



Original article

EPA guidance on the early detection of clinical high risk states of psychoses



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ABSTRACT

The aim of this guidance paper of the European Psychiatric Association is to provide evidence-based recommendations on the early detection of a clinical high risk (CHR) for psychosis in patients with mental problems. To this aim, we conducted a meta-analysis of studies reporting on conversion rates to psychosis in non-overlapping samples meeting any at least any one of the main CHR criteria: ultra-high risk (UHR) and/or basic symptoms criteria. Further, effects of potential moderators (different UHR criteria definitions, single UHR criteria and age) on conversion rates were examined. Conversion rates in the identified 42 samples with altogether more than 4000 CHR patients who had mainly been identified by UHR criteria and/or the basic symptom criterion 'cognitive disturbances' (COGDIS) showed considerable heterogeneity. While UHR criteria and COGDIS were related to similar conversion rates until 2-year follow-up, conversion rates of COGDIS were significantly higher thereafter. Differences in onset and frequency requirements of symptomatic UHR criteria or in their different consideration of functional decline, substance use and co-morbidity did not seem to impact on conversion rates. The 'genetic risk and functional decline' UHR criterion was rarely met and only showed an insignificant pooled sample effect. However, age significantly affected UHR conversion rates with lower rates in children and adolescents. Although more research into potential sources of heterogeneity in conversion rates is needed to facilitate improvement of CHR criteria, six evidence-based recommendations for an early detection of psychosis were developed as a basis for the EPA guidance on early intervention in CHR states.

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1. Introduction

In psychiatry, as in medicine, strenuous efforts are made to predict and, subsequently, prevent diseases before their first manifestation and the development of significant disability [13,51,127]. In psychosis research, this approach has already been

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pursued over the past two decades within the framework of indicated prevention in help-seeking samples [25,127]. Since a successful preventive intervention relies on the accuracy of risk detection, the present paper critically examines present research on the detection of clinical high risk (CHR) states to underpin the development of clinical recommendations that reflect current evidence in this sensitive and changing area of research. A second related paper (see Schmidt SJ et al.; this issue) will examine the evidence for preventive interventions in this area and provide clinical recommendations. Together, both papers offer up to date evidence-based guidance for both the prediction and the prevention of psychosis with special emphasis on potential developmental aspects.

1.1. Prevalence and burden of psychotic disorders

The defining characteristic of psychosis is the presence of positive symptoms, i.e. delusions, hallucinations and positive formal thought disorders, yet again confirmed as the key features of psychotic disorders in DSM-5 [4]. The lifetime prevalence of psychoses is estimated between 0.2 and 3.5% [83,125], their annual incidence between 0.01 and 0.035%, with growing numbers reported in Europe where, within 12 months, approximately 3.7 million adults (0.8%) had been affected in 2005 and as much as 5 million (1.2%) in 2011 [46,125]. The gender related incidence of affective and non-affective psychotic disorders depends on type of psychosis and age with a higher incidence of schizophrenia in men and a similar cumulative incidence of all psychoses at age 60 [19,34,35,38,47,65,114]. Approximately 10–15% of all psychoses are early-onset psychoses (EOP) manifesting before the age of 18, and approximately 1–3% are very-early-onset psychoses (VEOP) with an onset before the age of 13 [98,125].

Following psychotic episodes, negative symptoms commonly persist, and are associated with cognitive impairments and psychosocial disabilities. This is a main reason why such a relatively infrequent disorder is responsible for the sixth largest share of disability-adjusted life years (DALYs) in adults in Europe (i.e., 637,693 DALYs [125]), and the third largest (16.8 million DALYs) of all main brain disorders worldwide [16]. Despite the infrequency of (V)EOP, schizophrenia is one of the ten main causes of DALYs in 10- to 14-year-old boys and 15- to 19-year-old girls [31]. Thus, at € 93.9 billion of total direct health care, direct non-medical and indirect costs of brain disorders in Europe in 2010 attributed to psychoses, only the costs for mood disorders and dementia were higher [81]. In addition, the burden caused by stigma and discrimination is also among the highest in psychosis [89].

1.2. Etiological and pathogenetic aspects in psychoses

Psychoses are increasingly considered as a brain development disorder with polygenic heredity [36]. As with other complex diseases, research is now focusing on characterizing the polygenic factors and clarifying their variable phenotypic expression. This pathogenesis seems to be greatly influenced by both rare gene variants with large effects, and interactions between different genes of small effect as well as genes and environment [118]. Contributory environmental risk factors include exposure to viral agents in the second trimester of pregnancy, birth complications, childhood trauma, migration, the quality of the rearing environment, environment, socio-economic disadvantage, urban birth, living in urban areas and using illicit drugs, particularly cannabis. However, with odds ratios of around 2, each of these factors increase lifetime-risk for psychosis only slightly [117] and causality can be difficult to determine. Thus, to improve future prediction, research on gene $\times$ environment

interactions in development of psychoses is conducted intensively in Europe [22].

1.3. Rationale for a prevention of psychoses

The epidemiological, clinical and etiopathogenic aspects of psychoses outlined above, and the lack of a therapeutic breakthrough in the treatment of the disorder itself make psychotic disorders a worthwhile target for preventive measures prior to their first manifestation. In principle, prevention can be offered: universally to the general, unselected population; selectively to healthy individuals with a known risk factor of the disease; or by indication to persons already suffering from first complaints and impairments and who are actively seeking advice and help [73,127]. The universal and the selective approach cannot be implemented effectively—at least to date—due to: the low incidence of psychoses in the general population, lack of sufficient etiological knowledge and of risk factors of sufficiently large effect. The indicated approach is currently regarded as the most appropriate prevention strategy for psychoses [51], because the majority of first-episode psychosis patients report having suffered from mental problems including risk symptoms and increasing psychosocial impairment for an average 5-year period prior to the onset of psychosis [106] (Fig. 1). This strategy is supported by consistently reported negative effects of long duration of untreated illness and untreated psychosis on outcome [29,61] that may even be aggravated in EOP, because more pronounced neurodevelopmental and cognitive deficits, the insidious onset of less pronounced positive symptoms and/or the atypical clinical picture of the beginning EOP—potentially misinterpreted as ‘adolescent crisis’—might act as further delaying factors [96,97].

1.4. The clinical high risk (CHR) state of psychoses

Currently, there are two complementary approaches to the characterization of the CHR state of psychoses: the ultra-high risk (UHR) and the basic symptoms criteria (Fig. 1) [25,51]. The alternative UHR criteria, which comprise the attenuated psychotic symptom (APS) criterion, the brief limited intermittent psychotic symptom (BLIPS) criterion, and the genetic risk and functional decline (GRFD) criterion (Table 1), were originally developed with the explicit aim of detecting an imminent risk for psychoses, i.e., persons at risk for developing a first-episode within the next 12 months [84]. While their operationalization usually hardly differs with respect to these broad definitions, the associated requirements in particular of APS and BLIPS criteria can differ considerably between assessments (Table 2) [110]. Table 3 details instruments used for the assessment of UHR criteria.

In contrast to the UHR criteria, the criteria based on basic symptoms (the cognitive-perceptive basic symptoms (COPER) criterion and the cognitive disturbances (COGDIS) criterion (Table 4) [50,102,108]) were developed to detect the risk for psychosis as early as possible in the development of the illness, ideally before functional impairments appeared (Fig. 1). Basic symptoms are currently assessed with the Schizophrenia Proneness Instrument, Adult ((SPI-A [104]) or Child & Youth version (SPI-CY [109])).

