insufficient English	144	*group: ADULT)* - Gender: (male): EG: 62% / CG: 63% - Co-morbidities (total sample, >5%): Depressive disorder: 34%, dysthymic disorder: 7%, panic disorder with agoraphobia: 6%, panic disorder without agoraphobia: 11%, social phobia: 11%, specific phobia: 11%, generalized anxiety disorder: 9%, obsessive compulsive disorder: 8%	sessions, 6 months; plus up to 4 booster-sessions in the following 6 months;			doctors), FO (GAF)
Bechdolf et al., 2012 [x]; Bechdolf et al., 2007 [x]; **GE 1^{-}**	GER	RCT	Inclusion criteria: - At least one of 10 thought or perceptional basic symptoms (ERIraos) and/or - Reduction in the GAF Score (DSM-IV) of at least 30 points within the past year and at least one of these risk factors: first-degree relative with schizophrenia /schizophrenia spectrum disorder or pre-/perinatal complications; Exclusion criteria: - APS or BLIPS - Present or past diagnosis of a psychotic disorder, bipolar disorder, organic brain	128 EG: 63 CG: 65	- Age (yrs.): EG: 25.2±5.4 / CG: 26.8±6.2 *(Age group: ADULT)* - Gender: (male): 62% / 65% - Co-morbidities: not reported	Integrated treatment: : Individual CBT, multi-family psycho-education (group), social skills training (group), cognitive remediation 25 sessions, 12 months	Supportive counselling: coping with current problems, basic psycho-education; 30 sessions, 12 months	6, 12, 18, 24; EG / CG: 19%, / 12%	TR (DSM-IV), FO (SAS II)

			disorder, substance dependence - Mental retardation - Previous treatment with antipsychotics - Acute suicidality - < 17 years, > 35 years						
Van der Gaag et al., 2012 [x]; Rietdijk et al., 2010 [x]; **GE 1++**	NL	RCT	Inclusion criteria - 14 to 35 years - At-risk for psychosis (CAARMS 2006) - SOFAS score ≤ 50 and/or a reduction by 30% for at least 1 month in the past year Exclusion criteria: - Current or previous use of antipsychotic medication with ≥ 15 mg cumulative haloperidol equivalent - Severe learning impairment - Problems due to an organic condition - Insufficient competence in Dutch; - History of psychosis	201 EG: 98 CG: 103	- Age (yrs.): EG: 22.9±5.6 / CG: 22.6±5.5 *(Age group: ADULT)* - Gender (male): EG: 50% / CG: 49% - Co-morbidities: (total sample, > 5%): Anxiety disorders: 27%, depression: 26%, personality disorders: 8%, ADHD: 7%, addiction problems: 6%;	CBT + Treatment As Usual (TAU); max. 26 sessions, weekly; 6 months; additional evidence-based treatment for axis-I and axis-II disorders;	Treatment As Usual (TAU); additional evidence-based treatment for axis-I and axis-II disorders;	6, 12, 18; EG / CG: 15% / 12%	TR (CAARMS 2006), FO (SOFAS)
McGorry et al., 2013 [x]; Yung et al. 2011 [x]; **GE 1+**	AUS	RCT	Inclusion criteria: - Age 14-30 years - Melbourne metropolitan area - Risk for psychosis (CAARMS 2006) Exclusion criteria: - History of psychotic or manic episode - Medical condition that accounts for symptoms - Neurologic, biochemical or	72 EG: 44 CG: 28	- Age (yrs.): EG: 18.0±2.7 / CG: 18.8±3.7 *(Age group: YOUTH)* - Gender (male): EG: 49% / CG: 47% - Co-morbidities: not reported	EG : CBT + Placebo; 12 months; CBT: Weekly to monthly basis; 50-60 min./session with the number of sessions not determined	Supportive therapy + placebo; 12 months;	6, 12; EG: 34% / CG: 32%	TR (CAARMS 2006), FO GAF)

