

World Journal of *Psychiatry*

World J Psychiatry 2022 March 19; 12(3): 379-540



MINIREVIEWS

- 379 Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders
Zhao XP, Li H, Dai RP
- 393 Digital phenotyping in depression diagnostics: Integrating psychiatric and engineering perspectives
Kamath J, Leon Barriera R, Jain N, Keisari E, Wang B

ORIGINAL ARTICLE**Basic Study**

- 410 Magnesium-L-threonate exhibited a neuroprotective effect against oxidative stress damage in HT22 cells and Alzheimer's disease mouse model
Xiong Y, Ruan YT, Zhao J, Yang YW, Chen LP, Mai YR, Yu Q, Cao ZY, Liu FF, Liao W, Liu J

Observational Study

- 425 Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis
Schultze-Lutter F, Walger P, Francini M, Traber-Walker N, Osman N, Walger H, Schimmelmann BG, Flückiger R, Michel C
- 450 Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia
Edelkraut L, López-Barroso D, Torres-Prioris MJ, Starkstein SE, Jorge RE, Aloisi J, Berthier ML, Dávila G
- 470 Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients
Yu L, Qiu L, Ran H, Ma Q, Lu YR, Liu WB
- 483 Childhood maltreatment and suicide ideation: A possible mediation of social support
Ahouanse RD, Chang W, Ran HL, Fang D, Che YS, Deng WH, Wang SF, Peng JW, Chen L, Xiao YY
- 494 Personality traits and self-harm behaviors among Chinese children and adolescents: The mediating effect of psychological resilience
Jiao XY, Xu CZ, Chen Y, Peng QL, Ran HL, Che YS, Fang D, Peng JW, Chen L, Wang SF, Xiao YY
- 505 Trends in suicide by hanging, strangulation, and suffocation in Serbia, 1991-2020: A joinpoint regression and age-period-cohort analysis
Ilic M, Ilic I

Prospective Study

- 521 Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness
Drosos P, Johnsen E, Bartz-Johannessen CA, Larsen TK, Reitan SK, Rettenbacher M, Kroken RA

LETTER TO THE EDITOR

- 533** Therapeutic use of melatonin in schizophrenia-more than meets the eye!

Naguy A

- 536** Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach

Tirozzi A, Santonastaso F, de Gaetano G, Iacoviello L, Gialluisi A

ABOUT COVER

Peer Reviewer of *World Journal of Psychiatry*, Délio M Conde, MD, PhD, Professor, Department of Gynecology and Obstetrics, Federal University of Goiás, Goiânia 74605-050, Brazil. delioconde@ufg.br

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry (WJP, World J Psychiatry)* is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, etc.

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yan; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

March 19, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis

Frauke Schultze-Lutter, Petra Walger, Maurizia Franscini, Nina Traber-Walker, Naweed Osman, Helene Walger, Benno G Schimmelmann, Rahel Flückiger, Chantal Michel

Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Seeman MV

Received: April 14, 2021

Peer-review started: April 14, 2021

First decision: July 14, 2021

Revised: July 26, 2021

Accepted: September 19, 2021

Article in press: September 19, 2021

Published online: March 19, 2022



Frauke Schultze-Lutter, Petra Walger, Naweed Osman, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf 40629, North-Rhine Westphalia, Germany

Frauke Schultze-Lutter, Department of Psychology, Faculty of Psychology, Airlangga University, Surabaya 60286, Indonesia

Frauke Schultze-Lutter, Benno G Schimmelmann, Rahel Flückiger, Chantal Michel, University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern 3000, Switzerland

Maurizia Franscini, Nina Traber-Walker, Department of Child and Adolescent Psychiatry and Psychotherapy, University of Zürich, Zürich 8032, Germany

Helene Walger, Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich 80336, Bavaria, Germany

Benno G Schimmelmann, University Hospital of Child and Adolescent Psychiatry, University Hospital Hamburg-Eppendorf, Hamburg 20246, Germany

Corresponding author: Frauke Schultze-Lutter, MSc, PhD, Assistant Professor, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Bergische Landstraße 2, Düsseldorf 40629, North-Rhine Westphalia, Germany. frauke.schultze-lutter@lvr.de

Abstract**BACKGROUND**

In children and adolescents compared to adults, clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and less clinically relevant. Based on high rates of non-converters to psychosis, especially in children and adolescents, it was suggested that CHR criteria were: (1) Pluripotential; (2) A transdiagnostic risk factor; and (3) Simply a severity marker of mental disorders rather than specifically psychosis-predictive. If any of these three alternative explanatory models were true, their prevalence should differ between persons with and without mental disorders, and their severity should be associated with functional impairment as a measure of severity.

