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

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ABSTRACT

This guidance paper from the European Psychiatric Association (EPA) aims to provide evidence-based recommendations on early intervention in clinical high risk (CHR) states of psychosis, assessed according to the EPA guidance on early detection. The recommendations were derived from a meta-analysis of current empirical evidence on the efficacy of psychological and pharmacological interventions in CHR samples. Eligible studies had to investigate conversion rate and/or functioning as a 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 type of intervention were examined as potential moderators. Based on data from 15 studies (n = 1394), early intervention generally produced significantly reduced conversion rates at 6- to 48-month follow-up compared to control conditions. However, early intervention failed to achieve significantly greater functional improvements because both early intervention and control conditions produced similar positive effects. With regard to the type of intervention, 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. Seven evidence-based recommendations for early intervention in CHR samples could have been formulated, although more studies are needed to investigate the specificity of treatment effects and potential age effects in order to tailor interventions to the individual treatment needs and risk status.

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1. Introduction

Each year, 38.2% of the population of the European Union, i.e., 164.8 million persons, suffer from a mental disorder [120]. This is associated with huge societal and individual burden [34,119]. 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 [14,20,36].

1.1. Functional disability in psychotic disorders

Schizophrenia is among the seven leading causes of years lost to disability (YLDs) in adults in Europe [120]. 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 [44,106]. As a consequence, prevention of schizophrenia and psychotic disorders in general has attracted special interest [108].

Functional impairments are present before [1] and often worsen until the onset of psychosis [35]. Furthermore, they are one of the main predictors of poor clinical outcome including conversion to psychosis [28]. This emphasizes the need to intervene as early as possible to avoid or at least diminish these burdens and thereby to prevent transition to full blown 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 emerging psychosis, but do not meet diagnostic criteria. The ultimate goal of this approach is to prevent this condition from converting to psychosis [61,65,67]. Thus, indicated prevention faces two challenges: the accurate identification of the target population and their effective treatment. For the purpose of early detection, two complementary sets of clinical high risk (CHR) criteria have been developed: the ultra-high risk (UHR) [73,126] and the basic symptom approach [41,105]. The UHR criteria were originally developed to detect individuals with an inherent risk for a first episode of psychosis within the next 12 months, and comprise the attenuated psychotic symptom (APS) criterion, the brief limited intermittent psychotic symptom (BLIPS) criterion, and the genetic risk and functional decline criterion [126]. The basic symptom approach was developed to detect the risk for psychosis as early as possible as defined by the presence of the cognitive-perceptive basic symptoms (COPER) and the cognitive disturbances (COGDIS) criterion [41,105]. Recommendations for the use of the UHR and the basic symptom approach and a review of the underpinning evidence 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 [96]. 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, side effects of medication, financial loss) [24,51,83].

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, which are already present at the time of referral to an early detection and intervention service [50,99,98,110]. This is demonstrated by their high levels of hopelessness, depression, anxiety, and poor quality of life, in comparison to other help-seeking patients and patients with first-episode psychosis [30,31,95]. In fact, they often fulfill the diagnostic criteria for other mental disorders that require treatment, in particular depression, anxiety, and substance abuse or dependence [25,42,100]. Furthermore, CHR patients seem to exhibit poor coping skills, low self-efficacy, and excessive external attributions that resemble profiles of depressive patients [104].

CHR patients also demonstrate abnormalities in neuro- and social cognition that are usually intermediate between those of healthy controls and schizophrenia patients [12,22,27,112], and are associated with markedly impaired functional outcome and negative symptoms [15,56,71,101,102,107]. These neuro- and social-cognitive abnormalities are also accompanied by various abnormalities in functional and structural imaging [11,52,107], electrophysiological measures [10,85,118], and neurochemistry [19,33,55]. In summary, CHR patients are in need for treatment – independent of any potential risk to develop psychosis in the future [96].

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 [97,89,109]. With the primary goal of preventing conversion to psychosis, these studies have drawn upon well-established interventions for adult schizophrenia patients and used conversion to psychosis as their primary outcome [63,68,75]. Other more recently developed interventions take 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 psycho-education) [29,32,59]. Yet most "new generation" intervention studies have an uncontrolled single-group design, and therefore lack methodological rigor, and were not included in recent meta-analyses on the efficacy of interventions in CHR states using randomized controlled trials (RCTs) [23,43,57,92,109,117].

Current guidelines have not yet considered these "new generation" interventions [9,18,82]. Moreover, no sufficient evidence-based differential indication for the available interventions exists as this requires the evaluation of the type of intervention as a potential moderator variable in meta-analyses and/or in direct multi-head-to-head comparisons in large RCTs. 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.

1.5. Aims

The aim of this guidance paper on early intervention in CHR states was to evaluate the efficacy of interventions that aim at preventing the conversion to psychosis and/or a deterioration of functional outcome. We also considered the potential moderating effects of age and intervention type. From this analysis, we have derived evidence-based recommendations on early intervention in CHR states assessed according to the recommendations provided by the EPA guidance on 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) AND ((psychosis) OR (schizophrenia)). Furthermore, we inspected reference lists of all identified reviews and meta-analyses.

2.1.2. Selection criteria

We included all studies in our meta-analysis that: evaluated a psychological and/or pharmacological intervention including interventions with nutritional supplements and other substances, included a majority (>50%) of CHR patients as defined by the UHR and/or the basic symptom criteria, reported conversion rates and/or functional outcome as intervention outcome, and were published in English. Exclusion criteria were: studies with samples that were also sub-sets of other studies included in our analyses with a larger sample size and/or a longer follow-up period, studies that were only published as an abstract or trial protocol, case-reports, and studies that used an observational naturalistic design.

2.1.3. Selection process and quality assessment

Fig. 1 illustrates the flowchart of the study selection process following the PRISMA guidelines [74]. Two authors (S.J.S., S.R.) independently assessed trial quality using the methodology checklist of the Scottish Intercollegiate Guideline Network (SIGN) for randomized controlled trials. In cases of disagreement, discrepancies were discussed among the raters or supplementary information was requested from the authors until agreement was reached.

2.2. Literature analysis

2.2.1. Data extraction

The following variables were extracted from the included studies:

- study characteristics: country, sample sizes, design, inclusion/exclusion criteria, sample description, experimental and control condition, follow-up (defined as the time-period after baseline assessments), and drop-out rate;
- prevalence of psychosis at all available follow-up assessment points (conversion rates). Following an intention-to-treat (ITT) approach, the total number of persons randomized to each group was chosen as the point of reference in order to avoid higher conversions rates due to an increase of drop-outs during the course of the trial;
- means and standard deviations of functional outcome measures of the experimental (EG) and the control group (CG) at baseline and at each follow-up assessment.

2.2.2. Meta-analytic procedure

For binary data (i.e. conversion rates), we estimated relative risks (RR) with their 95% confidence intervals (CIs) [111]. Additionally, we calculated the number-needed-to-treat statistics (NNTs) with their 95% CIs for the combined studies [54]. Notably, RRs and NNTs cannot be calculated for uncontrolled intervention designs for lack of a normative conversion rate.

For continuous data (i.e. functional outcome), the effect size Hedges' g was estimated as the standardized mean difference. For between-group comparisons, i.e. intervention studies with a control group, Hedges' g_b was calculated as the difference of the mean scores of the treatment and the control group at the respective follow-up divided by their pooled standard deviation [21,38]. For within-group comparisons, i.e. controlled and uncontrolled intervention studies with pre- and post-assessments for each condition, Hedges' g_w was calculated by the difference of the respective mean scores at pre- and post-assessment divided by their pooled standard deviation [53]. To test if the within-group effect sizes differ between EG and CG, the Q_b-statistic was calculated [13].

For both binary and continuous data, heterogeneity between effect sizes was determined with the Q_w-statistic [37]. In addition, I^2 served as an estimate of the relative size of homogeneity. Values

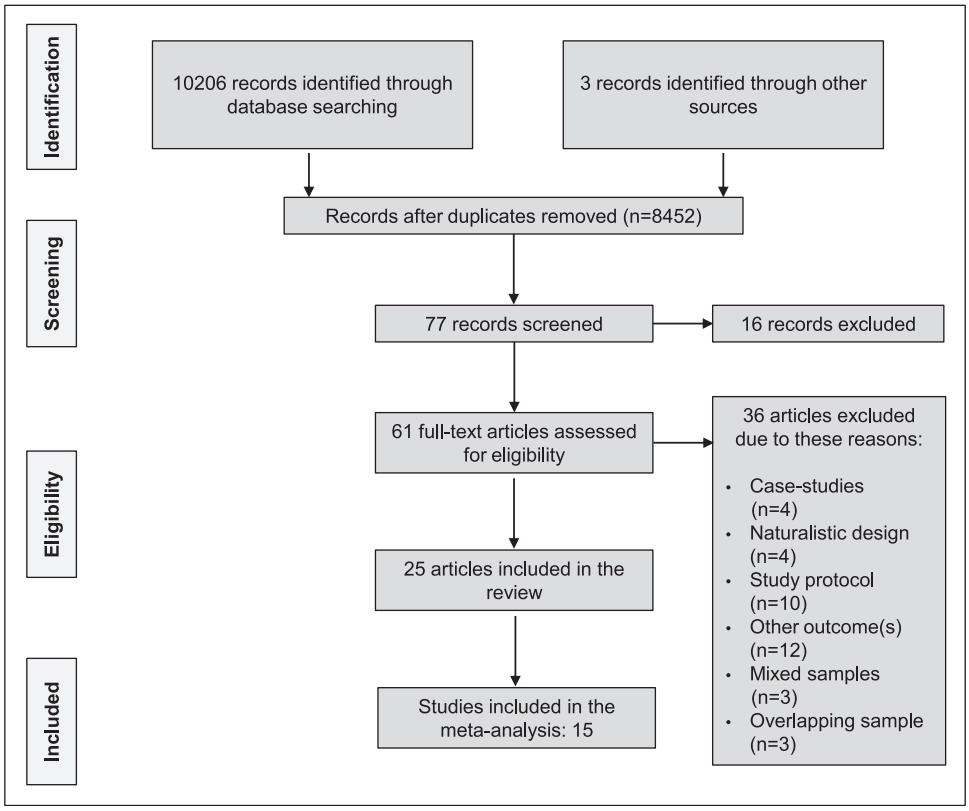

Fig. 1. Flow chart of the study selection process.

of 25, 50, and 75% are regarded as signifying low, moderate, and high heterogeneity [39]. If no substantial heterogeneity was detected, a fixed-effects model was applied. Otherwise, results of random-effects models are reported [13].

The meta-analytic calculations for this paper were conducted with the Review Manager (version 5.3) of the Cochrane Collaboration.