			hematologic abnormalities - Serious co-existing illnesses - Lifetime antipsychotic dose of 15mg or more of haloperidol - Any previous or current use of mood-stabilizing medication - History of severe drug allergy - IQ<70 - Pregnancy or lactation - Insufficient English			in advance;			
Miklowitz et al., 2014 [x]; O'Brien et al., 2014 [x]; **GE 1^{+}**	USA	RCT	Inclusion criteria: - 12 and 25 years - Speaks and writes English - At-risk for psychosis (SIPS) Exclusion criteria: - Current schizophrenia or schizoaffective disorders - Developmental disorders - Substance use disorders - Neurological disorders	129 EG: 66 CG: 63	- Age (yrs.): EG: 17.3±4.2 / CG: 17.4±3.9 *(Age group: YOUTH)* - Gender (male): EG: 59 % / CG: 56% - Co-morbidities (EG / CG, >10%): depressive disorder (40% / 29%), anxiety disorders (42% / 50%), ADD (21% / 18%), learning disorders (11% / 7%)	Family focused treatment; 18 sessions à 60 minutes, 6 months	Enhanced care; 3 weekly psycho-educational sessions, 1 month	6; EG: 17% / CG: 25%	TR (SIPS), FO (GAF)
O'Brien et al., 2007 [x]; **GE 2^{-}**	USA	No CG	Inclusion criteria: - 12-22 years - At-risk for psychosis (SIPS) Exclusion criteria: - DSM-IV diagnosis of a schizophrenia spectrum disorder - IQ<70 - Current drug or alcohol dependence	16	- Age (yrs.): 15.7 (range: 12.5-18.5) *(Age group: YOUTH)* - Gender: (male): 50% - Comorbidities (>10%): Mood disorders: 63%, depressive	Psycho-educational multi-family group; Weekly sessions à 90 minutes, 9 months	-	9; 45% declined or dropped out	FO (GAF)

			- Current neurological disorder		disorder: 31%, depressive disorder NOS: 19%, anxiety disorder NOS: 31%, generalized anxiety disorder: 19%, ADHD: 13%, eating disorder NOS: 19% / 0%				
Hooker et al., 2014 [x]; **GE 2⁻**	USA	No CG	Inclusion criteria: - 15-35 years - At-risk for psychosis (SIPS) Exclusion criteria: - Major medical / neurological illness - Non-fluent English - MR-contraindication - IQ<70	28 EG: 14 CG: 14	- Age (yrs.): 21.9±4.2 *(Age group: ADULT)* - Gender (male): 50%	CRT; neuro- and social-cognitive computerized exercises; 1h each day, 5 days/week, 8 weeks;	-	3; 18%	FO (Global Functioning Role and Social scales)
Pharmacological studies - with antipsychotics – (MED)									
McGlashan et al., 2006 [x]; McGlashan et al., 2003 [x]; Woods et al., 2003 [x]; **GE 1⁺**	USA	RCT	Inclusion criteria: - 12-45 years - Help-seeking - At-risk for psychosis (SIPS)¨ Exclusion criteria: - Past or current psychotic disorder - Treatable psychiatric disorder that could account for the prodromal symptoms - Suicidal or homicidal - Prodromal symptoms due to drug/alcohol use	60 EG:31 CG: 29	- Age (yrs.): EG: 18.2±5.5 / CG: 17.2±4.0 *(Age group: YOUTH)* - Gender (male): EG: 68% / CG: 62% - Co-morbidities: Current substance abuse or dependence (EG: 13% / CG: 4%)	Olanzapine; 5-15 mg/d, 12 months; Additional individual and family psychosocial treatment, varied across sites;	Placebo; 12 months; Additional individual and family psychosocial treatment, varied across sites;	2, 12, 24; EG: 55% / CG: 35%	TR (SIPS), FO (GAF)
Woods et al., 2007 [x];	USA	No CG	Inclusion criteria: - 13-40 years - Treatment seeking outpatients	15	- Age (yrs.): 17.1±5.5 *(Age group: YOUTH)* - Gender (male): 53%	Aripiprazole; Initial doses were 1st	-	2; 13%	FO (GAF, SFS)