1.5. Early detection of psychoses in children and adolescents

Since EOP were reported to present a slightly different onset and clinical picture compared to adult-onset psychoses [2,6,18,27,37,88,90,94,115,108], early detection in children and adolescents might be confronted with additional challenges. This is supported by first reports on conversion rates in adolescent risk samples between age 12 and 18 [122,135], indicating that lag time

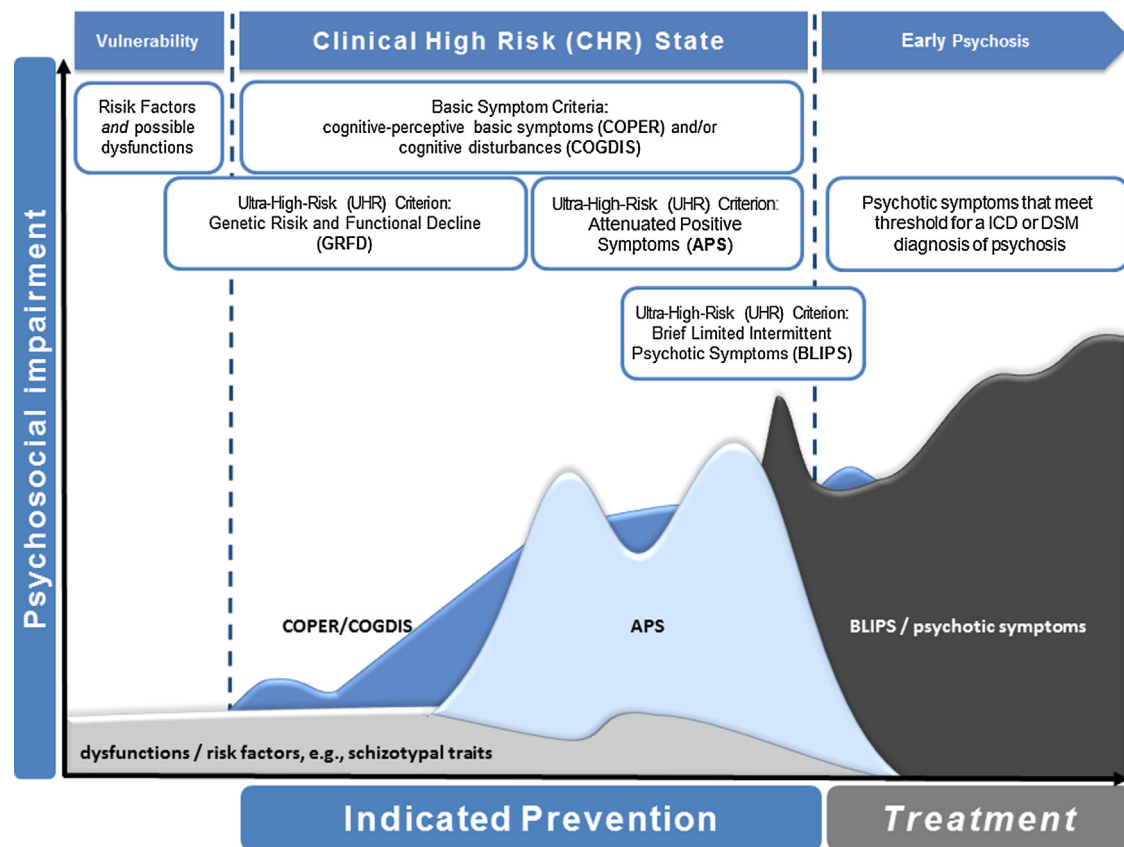


Fig. 1. Model of the early course of psychosis based on Fusar-Poli et al. (2012) [25].

to conversion might be longer and, consequently, conversion rates in the first years following initial risk assessment might be lower. Furthermore, recent studies reported high prevalence rates of (attenuated) psychotic symptoms [111], in particular of hallucinations, in children and young adolescents, which seem to decrease with age [43,44] and to remit spontaneously in about three quarters [7]. Thus, it was recently argued that the validity of current risk criteria needs to be examined in and possibly adapted to children and adolescents [23,95,99,107].

1.6. Aims

With studies on early detection of psychosis accumulating over the past 20 years and growing interest in this field from clinicians,

this paper aims to reflect the current state of evidence of the different CHR criteria in different age groups, and to make evidence-based recommendations for their clinical use in Europe.

2. Methods

2.1. Literature selection

2.1.1. Literature search

We conducted a systematic literature review in June 2014 in PubMed and Scopus that covered all journals included in Embase using the following search terms and syntax: ([early detection] OR [prediction] OR [early recognition]) AND ([conversion] OR [transition] OR [development]) AND ([psychosis] OR [schizophrenia]) AND ([risk] OR [prodrome]). Since the early detection of psychosis is a predominately psychiatric topic, an additional search in PsycInfo was not conducted as it covers fewer psychiatric journals than PubMed and Scopus.

2.1.2. Selection criteria

Inclusion criteria were:

- study was prospective with a (mean) follow-up of at least 6 months;
- study reported on a CHR sample according to the UHR or basic symptom criteria;
- primary or secondary outcome was psychosis and;
- paper was published in German or English.

Exclusion criteria were:

- study was published before 1996, i.e., before the first description of main CHR criteria;

Table 1
General definition of ultra-high risk (UHR) criteria.

Symptomatic approach
A. Presence of at least any 1 brief limited intermittent psychotic symptom (BLIPS)
Hallucinations
Delusions
Formal thought disorders
B. Presence of at least any 1 attenuated psychotic symptom (APS)
Ideas of reference
Odd beliefs or magical thinking, including ideas of grandiosity
Paranoid ideation
Unusual perceptual experiences
Odd thinking and speech
Constrictive 'state-trait' approach
C. Presence of a genetic risk factor (family history of psychosis; schizotypal personality disorder of person) in combination with a recent significant decline in psychosocial functioning (GRFD)
Presence of at least any one of A, B or C to meet UHR criteria

Table 2

Comparison of additional requirements of symptomatic ultra-high risk (UHR) criteria in the Structured Interview for Psychosis-Risk Syndromes (SIPS [64]) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) early versions [130] as well as latest 2006 version [131].

Scale	Onset	Frequency	Substance-use, co-morbidities	Functioning
<i>Attenuated psychotic symptoms (APS)</i>				
SIPS	Development or increase by 1 point in severity within the past year	Average frequency of at least once per week in the past month	Not the effect of substance use and not better explained by a mental disorder	Irrespective of current or past functioning
CAARMS early versions	Present for at least 1 week within the past year and not more than 5 years	Frequency of several times per week	Irrespective of relation to substance use or other mental disorders	Irrespective of current or past functioning
CAARMS 2006 version	Symptoms present in the past year	At least once a month to twice a week—more than one hour per occasion OR At least 3 to 6 times a week—less than one hour per occasion	Irrespective of relation to substance use or other mental disorders	30% drop in SOFAS score from premorbid level, sustained for a month and occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer
<i>Brief limited intermittent, i.e. transient psychotic symptoms (BLIPS)</i>				
SIPS	Development within the past 3 months	Several minutes a day at least 1/ month and no more than 1 hour a day for 4 days a week (on average) for 1 month	Symptoms are not seriously dangerous or disorganizing, not the effect of substance use and not better explained by a mental disorder	Irrespective of current or past functioning
CAARMS early versions	Occurrence within the past year	Duration of episode less than a week	Irrespective of relation to substance use or other mental disorders	Irrespective of current or past functioning
CAARMS 2006 version	Symptoms occurred during last year	At least 3 to 6 times a week—more than an hour per occasion OR At least daily—less than an hour per occasion	Irrespective of relation to substance use or other mental disorders	30% drop in SOFAS score from premorbid level, sustained for a month and occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer

SOFAS: Social and Occupational Functioning Assessment Scale [3].

- sample was part of a larger sample and/or longer follow-up reported in a study included in the meta-analysis and;
- study was only published as an abstract.

2.1.3. Selection process

As illustrated in Fig. 2, all titles that turned up in initial searches were first examined and assessed for relevance for the main question. Next, abstracts of selected papers were examined and assessed for relevance and appropriateness of the main question. Full texts of potentially relevant papers were obtained and independently reviewed by two authors (F.S.L. and C.M.). To rate the quality of the studies, we adapted the checklist for assessing the quality of cross-sectional diagnostic accuracy studies by [124] to the prospective design of early detection studies. Disagreement over inclusion and methodological quality of studies were discussed among the two raters until agreement was reached.

2.2. Literature analysis

2.2.1. Data extraction

For our purpose, we extracted the following variables from the literature:

- prevalence of psychosis at follow-up (conversion rates were recorded separately for CHR criteria where such information was provided). Thereby, the initial (sub)sample size was used as the base rate to avoid a bias towards overly high conversion rates at longer follow-ups that, even in the absence of additional conversions over time, would result from an increase of drop-outs/lost-to-follow-ups over time when earlier conversions are treated as observations-carried-forward;

- length of follow-up (conversion rates were recorded separately at 6-month, 1-year, 2-year, 3-year, 4-year and/or > 4-year follow-up where such information was provided; when only mean $\pm$ sd were provided, the follow-up category next to mean + sd was used, e.g., the 3-year follow-up category when mean = 26.3 and sd = 9.2 months [62]);
- type of CHR criteria (UHR incl. APS, BLIPS and GRFD, COPER and/or COGDIS) and their distribution;
- assessment of UHR criteria (i.e., SIPS, earlier CAARMS versions, latest CAARMS 2006 version, and other scales (Table 3) such as BSIP, ERIraos or PANSS);
- sample size and age distribution (age distribution was rated in four categories: almost entirely minors (≤ 18 years; CAD), almost entirely adults (minimum age 18 years or mean age > 18 with a lower sd only spanning patients ≥ 18 years; ADULT), $\geq 50\%$ minors (median or mean age ≤ 18 years or mean age ≤ 18 with an upper sd still spanning patients ≤ 18 years; YOUTH), and mixed samples with a proportion of minors of $< 50\%$ (MIX).