2.2.3. Potential moderator variables

Additionally, we investigated the impact of two potential moderator variables on treatment effects: intervention type and age. For this purpose, the meta-analytic calculations for between- (RR, Hedges' g_b) and within-group comparisons (Hedges' g_w) described above were performed separately for the respective sub-groups. Intervention type was distinguished by psychological interventions (PSY) and pharmacological interventions with antipsychotics or other substances (MED; Table 1). Age was rated in two categories: ≥50% minors (YOUTH), when the mean age ≤18 with an upper standard deviation still spanning patients ≤18 years, and samples with a proportion of minors of <50%, when the mean age >18 years (ADULT; Table 1). To test if the within-group effect sizes differ between the respective sub-groups, the Q_b-statistic was calculated as already described above.

2.3. Development of recommendations

In line with the EPA's methodological approach within the guidance project [26], the consensus process was restricted to the experts, i.e. authors. General consensus on recommendations was achieved by circulating results of the literature search and manuscript drafts prepared by the main authors (S.J.S., S.R.) to all co-authors for feedback and discussion after the following steps: compilation of studies to be included in meta-analyses, including their grade of evidence rating, conducting of analyses and first drafting of the manuscript, and recurrently adaptating after each feedback-related until full agreement among authors was reached on the manuscript's submission version. This step was also performed once more after receiving external review.

Furthermore, during the process of guidance development, the manuscript's submission version underwent review by the EPA Guidance Committee and EPA Board (see Acknowledgements) to guarantee that authors had adhered to the consented methodology. Only upon its approval by both committees, the manuscript was submitted for external review.

3. Results

3.1. Literature search

The process of the literature search is detailed in Fig. 1. The initial search produced 10,206 papers. After the exclusion of duplicate reports and screening of 8452 titles, 77 abstract were possibly relevant. They were further screened for inclusion and exclusion criteria, which reduced them to 61 full-text papers. These papers were especially checked for redundancies, i.e., significant overlap of samples, and presence of additional follow-up data in already included samples. Finally, 15 independent studies covered by 25 papers were included in the meta-analysis.

3.2. Evidence-base of the European Guidance

3.2.1. Sample and study characteristics of the included studies

Trial characteristics of the 15 studies that cover a total of 1394 participants are detailed in Table 1. Sample sizes at baseline ranged from 11 to 288 (mean = 87.12, S.D. = 73.82). Samples consisted mainly of young adults (mean = 20.44 years, S.D. = 3.29, range = 15.70–26.80). Nine samples (60.0%) included mainly adults, whereas six (40.0%) had a majority of minors. In eight studies (53.3%), more than half of the participants were male (range = 33.0–83.0%). Six studies (40.0%) provided information on co-morbidities consistently reporting the highest prevalence for affective (26.0–41.0%) and anxiety disorders (27.0–46.0%).

Ten studies (66.6%) were carried out in or at least involved well-established early detection and intervention services. Nine studies (60.0%) assessed conversion to psychosis. Two (13.3%) used the Positive and Negative Syndrome Scale (PANSS [46]), three (20.0%) the Structured Interview for Psychosis-Risk Syndromes (SIPS [64]), one (0.7%) the Early Recognition Inventory (ERIraos [60]), and three (20.0%) the Comprehensive Assessment of At-Risk Mental States (CAARMS [127]) in its original [78] and new version in 2006 [69,116]. Fourteen studies (93.3%) assessed functional outcome; most of them ($n = 11$, 78.6%) with the Global Assessment of Functioning Scale (GAF [3]). The follow-up duration ranged from 2 to 48 months (mean = 16.33 months, S.D. = 13.19). Twelve studies (80.0%) were RCTs, and three studies (20.0%) used an uncontrolled single-group design. Levels of evidence for RCTs according to SIGN varied between GE 1^- (i.e., RCTs with a high risk of bias) and GE 1^{++} (i.e., RCTs with a very low risk of bias). Studies with no control group were generally rated on GE 2^- (i.e., case-control studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal; Table 1).

3.2.2. Treatment characteristics of the included studies

3.2.2.1. Psychological interventions. Nine studies (60.0%) reported on the efficacy of psychological interventions with a mean therapy duration of 6.87 months (S.D. = 3.7, range = 2–12), a mean follow-up period of 16.67 months (S.D. = 10.40, range = 2–36), and a drop-out rate between 15.0 and 45.0% (Table 1). Five interventions used cognitive-behavioral therapy (CBT) techniques such as normalization, cognitive and behavioral experiments, and cognitive restructuring to improve stress- and symptom-management. These compared CBT with monitoring [75,78], supportive therapy [2], supportive therapy with placebo [69], and other evidence-based interventions for the disorders patients sought help [116]. One uncontrolled study evaluated cognitive remediation therapy (CRT) in CHR patients [40]. Moreover, a multi-family psycho-educational group program was evaluated first in one uncontrolled study [87], and next in a RCT with enhanced care as control condition [72]. One of the included RCTs [7] combined all of the aforementioned approaches with social skills training and compared this integrated psychological intervention with supportive therapy.

3.2.2.2. Pharmacological studies with antipsychotics or nutritional supplements. Six pharmacological studies (40.0%) have been published, two uncontrolled studies (33.3%) and four RCTs (66.7%). The mean therapy duration was 6.83 months (S.D. = 4.31, range = 2–12), the mean follow-up period was 15.29 months (S.D. = 16.23, range = 2–48), and the drop-out rate ranged between 13.0 and 55.0%. These trials investigated the efficacy of aripiprazole [123] and perospirone [113] using an uncontrolled design, and, as RCTs, olanzapine versus placebo [63], 'risperidone plus CBT' versus need-based intervention (NBI) [68], 'amisulpride plus NBI' versus NBI [94], and 'risperidone plus CBT' versus 'placebo plus supportive therapy' [69]. Only one included pharmacological study did not use antipsychotic medication but a neuroprotective approach, and investigated the effect of omega-3 polyunsaturated fatty acids (PUFAS) in CHR patients compared to placebo in a RCT [4]. Side effects of each pharmacological trial are listed in Table 1.

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

Psychological interventions (PSY)

Study	Country	Design	Inclusion and exclusion criteria	Sample size	Sample characteristics	Intervention	Control group	Follow-up (months after baseline); drop-out rate (post-therapy)	Extracted outcome; side effects
Morrison et al., 2004 [75], 2007 [76]; GE 1^{-}	UK	RCT	*Inclusion criteria:* risk for psychosis (PANSS), UHR *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: 30% CG: 30%	TR (PANSS)
Addington et al., 2011 [2]; Marshall et al., 2012 [58]; GE 1^{-}	CAN	RCT	*Inclusion criteria:* 14 to 30 years; risk for psychosis (SIPS), UHR *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: 30% CG: 33%	TR (SIPS), FO (GAF and SFS)
Morrison et al., 2012 [78]; Morrison et al., 2011 [77], 2013 [79]; GE $1^{\pm}$	UK	RCT	*Inclusion criteria:* risk for psychosis (CAARMS), UHR; 14–35 years; help-seeking *Exclusion criteria:* current or previous receipt of antipsychotic drugs; moderate to severe learning disability; organic impairments; insufficient English	288 EG: 144 CG: 144	Age (yrs): EG: 20.7 ± 4.2 / CG: 20.8 ± 4.5 (age 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%	CBT + monitoring; max. 26 sessions, 6 months; plus up to 4 booster-sessions in the following 6 months	Monitoring; monthly	6, 12, 18, 24 EG: 33% CG: 31%	TR (CAARMS or reports from family doctors), FO (GAF)
Bechdolf et al., 2012 [7]; Bechdolf et al., 2007 [5]; GE 1^{-}	GER	RCT	*Inclusion criteria:* at least one of 10 thought or perceptional basic symptoms (ERIraos); 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 disorder, substance dependence; mental retardation; previous treatment with antipsychotics, acute suicidality; <17 years, >35 years	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: 19% CG: 12%	TR (DSM-IV), FO (SAS II)
van der Gaag et al., 2012 [116]; Rietdijk et al., 2010 [93]; GE $1^{\pm\pm}$	NL	RCT	*Inclusion criteria:* 14 to 35 years; risk for psychosis (CAARMS 2006), UHR; 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): evidence-based treatment for axis-I and axis-II disorders for which patients were seeking help; max. 26 sessions, weekly; 6 months	Treatment as usual (TAU): evidence-based treatment for axis-I and axis-II disorders for which patients were seeking help	6, 12, 18 EG: 15% CG: 12%	TR (CAARMS 2006), FO (SOFAS)

Table 1 (*Continued*)

Study	Country	Design	Inclusion and exclusion criteria	Sample size	Sample characteristics	Intervention	Control group	Follow-up (months after baseline); drop-out rate (post-therapy)	Extracted outcome; side effects
Psychological interventions (PSY)									
McGorry et al., 2013 [69]; Yung et al., 2011 [128]; GE $1^{\pm}$	AUS	RCT	*Inclusion criteria:* age 14–30 years; Melbourne metropolitan area; risk for psychosis (CAARMS 2006), UHR *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 15 mg 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	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 in advance	Supportive therapy + placebo; 12 months	6, 12 EG: 34% CG: 32%	TR (CAARMS 2006), FO GAF)
Miklowitz et al., 2014 [72]; O'Brien et al., 2014 [88]; GE $1^{\pm}$	USA	RCT	*Inclusion criteria:* 12 and 25 years; speaks and writes English; risk for psychosis (SIPS), UHR *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 of 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 [87]; GE 2^{-}	USA	No CG	*Inclusion criteria:* 12–22 years; risk for psychosis (SIPS), UHR *Exclusion criteria:* DSM-IV diagnosis of a schizophrenia spectrum disorder; IQ < 70; current drug or alcohol dependence; current neurological disorder	16	Age (yrs): 15.7 (range: 12.5–18.5; age group: YOUTH) Gender: (male): 50% Co-morbidities (>10%): mood disorders: 63%, depressive disorder: 31%, depressive disorder NOS: 19%, anxiety disorder NOS: 31%, generalized anxiety disorder: 19%, ADHD: 13%, eating disorder NOS: 19% / 0%	Psycho-educational multi-family group; weekly sessions of 90 minutes, 9 months		9 45% declined or dropped out	FO (GAF)
Hooker et al., 2014 [40]; GE 2^{-}	USA	No CG	*Inclusion criteria:* 15–35 years; risk for psychosis (SIPS), UHR *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; 1 h 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 [63]; McGlashan et al., 2003 [62]; Woods et al., 2003 [121]; GE $1^{\pm}$	USA	RCT	*Inclusion criteria:* 12–45 years; help-seeking; risk for psychosis (SIPS), UHR *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); side effects: extrapyramidal symptoms, cholesterol, and blood glucose did not differ between groups, 61% weight gain in EG, 29% fatigue