AIM

To compare the prevalence and severity of CHR criteria/symptoms in children and adolescents of the community and inpatients.

METHODS

In the mainly cross-sectional examinations, 8–17-year-old community subjects ($n = 233$) randomly chosen from the population register of the Swiss Canton Bern, and inpatients ($n = 306$) with primary diagnosis of attention-deficit/hyperactivity disorder ($n = 86$), eating disorder ($n = 97$), anxiety including obsessive-compulsive disorder ($n = 94$), or autism spectrum disorder ($n = 29$), not clinically suspected to develop psychosis, were examined for CHR symptoms/criteria. Positive items of the Structured Interview for Psychosis-Risk Syndromes (SIPS) were used to assess the symptomatic ultra-high-risk criteria, and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY) was used to assess the 14 basic symptoms relevant to basic symptom criteria. We examined group differences in frequency and severity of CHR symptoms/criteria using χ^2 tests and nonparametric tests with Cramer's V and Rosenthal's r as effect sizes, and their association with functioning using correlation analyses.

RESULTS

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups, while the frequency and severity of CHR symptoms differed only minimally. Group differences were found in only four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS [$\chi^2(4) = 9.425$; $P = 0.051$, Cramer's $V = 0.132$; and $Z = -4.281$, $P < 0.001$; Rosenthal's $r = 0.184$], and *thought pressure* [$\chi^2(4) = 11.019$; $P = 0.026$, Cramer's $V = 0.143$; and $Z = -2.639$, $P = 0.008$; Rosenthal's $r = 0.114$], *derealization* [$\chi^2(4) = 32.380$; $P < 0.001$, Cramer's $V = 0.245$; and $Z = -3.924$, $P < 0.001$; Rosenthal's $r = 0.169$] and *visual perception disturbances* [$\chi^2(4) = 10.652$; $P = 0.031$, Cramer's $V = 0.141$; and $Z = -2.822$, $P = 0.005$; Rosenthal's $r = 0.122$] of the SPI-CY. These were consistent with a transdiagnostic risk factor or dimension, *i.e.*, displayed higher frequency and severity in inpatients, in particular in those with eating, anxiety/obsessive-compulsive and autism spectrum disorders. Low functioning, however, was at most weakly related to the severity of CHR criteria/symptoms, with the highest correlation yielded for *suspiciousness/persecutory ideas* (Kendall's tau = -0.172 , $P < 0.001$).

CONCLUSION

The lack of systematic differences between inpatients and community subjects does not support suggestions that CHR criteria/symptoms are pluripotential or transdiagnostic syndromes, or merely markers of symptom severity.

Key Words: Psychotic disorders; Risk assessment; Minors; Community; Inpatients; Psychosocial functioning

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and clinically relevant in minors compared to adults, and, therefore, alternatively proposed as pluripotential, transdiagnostic risk factors, or severity markers of mental disorders. If any of these explanatory models were true, their prevalence should differ between 8–17-year-old community subjects ($n = 233$) and inpatients ($n = 306$), included in our study, and their severity should be associated with psychosocial functioning. Yet, CHR criteria and symptoms hardly differed between groups and were at most weakly associated with functioning. Consequently, our study did not support any alternative explanatory model of CHR criteria.

Citation: Schultze-Lutter F, Walger P, Francini M, Traber-Walker N, Osman N, Walger H, Schimmelmann BG, Flückiger R, Michel C. Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis. *World J Psychiatry* 2022; 12(3): 425-449

URL: <https://www.wjgnet.com/2220-3206/full/v12/i3/425.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v12.i3.425>