2.2.2. Meta-analyses

Analyses and formulae used are specified in the [Supplementary Material S1](#). In brief, the procedure was as follows: as recommended for meta-analyses of univariate studies, proportions of conversions at follow-up were used as measure of effect in a fixed-effects model. The inverse variance was used as weight to account for the different sample size of studies. Heterogeneity between effect sizes of studies was tested by the Q-statistic, and, in case of significance, a random-effects model was applied.

Table 3

Overview of instruments used for the assessment of symptomatic ultra-high risk (UHR) criteria.

Instrument	Structure and subscales relevant in the rating of APS and BLIPS
SIPS: Structured Interview for Psychosis-Risk Syndromes [64]	Modelled on the 'Positive and Negative Syndrome Scale' (PANSS) [41] Contains 4 subscales: positive, negative, disorganized, and general symptoms Five positive symptoms are used for the assessment of APS and BLIPS: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication/speech
CAARMS early (before 2006) versions: Comprehensive Assessment of At-Risk Mental States [130]	Modelled on various scales including the 'Brief Psychiatric Rating Scale' (BPRS) [82] Contains 8 subscales: disorders of thought content, perceptual abnormalities, conceptual disorganization, motor changes, concentration and attention, emotion and affect, subjectively impaired energy, and impaired tolerance to normal stress Three subscales are used for the assessment of APS and BLIPS: disorder of thought content, perceptual abnormalities, disorganized speech
CAARMS 2006 version: Comprehensive Assessment of At-Risk Mental States [131]	Modelled on earlier versions of CAARMS [130] Contains 7 subscales: positive symptoms, cognitive change attention/concentration, emotional disturbances, negative symptoms, behavioural change, motor/physical changes, and general psychopathology Four positive symptoms are used for the assessment of APS and BLIPS: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech
BSIP: Basel Screening Instrument for Psychosis [86]	Modelled on the BPRS [82] 46-item checklist used in combination with the BPRS Three symptoms of the BPRS are used for the assessment of APS: hallucinations, unusual thought content, and suspiciousness Four symptoms of the BPRS are used for the assessment of BLIPS: hallucinations, unusual thought content, suspiciousness, and conceptual disorganisation
ERIsa: The Early Recognition Inventory [63]	Modelled on the 'Instrument for the Retrospective Assessment of the Onset of Schizophrenia' (IRAOS) [33] Consists of a symptom list with 110 items, which is further structured into 12 sections Five sections include items used for the assessment of APS, BLIPS and also COPER: thought disorder, disorders of self and delusions, impaired bodily sensations, abnormal perceptions, and observation-based items
PANSS: Positive and Negative Syndrome Scale [41]	Contains 3 subscales: positive, negative and general psychopathology Four positive symptoms are used for the assessment of APS and BLIPS: delusions, hallucinations, suspiciousness, and conceptual disorganization
BPRS: Brief Psychiatric Rating Scale [82]	Contains 24 subscales: somatic concern, anxiety, depression, suicidality, guilt, hostility, elated mood, grandiosity, suspiciousness, hallucinations, unusual thought content, bizarre behaviour, self-neglect, disorientation, conceptual disorganisation, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerisms and posturing Four subscales of the BPRS are used for the assessment of APS and BLIPS: unusual thought content, hallucinations, suspiciousness, and conceptual disorganisation

APS: Attenuated Psychotic Symptoms; BLIPS: Brief Limited Intermittent Psychotic Symptoms; COPER: Cognitive-Perceptive basic symptoms.

2.2.3. Sensitivity analyses

To estimate the influence of assessment scales and, relatedly, definitions of UHR criteria (SIPS, CAARMS, CAARMS 2006), type of CHR criteria and combinations (APS, BLIPS, GRFD, COPER, COGDIS, UHR plus COGDIS, UHR and/or COGDIS), and age characteristic of the sample (CAD, YOUTH or ADULT), the same analyses (Supplementary Material S1 and S2) were repeated using these subgroups. Effect sizes in different subgroups were compared for significant differences using exploratory one-dimensional χ^2 -tests.

2.3. Development of recommendations

In line with the EPA's methodological approach within the guidance project [28], 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 (F.S.-L. and J.K.) 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 adapting 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

Our preliminary search identified 3467 titles with substantial overlap between the two databases (Fig. 2). After exclusion of titles published before 1996, the remaining 3054 titles were screened and 604 abstracts were examined in more detail for inclusion and exclusion criteria. Altogether 77 papers were deemed potentially relevant for the meta-analysis and further examined, in particular for likely redundancy of data (i.e., for the inclusion of the sample in a larger sample and/or longer follow-up). From this, 41 papers resulted that were complimented by four additional papers that reported conversion rates but had a different focus; thus, 45 papers on 42 samples were finally selected into our meta-analysis (Fig. 2).

3.2. Included studies and study design

Supplementary Table 1 gives the description of included studies that generally were rated on levels of evidence according to the Scottish Intercollegiate Guideline Network (SIGN) as '2+' (i.e., cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal). Seven samples (16.7%) each were from North America [1,12,14,15,42,100,126] and Australia [8,62,77–79,123,132,133], six (14.3%) from

Table 4

Basic symptom criteria.

Cognitive-Perceptive Basic Symptoms (COPER)
Presence of ≥ 1 of the following 10 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months and first occurrence ≥ 12 months ago
Thought interference ^a
Thought perseveration
Thought pressure ^a
Thought blockages ^a
Disturbance of receptive speech ^a
Decreased ability to discriminate between ideas/perception, fantasy/true memories
Unstable ideas of reference ^a
Derealisation
Visual perception disturbances (excl. hypersensitivity to light and blurred vision)
Acoustic perception disturbances (excl. hypersensitivity to sounds)
Cognitive Disturbances (COGDIS)
Presence of ≥ 2 of the following 9 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months
Inability to divide attention
Thought interference ^a
Thought pressure ^a
Thought blockages ^a
Disturbance of receptive speech ^a
Disturbance of expressive speech
Unstable ideas of reference ^a
Disturbances of abstract thinking
Captivation of attention by details of the visual field

SPI-A: Schizophrenia Proneness Instrument, Adult version [104].

^a Indicates basic symptoms included in both COPER and COGDIS.

Germany [9,11,50,55,91,103,105,112], three (7.1%) each from the Netherlands [116,120,135] and the UK [26,69–72], two (4.8%) each from Switzerland [87,113] and Finland [59,60], and six (14.3%) each from other European [5,24,48,53,58,92] and from Asian countries [40,45,52,56,57,134]. All but one [60] were help-seeking clinical samples: 25 (59.5%) of established early detection and intervention (EDI) services and 16 (38.1%) recruited in mental health services for the purpose of an EDI study. CHR patients generally received some kind of treatment, yet for the six (14.3%) treatment trials included in the meta-analysis, we considered only the control groups [1,5,9,69–72,116]. Six (14.3%) CHR samples were complemented by a CHR-negative group [40,59,60,112,113,132,133].

Baseline CHR sample sizes ranged from seven [60] to 817 [77] including altogether 4952 CHR subjects. With regard to age at baseline, the age range of CHR samples was almost always somewhere between 12 and 40 years; one sample [56] included patients as young as 6 years, and one other [50] patients as old as 53 years. Fifteen (35.7%) samples almost entirely included adults, ten (23.8%) a majority of patients aged ≤ 18 years, six (14.3%) almost entirely minors, and 10 (23.8%) mixed samples with a dominance of adults; one study lacked information on age [48]. In 28 samples (66.7%), $\geq 50\%$ were males; two (4.8%) studies did not provide data on gender distribution [48,53]. On 22 (52.4%) samples information on co-morbidities at baseline was provided that were mainly affective disorders (23.1–75.8%) and anxiety disorders (8.7–57.6%).

Participation rates of eligible samples at baseline were reported for 24 (57.1%) samples (39.1–100%); the drop-out or non-participation rates at last follow-up reported for 36 (85.7%) samples were between 0 and 91.6%.