GE 2⁻			- Met diagnostic criteria for a possible prodromal syndrome (SIPS) Exclusion criteria: - Past or current DSM-IV criteria for any lifetime psychotic disorder - Psychiatric disorder which could account for the symptoms - Symptoms primarily as sequelae to drug or alcohol use - Alcohol or drug misuse or dependence in the past 3 months - Use of antipsychotic medication in the previous 3 months - Change in dosage of any antidepressant within 6 weeks, stimulant medication within 4 weeks or mood stabiliser within 4 weeks		- Co-morbidities: not reported	Week: 5 mg/d, 2nd Week: 10 mg/d 3rd week: 15 mg/d, 4th Week: 20mg/d and if needed to 30mg/d; 6 weeks			
Tsujino et al., 2013 [x]; **GE 2⁻**	JPN	No CG	Inclusion criteria: - 15-39 years - Help-seeking outpatients - At-risk for psychosis (SIPS) Exclusion criteria: - Previous diagnosis of any psychotic disorder (DSM-IV) - Symptoms fully accounted for by an Axis 1 disorder or sequelae of drug/alcohol use - Abuse of alcohol or drugs - Antipsychotic medication use	11	- Age (yrs.): 26.7±6.5 *(Age group: ADULT)* - Gender (male): 46% - Co-morbidities: not reported	Perospirone ; dosing according to a flexible schedule; psychosocial therapy available; 26 weeks	-	6; 25%	FO (GAF)

Pharmacological studies - combined with psychological interventions – (MED)									
McGorry et al. 2002 [x]**;** Phillips et al., 2007 [x]; **GE 1**[-]	AUS	RCT	Inclusion criteria: - 14-30 years - Live in the Melbourne metropolitan area - Risk for psychosis (CAARMS) Exclusion criteria: - Previous psychotic or manic episode - Previous treatment with an antipsychotic or mood stabilizing agent - Substance-induced psychotic disorder - IQ<70 - Inadequate command of English	59 EG: 31 CG: 28	- Age (yrs.): EG: 20±4/ CG: 20±3 *(Age group: ADULT)* - Gender (male): EG: 65% / CG: 50%	Risperidone (1-2 mg/d) + CBT + Needs-based intervention (NBI); 6 months; NBI on-going;	Needs-based intervention (NBI); 6 months; NBI on-going;	6, 12, 36-48; months; Drop-out rate: not reported, 41% non-adherent to Risperidone;	FO (GAF)
Ruhrmann et al., 2007 [x]; **GE 1**[-]	GER	RCT	Inclusion criteria: - Older than 18 years - Risk for psychosis (ERIraos) Exclusion criteria: - Lifetime DSM–IV diagnosis of schizophrenia spectrum disorder, brief psychotic episode (>1 week), delirium, dementia, amnestic and other cognitive disorders - Mental retardation - Mental disorders due to a general medical condition or psychotropic substances - Abuse of alcohol or drugs within the past 3 months or the past 4 weeks for cannabis - Any lifetime continuous treatment with high-potency	124 EG: 65 CG: 59	- Age (yrs.): EG: 25.1±6.6 / CG: 26.1±6.1 *(Age group: ADULT)* - Gender: (male): 48% / 60% - Co-morbidities: not reported	Needs-focused intervention + Amisulpride; 12 weeks; 50-800 mg/d, with increments of 50 mg at first step and 100 mg at further steps; dosage was increased as long as APS and BLIPS were	Needs-focused intervention; 12 weeks	3; EG: 29% / CG: 49%	FO (GAF)

			antipsychotics (> 1 week) or antipsychotics during 6 months prior to the study - Any contraindication for amisulpride - Women of childbearing risk not using contraception			present;			
McGorry et al., 2013 [x]; Yung et al. 2011 [x]; **GE 1+**	AUS	RCT	Inclusion criteria: - Age 14-30 years - Melbourne metropolitan area - Risk for psychosis (CAARMS, 2005) Exclusion criteria: - History of psychotic or manic episode - Medical condition that accounts for symptoms - Neurologic, biochemical or hematologic abnormalities - Serious co-existing illnesses - Lifetime antipsychotic dose of 15mg or more of haloperidol - Any previous or current use of mood-stabilizing medication - History of severe drug allergy - IQ<70 - Pregnancy or lactation - Insufficient English	71 EG: 43 CG: 28	- Age (yrs.): EG: 17.6 ±3.0) / CG: 18.8±3.7 *Age group: YOUTH)* - Gender (male): EG: 45% / CG: 47% - Co-morbidities: not reported	EG: CBT + Risperidone (0.5-2 mg/d); 12 months; CBT: Weekly to monthly basis; 50-60 min./session ; number of sessions not predetermined;	Supportive therapy + placebo; 12 months;	6, 12; EG 37% / CG: 32%	TR (CAARMS 2006), FO GAF)
Pharmacological studies - with nutritional supplements – (MED)									
Amminger et al., 2010 [x]; Mossaheb et al., 2013 [x];	AUT	RCT	Inclusion criteria: - At-risk for psychosis (PANSS) Exclusion Criteria: - History of previous psychotic disorder or manic episode - Substance-induced psychotic	81 EG: 41 CG:40	- Age (yrs.): EG: 16.8±2.4 / CG: 16.0±1.7 *(Age group: YOUTH)* - Gender (male): EG: 34% / CG: 33%	1.2 g/d ω-3 PUFAS; 12 weeks; 9 additional sessions of psychologic	Placebo (coconut oil); 12 weeks; psychologic al and	12; EG: 7% / 5%;	TR (PANSS), FO (GAF)