Table 1 (*Continued*)

Pharmacological studies – with antipsychotics – (MED)									
Woods et al., 2007 [123]; GE 2⁻	USA	No CG	*Inclusion criteria:* 13–40 years; treatment seeking outpatients; met diagnostic criteria for a possible prodromal syndrome (SIPS), UHR *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 stabilizer within 4 weeks	15	Age (yrs): 17.1 ± 5.5 (age group: YOUTH) Gender (male): 53% Co-morbidities: not reported	Aripiprazole; initial doses were 1st week: 5 mg/d, 2nd week: 10 mg/d, 3rd week: 15 mg/d, 4th week: 20 mg/d and if needed to 30 mg/d; 6 weeks		2 13%	FO (GAF, SFS); side effects: 33% irritability, 27% increased appetite, 20% sedation, 13% insomnia, 13% nervousness, 13% impaired memory, 13% impaired perception, 13% increased saliva, 13% increased libido, 13% excessive sweating
Tsujino et al., 2013 [113]; GE 2⁻	JPN	No CG	*Inclusion criteria:* 15–39 years; help-seeking outpatients; risk for psychosis (SIPS), UHR *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); side effects: No serious side events (hyperglycemia, diabetes mellitus) occurred
Pharmacological studies – combined with psychological interventions – (MED)									
McGorry et al., 2002 [68]; Phillips et al., 2007 [91]; GE 1⁻	AUS	RCT	*Inclusion criteria:* 14–30 years; live in the Melbourne metropolitan area; risk for psychosis (CAARMS), UHR *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 ongoing	Needs-based intervention (NBI); 6 months; NBI ongoing	6, 12, 36–48 EG: 0%, 41% non-adherent to risperidone	FO (GAF); side effects: minor rigidity (3%), mild sedation (10%)
Ruhrmann et al., 2007 [94]; GE 1⁻	GER	RCT	*Inclusion criteria:* older than 18 years; risk for psychosis (ERIraos), UHR (APS and/or BLIPS) *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 antipsychotics (>1 week) or antipsychotics during 6 months prior to the study; any contraindication for amisulpride; women of childbearing risk not using contraception	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 present	Needs-focused intervention; 12 weeks	3 EG: 29% CG: 49%	FO (GAF); side effects: significantly more asthenia/fatigability (66% vs. 40%), memory problems (49% vs. 23%), dream activity (26% vs. 0%), sweating (20% vs. 0%), diminished sexual desire (34% vs. 10%)

Table 1 (*Continued*)

Pharmacological studies – combined with psychological interventions – (MED)									
McGorry et al., 2013 [69]; Yung et al., 2011 [128]; GE 1±	AUS	RCT	*Inclusion criteria:* age 14–30 years; Melbourne metropolitan area; risk for psychosis (CAARMS 2006), UHR *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 15 mg 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 pre-determined	Supportive therapy + placebo; 12 months	6, 12 EG: 37% CG: 32%	TR (CAARMS 2006), FO GAF); side effects: No significant differences between risperidone and placebo; most common were fatigue, depression, concentration difficulties, orthostatic dizziness
Pharmacological studies – with nutritional supplements – (MED)									
Amminger et al., 2010 [4]; Mossaheb et al., 2013 [80]; GE 1±	AUT	RCT	*Inclusion criteria:* risk for psychosis (PANSS), UHR *Exclusion criteria:* history of previous psychotic disorder or manic episode; substance-induced psychotic 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	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% Co-morbidities: not reported	1.2 g/d ω-3 fatty acids; 12 weeks; 9 additional sessions of psychological and psychosocial interventions	Placebo (coconut oil); 12 weeks; psychological and psychosocial interventions	12 EG: 7% CG: 5%	TR (PANSS), FO (GAF); side effects: no significant differences between EG and CG; side effects >5%: 10% tension, 7% nausea, 7% reduced duration of sleep, 7% fatigue

APS: attenuated psychotic symptoms; AUS: Australia; AUT: Austria; BLIPS: brief limited intermittent psychotic symptoms; BS: basic symptom approach; CA: Canada; EG: experimental group; CG: control group; GER: Germany; JPN: Japan; NL: Netherlands; RCT: randomized controlled trial; UK; United Kingdom; UHR: ultra-high risk approach; USA: United States of America.

3.2.3. Excluded studies and ongoing trials

Studies that had to be excluded because their trials are still underway or their results have not been published yet are briefly summarized below, as they may entail important information on current developments in early intervention in CHR states.

Recent psychological trials paid special attention, not only to risk symptoms, but also to other common features or stressors of CHR samples such as deficits in neuro- and social cognition and in coping. Studies in adolescents that were excluded due to their naturalistic design emphasized the importance of good and frequent net-working of multi-professional teams in achieving not only symptomatic and functional gains but also reductions in depression, hopelessness, and anxiety [29,32]. One additional trial investigated the potential beneficial effects of CBT based on the intervention of Morrison et al. [75] in CHR samples [48] with further trials being underway using CRT [70,114,115].

Recent ongoing RCTs have been designed to disentangle the effects of pharmacological and psychological interventions [6] and to replicate the neuroprotective effect of PUFAS [66,84]. Other studies used lithium as a neuroprotective agent [8] or followed the glutamate hypothesis of psychosis and investigated glycine [122,124] or – still ongoing – d-serine [81]. Results for lithium and glycine are promising but no effects on conversion rates or functional outcome were reported. Other pharmacological trials of antidepressants [16,86] and aspirin [125] used a naturalistic design and/or are still ongoing.

3.3. Meta-analytic results

3.3.1. Conversion rates

All seven RCTs [2,7,68,72,75,78,116] (n = 916) that investigated psychological and/or pharmacological interventions reported on the conversion rates at 6-month follow-up (Fig. 2a). As there was no relevant heterogeneity among the study effects, the results of

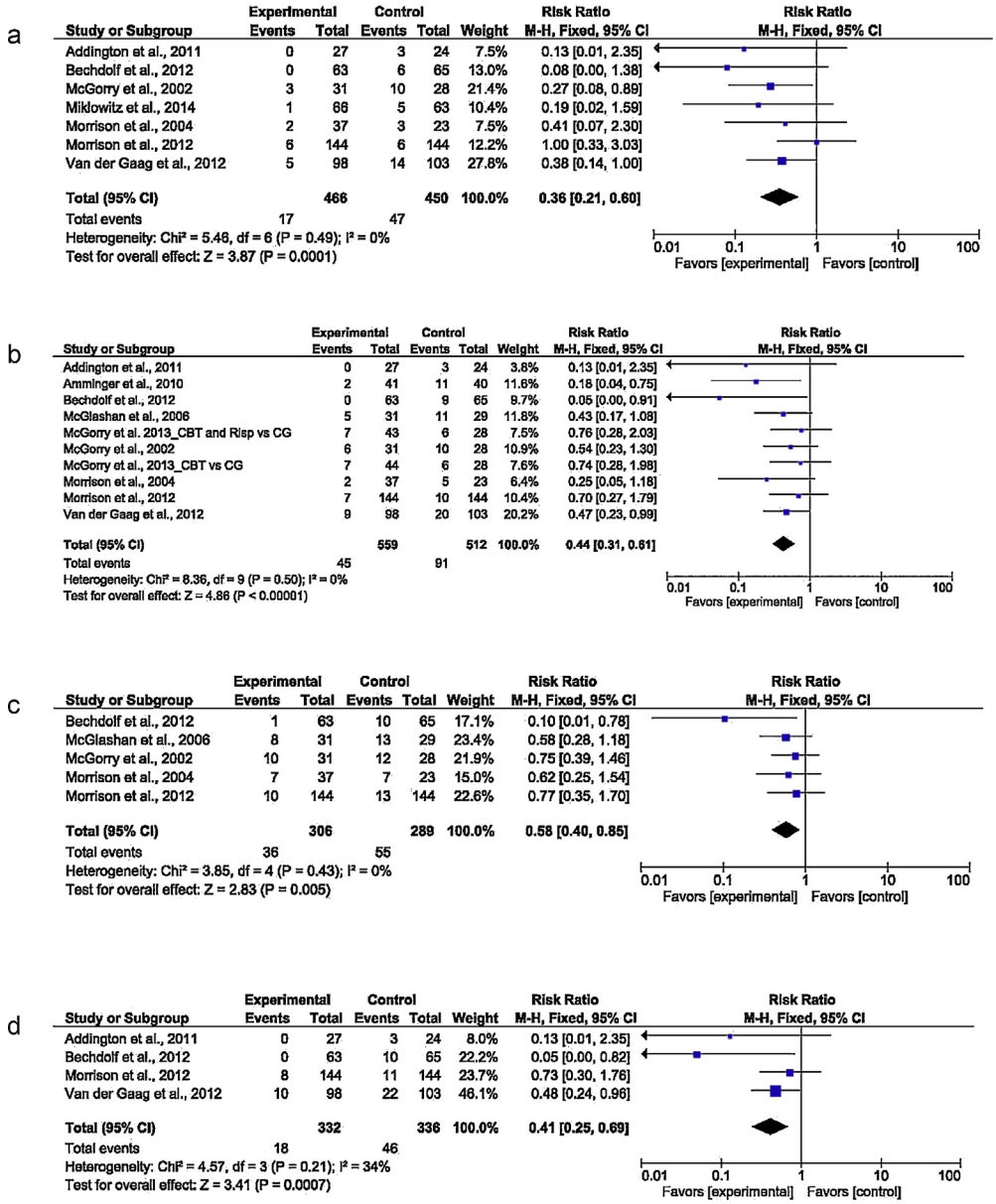

Fig. 2. a: conversion rates at 6-month follow-up; b: conversion rates at 12-month follow-up; c: conversion rates at 18-month follow-up; d: conversion rates at 24- to 48-month follow-up.

the fixed-effects model are reported. On average, 10.4% of the control and 3.6% of the experimental group converted to psychosis within six months after baseline assessment. The experimental condition significantly reduced the risk for conversion to first episode psychosis by 64.0% relative to the control condition as indicated by an overall pooled RR of 0.36 (95% CIs = 0.21, 0.60; $P < 0.001$). NNT based on the pooled risk difference (RD) of −0.07 (95% CIs = −0.10, −0.04; $P < 0.001$) was 15 (95% CIs = 10, 25).