For the identification of an CHR according to UHR criteria, in 17 (40.5%) samples the SIPS was employed, in twelve (28.6%) an early CAARMS version (of before 2006; in two studies [77,79], CAARMS and BRPS data were mixed), in six (14.3%) the latest 2006 CAARMS version including the general obligate functional decline criterion (Tab. 2), in two (4.8%) each the PANSS and ERIRaos, and in one (2.4%) the BSIP. For eleven (26.2%) UHR samples differential

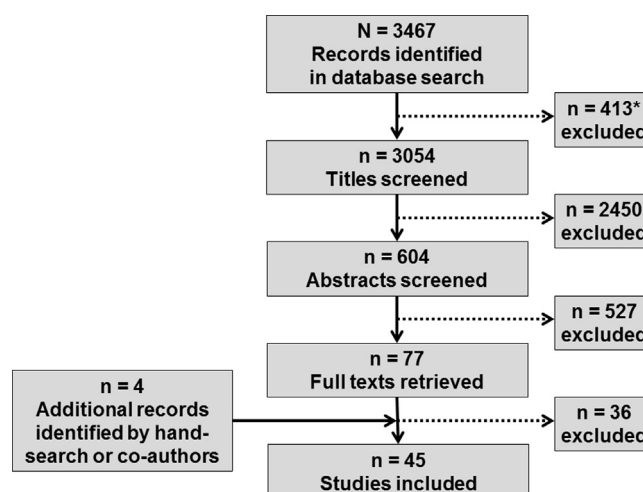


Fig. 2. Flow of studies retrieved by the systematic literature search with the algorithm detailed in 2.1.1. * published before 1996, i.e. before the first description of current UHR criteria (Yung and McGorry, 1996) [128].

conversion rates for the three UHR criteria were reported. For the identification of a CHR according to basic symptoms criteria, the 'Bonn Scale for the Assessment of Basic Symptoms' (BSABS; [32]) was used in two (4.8%) samples (in one in combination with the CAARMS), the SPI-A in six (14.3%; in five in combination with the SIPS) and the ERIRaos in one (2.4%). Assessments were generally carried out by clinicians specifically trained in the application of the respective instruments.

The majority of information on conversion to psychosis was available for the 2-year follow-up (on 23 samples; 54.8%, incl. reports on 18-month conversion rates). Conversion rates at 6 months were reported for ten (23.8%) samples and at 12 months for 20 (47.6%). Information on 3-year conversion rates (incl. reports on 2.5-year conversion rates) was obtained from ten (23.8%), on 4-year conversion rates from eight (19.0%) and on longer follow-ups from five (11.9%) samples.

Conversion was mainly to a non-affective schizophrenic or schizophreniform psychosis according to DSM-IV (71.4–100% of converters). A conversion to an affective psychosis was generally rare, with reported rates in converters between 2 and 28.6%. For 15 (35.7%) samples, information on type of psychosis was not provided.

3.3. Heterogeneity analyses of fixed-effects models

The Q -statistic indicated that there was significant heterogeneity between the conversion rate estimates in UHR, COPER and COGDIS samples at the different follow-ups with the exception of the 1-year conversion rates of two COGDIS studies ($Q_{(1)} = 0.10$; $I^2 = 39\%$). In all other cases, I^2 was between 54% and 98% and, consequently, $\bar{E}^*$ s and their 95% CIs were calculated according to the random-effects model.

3.4. Conversion rates to psychosis

Overall, the pooled conversion rate in UHR samples increased from 9.6% at 6 months to 37.0% at > 4 -year follow-up (Fig. 3a–e). In COGDIS samples, the respective numbers ranged from 25.3% at 1 year to 61.3% at > 4 years; a 6-month conversion rate of 13.9% was only reported by one study, thus not allowing the calculation of $\bar{E}^*$ (Fig. 4). For COPER, $\bar{E}$ and $\bar{E}^*$ could be calculated for 1- and 2-year follow-ups for that they were 14.4% and 21.1% (Supplementary Table 2). Overall, z -values of $\bar{E}/\bar{E}^*$ were > 2.58 indicating

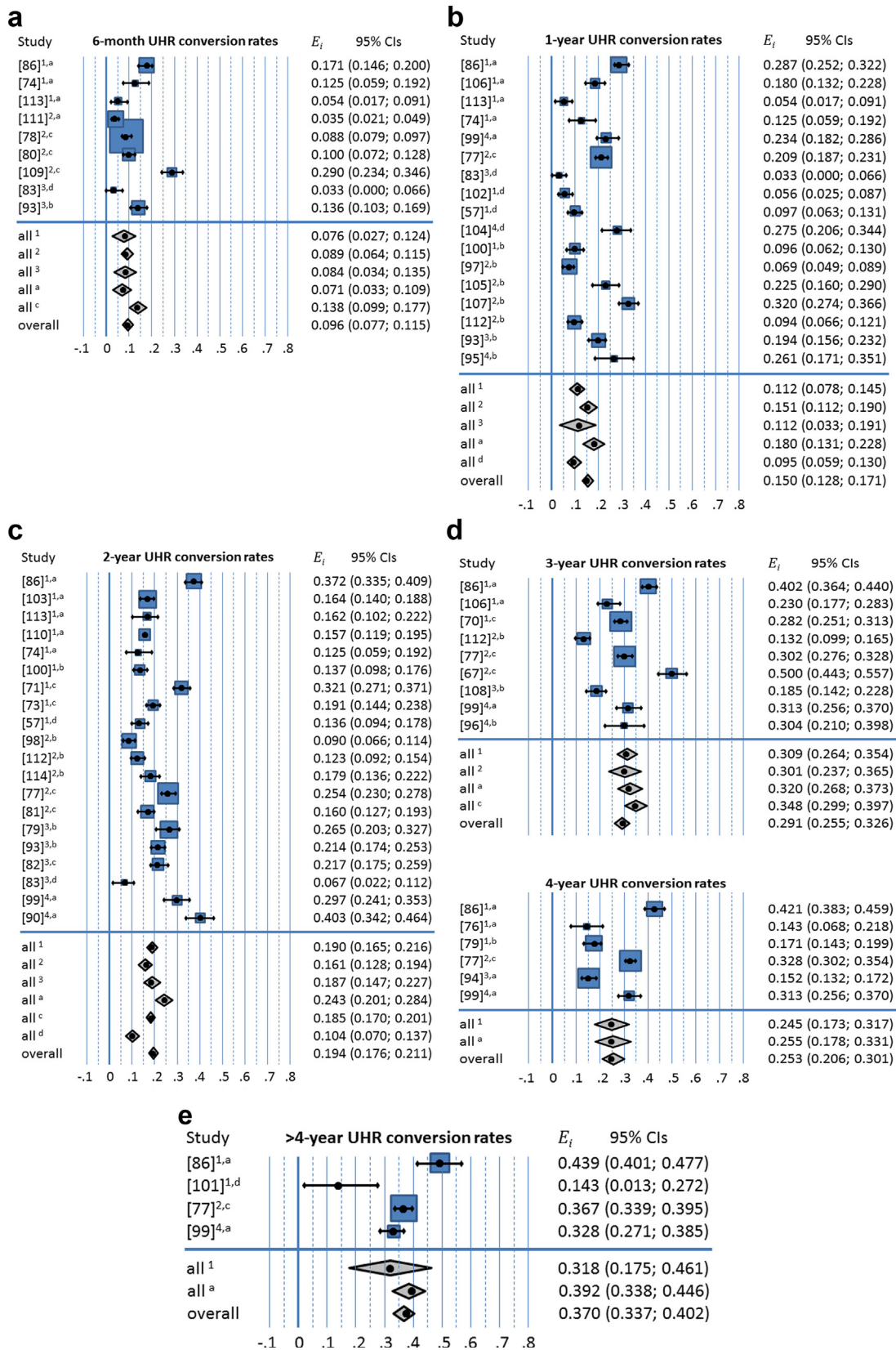


Fig. 3. a–e Conversion rates at different follow-ups in samples meeting any one ‘Ultra-high risk’ (UHR) criterion (irrespective of the potential presence of basic symptom criteria). Upper number indicates scale used for the assessment of UHR criteria (1: SIPS; 2: CAARMS; 3: CAARMS 2006 version; and 4: other scale). Upper small letter indicates age group of sample (a: ADULT; b: MIX; c: YOUTH; and d: CAD). F: according to fixed-effects model.

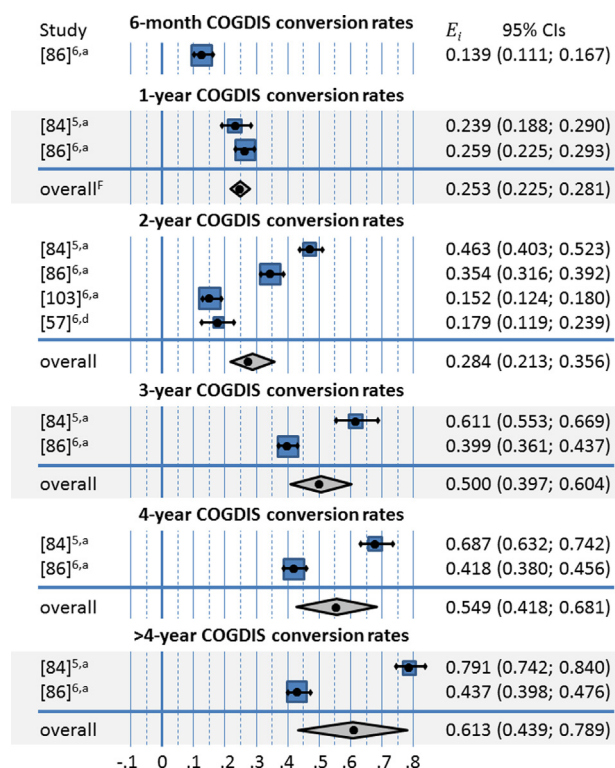


Fig. 4. Conversion rates at different follow-ups in samples meeting the 'Cognitive disturbances' (COGDIS) criterion (irrespective of the potential presence of COPER or UHR criteria). Upper number indicates scale used for the assessment of COGDIS (5: BSABS; and 6: SPI-A). Upper small letter indicates age group of sample (a: ADULT; and d: CAD). F: according to fixed-effects model.

significant pooled sample effect of UHR, COPER and COGDIS samples on conversion rates to psychosis at an at least 5% error level.