GE 1[+]			disorder - Acute suicidal or aggressive behavior - Current DSM-IV diagnosis of substance dependence (except cannabis dependence) - Neurological disorders - IQ<70 - Structural brain changes apparent on magnetic resonance imaging - Previous treatment with an antipsychotic or mood-stabilizing agent (>1 week) - ω-3 supplements within 8 weeks of being included in the trial - Laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, C-reactive protein, or bleeding parameters - Another severe intercurrent illness		- Co-morbidities: not reported	al and psychosocial interventions;	psychosocial interventions;		

Table 2 Within-group effect sizes at different follow-ups for improvements in functional outcome						
Follow-up	**2 to 6 months**		**9 to 12 months**		**18 months**	
Study	*EG* g_w	*CG* g_w	*EG* g_w	*CG* g_w	*EG* g_w	*CG* g_w
Addington[x]$_a$	0.18	-0.03	0.45	0.53	0.07	0.29
Addington[x]$_b$	0.36	0.25	0.28	0.37	0.92	0.43
Amminger[x]			7.62	2.97		
Bechdolf[x]			0.44	0.60		
Hooker[x]$_a$	-0.25					
Hooker[x]$_b$	-0.06					
McGlashan[x]	0.54	0.27	0.87	0.52		
McGorry[x]			0.01	0.35	0.34	0.03
McGorry[x]$_{Risperidone}$	0.29	0.90	1.26	0.57		
McGorry[x]$_{CBT}$	0.09	1.52				
Miklowitz[x]	2.79	2.24				
Morrison[x]	0.62	0.84	0.72	0.57	1.04	0.77
O`Brien[x]			0.87			
Ruhrmann[x]	0.72	0.19				
Tsujino[x]	0.97					
Van der Gaag[x]	0.99	0.72	1.20	1.19	1.66	1.46
Woods[x]$_a$	-0.06					
Woods[x]$_b$	1.40					
Pooled g_w (g_w, 95% CIs)	**0.62*** (0.26,0.98)**	**0.68** (0.26,1.10)**	**0.84*** (0.41,1.26)**	**1.22*** (0.66,1.78)**	**0.69 (-0.01,1.39)**	**0.64* (0.12,1.17)**
Heterogeneity	$Q_{w(13)=}$**101.65*** I^2=87%**		$Q_{w(19)=}$**201.02*** I^2=91%**		$Q_{w(9)=}$**67.27*** I^2=87%**	
Between-group differences	$Q_{b(1)=}$**0.04, p=0.83**		$Q_{b(1)=}$**1.12, p=0.29**		$Q_{b(1)=}$**0.01, p=0.91**	

Note. * < 0.05, ** < 0.01, ***< 0.001; Effect sizes are presented in a way that positive values indicate an improvement in functional outcome.
Abbreviations: CG, control group; EG, experimental group; g_w: standardized mean difference for pre-post improvements in the respective group;