At 12-month follow-up, nine RCTs [2,4,7,63,68,69,75,78,116] ($n = 1071$) provided data for 10 comparisons (Fig. 2b). Again, study effects were homogeneous, and the experimental condition significantly reduced the conversion risk on average by 56.0%. While 17.8% of the control group converted to psychosis, only 8.1% of the experimental group did. This corresponds to a significant pooled RR of 0.44 (95% CIs = 0.31, 0.61; $P < 0.001$) and a NNT of 10 (95% CIs = 8, 17; RD = −0.1, 95% CIs = −0.14, −0.06; $P < 0.001$).

All four RCTs [2,7,78,116] ($n = 668$) that investigated conversion rates at 18-month follow-up had offered CBT for up to 12 months and assessed study subjects at least six months after the end of treatment (Table 1). The conversion rates were 13.7% in the control and 5.4% in the EG group. The heterogeneity between the study effects increased compared to 6- and 12-month follow-up but was still moderate and insignificant. Using the fixed-effects model resulted in a pooled RR of 0.41 (95% CIs = 0.25, 0.69; $P < 0.001$), an average risk reduction of 59.0%, and a NNT of 13 (95% CIs = 8, 25; RD = −0.08, 95% CIs = −0.13, −0.04; $P = 0.01$; Fig. 2c).

We pooled the conversion rates of five studies ($n = 595$) that investigated a follow-up period of more than 18 months: three studies reported conversion rates at 24 months [7,63,78], one study [75] at 36 months, and one study [68] at 36 to 48 months (Table 1). No significant heterogeneity was present. Again, the pooled RR of 0.58 demonstrates a significant risk reduction by the experimental condition (95% CIs = 0.40, 0.85; Fig. 2d). NNT was 13 (95% CIs = 8, 34; RD = −0.08, 95% CIs = −0.14, −0.03; $P < 0.01$). Conversion rates of 19.0% in the CG and of 11.8% in the EG were the highest during the follow-up period.

3.3.2. Functional outcome

Seven RCTs [2,63,69,72,78,94,116] ($n = 869$) assessed the functional outcome after a short-term follow-up of between two and six months (Table 1). Due to significant heterogeneity a random-effects model was applied that revealed no significant overall between-group effect for the experimental condition compared to the control condition (Hedges' $g_b = 0.05$, 95% CIs = −0.22, 0.32; $P = 0.70$; Fig. 3a). However, $I^2 = 73\%$ indicated high heterogeneity which was mainly introduced by one study [69] with a slightly negative effect of the experimental condition (Hedges' $g_b = -0.22$, 95% CIs = −0.74, 0.30; $P = 0.40$) and could be reduced to a moderate degree ($Q_{w(6)} = 9.88$, $P = 0.13$; $I^2 = 39.0\%$) by its exclusion. This resulted in a significant improvement in functional outcome favoring the experimental condition (Hedges' $g_b = 0.22$, 95% CIs = 0.02, 0.42; $P = 0.03$).

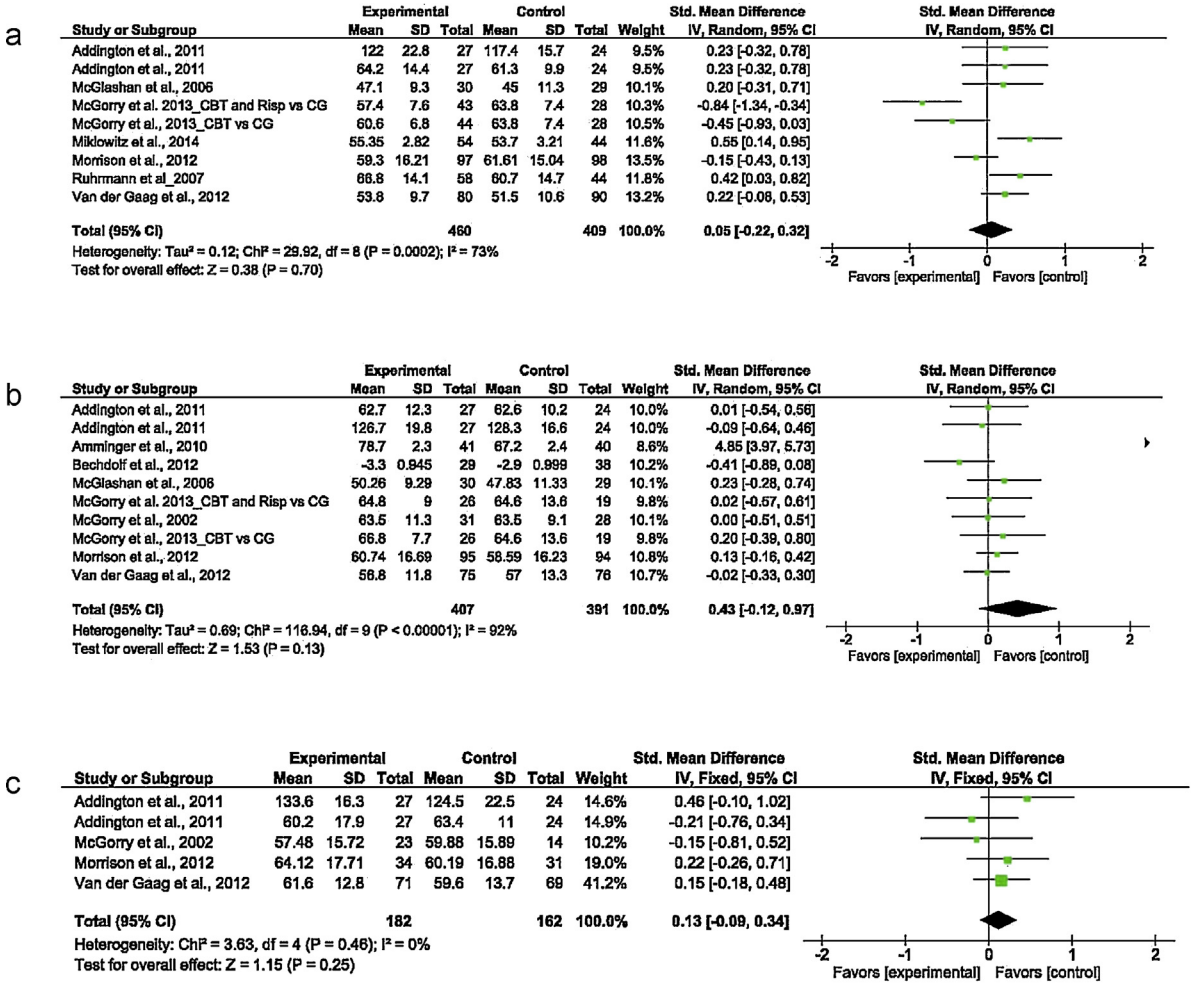

Fig. 3. a: improvement in functional outcome at 2- to 6-month follow-up; b: improvement in functional outcome at 9- to 12-month follow-up; c: improvement in functional outcome at 18- to 48-month follow-up.

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 to 48 months	
Study	Intervention type and age group	Design	EG g_w	CG g_w	EG g_w	CG g_w	EG g_w	CG g_w
Addington et al.[a] [2]	PSY, ADULT	RCT	0.18 [−0.36, 0.71]	−0.03 [−0.59, 0.54]	0.45 [−0.09, 0.99]	0.53 [−0.05, 1.10]	0.92 [0.36, 1.49]	0.29 [−0.28, 0.86]
Addington et al.[b] [2]	PSY, ADULT	RCT	0.36 [−0.17, 0.90]	0.25 [−0.32, 0.82]	0.28 [−0.26, 0.81]	0.37 [−0.20, 0.94]	0.07 [−0.46, 0.60]	0.43 [−0.15, 1.00]
Amminger et al. [4]	MED, YOUTH	RCT			7.62 [6.35, 8.90]	2.97 [2.33, 3.62]		
Bechdolf et al. [7]	PSY, ADULT	RCT			0.44 [−0.08, 0.96]	0.60 [0.14, 1.06]		
Hooker et al.[a] [40]	PSY, ADULT	No CG	−0.06 [−0.80, 0.68]					
Hooker et al.[b] [40]	PSY, ADULT	No CG	−0.25 [−0.99, 0.50]					
McGlashan et al. [63]	MED, YOUTH	RCT	0.54 [0.03, 1.06]	0.27 [−0.25, 0.79]	0.87 [0.34, 1.41]	0.52 [−0.01, 1.04]		
McGorry et al. [68]	MED, ADULT	RCT			0.01 [−0.49, 0.51]	0.35 [−0.17, 0.88]	−0.34 [−0.92, 0.25]	0.03 [−0.71, 0.78]
McGorry et al. [69] Risperidone and CBT	MED, YOUTH	RCT	0.29 [−0.14, 0.71]	0.90 [0.35, 1.46]	1.26 [0.66, 1.86]	0.57 [−0.08, 1.22]		
McGorry et al. [69] CBT	PSY, YOUTH	RCT	0.09 [−0.33, 0.51]		1.52 [0.90, 2.14]			
Miklowitz et al. [72]	PSY, YOUTH	RCT	2.79 [2.27, 3.30]	2.24 [1.74, 2.73]				
Morrison et al. [78]	PSY, ADULT	RCT	0.62 [0.36, 0.89]	0.84 [0.57, 1.11]	0.72 [0.45, 0.99]	0.57 [0.31, 0.84]	1.04 [0.66, 1.43]	0.77 [0.37, 1.17]
O'Brien et al. [87]	PSY, YOUTH	No CG			0.87 [0.14, 1.60]			
Ruhrmann et al. [94]	MED, ADULT	RCT	0.72 [0.35, 1.10]	0.19 [−0.23, 0.61]				
Tsujino et al. [113]	MED, ADULT	No CG	0.97 [0.08, 1.87]					
van der Gaag et al. [116]	PSY, ADULT	RCT	0.99 [0.67, 1.30]	0.72 [0.43, 1.01]	1.20 [0.87, 1.53]	1.19 [0.87, 1.52]	1.66 [1.30, 2.02]	1.46 [1.11, 1.80]
Woods et al.[a] [123]	MED, YOUTH	No CG	−0.06 [−0.83, 0.70]					
Woods et al.[b] [123]	MED, YOUTH	No CG	1.40 [0.59, 2.21]					
Pooled g_w [g_w, 95% CI]			EG: 0.62*** [0.26, 0.98]	CG: 0.68** [0.26, 1.10]	EG: 1 22*** [0.66, 1.78]	CG: 0.84*** [0.41, 1.26]	EG: 0.69 [−0.01, 1.39]	CG: 0.64* [0.12, 1.17]
Pooled g_w [g_w, 95% CI]			EG_{PSY}: 0.61* [0.04, 1.18] EG_{MED}: 0.59*** [0.27, 0.92] EG_{YOUTH}: 0.84 [−0.05, 1.73] EG_{ADULT}: 0.51*** [0.24, 0.78]	CG_{PSY}: 0.83** [0.32, 1.34] CG_{MED}: 0.43 [0.01, 0.85] CG_{YOUTH}: 1.14 [−0.03, 2.31] CG_{ADULT}: 0.46** [0.13, 0.78]	EG_{PSY}: 0.78*** [0.47, 1.09] EG_{MED}: 2.34* [0.34, 4.34] EG_{YOUTH}: 0.55** [0.20, 0.90] EG_{ADULT}: 2.32** [0.81, 3.83]	CG_{PSY}: 0.68** [0.40, 0.95] CG_{MED}: 1.27 [−0.27, 2.81] CG_{YOUTH}: 1.35 [−0.20, 2.89] CG_{ADULT}: 0.64*** [0.36, 0.92]	EG_{PSY}: 0.94** [0.31, 1.58] EG_{MED}: −0.34 [−0.92, 0.25]	CG_{PSY}: 0.77** [0.22, 1.32] CG_{MED}: 0.03 [−0.71, 0.78]
Heterogeneity (EG vs. CG)			$Q_{w(21)} = 157.80$***, $I^2 = 87.0\%$		$Q_{w(19)} = 201.02$***, $I^2 = 91.0\%$		$Q_{w(9)} = 67.27$***, $I^2 = 87.0\%$	
Heterogeneity (EG: PSY vs. MED, YOUTH vs. ADULT)			$Q_{w(13)} = 101.65$***, $I^2 = 87.0\%$		$Q_{w(10)} = 140.34$***, $I^2 = 93.0\%$		$Q_{w(4)} = 44.53$***, $I^2 = 91.0\%$	
Heterogeneity (CG: PSY vs. MED, YOUTH vs. ADULT)			$Q_{w(8)} = 56.18$***, $I^2 = 86.0\%$		$Q_{w(8)} = 60.26$***, $I^2 = 87.0\%$		$Q_{w(4)} = 22.57$***, $I^2 = 82.0\%$	
Between-group difference (EG vs. CG)			$Q_{b(1)} = 0.04$, $P = 0.83$		$Q_{b(1)} = 1.12$, $P = 0.29$		$Q_{b(1)} = 0.01$, $P = 0.91$	
Between-group difference (EG: MED vs. PSY)			$Q_{b(1)} = 0.00$, $P = 0.96$		$Q_{b(1)} = 2.27$, $P = 0.13$		$Q_{b(1)} = 8.45$, $P < 0.001$	
Between-group difference (EG: YOUTH vs. ADULT)			$Q_{b(1)} = 0.49$, $P = 0.49$		$Q_{b(1)} = 5.02$, $P = 0.02$			
Between-group differences (CG: MED vs. PSY)			$Q_{b(1)} = 1.41$, $P = 0.24$		$Q_{b(1)} = 0.55$, $P = 0.46$		$Q_{b(1)} = 2.44$, $P = 0.12$	
Between-group difference (CG: YOUTH vs. ADULT)			$Q_{b(1)} = 1.22$, $P = 0.27$		$Q_{b(1)} = 0.78$, $P = 0.38$			