A significant pooled sample effect was mainly missing in the samples not considered at CHR (Supplementary Table 2) that showed mainly homogeneous conversion rates; of these, only the 9.8% conversion rate at > 4-year follow-up revealed a significant pooled sample effect. Thus, compared to even the lowest conversion rate in UHR, COPER or COGDIS samples at any follow-up (Figs. 3 and 4; Supplementary Table 2), conversion rates of help-seeking patients not meeting the examined CHR criteria were clearly significantly lower ($\chi^2_{(1)} \geq 5.175$; $P < 0.025$).

Irrespective of a potential co-occurrence of criteria, UHR, COPER and COGDIS samples did not significantly differ in 6-month, 1- and 2-year conversion rates ($\chi^2_{(2)} \leq 4.118$; $P > 0.10$) but only in longer term conversion rates ($\chi^2_{(2)} \geq 6.767$; $P < 0.05$) due to higher rates in both COPER and COGDIS compared to UHR samples ($\chi^2_{(1)} \geq 5.522$; $P < 0.05$).

3.5. Sensitivity analyses

3.5.1. Single and combined CHR criteria

With regard to the analyses of UHR studies reporting conversion rates separately for the three UHR criteria (APS, BLIPS and GRFD), except for the conversion rates of APS at 3 and that of BLIPS at 2 years (Supplementary Table 2), fixed-effects models were chosen for their non-significant Q-statistic or negative τ^2 -value.

As detailed in Supplementary Table 2, the pooled conversion rate in APS samples ranged from 7.7% at 6 months to 14.9% at > 4-year follow-ups of CAD samples [15,60]; and all pooled sample effects were significant. Data on the 4-year conversion rate

in APS samples was not available. Data on conversion rates in BLIPS samples were even less available (Supplementary Table 2), and pooled conversion rates could only be calculated for 2-year and 3-year follow-ups with a significant pooled sample effect only at 3 years due to the 3 BLIPS-non-converters [113] at 2 years. Pooled 2- and 3-year conversion rates in GRFD samples (Supplementary Table 2) were much lower, showed no significant pooled sample effect, and were equal to or even lower than conversion rates of CHR-negative samples (Supplementary Table 3).

Pooled conversion rates between the three UHR criteria differed significantly at 1-, 2- and 3-year follow-ups ($\chi^2_{(2)} \geq 15.200$; $P < 0.001$), mainly due to higher conversion rates in BLIPS and/or lower in GRFD samples (Supplementary Table 3).

Since recent studies have suggested that the combined assessment of UHR and BS criteria, especially COGDIS, was advantageous to their exclusive assessment in identifying an CHR [92,112], we also analyzed pooled effects of both 'UHR plus COGDIS' and 'UHR and/or COGDIS' on 2-year conversion rates. For both combinations, most conversion rates of studies were significantly heterogeneous; and pooled conversion rates of random-effects models were 26.7% for 'UHR plus COGDIS' and 19.9% for 'UHR and/or COGDIS' (Supplementary Table 2); both indicated a significant pooled sample effect that did not significantly differ from each other ($\chi^2_{(1)} = 0.992$; $P > 0.25$) or from UHR ($\chi^2_{(2)} = 1.461$; $P > 0.25$) or COGDIS ($\chi^2_{(2)} = 1.618$; $P > 0.25$) when these were considered irrespective but not exclusive of each other as in the two earlier studies [92,112].

3.5.2. UHR criteria assessment scales

For the differences in requirements of onset, recency, frequency and psychosocial functioning in symptomatic UHR criteria of different scales [110] (Table 2), conversion rates in UHR samples were additionally calculated separately for SIPS-, early CAARMS- and CAARMS 2006-assessed samples (Fig. 3a–e; Supplementary Table 4). Overall, there was no indication of a significant effect of the applied scale and, relatedly, UHR definition; only at 4-year follow-up, there was some weak indication of a difference between UHR assessments ($\chi^2_{(2)} = 6.416$; $P < 0.05$) due to a lower single effect of CAARMS 2006 [53] in comparison with the single effect of CAARMS early versions [79] (Supplementary Table 4).

3.5.3. Age group

To examine a potential age effect in UHR samples, we compared three age groups (CAD, YOUTH and ADULT) for available conversion rates on 6-month, 1-, 2- and > 4-year follow-ups (Fig. 3a–c,e). Pairwise comparisons indicated lower conversion rates in CAD compared to YOUTH throughout, and additionally to ADULT at 2 and > 4 years (Supplementary Table 5). YOUTH conversion rates never differed significantly from those in ADULT. The only significant difference to the total sample conversion rates occurred for CAD at > 4 years with an additional trend result at 6 months and 2 years (Supplementary Table 5).

4. Recommendations

4.1. Meta-analysis of studies as the evidence base of the European Guidance

Based on the results of our meta-analyses, we found that recommendations can be formulated with sufficient evidence based on studies mainly given SIGN '2+' rating (due to the unfeasibility of RCTs in early detection research) at a grade of recommendation of 'C' for recommendations 1–5 and at grade 'D' for the expert consensus-based recommendation 6.

4.2. Proposed recommendations of the European Guidance Project

4.2.1. Recommendation 1

The EPA considers that the following three CHR criteria should be alternatively used in the early detection of psychosis when past or present psychosis and causation by a somatic illness had been ruled out:

- at least any one attenuated psychotic symptom (i.e., (1) unusual thought contents or delusional ideas not held with full conviction, including ideas of reference not immediately rectified by cognition, (2) perceptual aberrations or hallucination with remaining insight, or (3) disorganized communication or speech that is still comprehensible and responds to structuring in the interview) that meets the additional requirements of either SIPS or early CAARMS (Table 2);
- at least any two self-experienced and self-reported cognitive basic symptoms rated irrespective of their appearance in the interview (i.e., (1) interference of completely insignificant thought contents, (2) blockage of thoughts not explained by lack of concentration or attention, (3) thought pressure by thoughts unrelated to a common topic, (4,5) disturbances of receptive or expressive speech in everyday use of native language, (6) inability to divide attention between tasks relating to different senses and generally not requiring full attention each such as making a sandwich and talking to someone, (7) disturbance in the immediate recognition and understanding of any kind of abstract, figurative or symbolic phrases or contents, (8) subjective experience of self-reference that are almost immediately rectified by cognition, and (9) captivation of attention by insignificant details of the visual field that impairs paying attention to more relevant stimuli) that have not been present in what the patient considers his/her premorbid stage, have occurred at least on a weekly basis for some time in the past 3 months and are not an effect of drug use;
- at least any one transient psychotic symptom (i.e., delusion, hallucination, formal thought disorder) that meets the additional requirements of either SIPS or early CAARMS (Table 2).

4.2.2. Recommendation 2

The EPA considers that a genetically increased risk of psychosis by a positive family history of psychosis in at least one first-degree biological relative should not be used as a clinical indicator of a CHR on its own, even if accompanied by functional deficits and mental problems. Rather, it should be regarded as a general risk factor indicating an already increased pre-CHR assessment risk for psychosis that should be taken into account in patients meeting the above CHR criteria. Patients not presenting the above CHR criteria but a genetic risk and other mental problems should however be encouraged to present again for a CHR assessment should they note the onset of mental problems resembling CHR symptoms.

4.2.3. Recommendation 3

In line with the general EPA guidance on prevention of mental disorders [13] whose aims include reduction of the burden of mental disorders by improvement in quality of life and productivity of individuals, the EPA considers that a significant decline in occupational and/or social functioning (and, relatedly, in productivity) should not be an obligate requirement in the above CHR criteria for the lack of evidence for an improvement of prediction by this addition. However, it should be considered as an indication of an imminence of risk of conversion and CHR patients with a significant functional decline should be considered at high need for treatment.

4.2.4. Recommendation 4

The EPA considers that the above CHR criteria should only be applied in persons already distressed by mental problems and seeking help for them or persons seeking clarification of their current risk for a vulnerability for psychosis, e.g., by genetic risk. Any clinical screening of other persons seems not warranted by current scientific evidence.