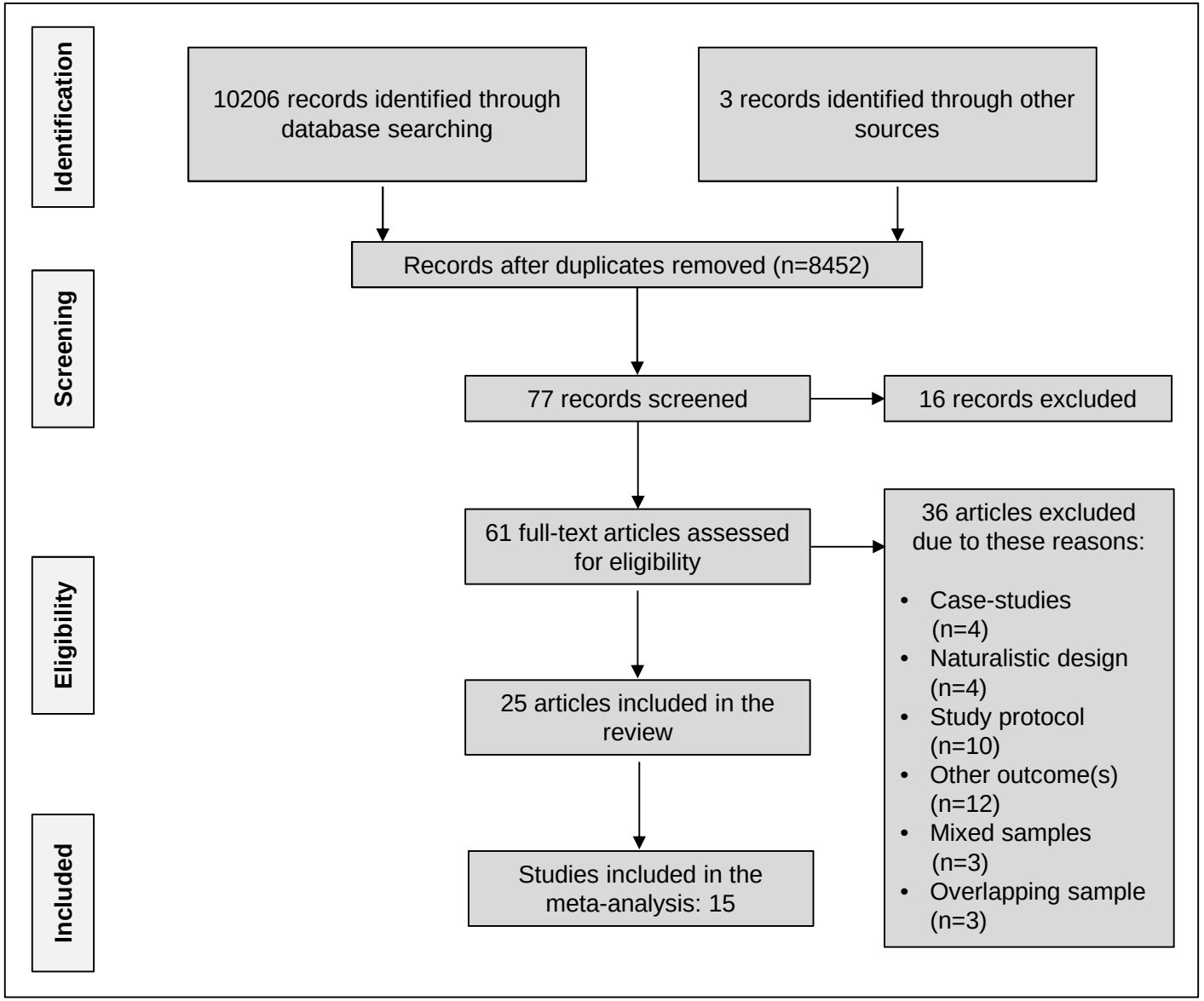
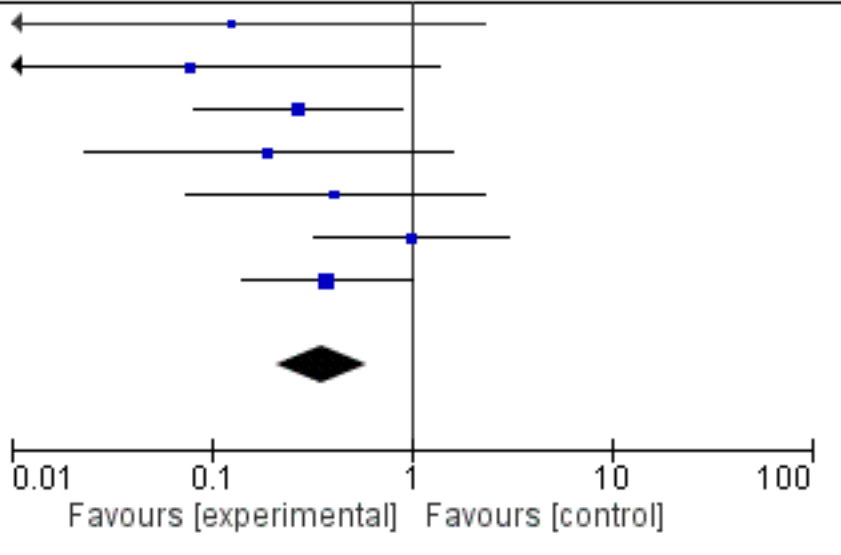