CG: control group; EG: experimental group; g_w: standardized mean difference for pre-post improvements in the respective group; MED: pharmacological intervention; PSY: psychological intervention; * <0.05; ** <0.01; *** <0.001; effect sizes are presented in a way that positive values indicate an improvement in functional outcome.
a and b refer to two different tests that were used in a study to assess functional outcome.

At 12-month follow-up, eight RCTs [2,4,7,63,68,69,78,116] (n = 798) assessed functional outcome (Table 1). Again, significant heterogeneity between effect sizes was present. No significant treatment effect on functional outcome was detected (Hedges' g_b = 0.43, 95% CIs = −0.12, 0.97; P = 0.13; Fig. 3b). Testing successively the effect of excluding each single study revealed that high levels of heterogeneity (I^2 = 92%) between effect sizes were mainly due to the large positive effect (Hedges' g_b = 4.85, 95%s CI = 3.97, 5.73; $P < 0.001$) in the study of Amminger et al. [4]. When this study was excluded from the analysis, heterogeneity decreased substantially ($Q_{w(8)}$ = 4.71, P = 0.79; I^2 = 0.0%) but the overall effect on functional outcome remained insignificant (Hedges' g_b = −0.02, 95% CIs = −0.13, 0.17; P = 0.77).

Only four RCTs assessed functional outcome at least 18 months after baseline: two at 18 months [2,116], one at 24 months [78], and one between 36 to 48 months [68]. Therefore, we summarized the effect of these four studies. No significant heterogeneity among the four RCTs (n = 344) was detected, and again no significant effect on functional outcome was revealed (Hedges' g_b = 0.13, 95% CIs = −0.09, 0.34; P = 0.25; Fig. 3c).

Within-group effect sizes (Hedges' g_w) were calculated for the experimental and the control group separately. Random-effects model were applied to all sub-group comparisons because significant heterogeneity was present at all follow-up assessments (Table 2). Notably, both experimental and control group demonstrated significant functional improvements at short-term follow-up (2–6 months; Hedges' $g_w \geq 0.62$, $P \leq 0.002$) and at between 9- to 12-month follow-up (Hedges' $g_w \geq 0.84$, $P < 0.001$). These within-group effects on the control group were larger than those on the experimental group but these differences were not significant at both follow-ups ($Q_{b(1)} \leq 1.12$, $P \geq 0.29$). The control group still demonstrated significant functional gains at between 18 to 48 months (Hedges' g_w = 0.64, 95% CIs = 0.12, 1.17; P = 0.02) but not the experimental group. Yet again these between-group differences were not significant ($Q_{b(1)}$ = 0.01, P = 0.91; Table 2).

3.4. Moderator analysis

3.4.1. Intervention approach

At 6- and 12-month follow-up, both conditions significantly reduced the conversion rates, and no differential treatment effect between both groups could be detected (Table 3). No comparative data was available for the 18-month follow-up, as all available studies administered PSY (Table 1). Between the 24- to 48-month follow-up, only PSY significantly reduced the risk for conversion to psychosis. However, the between-group effect was again insignificant.

With regard to functional outcome, the comparison of between-group effects (Hedges' g_b) of RCTs revealed that PSY and MED did not differ in their effects on functional outcome at any follow-up assessment ($Q_{b(1)} \leq 1.96$, $P \geq 0.16$). This negative finding was likely caused by the general lack of significant effects in functional improvement between the experimental and control conditions (see above). When within-group effects (Hedges' g_w) were compared between PSY and MED, both PSY and MED showed significant improvements in the experimental condition that did not differ significantly from each other (Table 2). Notably, at medium-term follow-up (18–48 months), only PSY revealed a significant within-group effect on functional outcome in the experimental condition but not MED. This between-sub-group difference was significant, but MED comprised only one study [68]. With regard to the control condition, only PSY achieved significant improvements in functional outcome.

3.4.2. Age group

ADULT demonstrated a significant reduction of conversion rate at 6-, 12-, 18-month, and medium-term follow-up (24–48 months; Table 3). YOUTH generally had a lower risk reduction which was significantly larger at 12 months but not at 6- and 24 to 48-month follow-ups. However, all other differences between sub-groups were insignificant.

With regard to functional outcome, potential age effects could only be investigated after 6 and 12 months because studies with longer follow-up periods included only ADULT samples (Table 1). Both ADULT and YOUTH in the experimental condition did not increase their functional outcome after 6 and 12 months relative to the control condition ($Q_{b(1)} \leq 2.10$, $P \geq 0.15$). With regard to changes in functional outcome within each age group, ADULT benefited from both the experimental condition and the control condition, and improved their functional outcome significantly at 6 and 12 months independent of the treatment condition. YOUTH however only demonstrated functional gains in the experimental condition and only at 12 months but they were significantly larger than those of ADULT. Yet again, all other between-sub-group differences were insignificant (Table 2).

4. Recommendations

4.1. Literature review and meta-analysis as evidence-base

Based on the described evidence-base, seven recommendations were derived with different degrees of evidence and grades of recommendations according to the methodology checklist of the Scottish Intercollegiate Guideline Network (SIGN) for randomized controlled trials. Grades of recommendations were A (''meta-analysis, systematic review, or RCTs with very low risk for bias''), C (''large body of evidence including well-conducted case-control, or cohort studies with a low risk of bias''), and D (''expert opinion'').

4.2. Proposed recommendations of the European guidance

4.2.1. Recommendation 1 (grade of recommendation: D)

In line with the general EPA guidance on prevention of mental disorders [14], the EPA considers that an early intervention in patients presenting with a clinical high risk (CHR) of psychosis should not only aim to prevent the first episode of an affective or non-affective psychotic disorder but also the development or persistence of functional, i.e. social, educational, or vocational deficits.

4.2.2. Recommendation 2 (grade of recommendation: C)

The EPA considers that any psychosis-preventive intervention requires that the CHR status was assessed in full accordance with the EPA guidance on early detection of psychosis (Schultze-Lutter et al., this issue).

4.2.3. Recommendation 3 (grade of recommendation: A)

The EPA considers that psychological, in particular CBT, as well as pharmacological interventions are able to prevent or at least postpone a first psychotic episode in adult CHR patients.

4.2.4. Recommendation 4 (grade of recommendation: D)

The EPA considers that in adult CHR patients a staged intervention model should be applied with the least restrictive service approach, i.e., CBT, being offered as first choice. Where psychological interventions have proved ineffective, they should be complemented by low dose second-generation antipsychotics in adult CHR patients if severe and progressive CHR symptomatology (APS with only minimal or clearly declining insight, or BLIPS in higher or increasing frequency) is present and with the primary aim to achieve a degree of symptomatic stabilization that

Table 3
Conversion rates at different follow-ups dependent on intervention type and age group.

