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

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A R T I C L E  I N F O

Article history:
Received 10 November 2014
Received in revised form 29 January 2015
Accepted 29 January 2015
Available online 27 February 2015

Keywords:
Meta-analysis
Prevention of psychosis in Europe
Attenuated psychotic symptoms (APS)
Transient psychotic symptoms (BLIPS)
Cognitive disturbances (COGDIS)
Children and adolescents

A B S T R A C T

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

1.3. Rationale for a prevention of psychoses

The epidemiological, clinical and etiopathogenetic 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
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 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].

<table>
<thead>
<tr>
<th>Scale</th>
<th>Onset</th>
<th>Frequency</th>
<th>Substance-use, co-morbidities</th>
<th>Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>attenuated psychotic symptoms (APS)</td>
<td>Development/increase by 1 point in severity within the past year</td>
<td>Average frequency of at least once per week in the past month</td>
<td>Not the effect of substance use and not better explained by a mental disorder</td>
<td>Irrespective of current or past functioning</td>
</tr>
<tr>
<td>SIPS</td>
<td>Present for at least 1 week within the past year and not more than</td>
<td>Frequency of several times per week</td>
<td>Irrespective of relation to substance use or other mental disorders</td>
<td>Irrespective of current or past functioning</td>
</tr>
<tr>
<td>CAARMS early versions</td>
<td>5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAARMS 2006 version</td>
<td>Symptoms present in the past year</td>
<td>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</td>
<td>Irrespective of relation to substance use or other mental disorders</td>
<td>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</td>
</tr>
<tr>
<td>brief limited intermittent, i.e. transient psychotic symptoms (BLIPS)</td>
<td>Development within the past 3 months</td>
<td>Several minutes a day at least 1/4 day for 4 days a week (on average) for 1 month</td>
<td>Symptoms are not seriously dangerous or disorganizing, not the effect of substance use and not better explained by a mental disorder</td>
<td>Irrespective of current or past functioning</td>
</tr>
<tr>
<td>SIPS</td>
<td>Occurrence within the past year</td>
<td>Duration of episode less than a week</td>
<td>Irrespective of relation to substance use or other mental disorders</td>
<td>Irrespective of current or past functioning</td>
</tr>
<tr>
<td>CAARMS early versions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAARMS 2006 version</td>
<td>Symptoms occurred during last year</td>
<td>At least 3 to 6 times a week–more than an hour per occasion OR At least daily–less than an hour per occasion</td>
<td>Irrespective of relation to substance use or other mental disorders</td>
<td>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</td>
</tr>
</tbody>
</table>

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 adopted 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 ± 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), ≥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.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Structure and subscales relevant in the rating of APS and BLIPS</th>
</tr>
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<tbody>
<tr>
<td>SIPS: Structured Interview for Psychosis-Risk Syndromes [64]</td>
<td>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</td>
</tr>
<tr>
<td>CAARMS early (before 2006) versions: Comprehensive Assessment of At-Risk Mental States [130]</td>
<td>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</td>
</tr>
<tr>
<td>CAARMS 2006 version: Comprehensive Assessment of At-Risk Mental States [131]</td>
<td>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</td>
</tr>
<tr>
<td>BSIP: Basel Screening Instrument for Psychosis [86]</td>
<td>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</td>
</tr>
<tr>
<td>ERIIacs: The Early Recognition Inventory [63]</td>
<td>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</td>
</tr>
<tr>
<td>PANSS: Positive and Negative Syndrome Scale [41]</td>
<td>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</td>
</tr>
<tr>
<td>BPRS: Brief Psychiatric Rating Scale [82]</td>
<td>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</td>
</tr>
</tbody>
</table>

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 \(\chi^2\)-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
- Thought perseveration
- Thought pressure
- Thought blockages
- Disturbance of receptive speech
- Decreased ability to discriminate between ideas/perception, fantasy/true memories
- Unstable ideas of reference
- 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
- Thought pressure
- Thought blockages
- Disturbance of receptive speech
- Disturbance of expressive speech
- Unstable ideas of reference
- Disturbances of abstract thinking
- Captivation of attention by details of the visual field

SPI-A: Schizophrenia Proneness Instrument, Adult version [104].
* 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 complimented 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%), ≥ 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 ERlraos, and in one (2.4%) the BSIP. For eleven (26.2%) UHR samples differential 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 ERlraos 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 schizoprophiciform 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 trials at the different follow-ups with the exception of the 1-year conversion rates of two COGDIS studies (Q_{1,1} = 0.10; I^2 = 39%). In all other cases, I^2 was between 54% and 98% and, consequently, ESS 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 E (Fig. 4). For COPER, E and E^2 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 E/E^2 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.
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 ($\chi^2 > 5.175, P < 0.025$).

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 ($\chi^2 > 4.118; P > 0.10$) but only in longer term conversion rates ($\chi^2 > 6.767; P < 0.05$) due to higher rates in both COPER and COGDIS compared to UHR samples ($\chi^2 > 5.522; P > 0.05$).

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 CHR 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 $\tau^2$-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 criteria between the three UHR criteria differed significantly at 1-, 2- and 3-year follow-ups ($\chi^2 > 15.200; P < 0.001$), 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 ($\chi^2 > 0.992; P > 0.25$) or from UHR ($\chi^2 > 1.461; P > 0.25$) or COGDIS ($\chi^2 > 1.618; P > 0.25$) 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 ($\chi^2 > 6.416; P < 0.05$) 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-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 utmost 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 COPPER 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.

Acknowledgements

Obtaining of required approval of EPA Guidance Committee and EPA Board was coordinated by the EPA President, Wolfgang Gaebel (Germany). In alphabetical order, EPA Guidance Committee members were: Dinesh Bhugra (UK), Peter Falkai (Germany), Andrea Fiorillo (Italy), Wolfgang Gaebel, Reinhard Heun (UK), Hans-Jürgen Möller (Germany), Michael Musalek (Austria) and Danuta Wasserman (Sweden); EPA Board members were: Sue Bailey (UK), Julian Beehold (UK), Geert Dom (Belgium), Peter Falkai, Andrea Fiorillo, Wolfgang Gaebel, Silvana Galderisi (Italy), Paz García-Portilla (Spain), Philip Gorwood (France), Cécile Hanon (France), Andreas Heinz (Germany), Marianne Kastrup (Denmark), Levent Küey (Turkey), Tamas Kurimany (Hungary), Michael Musalek, Wulf Rössler (Switzerland), Jerzy Samochowiec (Poland), Rutger J. van der Gaag (Netherlands) and Danuta Wasserman (source: www.europsy.net).

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.

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