Figure 1. Flow chart of the study selection process

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Addington et al., 2011	0	27	3	24	7.5%	0.13 [0.01, 2.35]
Bechdolf et al., 2012	0	63	6	65	13.0%	0.08 [0.00, 1.38]
McGorry et al., 2002	3	31	10	28	21.4%	0.27 [0.08, 0.89]
Miklowitz et al., 2014	1	66	5	63	10.4%	0.19 [0.02, 1.59]
Morrison et al., 2004	2	37	3	23	7.5%	0.41 [0.07, 2.30]
Morrison et al., 2012	6	144	6	144	12.2%	1.00 [0.33, 3.03]
Van der Gaag et al., 2012	5	98	14	103	27.8%	0.38 [0.14, 1.00]
Total (95% CI)		**466**		**450**	**100.0%**	**0.36 [0.21, 0.60]**
Total events	17		47			

Heterogeneity: $Chi^2 = 5.46$, df = 6 (P = 0.49); $I^2 = 0\%$

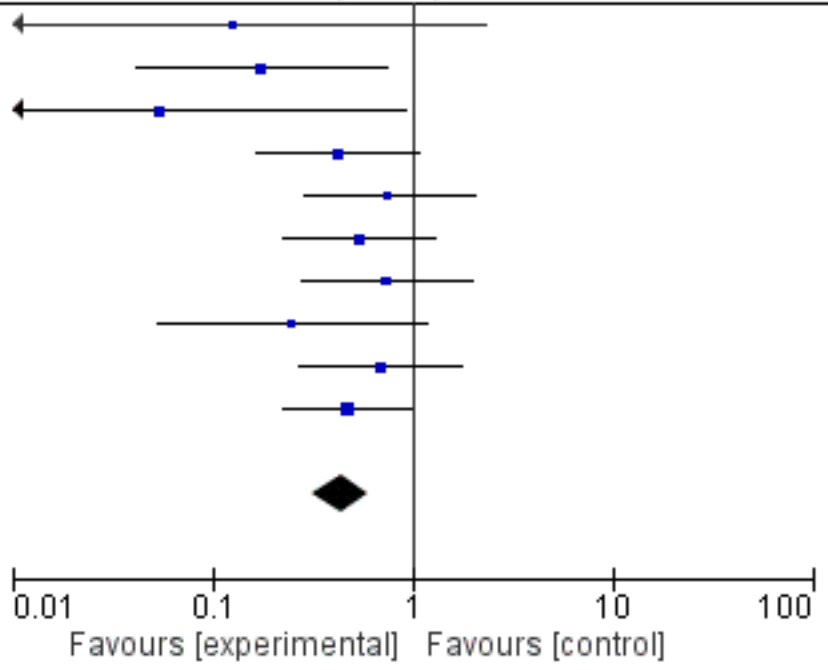
Test for overall effect: Z = 3.87 (P = 0.0001)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Addington et al., 2011	0	27	3	24	3.8%	0.13 [0.01, 2.35]
Amminger et al., 2010	2	41	11	40	11.6%	0.18 [0.04, 0.75]
Bechdolf et al., 2012	0	63	9	65	9.7%	0.05 [0.00, 0.91]
McGlashan et al., 2006	5	31	11	29	11.8%	0.43 [0.17, 1.08]
McGorry et al. 2013_CBT and Risp vs CG	7	43	6	28	7.5%	0.76 [0.28, 2.03]
McGorry et al., 2002	6	31	10	28	10.9%	0.54 [0.23, 1.30]
McGorry et al., 2013_CBT vs CG	7	44	6	28	7.6%	0.74 [0.28, 1.98]
Morrison et al., 2004	2	37	5	23	6.4%	0.25 [0.05, 1.18]
Morrison et al., 2012	7	144	10	144	10.4%	0.70 [0.27, 1.79]
Van der Gaag et al., 2012	9	98	20	103	20.2%	0.47 [0.23, 0.99]
Total (95% CI)		**559**		**512**	**100.0%**	**0.44 [0.31, 0.61]**
Total events	45		91			