Follow-up			6 months	12 months	18 months	24–48 months
Study	Intervention type and age group	Design	RR	RR	RR	RR
Addington et al. [2]	PSY, ADULT	RCT	0.13 [0.01, 2.35]	0.13 [0.01, 2.35]	0.13 [0.01, 2.35]	
Amminger et al. [4]	MED, YOUTH	RCT		0.18 [0.04, 0.75]		
Bechdolf et al. [7]	PSY, ADULT	RCT	0.08 [0.00, 1.38]	0.05 [0.00, 0.91]	0.05 [0.00, 0.82]	0.10 [0.01, 0.78]
McGlashan et al. [63]	MED, YOUTH	RCT		0.43 [0.17, 1.08]		0.58 [0.28, 1.18]
McGorry et al. [68]	MED, ADULT	RCT	0.27 [0.08, 0.89]	0.54 [0.23, 1.30]		0.75 [0.39, 1.46]
McGorry et al. [68] Risp. and CBT	MED, ADULT	RCT	0.76 [0.28, 2.03]			
McGorry et al. [69] CBT	PSY, YOUTH	RCT		0.74 [0.28, 1.98]		
Miklowitz et al. [72]	PSY, YOUTH	RCT	0.19 [0.02, 1.59]			
Morrison et al. [75]	PSY, ADULT	RCT	0.41 [0.07, 2.30]	0.25 [0.05, 1.18]		0.62 [0.25, 1.54]
Morrison et al. [78]	PSY, ADULT	RCT	1.00 [0.33, 3.03]	0.70 [0.27, 1.79]	0.73 [0.30, 1.76]	0.77 [0.35, 1.70]
van der Gaag et al. [116]	PSY, ADULT	RCT	0.38 [0.14, 1.00]	0.47 [0.23, 0.99]	0.48 [0.24, 0.96]	
Pooled RR [95% CIs]			$RR_{PSY} = 0.43^{*}$ [0.23, 0.80] $RR_{MED} = 0.27^{**}$ [0.08, 0.89] $RR_{YOUTH} = 0.19$ [0.02, 1.59] $RR_{ADULT} = 0.41^{**}$ [0.23, 0.72]	$RR_{PSY} = 0.43^{***}$ [0.28, 0.68] $RR_{MED} = 0.45^{**}$ [0.27, 0.73] $RR_{YOUTH} = 0.48^{**}$ [0.29, 0.80] $RR_{ADULT} = 0.41^{***}$ [0.27, 0.64]	$RR_{PSY} = 0.41^{***}$ [0.25, 0.69] $RR_{ADULT} = 0.41^{***}$ [0.25, 0.69]	$RR_{PSY} = 0.52^{*}$ [0.30, 0.91] $RR_{MED} = 0.66$ [0.30, 0.91] $RR_{YOUTH} = 0.58$ [0.28, 1.18] $RR_{ADULT} = 0.59^{*}$ [0.38, 0.90]
Heterogeneity			$Q_{w(6)} = 5.46$, $I^2 = 0.0\%$	$Q_{w(9)} = 8.36$, $I^2 = 0.0\%$	$Q_{w(i)} = 4.57$, $I^2 = 34.0\%$	$Q_{w(i)} = 3.85$, $I^2 = 0.0\%$
Between-group differences: MED vs. PSY			$Q_{b(i)} = 0.25$, $P = 0.62$	$Q_{b(i)} = 0.01$, $P = 0.91$	–	$Q_{b(i)} = 0.40$, $P = 0.53$
Between-group difference: YOUTH vs. ADULT			$Q_{b(i)} = 0.37$, $P = 0.55$	$Q_{b(i)} = 0.19$, $P = 0.66$	–	$Q_{b(i)} = 0.00$, $P = 0.96$

MED: pharmacological intervention; PSY: psychological intervention; RR: risk ratio; * <0.05; ** <0.01; ***<0.001; effect sizes are presented in a way that positive values indicate a reduction in conversion rates.

is required for psychological interventions to be effective. Thus, any long-term antipsychotic treatment with a primarily preventive purpose is not recommended.

4.2.5. Recommendation 5 (grade of recommendation: D)

The EPA considers that any intervention in CHR should also address current individual needs and other mental disorders present (co-morbidities), in particular depression and anxiety, according to their respective treatment guidelines. These disorders should be thoroughly assessed and monitored regularly by a specialist (psychiatrist, clinical psychologist, or equivalent mental health professional).

4.2.6. Recommendation 6 (grade of recommendation: A)

The EPA considers that the current evidence for the psychosis-predictive value of CHR criteria (Schultze-Lutter et al., this issue) and for the efficacy of psychological and pharmacological interventions in children and young adolescents is not sufficient to justify primarily preventive interventions.

4.2.7. Recommendation 7 (grade of recommendation: D)

The EPA considers that in children and adolescents, specific psychological interventions with the aim to improve functioning should be provided as part of an overall treatment plan and complemented by interventions for other psychosocial problems and co-morbid mental disorders according to their treatment guidelines. CHR symptoms should be carefully monitored and assessed for a potential progression over an extended period, and the treatment plan should be adapted according to their course.

5. Discussion

We found that recommendations for early intervention in CHR states could be derived from the current evidence-base. In line with the available treatment guidelines [9,18,82], this guidance paper emphasizes the need to target both conversion rates and functional impairments. CBT is regarded as the first choice intervention for the prevention of conversion to psychosis but it might be complemented by pharmacological interventions with low dose second-generation antipsychotics for symptomatic stabilization, if risk symptoms limit the efficacy of CBT. Our recommendations advance existing guidelines in that they provide guidance on a differential application of early interventions in psychoses with respect to developmental aspects and type of intervention, despite limited availability of evidence.

Our results suggest that early interventions can significantly reduce conversion rates in adult CHR patients at short- to medium-term follow-up. However, the effect of these interventions may only be specific for conversion rates but not for functional outcome because the experimental conditions did not achieve larger functional improvements than the control conditions, i.e., monitoring, supportive therapy, and TAU including evidence-based treatment for axis-I and axis-II disorders. This indicates that patients have functionally benefited from control interventions to a similar degree. This may be due to the fact that this particular patient group is quite heterogeneous, for example, with regard to their individual vulnerability, their developmental status, their level of functional impairments, different environmental factors [49], and the prevalence of co-morbid mental health issues.

Therefore, it seems likely that a 'one-fits-all' approach may not sufficiently address the intra- and inter-individual heterogeneity of CHR patients. Consequently, future early intervention programs should be optimized with regard to their effect on functional outcome by allowing a need- and evidence-based tailored service provision derived, for example, from personalized risk stratification by a prognostic index that does not only stratify risk for psychosis but also for disabling functional impairment [96,97]. Another implication of the lack of a differential treatment effect but significant within-group effect on functional outcome is that control interventions are also effective in improving functional outcome and, from the exclusive point of view of functional improvement, may be an alternative treatment option for current early intervention programs.

The identification of moderator variables such as age is another means of optimizing treatment approaches by identifying subgroups of patients that can be targeted most successfully with an intervention adjusted to be developmentally appropriate [103]. Our meta-analysis provides preliminary evidence that early intervention programs are less effective in reducing conversion to psychosis in youth compared to adult patients. This may be due to the lower conversion rates generally found in children and adolescents (Schultze-Lutter et al., this issue) but needs to be interpreted cautiously due to the lack of studies consisting of youth samples, in particular with regard to conversion rates. However, together with the result that youth also achieved lower functional improvements than adults this suggests that current intervention programs do not sufficiently address the special needs and developmental stage of younger CHR patients.

There are additional limitations to our study that need to be considered. Almost all pharmacological interventions also offered some kind of psychosocial and/or psychological intervention, and in psychological trials patients were also allowed to take medication. Therefore, the positive treatment effects of most trials cannot be clearly attributed to one intervention approach. Furthermore, the number of studies included with a follow-up longer than 12 months was small. Therefore, no recommendations with regard to the optimal treatment duration and no firm conclusions about the maintenance of the effects can be derived. However, because of their unfavorable side effect profiles [17,47], pharmacological interventions with antipsychotics should only be applied following thorough cost-benefit considerations and only for a limited time-period with the primary aim to achieve symptomatic stabilization as a starting point for psychological interventions but not with the aim to prevent conversion to psychosis. Pharmacological interventions with PUFAS and antidepressants seem promising so far but require further replication.

Another limitation is the use of the GAF scale to assess functional outcome as it is confounded with the current level of psychiatric symptoms. As a consequence, one cannot conclude if positive within-group effects in functional outcome were mediated by symptomatic improvements, if they are only a spurious effect of these, or if both current early intervention programs and their respective control conditions indeed improved functional outcome directly. Therefore, future studies need to investigate symptomatic and functional improvements separately. Furthermore, at follow-ups several studies reported the mean scores of functional outcome of the remaining sample without converters. This may have led to samples that are biased in that they demonstrate fewer functional deficits than ITT samples and consequently less possibility to achieve functional improvements because converters usually exhibit more pronounced functional deficits than non-converters [45]. Both limitations may explain why we did not find significant improvements favoring the experimental condition at all follow-ups.

6. Conclusions and perspectives

The accumulating evidence on early intervention in CHR states of psychoses allowed us to derive some first evidence-based recommendations. Yet, our results also demonstrate the need for individualization of treatment and for the development of differential treatment indication. With regard to the still increasing conversion rates beyond 24-month follow-up in observational studies (Schultze-Lutter et al., this issue), interventions should also include longer follow-ups. Moreover, the focus of interventions in CHR patients needs to be broadened with regard to outcomes and intervention approaches (e.g., vocational rehabilitation).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References

[1] Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. Schizophr Res 2008;99(1–3):119–24.
[2] Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB. A randomized controlled trial of cognitive-behavioral therapy for individuals at clinical high risk of psychosis. Schizophr Res 2011;125(1):54–61.
[3] American Psychiatric Association. Diagnostic and statistical manual of mental health disorders (DSM-IV), 4th ed, Washington, DC: American Psychiatric Press; 1994.
[4] Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010;67(2):146–54.
[5] Bechdolf A, Wagner M, Veith V, Ruhrmann S, Pukrop R, Brockhaus-Dumke A, et al. Randomized controlled multicenter trial of cognitive behaviour therapy in the early initial prodromal state: effects on social adjustment post treatment. Early Interv Psychiatry 2007;1:71–8.
[6] Bechdolf A, Müller H, Stützer H, Wagner M, Maier W, Lautenschlager M, et al. Rationale and baseline characteristics of PREVENT: a second-generation intervention trial in subjects at-risk (prodromal) of developing first-episode psychosis evaluating cognitive behavior therapy, aripiprazole, and placebo for the prevention of psychosis. Schizophr Bull 2011;37(2):111–21.
[7] Bechdolf A, Wagner M, Ruhrmann S, Harrigan S, Putzfeld V, Pukrop R, et al. Preventing progression to first-episode psychosis in early initial prodromal states. Br J Psychiatry 2012;200(1):22–9.
[8] Berger GE, Wood SJ, Ross M, Hamer CA, Wellard RM, Pell G, et al. Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. Curr Pharm Des 2012;18(4):570–5.
[9] Bertolote JM, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. Br J Psychiatry 2005;48(Suppl.):116–9.