4.2.5. Recommendation 5

The EPA considers that the above CHR criteria should only be used and communicated with outmost care in children and young adolescents in whom they should nevertheless be assessed and monitored (see Schmidt SJ et al.; this issue). In late adolescence, however, the CHR criteria seem to be as applicable as in adults.

4.2.6. Recommendation 6

The EPA considers that a trained specialist (psychiatrist, clinical psychologist or equivalent mental health professional) with sufficient experience in CHR should carry out the assessment; if referral to a specialist is not possible, the responsible clinician should consult a trained specialist on the case, e.g. by phone; and specialized early detection services should be prepared to give such advice, e.g., within the framework of telephone consultation hours. Case conferences with experts in early detection of psychoses are even advised for mental health specialists.

5. Discussion

From our meta-analyses, evidence-based recommendations for early detection of psychosis were formulated that improve upon those of previous expert consensus guidelines [10,20,74–76]. While the evidence for the psychosis-predictive value of UHR criteria, especially APS and BLIPS, and basic symptom criteria, especially COGDIS, continue to accumulate, the heterogeneity of conversion rates between CHR samples strongly suggests the presence of moderating variables. Of these, single CHR criteria, their assessment mode and definition, and age were analyzed based on the limited available data. Generally, the lack of detailed information on the relationship of sample, presence and kind of treatment and study characteristics, and clinical variables with conversion rates impeded our analyses. Thus, for example, the frequent specification of simply mean follow-up times along with the frequent lack of time-dependent survival analyses only allowed estimates of the impact of observation time on conversion rate. This lack of information also precluded the simultaneous consideration of our considered moderators and might have introduced some bias. For example, the pooled conversion rate in APS samples with > 4-year follow-up was lower than at 2- or 3-year follow-up, yet these shorter follow-ups were in older samples than the > 4-year follow-ups on that data were provided only by CAD samples, and significantly lower conversion rates can be assumed for this age range. Furthermore, our estimates might somewhat underestimate the true effect of a CHR on conversion to psychosis as we conservatively treated the often considerable numbers of drop-outs and/or cases with shorter than the allocated follow-up as non-converters. Despite these shortcomings, some consistent patterns occurred that allowed the formulation of detailed recommendations including age considerations for the first time.

These recommendations did not include the basic symptom criterion COPER because of its large overlap with COGDIS and, compared to COGDIS, its lesser degree of evidence due to the very small number of studies of that only the study on that the basic symptom criteria were developed [50,103] exceeded 2-year follow-up. Moreover, the recommendations did not adopt the recent addition of an obligate functional decline criterion to the

symptomatic UHR criteria, as our analyses did not support the presumption that it would improve prediction of psychosis in help-seeking samples. The addition had been put forward on the basis of consistent reports of significantly lower functioning in converters in group mean comparisons and the frequent inclusion of functional deficits in prediction models [14,17,21,30,39,62,92,93,119,121,129,136]. However, such group mean-based results seem to fail to translate into an improved prediction in practice, highlighting the general need for more translational research on predictors using, for example, existing norms or clearly defined and tested cut-offs [67,101]. Furthermore, a 'one-fits-all' approach most likely does not measure up to the considerable heterogeneity of conversion rates even in CHR samples of equal intake criteria. Future early detection approaches should therefore define different CHR groups that are identified, for example, by a risk stratification approach, which might consider most likely level of functioning but also other potential predictors such as neurocognitive or neurobiological abnormalities [5,11,54,67,80,87].

6. Conclusions and perspectives

The young field of preventive research in psychosis has already resulted in sufficient evidence to formulate recommendations for an early detection of psychosis in the clinical practice. Yet, our analysis has also revealed significant heterogeneity of conversion rates that needs to be addressed in future studies in order to develop more sophisticated prediction models that can be easily translated into clinical practice and address the special characteristics and treatment needs of different patient groups. Furthermore, the success of preventive approaches also depends on a sufficiently high rate of target persons who are reached by it. Thus, to reach also CHR persons who do not actively seek help for their mental problems, more research in the general population is needed to develop ethically justified means such as well-validated and reliable screeners [68] on the basis of those already proposed [49,66,85].

Disclosure of interest

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eurpsy.2015.01.010>.

References

- [1] 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.
- [2] Alaghband-Rad J, McKenna K, Gordon CT, Albus KE, Hamburger SD, Rumsey JM, et al. Childhood-onset schizophrenia: the severity of premorbid course. *J Am Acad Child Adolesc Psychiatry* 1995;34(10):1273–83.
- [3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV), 4th ed., Washington, DC: American Psychiatric Press; 1994.
- [4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5), 5th ed., Washington, DC: American Psychiatric Press; 2013.
- [5] 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.
- [6] Ballageer T, Malla A, Manchanda R, Takhar J, Haricharan R. Is adolescent-onset first-episode psychosis different from adult onset? *J Am Acad Child Adolesc Psychiatry* 2005;44(8):782–9.
- [7] Bartels-Velthuis AA, van de Willige G, Jenner JA, van Os J, Wiersma D. Course of auditory vocal hallucinations in childhood: 5-year follow-up study. *Br J Psychiatry* 2011;199(4):296–302.
- [8] Bechdolf A, Thompson A, Nelson B, Cotton S, Simmons MB, Amminger GP, et al. Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. *Acta Psychiatr Scand* 2010;121(5):377–84.
- [9] 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.
- [10] Bertolote J, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. *Br J Psychiatry* 2005;48(Suppl.):116–9.
- [11] Bodatsch M, Ruhrmann S, Wagner M, Müller R, Schultze-Lutter F, Frommann I, et al. Prediction of psychosis by mismatch negativity. *Biol Psychiatry* 2011;69(10):959–66.
- [12] Buchy L, Perkins D, Woods SW, Liu L, Addington J. Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. *Schizophr Res* 2014;156(2–3):277–80.
- [13] 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.
- [14] Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008;65(1):28–37.
- [15] Carrión 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] Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. *Nature* 2011;475(7354):27–30.
- [17] Cornblatt BA, Carrión RE, Addington J, Seidman L, Walker EF, Cannon TD, et al. Risk factors for psychosis: impaired social and role functioning. *Schizophr Bull* 2012;38(6):1247–57.
- [18] David CN, Greenstein D, Clasen L, Gochman P, Miller R, Tossell JW, et al. Childhood onset schizophrenia: high rate of visual hallucinations. *J Am Acad Child Adolesc Psychiatry* 2011;50(7):681–6.
- [19] De Girolamo G, Dagani J, Purcell R, Cocchi A, McGorry PD. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. *Epidemiol Psychiatr Sci* 2012;21(1):47–57.
- [20] Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN). Behandlungsleitlinie Schizophrenie. Darmstadt: Steinkopff Verlag; 2006.
- [21] Dragt S, Nieman DH, Veltman D, Becker HE, van de Fliert R, de Haan L, et al. Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. *Schizophr Res* 2011;125(1):69–76.
- [22] The European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions (EU-GEI). Schizophrenia aetiology: do gene-environment interactions hold the key? *Schizophr Res* 2008;102(1–3):21–6.
- [23] Fiori Nastro P, Schimmelmann BG, Gebhardt E, Monducci E, Resch F, Koch E, et al. [Challenges in the early detection of psychosis in children and adolescents]. *Riv Psichiatr* 2012;47(2):116–25.
- [24] Fusar-Poli P, Hobson R, Raduelli M, Balottin U. Reliability and validity of the comprehensive assessment of the at risk mental state, Italian version (CAARMS-I). *Curr Pharm Des* 2012;18(4):386–91.
- [25] 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.
- [26] Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in south London (OASIS), 2001–2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. *Eur Psychiatry* 2013;28(5):315–26.
- [27] Fux L, Walger P, Schimmelmann BG, Schultze-Lutter F. The schizophrenia proneness instrument, child and youth version (SPI-CY): practicability and discriminative validity. *Schizophr Res* 2013;146(1–3):69–78.