INTRODUCTION

Delays in treatment of beginning or first psychosis in children and adolescents

Psychotic disorders are severe mental disorders with often chronic course that incur high costs and burden to both society and affected patients[1-4]. Since the 1980s, multiple retrospective studies reported an association of a negative outcome of first-episode psychosis with a longer duration of untreated – or rather, inadequately treated – first-episode psychosis, as well as with untreated illness, *i.e.*, the untreated duration of both the initial prodrome and first-episode psychosis[5-8]. These negative effects of the duration of untreated psychosis or of untreated illness also occurred when patients had sought professional help for mental problems early but were not recognized as suffering from psychotic symptoms or a developing psychotic disorder[9]. Consequently, patients were treated for other, apparently more predominant complaints, frequently depressive or anxiety disorders[9]. Such delays in providing adequate treatment were further prolonged when the psychosis and/or the prodrome had an early onset in childhood and adolescence, that is, before age of 18 years[5,10,11]. This possibly explains the assumed inherent more negative course of early-onset compared to adult-onset psychoses[11]. Potential explanations of the longer duration of untreated psychosis and of untreated illness in children and adolescents with a psychotic disorder include the masking of the emergence of a psychotic disorder by other comorbid conditions such as substance abuse, depressive and anxiety syndromes, and a higher risk to overlook positive symptoms – especially if parents and primary care providers assume that the adolescents' symptoms are the expression of a sort of adolescent crisis[11-13]. Additionally, insufficient awareness and training of the general and mental health network (pediatricians, general physicians, school psychologists, and child and adolescent psychiatrists) might result in failures to adequately and routinely assess psychotic symptomatology in adolescents[12]. Finally, the greater frequency of insidious-onset illness trajectories[10-12] may further impede a timely detection. Thus, it was concluded that children and adolescents with developing, or already manifest, psychotic disorders would require specific early detection strategies to reduce duration of untreated psychosis and of untreated illness, in order to improve long-term outcomes[12,13].

Early detection of psychosis – the clinical high-risk approach

Based on findings regarding the negative effects of extended duration of untreated psychosis and of untreated illness, and the need to specifically intervene earlier in the course of illness, clinical high-risk for psychosis (CHR) criteria were gradually developed and initially validated in adult patient samples within the 1990s[14-17].

The two dominant current CHR approaches are the ultra-high-risk (UHR) approach developed to detect psychosis in the year before the onset of the first episode[16,17] and the basic symptom approach developed to detect signs of emerging psychosis as early as possible[14,15,18]. The UHR approach (Table 1) consists of three criteria, of which only the attenuated psychotic symptoms (APS) syndrome and the brief intermittent psychotic symptoms (BIPS) syndrome demonstrated sufficient psychosis-predictive validity in meta-analyses[19,20]. The third criterion, combining genetic risk and functional deterioration, was not uniquely related to an elevated psychosis risk[19,20].

The basic symptom approach (Table 1) consists of two partly symptomatically overlapping criteria: Cognitive Disturbances (COGDIS) and Cognitive-Perceptive Basic Symptoms (COPER), of which COPER thus far did not demonstrate sufficient evidence in terms of sufficient number of studies[19].

Consequently, within the framework of the Guidance Project of the European Psychiatric Association (EPA), the APS and BIPS syndromes of the UHR approach and COGDIS of the basic symptom approach (henceforth: EPA criteria) were recommended for alternative use in the early detection of psychosis in the clinic[19]. While both the UHR and the basic symptom approach – irrespective of each other – performed equally well in predicting conversion to psychosis within 6 months to 2 years, at which time they were associated with a conversion rate of 20%–30%, the basic symptom criteria were associated with significantly higher conversion rates at longer observation times compared to the UHR criteria[19].

In clinical samples, however, CHR criteria were associated with a significantly lower risk of conversion to psychosis in children and adolescents compared to adults[19,21]. Furthermore, in the community, children and adolescents reported CHR symptoms and criteria more frequently compared to adults[22,23]. These findings suggested that APS and BIPS may be less clinically relevant below the age threshold of 16 years, while perceptual and cognitive basic symptoms may be less clinically relevant below the age threshold of 18 and 23 years, respectively [22,23].

Taken together, these findings emphasize a need to account for developmental aspects in the early detection of psychosis[12,13] and to improve the specificity of the CHR approach by adding other predictors, for example, in a stepwise manner[24].

Alternative explanatory models of clinical high-risk states

In light of the moderate conversion rates and an undisputed need for further improvement of CHR criteria as well as the reported various nonpsychotic outcomes of CHR patients[25,26], it was also argued that CHR criteria, in particular the APS and BIPS syndromes, would not be specific to the development of psychosis[27-30]. Rather, it was argued that these would represent a pluripotent

Table 1 Clinical high-risk criteria: (1) Ultra-high risk criteria in the definition of the criteria of psychosis-risk syndromes of the structured interview for Psychosis-Risk Syndromes, Structured Interview for Psychosis-Risk Syndromes[43] and (2) the basic symptom criteria in the definition of the Schizophrenia Proneness Instrument, Child and Youth version[44]

(1) Ultra-high risk criteria

Brief intermittent psychotic symptom (BIPS) syndrome

At least 1 of the following SIPS positive items scored 6 "severe and psychotic"

P1 Unusual thought content/delusional ideas

P2 Suspiciousness/persecutory ideas

P3 Grandiose ideas

P4 Perceptual abnormalities/hallucinations

P5 Disorganized communication

Symptoms reached a psychotic level of intensity in the past 3 mo

Present for at least several minutes per day at a frequency of at least once per month but less than required for rating of a conversion to psychosis, *i.e.*, less than at least 1 h per day at an average frequency of 4 d/wk over 1 mo