[10] Bodatsch M, Ruhrmann S, Wagner M, Muller R, Schultze-Lutter F, Frommann I, et al. Prediction of psychosis by mismatch negativity. Biol Psychiatry 2011;69:959–66.
[11] Bois C, Whalley H, McIntosh A, Lawrie S. Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: a review of familial and clinical high risk population studies. J Psychopharmacol 2015;29(2):144–54.
[12] Bora E, Pantelis C. Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: systematic review and meta-analysis. Schizophr Res 2013;144(1–3):31–6.
[13] Borenstein M. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors. Introduction to meta-analysis. United Kingdom: John Wiley & Sons; 2008 p. 33–41.
[14] Campion J, Bhui K, Bhugra D, European Psychiatric Association. European Psychiatric Association (EPA) guidance on prevention of mental disorders. Eur Psychiatry 2012;27(2):68–80.
[15] Carrion RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, et al. Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry 2013;70(11):1133–42.
[16] Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. J Clin Psychiatry 2007;68(4):546–57.
[17] Datta SS, Kumar A, Wright SD, Furtado VA, Russell PS. Evidence-base for using atypical antipsychotics for psychosis in adolescents. Schizophr Bull 2014;40(2):252–4.
[18] Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN). Behandlungsleitlinie Schizophrenie. Darmstadt: Steinkopff Verlag; 2006.
[19] Egerton A, Stone JM, Chaddock CA, Barker GJ, Bonoldi I, Howard RM, et al. Relationship between brain glutamate levels and clinical outcome in individuals at ultra-high risk of psychosis. Neuropsychopharmacology 2014;39(12): 2891–9.
[20] European Commission. Green paper – Improving the mental health of the population: towards a strategy on mental health for the European Union. Summary of consultation meetings Brussels: European Commission; 2005.
[21] Fritz CO, Morris PE. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 2012;141(1):2–18.
[22] Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, et al. Cognitive functioning in prodromal psychosis: a meta-analysis. Arch Gen Psychiatry 2012;69(6):562–71.
[23] Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 2013;70(1):107–20.
[24] Fusar-Poli P, Carpenter WT, Woods SW, McGlashan TH. Attenuated psychosis syndrome: ready for DSM-5.1? Annu Rev Clin Psychol 2014;10:155–92.
[25] Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Are we really mapping psychosis risk? Neuroanatomical signature of affective disorders in subjects at ultra-high risk. Schizophr Bull 2014;40(1):120–31.
[26] Gaebel W, Möller HJ. European guidance – a project of the European Psychiatric Association. Eur Psychiatry 2012;27:65–7.
[27] Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ. Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. Curr Pharm Des 2012;18(4):399–415.
[28] Granö N, Kallionpää S, Karjalainen M, Edlund V, Saari E, Itkonen A, et al. Lower functioning predicts identification of psychosis risk screening status in help-seeking adolescents. Early Interv Psychiatry 2014. http://dx.doi.org/10.1111/eip.12118.
[29] Granö N, Karjalainen M, Anto J, Itkonen A, Edlund V, Roine M. Associations between number of different type of care meetings with social network and improvement in mental well-being in adolescents at risk of first-episode psychosis. Early Interv Psychiatry 2011;5(3):212–8.
[30] Granö N, Karjalainen M, Edlung V, Saari E, Itkonen A, Anto J, et al. Anxiety symptoms in adolescents at risk for psychosis: a comparison among help seekers. Child Adolesc Ment Health 2014;19(2):97–101.
[31] Granö N, Karjalainen M, Edlund V, Saari E, Itkonen A, Anto J, et al. Health-related quality of life among adolescents: a comparison between subjects at risk for psychosis and other help seekers. Early Interv Psychiatry 2014;8(2): 163–9.
[32] Granö N, Karjalainen M, Edlund V, Saari E, Itkonen A, Anto J, et al. Changes in depression, anxiety and hopelessness symptoms during family- and community-oriented intervention for help-seeking adolescents and adolescents at risk of psychosis. Nord J Psychiatry 2014;68(2):93–9.
[33] Grant P, Gabriel F, Kuepper Y, Wielpuetz C, Hennig J. Psychosis-proneness correlates with expression levels of dopaminergic genes. Eur Psychiatry 2014;29(5):304–6.
[34] Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(10):718–79.
[35] Häfner H, an der Heiden W. The course of schizophrenia in the light of modern follow-up studies: the ABC and WHO studies. Eur Arch Psychiatry Clin Neurosci 1999;249(Suppl. 4):14–26.
[36] Haro JM, Ayuso-Mateos JL, Bitter I, Demotes-Mainard J, Leboyer M, Lewis SW, et al. ROAMER: roadmap for mental health research in Europe. Int J Methods Psychiatr Res 2014;23(Suppl. 1):1–14.
[37] Hedge LV, Olkin I. Statistical methods for meta-analysis, 1st ed, Orlando: Academic Press; 1985.
[38] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration; 2011.
[39] Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
[40] Hooker CI, Carol EE, Eisenstein TJ, Yin H, Lincoln SH, Tully LM, et al. A pilot study of cognitive training in clinical high risk for psychosis: initial evidence of cognitive benefit. Schizophr Res 2014;157(1–3):314–6.
[41] Huber G. Reine Defektsyndrome und Basisstadien endogener Psychosen. Fortschr Neurol Psychiatr 1966;34:409–26.
[42] Hui C, Morcillo C, Russo DA, Stochl J, Shelly GF, Painter M, et al. Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr Res 2013;148(1–3):175–80.
[43] Hutton P, Taylor PJ. Cognitive behavioural therapy for psychosis prevention: a systematic review and meta-analysis. Psychol Med 2014;44(3):449–68.
[44] Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 2013;39(6):1296–306.
[45] Jang JH, Shin NY, Shim G, Park HY, Kim E, Jang GE, et al. Longitudinal patterns of social functioning and conversion to psychosis in subjects at ultra-high risk. Aust N Z J Psychiatry 2011;45(9):763–70.
[46] Kay SR, Fiszbein A, Opfer LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261–76.
[47] Khanna P, Suo T, Komossa K, Ma H, Rummel-Kluge C, El-Sayeh HG, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2014. http://dx.doi.org/10.1002/14651858.CD006569.pub5.
[48] Kim KR, Lee SY, Kang JI, Kim BR, Choi SH, Park JY, et al. Clinical efficacy of individual cognitive therapy in reducing psychiatric symptoms in people at ultra-high risk for psychosis. Early Interv Psychiatry 2011;5(2):174–8.
[49] Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. Arch Gen Psychiatry 2006;63:250–8.
[50] Kline E, Thompson E, Bussell K, Pitts S, Reeves G, Schiffman J. Psychosis-like experiences and distress among adolescents using mental health services. Schizophr Res 2014;152(2–3):498–502.
[51] Klosterkötter J, Schultze-Lutter F. Prevention and early treatment. In: Helmchen H, Sartorius N, editors. Ethics in psychiatry – European contributions. Heidelberg: Springer Science + Business Media B.V.; 2010. p. 235–62.
[52] Koutsouleris N, Riecher-Rössler A, Meisenzahl EM, Smieskova R, Studerus E, Kambeitz-Ilankovic L, et al. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. Schizophr Bull [pii: sbu078].
[53] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for *t*-tests and ANOVAs. Front Psychol 2013;4:863.
[54] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373(9657):31–41.
[55] Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2012;2:e94.
[56] Lin A, Wood SJ, Nelson B, Brewer WJ, Spiliotacopoulos D, Bruxner A, et al. Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. Schizophr Res 2011;132(1): 1–7.
[57] Marshall M, Rathbone J. Early intervention for psychosis. Schizophr Bull 2011;37(6):1111–4.
[58] Marshall C, Addington J, Epstein I, Liu L, Deighton S, Zipursky R. Treating young individuals at clinical high risk for psychosis. Early Interv Psychiatry 2012;6:60–8.
[59] Marvin SE, Miklowitz DJ, O'Brien MP, Cannon TD. Family-focused therapy for individuals at clinical high risk for psychosis: treatment fidelity within a multisite randomized trial. Early Interv Psychiatry 2014. http://dx.doi.org/10.1111/eip.12144.
[60] Maurer K, Hörrmann F, Trendler G, Schmidt M, Haefner H. Identification of psychosis risk by the Early Recognition Inventory (ERIraos) – Description of the schedules and preliminary results on reliability and validity of the checklist. Nervenheilkunde 2006;25(1):11–6.
[61] McGlashan TH, Johannessen JO. Early detection and intervention with schizophrenia: rationale. Schizophr Bull 1996;22(2):201–22.
[62] McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. Schizophr Res 2003;61: 7–18.
[63] McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 2006;163(5): 790–9.
[64] McGlashan T, Walsh B, Woods S. The psychosis-risk syndrome. Handbook for diagnosis and follow-up. New York, NY: Oxford University Press; 2010.
[65] McGorry PD. "A stitch in time". The scope for preventive strategies in early psychosis. Eur Arch Psychiatry Clin Neurosci 1998;248(1):22–31.
[66] McGorry P, et al. A comparison study of fish oil capsules and psychological therapy versus placebo capsules and psychological therapy in patients at risk