- [28] Gaebel W, Möller HJ. European guidance—a project of the European Psychiatric Association. *Eur Psychiatry* 2012;27:65–7.
- [29] Gater R, Jordanova V, Maric N, Alikaj V, Bajcs M, Cavic T, et al. Pathways to psychiatric care in Eastern Europe. *Br J Psychiatry* 2005;186:529–35.
- [30] González-Pinto A, Ruiz de Azúa S, Ibáñez B, Otero-Cuesta S, Castro-Fornieles J, Graell-Berna M, et al. Can positive family factors be protective against the development of psychosis? *Psychiatry Res* 2011;186(1):28–33.
- [31] Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 2011;377(9783):2093–102.
- [32] Gross G, Huber G, Klosterkötter J, Linz M. Bonner Skala für die Beurteilung von Basis-symptomen.BSABS; Bonn Scale for the assessment of basic symptoms Berlin: Springer-Verlag; 1987.
- [33] Häfner H, Riecher-Rössler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, et al. IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophr Res* 1992;6(3):209–23.
- [34] Häfner H, Maurer K, Löffler W, Riecher-Rössler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry* 1993;162:80–6.
- [35] Häfner H, Maurer K, Löffler W, Fätkenheuer B, an der Heiden W, Riecher-Rössler A, et al. The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. *Br J Psychiatry* 1994;Suppl.(23):29–38.
- [36] Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression and neuropathology on the matter of their convergence. *Mol Psychiatry* 2005;10(Suppl. 3):40–68.
- [37] Hlastala SA, McClellan J. Phenomenology and diagnostic stability of youths with atypical psychotic symptoms. *J Child Adolesc Psychopharmacol* 2005;15(3):497–509.
- [38] Jackson D, Kirkbride J, Croudace T, Morgan C, Boydell J, Errazuriz A, et al. Meta-analytic approaches to determine gender differences in the age-incidence characteristics of schizophrenia and related psychoses. *Int J Methods Psychiatr Res* 2013;22(1):36–45.
- [39] 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.
- [40] Katsura M, Ohmuro N, Obara C, Kikuchi T, Ito F, Miyakoshi T, et al. A naturalistic longitudinal study of at-risk mental state with a 2.4-year follow-up at a specialized clinic setting in Japan. *Schizophr Res* 2014;158(1–3):32–8. <http://dx.doi.org/10.1016/j.schres.2014.06.013>.
- [41] Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261–76.
- [42] Kayser J, Tenke CE, Kropmann CJ, Alschuler DM, Ben-David S, Fekri S, et al. Olfaction in the psychosis prodrome: electrophysiological and behavioral measures of odor detection. *Int J Psychophysiol* 2013;90(2):190–206.
- [43] Kelleher I, Murtagh A, Molloy C, Roddy S, Clarke MC, Harley M, et al. Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. *Schizophr Bull* 2012;38(2):239–46.
- [44] Kelleher I, Keeley H, Corcoran P, Lynch F, Fitzpatrick C, Devlin N, et al. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *Br J Psychiatry* 2012;201(1):26–32.
- [45] Kim E, Jang JH, Park HY, Shim G, Hwang JY, Kim SN, et al. Pharmacotherapy and clinical characteristics of ultra-high-risk for psychosis according to conversion status: a naturalistic observational study. *Early Interv Psychiatry* 2012;6(1):30–7.
- [46] 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(3):250–8.
- [47] Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analysis. *PLoS One* 2012;7(3):e31660.
- [48] Kiss I, Kelemen O, Kéri S. Decreased peripheral expression of neuregulin 1 in high-risk individuals who later converted to psychosis. *Schizophr Res* 2012;135(1–3):198–9.
- [49] Kline E, Schiffman J. Psychosis risk screening: a systematic review. *Schizophr Res* 2014;158(1–3):11–8. <http://dx.doi.org/10.1016/j.schres.2014.06.036>.
- [50] Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001;58(2):158–64.
- [51] Klosterkötter J, Schultze-Lutter F, Bechdolf A, Ruhrmann S. Prediction and prevention of schizophrenia: what has been achieved and where to go next? *World Psychiatry* 2011;10(3):165–74.
- [52] Koike S, Takano Y, Iwashiro N, Satomura Y, Suga M, Nagai T, et al. A multimodal approach to investigate biomarkers for psychosis in a clinical setting: the integrative neuroimaging studies in schizophrenia targeting for early intervention and prevention (IN-STEP) project. *Schizophr Res* 2013;143(1):116–24.
- [53] Kotlicka-Antczak M, Pawelczyk T, Rabe-Jabłońska J, Pawelczyk A. PORT (Programme of Recognition and Therapy): the first Polish recognition and treatment programme for patients with an at-risk mental state. *Early Interv Psychiatry* 2014. <http://dx.doi.org/10.1111/eip.12146> [Epub ahead of print].
- [54] Koutsouleris N, Riecher-Rössler A, Meisenzahl EM, Smieskova R, Studerus E, Kambaitz-Iankovic L, et al. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. *Schizophr Bull* 2014. <http://dx.doi.org/10.1093/schbul/sbu078> [Epub ahead of print].
- [55] Koutsouleris N, Meisenzahl EM, Davatzikos C, Bottlender R, Frodl T, Scheuer-ecker J, et al. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Arch Gen Psychiatry* 2009;66(7):700–12.
- [56] Lam MM, Hung SF, Chen EY. Transition to psychosis: 6-month follow-up of a Chinese high-risk group in Hong Kong. *Aust N Z J Psychiatry* 2006;40(5):414–20.
- [57] Lee J, Rekhi G, Mitter N, Bong YL, Kraus MS, Lam M, et al. The longitudinal youth at risk study (LYRIKS)—an Asian UHR perspective. *Schizophr Res* 2013;151(1–3):279–83.
- [58] Lemos-Giráldez S, Vallina-Fernández O, Fernández-Iglesias P, Vallejo-Seco G, Fonseca-Pedrero E, Paño-Piñeiro M, et al. Symptomatic and functional outcome in youth at ultra-high risk for psychosis: a longitudinal study. *Schizophr Res* 2009;115(2–3):121–9.
- [59] Lindgren M, Manninen M, Kalska H, Mustonen U, Laajasalo T, Moilanen K, et al. Predicting psychosis in a general adolescent psychiatric sample. *Schizophr Res* 2014;158(1–3):1–6. <http://dx.doi.org/10.1016/j.schres.2014.06.028>.
- [60] Manninen M, Lindgren M, Therman S, Huttunen M, Ebeling H, Moilanen I, et al. Clinical high-risk state does not predict later psychosis in a delinquent adolescent population. *Early Interv Psychiatry* 2014;8(1):87–90.
- [61] Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005;62(9):975–83.
- [62] Mason O, Startup M, Halpin S, Schall U, Conrad A, Carr V. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. *Schizophr Res* 2004;71(2–3):227–37.
- [63] Maurer K, Hörmann 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.
- [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] McGrath J, Saha S, Welham J, El SO, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med* 2004;2:13.
- [66] Meneghelli A, Alpi A, Cascio MT, Häfner H, Maurer K, Preti A, et al. Italian validation of the early recognition inventory for the retrospective assessment of the onset of schizophrenia checklist: reliability, validity and instructions for use. *J Psychopathol* 2013;19(1–2):1–9.
- [67] Michel C, Ruhrmann S, Schimmelmann BG, Klosterkötter J, Schultze-Lutter F. A stratified model for psychosis prediction in clinical practice. *Schizophr Bull* 40(6):1533–42. doi:10.1093/schbul/sbu025.
- [68] Michel C, Schultze-Lutter F, Schimmelmann BG. Screening instruments in child and adolescent psychiatry: general and methodological considerations. *Eur Child Adolesc Psychiatry* 23(9):725–7. doi:10.1007/s00787-014-0608-x.
- [69] 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.
- [70] 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.
- [71] 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.
- [72] 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;344:e2233.
- [73] Mrazek PJ, Haggerty HJ. Reducing risks for mental disorders: frontiers for preventive research. Washington, DC: Academy Press; 2013.
- [74] National Institute for Health, Clinical Excellence (NICE). Psychosis with coexisting substance misuse: assessment and management in adults and young people; [Online] 2011 [Available at: <https://www.nice.org.uk/guidance/published?type=Guidelines> (Accessed: 25 August 2014)].
- [75] National Institute for Health, Clinical Excellence (NICE). Psychosis and schizophrenia in children and young people: recognition and management; [Online] 2013 [Available at: <https://www.nice.org.uk/guidance/published?type=Guidelines> (Accessed: 25 August 2014)].
- [76] National Institute for Health, Clinical Excellence (NICE). Psychosis and schizophrenia in adults: treatment and management; [Online] 2014 [Available at: <https://www.nice.org.uk/guidance/published?type=Guidelines> (Accessed: 25 August 2014)].
- [77] Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? *Schizophr Res* 2011;125(1):62–8.
- [78] Nelson B, Thompson A, Yung AR. Basic self-disturbance predicts psychosis onset in the ultra high risk for psychosis “prodromal” population. *Schizophr Bull* 2012;38(6):1277–87.
- [79] Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, et al. Long-term follow-up of a group at ultra high risk (“prodromal”) for psychosis: the PACE 400 study. *JAMA Psychiatry* 2013;70(8):793–802.
- [80] 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* 40(6):1482–90, doi:10.1093/schbul/sbt145.