Heterogeneity: $Chi^2 = 8.36$, $df = 9$ ($P = 0.50$); $I^2 = 0\%$

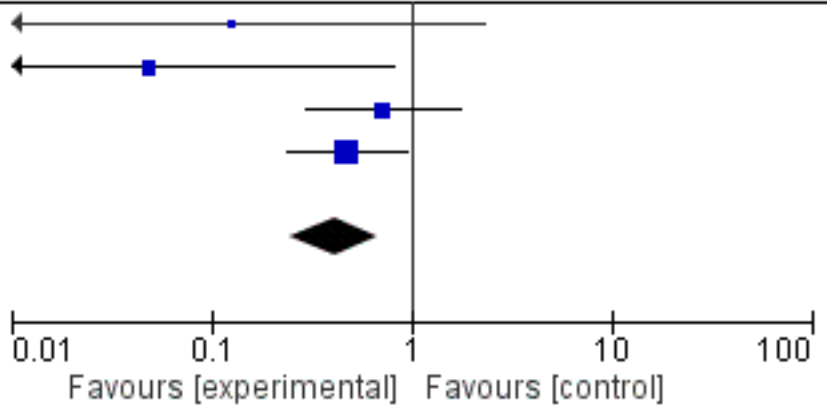
Test for overall effect: $Z = 4.86$ ($P < 0.00001$)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Addington et al., 2011	0	27	3	24	8.0%	0.13 [0.01, 2.35]
Bechdolf et al., 2012	0	63	10	65	22.2%	0.05 [0.00, 0.82]
Morrison et al., 2012	8	144	11	144	23.7%	0.73 [0.30, 1.76]
Van der Gaag et al., 2012	10	98	22	103	46.1%	0.48 [0.24, 0.96]
Total (95% CI)		**332**		**336**	**100.0%**	**0.41 [0.25, 0.69]**
Total events	18		46			

Heterogeneity: $Chi^2 = 4.57$, $df = 3$ ($P = 0.21$); $I^2 = 34\%$

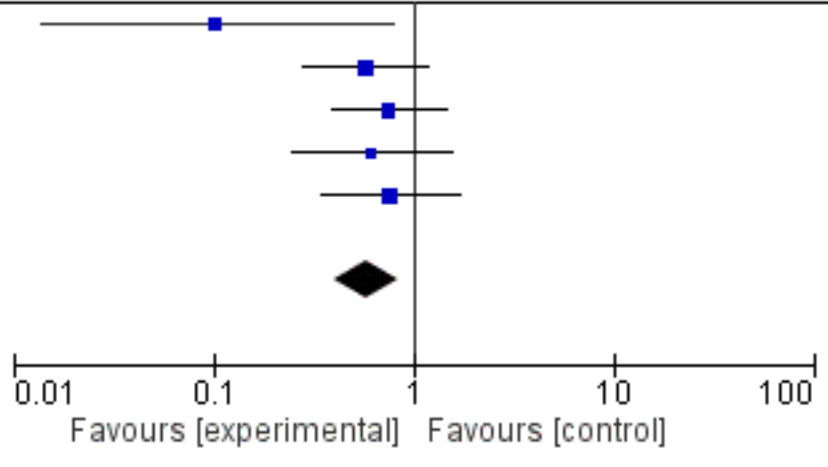
Test for overall effect: $Z = 3.41$ ($P = 0.0007$)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bechdolf et al., 2012	1	63	10	65	17.1%	0.10 [0.01, 0.78]
McGlashan et al., 2006	8	31	13	29	23.4%	0.58 [0.28, 1.18]
McGorry et al., 2002	10	31	12	28	21.9%	0.75 [0.39, 1.46]
Morrison et al., 2004	7	37	7	23	15.0%	0.62 [0.25, 1.54]
Morrison et al., 2012	10	144	13	144	22.6%	0.77 [0.35, 1.70]
Total (95% CI)		**306**		**289**	**100.0%**	**0.58 [0.40, 0.85]**
Total events	36		55			