of developing a psychotic disorder. In: Australian New Zealand Clinical Trials Registry, 2010 [Internet]. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=83121 [identifier: ACTRN12608000475347].
[67] McGorry PD, Killackey EJ. Early intervention in psychosis: a new evidence-based paradigm. Epidemiol Psichiatr Soc 2002;11(4):237–47.
[68] McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002;59(10):921–8.
[69] McGorry PD, Nelson B, Phillips LJ, Yuen HP, Francey SM, Thampi A, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. J Clin Psychiatry 2013;74(4):349–56.
[70] Mental Health Services in the Capital Region. Effects of neurocognitive and social-cognitive remediation in patients at ultra-high risk of psychosis (FOCUS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27 2014; NLM identifier: NCT02098408] https://clinicaltrials.gov/ct2/show/NCT02098408?term=NCT02098408&rank=1.
[71] Meyer EC, Carrión RE, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, et al. The relationship of neurocognition and negative smyptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. Schizophr Bull 2014;40(6):1452–61.
[72] Miklowitz DJ, O'Brien MP, Schlosser DA, Addington J, Candan KA, Marshall C, et al. Family-focused treatment for adolescents and young adults at high risk for psychosis: results of a randomized trial. J Am Acad Child Adolesc Psychiatry 2014;53(8):848–58.
[73] Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 2003;29(4):703–15.
[74] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Guidance for developers of health research reporting guidelines. PLoS med 2010;7(2):1–9.
[75] Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. Br J Psychiatry 2004;185:291–7.
[76] Morrison AP, French P, Parker S, Roberts M, Stevens H, Bentall RP, et al. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. Schizophr Bull 2007;33(3):682–7.
[77] Morrison AP, Stewart SL, French P, Bentall RP, Birchwood M, Byrne R, et al. Early detection and intervention evaluation for people at high-risk of psychosis-2 (EDIE-2): trial rationale, design and baseline characteristics. Early Interv Psychiatry 2011;5(1):24–32.
[78] Morrison AP, French P, Stewart SL, Birchwood M, Fowler D, Gumley AI, et al. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 2012;5(344):e2233.
[79] Morrison AP, Birchwood M, Pyle M, Flach C, Stewart SL, Byrne R, et al. Impact of cognitive therapy on internalised stigma in people with at-risk mental states. Br J Psychiatry 2013;203(2):140–5.
[80] Mossaheb N, Schäfer MR, Schlögelhofer M, Klier CM, Cotton SM, McGorry P, et al. Effect of omega-3 fatty acids for indicated prevention of young patients at risk for psychosis: when do they begin to be effective. Schizophr Res 2013;148:163–7.
[81] Nathan Kline Institute for Psychiatric Research. D-serine for the schizophrenia prodrome. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27; NLM identifier: NCT01429454]https://clinicaltrials.gov/ct2/show/NCT00826202?term=d-serine&rank=5.
[82] National Institute for Health and Clinical Excellence (NICE). Psychosis and schizophrenia in adults: treatment and management;[Online] 2014 [accessed: 25 August 2014]https://www.nice.org.uk/guidance/published?type=Guidelines.
[83] Nelson B. Attenuated psychosis syndrome: don't jump the gun. Psychopathology 2014;47(5):292–6.
[84] Nelson B, McGorry P, Yung A, Amminger P, Francey S, Berk M, et al. The NEURAPRO (North America, Europe, Australia prodrome) study: a multicentre RCT of treatment strategies for symptomatic patients at ultra-high risk for progression to schizophrenia and related disorders. Design and study plan. Schizophr Res 2008;102(1–3):155.
[85] Nieman DH, Ruhrmann S, Dragt S, Soen F, van Tricht MJ, Koelman JH, et al. Psychosis prediction: stratification of risk estimation with information-processing and premorbid functioning variables. Schizophr Bull 2014;40(6):1482–90.
[86] North Shore Long Island Jewish Health System. Antidepressant and antipsychotic to treat attenuated positive and negative symptoms. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27; NLM identifier: NCT00169988]https://clinicaltrials.gov/ct2/show/NCT00169988?term=NCT00169988&rank=1.
[87] O'Brien MP, Zinberg JL, Bearden CE, Daley M, Niendam TA, Kopelowicz A, et al. Psycho-educational multi-family group treatment with adolescents at high risk for developing psychosis. Early Interv Psychiatry 2007;1(4):325–32.
[88] O'Brien MPO, Miklowitz DJ, Candan KA, Marshall C, Domingues I, Walsh BC, et al. A randomized trial of family focused therapy with populations at clinical high risk for psychosis: effects on interactional behavior. J Consult Clin Psychol 2014;82(1):90–101.
[89] Okuzawa N, Kline E, Fuertes J, negi S, Reeves G, Himelhoch S, et al. Psychotherapy for adoescents and young adults at high risk for psychosis: a systematic review. Early Interv Psychiatry 2014;8(4):307–22.
[91] Phillips LJ, McGorry P, Yuen HP, Ward J, Donovan K, Kelly D, et al. Medium-term follow-up of a randomized controlled trial of interventions for young people at ultra-high risk of psychosis. Schizophr Res 2007;96:25–33.
[92] Preti A, Cella M. Randomized-controlled trials in people at ultra-high risk of psychosis: a review of treatment effectiveness. Schizophr Res 2010;123(1):30–6.
[93] Rietdijk J, Dragt S, Klaassen R, Ising H, Nieman D, Wunderink L, et al. A single blind randomized controlled trial of cognitive behavioural therapy in a help-seeking population with an at risk mental state for psychosis: the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial. Trials 2010;11:30.
[94] Ruhrmann S, Bechdolf A, Kühn KU, Wagner M, Schultze-Lutter F, Janssen B, et al. Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. Br J Psychiatry 2007;191(Suppl. 51):S96–101.
[95] Ruhrmann S, Paruch J, Bechdolf A, Pukrop R, Wagner M, Berning J, et al. Reduced subjective quality of life in persons at risk for psychosis. Acta Psychiatr Scand 2008;117:357–68.
[96] Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Probably at-risk, but certainly ill – Advocating the introduction of a psychosis spectrum disorder in DSM-V. Schizophr Res 2010;120(1–3):23–37.
[97] Ruhrmann S, Klosterkötter J, Bodatsch M, Bechdolf A, Schimmelmann BG, Nikolaides A, et al. Pharmacological prevention and treatment in clinical at-risk states for psychosis. Curr Pharm Des 2012;18(4):550–7.
[98] Rüsch N, Müller M, Heekeren K, Theodoridou A, Metzler S, Dvorsky D, et al. Longitudinal course of self-labeling, stigma stress and well-being among young people at risk of psychosis. Schizophr Res 2014;158(1–3):82–4.
[99] Rüsch N, Corrigan PW, Heekeren K, Theodoridou A, Dvorsky D, Metzler S, et al. Well-being among persons at risk of psychosis: the role of self-labeling, shame, and stigma stress. Psychiatr Serv 2014;65(4):483–9.
[100] Salokangas RKR, Ruhrmann S, von Reventlow HG, Heinimaa M, Svirskis T, From T, et al. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245clinical high-risk outpatients in four countries 2012;138(2–3):192–7.
[101] Salokangas RKR, Nieman DH, Heinimaa M, Svirskis T, Luutonen S, From T, et al. Psychosocial outcome in patients at clinical high risk of psychosis: a prospective follow-up. Soc Psychiatry Psychiatr Epidemiol 2013;48(2):303–11.
[102] Salokangas RKR, Heinimaa M, From T, Löyttyniemi E, Ilonen T, Luutonen S, et al. Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. Eur Psychiatry 2014;29(6):371–80.
[103] Schmidt SJ, Schimmelmann BG. Evidence-based psychotherapy in children and adolescents: advances, methodological and conceptual limitations, and perspectives. Eur Child Adolesc Psychiatry 2013;22(5):265–8.
[104] Schmidt SJ, Grunert VM, Schimmelmann BG, Schultze-Lutter F, Michel C. Differences in coping, self-efficacy, and external control beliefs between patients at-risk for psychosis and patients with first-episode psychosis. Psychiatry Res 2014;219(1):95–102.
[105] Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. Schizophr Bull 2009;35(1):5–8.
[106] Shivashankar S, Telfer S, Arunagiriraj J, McKinnon M, Jauhar S, Krishnadas R, et al. Has the prevalence, clinical presentation and social functioning of schizophrenia changed over the last 25 years? Nithsdale schizophrenia survey revisited. Schizophr Res 2013;146(1–3):349–56.
[107] Smieskova R, Marmy J, Schmidt A, Bendfeldt K, Riecher-Rössler A, Walter M, et al. Do subjects at clinical high risk for psychosis differ from those with a genetic high risk? – A systematic review of structural and functional brain abnormalities. Curr Med Chem 2013;20(3):467–81.
[108] Solis M. Prevention: before the break. Nature 2014;508(7494):12–3.
[109] Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. BMJ 2013. http://dx.doi.org/10.1136/bmj.f185.
[110] Stowkowy J, Perkins DO, Woods SW, Nyman K, Addington J. Personal beliefs about experiences in those at clinical high risk for psychosis. Behav Cogn Psychother 2014. http://dx.doi.org/10.1017/S1352465814000307.
[111] Sullivan GM, Feinn R. Using effect size – or why the *P*-value is not enough. J Grad Med Educ 2012;4(3):279–82.
[112] Thompson A, Papas A, Bartholomeusz C, Allott K, Amminger GP, Nelson B, et al. Social cognition in clinical "at risk" for psychosis and first episode psychosis populations. Schizophr Res 2012;141(2–3):204–9.
[113] Tsujino N, Nemoto T, Morita K, Katagiri N, Ito S, Mizuno M. Long-term efficacy and tolerability of perospirone for young help-seeking people at clinical high risk: a preliminary open trial. Clin Psychopharmacol Neurosci 2013;11(3):132–6.
[114] University of Calgary. Effects of cognitive remediation on cognition in young people at clinical high risk of psychosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27; NLM identifier: NCT01619319]https://clinicaltrials.gov/ct2/show/NCT01619319?term=NCT01619319&rank=1.
[115] University of California. Effectiveness of neuroadaptive cognitive training in adolescents at risk for psychosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27; NLM identifier: NCT00655239]https://clinicaltrials.gov/ct2/show/NCT00655239?term=NCT00655239&rank=1.

[116] van der Gaag M, Nieman DH, Rietdijk J, Dragt S, Ising HK, Klaassen RM, et al. Cognitive-behavioral therapy for subjects at ultrahigh risk for developing psychosis: a randomized controlled clinical trial. Schizophr Bull 2012;38(6): 1180–8.
[117] van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 months and longer-term follow-ups. Schizophr Res 2013;149(1–3):56–62.
[118] Van Tricht MJ, Ruhrmann S, Arns M, Muller R, Bodatsch M, Velthorst E, et al. Can quantitative EEG measures predict clinical outcome in subjects at clinical high risk for psychosis? A prospective multicenter study. Schizophr Res 2014;153:42–7.
[119] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382(9904):1575–86.
[120] Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(9):655–79.
[121] Woods SW, Breier A, Zipursky RB, Perkins DO, Addington J, Miller TJ, et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. Biol Psychiatry 2003;54: 453–64.
[122] Woods SW, Walsh B, Pearlson GD, McGlashan TH, Simonsen E. WC2E glycine treatment of prodromal symptoms. Schizophr Res 2006;86(Suppl.):S7.
[123] Woods SW, Tully EM, Walsh BC, Hawkins KA, Callahan JL, Cohen SJ, et al. Aripiprazole in the treatment of the psychosis prodrome: an open-label pilot study. Br J Psychiatry 2007;191(Suppl. 51):96–101.
[124] Woods SW, Walsh BC, Hawkins KA, Miller TJ, Saksa JR, D'Souza DC, et al. Glycine treatment of the risk syndrome for psychosis: report of two pilot studies. Eur Neuropsychopharmacol 2013;23(8):931–40.
[125] Yale University. Randomized controlled trial of aspirin vs placebo in the treatment of pre-psychosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 [2014 August 27; NLM identifier: NCT02047539]https://www.clinicaltrials.gov/ct2/show/NCT02047539?term=NCT02047539&rank=1.
[126] Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005;39(11–12):964–71.
[127] Yung AR, Phillips LJ, Simmons MB, Ward J, Thompson P, French P, et al. CAARMS. Comprehensive Assessment of at Risk Mental States. Parkville Victoria: The PACE Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry; 2006.
[128] Yung AR, Phillips LJ, Nelson B, Francey SM, PanYuen H, Simmons MB, et al. Randomized controlled trial of interventions for young people at ultra-high risk for psychosis: a 6-month analysis. J Clin Psychiatry 2011;72(4):430–40.