- [81] Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B, CDBE2010 study group, et al. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012;19(1):155–62.
- [82] Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep* 1962;10:799–812.
- [83] Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007;64(1):19–28.
- [84] Phillips LJ, Yung AR, McGorry PD. Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *Aust N Z J Psychiatry* 2000;34(Suppl.):164–9.
- [85] Raballo A, Meneghelli A, Cocchi A, Sisti D, Rocchi MB, Alpi A, et al. Shades of vulnerability: latent structures of clinical caseness in prodromal and early phases of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2014;264(2):155–69.
- [86] Riecher-Rössler A, Aston J, Ventura J, Merlo M, Borgwardt S, Gschwandtner U, et al. [The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity]. *Fortschr Neurol Psychiatr* 2008;76(4):207–16.
- [87] Riecher-Rössler A, Pflueger MO, Aston J, Borgwardt SJ, Brewer WJ, Gschwandtner U, et al. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. *Biol Psychiatry* 2009;66(11):1023–30.
- [88] Ross RG, Heinlein S, Tregellas H. High rates of comorbidity are found in childhood-onset schizophrenia. *Schizophr Res* 2006;88(1–3):90–5.
- [89] Rössler W, Salize HJ, van Os J, Riecher-Rössler A. Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol* 2005;15(4):399–409.
- [90] Rubio JM, Sanjuán J, Flórez-Salamanca L, Cuesta MJ. Examining the course of hallucinatory experiences in children and adolescents: a systematic review. *Schizophr Res* 2012;138(2–3):248–54.
- [91] 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;51(Suppl.):88–95.
- [92] Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, et al. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry* 2010;67(3):241–51.
- [93] Salokangas RK, Patterson P, Heinimaa M, Svriskis T, From T, Vaskelainen L, et al. Perceived negative attitude of others predicts transition to psychosis in patients at risk of psychosis. *Eur Psychiatry* 2012;27(4):264–6.
- [94] Schaeffer JL, Ross RG. Childhood-onset schizophrenia: premorbid and prodromal diagnostic and treatment histories. *J Am Acad Child Adolesc Psychiatry* 2002;41(5):538–45.
- [95] Schimmelmänn BG, Schultze-Lutter F. Early detection and intervention of psychosis in children and adolescents: urgent need for studies. *Eur Child Adolesc Psychiatry* 2012;21(5):239–41.
- [96] Schimmelmänn BG, Conus P, Cotton S, McGorry PD, Lambert M. Pre-treatment, baseline, and outcome differences between early-onset and adult-onset psychosis in an epidemiological cohort of 636 first-episode patients. *Schizophr Res* 2007;95(1–3):1–8.
- [97] Schimmelmänn BG, Huber CG, Lambert M, Cotton S, McGorry PD, Conus P. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. *J Psychiatr Res* 2008;42(12):982–90.
- [98] Schimmelmänn BG, Schmidt SJ, Carlson M, Correll CU. Treatment of adolescents with early-onset schizophrenia spectrum disorders: in search of a rational, evidence-informed approach. *Curr Opin Psychiatry* 2013;26(2):219–30.
- [99] Schimmelmänn BG, Walger P, Schultze-Lutter F. The significance of at-risk symptoms for psychosis in children and adolescents. *Can J Psychiatry* 2013;58(1):32–40.
- [100] Schlosser DA, Jacobson S, Chen Q, Sugar CA, Niendam TA, Li G, et al. Recovery from an at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. *Schizophr Bull* 2012;38(6):1225–33.
- [101] Schmidt SJ, Grunert VM, Schimmelmänn 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.
- [102] Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr Bull* 2009;35(1):5–8.
- [103] Schultze-Lutter F, Ruhrmann S, Klosterkötter J. In: Johannessen JO, Martindale B, Cullberg J, editors. *Evolving psychosis. Different stages, different treatments*. London, New York: Routledge; 2006. p. 104–23.
- [104] Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. Schizophrenia proneness instrument adult version (SPI-A). Rome: Giovanni Fioriti Editore s.r.l.; 2007.
- [105] Schultze-Lutter F, Klosterkötter J, Picker H, Steinmeyer EM, Ruhrmann S. Predicting first-episode psychosis by basic symptom criteria. *Clin Neuropsychiatry* 2007;4(1):11–22.
- [106] Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, Klosterkötter J. Basic symptoms and ultrahigh risk criteria: symptom development in the initial prodromal state. *Schizophr Bull* 2010;36(1):182–91.
- [107] Schultze-Lutter F, Resch F, Koch E, Schimmelmänn BG. Früherkennung von Psychosen bei Kindern und Adoleszenten – sind entwicklungsbezogene Besonderheiten ausreichend berücksichtigt? *Z Kinder Jugendpsychiatr Psychother* 2011;39(5):301–11.
- [108] Schultze-Lutter F, Ruhrmann S, Fusar-Poli P, Bechdolf A, Schimmelmänn BG, Klosterkötter J. Basic symptoms and the prediction of first-episode psychosis. *Curr Pharm Des* 2012;18(4):351–7.
- [109] Schultze-Lutter F, Marshall M, Koch E. Schizophrenia proneness instrument, child and youth version; extended English translation (SPI-CY EET). Rome: Giovanni Fioriti Editore s.r.l.; 2012.
- [110] Schultze-Lutter F, Schimmelmänn BG, Ruhrmann S, Michel C. 'A rose is a rose is a rose', but at-risk criteria differ. *Psychopathology* 2013;46(2):75–87.
- [111] Schultze-Lutter F, Michel C, Schimmelmänn BG. Prevalence of at-risk criteria of psychosis in children and adolescents, and in young adults: results from two Swiss community samples. *Schizophr Res* 2014;153(Suppl. 1):134 [Abstract].
- [112] Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophr Res* 2014;154(1–3):100–6.
- [113] Simon AE, Grädel M, Cattapan-Ludewig K, Gruber K, Ballinari P, Roth B, et al. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophr Res* 2012;142(1–3):108–15.
- [114] Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med* 2007;37(4):479–84.
- [115] Tolbert HA. Psychoses in children and adolescents: a review. *J Clin Psychiatry* 1996;57(Suppl. 3):4–8 [discussion 46–7].
- [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 Os J, Kapur S. Schizophrenia. *Lancet* 2009;374(9690):635–45.
- [118] van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature* 2010;468(7321):203–12.
- [119] Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. *Schizophr Res* 2009;109(1–3):60–5.
- [120] Velthorst E, Derks EM, Schothorst P, Becker H, Durston S, Ziermans T, et al. Quantitative and qualitative symptomatic differences in individuals at Ultra-High Risk for psychosis and healthy controls. *Psychiatry Res* 2013;210(2):432–7.
- [121] Velthorst E, Nelson B, Wiltink S, de Haan L, Wood SJ, Lin A, et al. Transition to first episode psychosis in ultra high risk populations: does baseline functioning hold the key? *Schizophr Res* 2013;143(1):132–7.
- [122] Walder DJ, Mittal V, Trotman HD, McMillan AL, Walker EF. Neurocognition and conversion to psychosis in adolescents at high-risk. *Schizophr Res* 2008;101(1–3):161–8.
- [123] Welsh P, Tiffin PA. The 'at-risk mental state' for psychosis in adolescents: clinical presentation, transition and remission. *Child Psychiatry Hum Dev* 2014;45(1):90–8.
- [124] Whithing J, Rutjes AW, Dinnes J, Reitsma BJ, Bossuyt PM, Kleijnen J. Development and validation of methods assessing the quality of diagnostic accuracy studies. *Health Tech Assess* 2004;8(25):1–234 [iii].
- [125] 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.
- [126] Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. *Schizophr Res* 2010;123(2–3):188–98.
- [127] World Health Organization. Prevention of mental disorders: effective interventions and policy options. Geneva: World Health Organization; 2004.
- [128] Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry* 1996;30(5):587–99.
- [129] Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res* 2003;60(1):21–32.
- [130] Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olivo 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.
- [131] Yung AR, Phillips LJ, Simmons MB, Ward J, Thompson P, French P, et al. CAARMS. Comprehensive assessment at risk mental states. Parkville Victoria: The PACE Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry; 2006.
- [132] Yung AR, Stanford C, Cosgrave E, Killackey E, Phillips L, Nelson B, et al. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophr Res* 2006;84(1):57–66.
- [133] Yung AR, Nelson B, Stanford C, Simmons MB, Cosgrave EM, Killackey E, et al. Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2-year follow-up. *Schizophr Res* 2008;105(1–3):10–7.
- [134] Zhang T, Li H, Woodberry KA, Seidman LJ, Zheng L, Li H, et al. Prodromal psychosis detection in a counseling center population in China: an epidemiological and clinical study. *Schizophr Res* 2014;152(2–3):391–9.
- [135] Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. *Schizophr Res* 2011;126(1–3):58–64.
- [136] Zimmermann R, Gschwandtner U, Wilhelm FH, Pflueger MO, Riecher-Rössler A, Fuhr P. EEG spectral power and negative symptoms in at-risk individuals predict transition to psychosis. *Schizophr Res* 2010;123(2–3):208–16.