Heterogeneity: $Chi^2 = 3.85$, $df = 4$ ($P = 0.43$); $I^2 = 0\%$

Test for overall effect: $Z = 2.83$ ($P = 0.005$)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington et al., 2011	64.2	14.4	27	61.3	9.9	24	9.5%	0.23 [-0.32, 0.78]
Addington et al., 2011	122	22.8	27	117.4	15.7	24	9.5%	0.23 [-0.32, 0.78]
McGlashan et al., 2006	47.1	9.3	30	45	11.3	29	10.1%	0.20 [-0.31, 0.71]
McGorry et al. 2013_CBT and Risp vs CG	57.4	7.6	43	63.8	7.4	28	10.3%	-0.84 [-1.34, -0.34]
McGorry et al., 2013_CBT vs CG	60.6	6.8	44	63.8	7.4	28	10.5%	-0.45 [-0.93, 0.03]
Miklowitz et al., 2014	55.35	2.82	54	53.7	3.21	44	11.6%	0.55 [0.14, 0.95]
Morrison et al., 2012	59.3	16.21	97	61.61	15.04	98	13.5%	-0.15 [-0.43, 0.13]
Ruhrmann et al_2007	66.8	14.1	58	60.7	14.7	44	11.8%	0.42 [0.03, 0.82]
Van der Gaag et al., 2012	53.8	9.7	80	51.5	10.6	90	13.2%	0.22 [-0.08, 0.53]
Total (95% CI)			**460**			**409**	**100.0%**	**0.05 [-0.22, 0.32]**

Heterogeneity: Tau² = 0.12; Chi² = 29.92, df = 8 (P = 0.0002); I² = 73%
Test for overall effect: Z = 0.38 (P = 0.70)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Addington et al., 2011	62.7	12.3	27	62.6	10.2	24	11.1%	0.01 [-0.54, 0.56]
Addington et al., 2011	126.7	19.8	27	128.3	16.6	24	11.1%	-0.09 [-0.64, 0.46]
Amminger et al., 2010	78.7	2.3	41	67.2	2.4	40	9.7%	4.85 [3.97, 5.73]
Bechdolf et al., 2012	-3.3	0.945	29	-2.9	0.999	38	11.3%	-0.41 [-0.89, 0.08]
McGlashan et al., 2006	50.26	9.29	30	47.83	11.33	29	11.2%	0.23 [-0.28, 0.74]
McGorry et al. 2013_CBT and Risp vs CG	64.8	9	26	64.6	13.6	19	10.9%	0.02 [-0.57, 0.61]
McGorry et al., 2013_CBT vs CG	66.8	7.7	26	64.6	13.6	19	10.9%	0.20 [-0.39, 0.80]
Morrison et al., 2012	60.74	16.69	95	58.59	16.23	94	11.9%	0.13 [-0.16, 0.42]
Van der Gaag et al., 2012	56.8	11.8	75	57	13.3	76	11.8%	-0.02 [-0.33, 0.30]
Total (95% CI)			**376**			**363**	**100.0%**	**0.48 [-0.12, 1.08]**

Heterogeneity: $Tau^2 = 0.78$; $Chi^2 = 116.57$, df = 8 ($P < 0.00001$); $I^2 = 93\%$

Test for overall effect: $Z = 1.56$ ($P = 0.12$)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Addington et al., 2011	133.6	16.3	27	124.5	22.5	24	14.6%	0.46 [-0.10, 1.02]
Addington et al., 2011	60.2	17.9	27	63.4	11	24	14.9%	-0.21 [-0.76, 0.34]
McGorry et al., 2002	57.48	15.72	23	59.88	15.89	14	10.2%	-0.15 [-0.81, 0.52]
Morrison et al., 2012	64.12	17.71	34	60.19	16.88	31	19.0%	0.22 [-0.26, 0.71]
Van der Gaag et al., 2012	61.6	12.8	71	59.6	13.7	69	41.2%	0.15 [-0.18, 0.48]
Total (95% CI)			**182**			**162**	**100.0%**	**0.13 [-0.09, 0.34]**

Heterogeneity: $Chi^2 = 3.63$, $df = 4$ ($P = 0.46$); $I^2 = 0\%$

Test for overall effect: $Z = 1.15$ ($P = 0.25$)