Attenuated positive symptom (APS) syndrome

At least 1 of the 5 SIPS positive items (see above) scored 3 "moderate" to 5 "severe but not psychotic"

Symptoms have begun within the past year or currently rate one or more scale points higher compared to 12 mo ago

Symptoms have occurred at an average frequency of at least once per week in the past month

Genetic risk and functional deterioration syndrome

Patient meets criteria for schizotypal personality disorder according to SIPS

Patient has first-degree relative with a psychotic disorder

Patient has experienced at least 30% drop in the Global Assessment of Functioning score over the last month compared to 12 mo ago

[1 and 3] or [2 and 3] or all are met

(2) Basic symptom criteria

A general requirement for basic symptoms is that they deviate from what is considered the 'normal' self and, thus, have not always been present in the same severity

Cognitive-perceptive basic symptoms (COPER)

At least 1 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: thought interference; thought perseveration; thought pressure; thought blockages¹; disturbance of receptive speech; decreased ability to discriminate between ideas and perception, fantasy and true memories; unstable ideas of reference; derealization; visual perception disturbances (excl. hypersensitivity to light or blurred vision); acoustic perception disturbances (excl. hypersensitivity to sounds); first occurrence \geq 12 mo ago

Cognitive disturbances (COGDIS)

At least 2 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: inability to divide attention; thought interference; thought pressure; thought blockages¹; disturbance of receptive speech; disturbance of expressive speech; unstable ideas of reference; disturbances of abstract thinking¹; captivation of attention by details of the visual field

¹Assessable only from age of 13 yr onwards.

syndrome[27,28], a transdiagnostic risk factor[29], a transdiagnostic dimension of psychopathology[30], or merely a marker for the severity of nonpsychotic states[30]. Despite them frequently being used in synonym[29], pluripotential and transdiagnostic relate to different concepts.

Being derived from biology and initially applied to (embryonic) cells, pluripotent is defined as "not fixed as to potential development", and used to describe precursor cells that are only found in early embryonic states[31]. Thus, translated to psychiatric disorders, a pluripotential syndrome would be the first diagnostically neutral stage of potentially more severe psychopathology, which only later would acquire a degree of diagnostic specificity[27,28]. In this case, similar to embryonic pluripotent cells, a CHR state would completely transform into another disorder in that it would not be recognizable anymore. Examples are APS that will not be detectable once they have been transformed into frank psychotic symptoms, *i.e.*, after the conversion to psychosis.

In contrast, transdiagnostic risk factors would be distributed across the community and would be present in various disorders, in which they would still be assessable, and mediate the association between environmental exposures and disorders[32]. Similarly, a transdiagnostic dimension of psychopathology may be present in various disorders but not at all or only in very mild subclinical forms in the

community outside states of mental ill health. In these cases, CHR symptoms would develop in the wake of other mental problems.

Lastly, a severity marker of psychopathology would be generally present in mental disorders, in which it would be most pronounced or frequent in those with severe mental disorders and/or most functional impairment due to their mental problems. Furthermore, it would be more frequent in acute states of illness compared to (partly) remitted states. In this case, CHR symptoms and criteria should be increasingly present with declining functioning.

Mental problems in childhood and adolescence often lack continuity into adulthood[33] and specificity for mental disorders[34], and frequently present as insidious onset of disorders, initially with mild forms of mental problems[12,35]. Consequently, children and adolescents represent an excellent age group to study the nature of symptoms and syndromes, such as CHR symptoms and criteria[36], and in particular, to study which of the three alternative models best fits the data.

Study aims

The aim of this study was to examine which of these alternative explanatory models of CHR criteria and symptoms – pluripotential syndrome, transdiagnostic risk factor/dimension, and severity marker – best fits the data of an age group in which CHR criteria and symptoms are likely the least psychosis-specific [19,21]. To that end, we cross-sectionally studied the frequency of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community and in 8–17-year-old inpatients whose main diagnosis was a disorder that, earlier, had been longitudinally associated with an elevated risk to develop psychosis in adulthood[36,37] (Supplementary Table 1). The three alternative explanatory models were associated with in the following differential premises: (1) In the case of the CHR criteria and symptoms acting as a pluripotential syndrome, these should not be detectable after the onset of severe mental disorder, *i.e.*, after their transformation in a diagnostically specific disorder in the inpatient group. Rather, CHR criteria and symptoms should still be detectable as a potential precursor state in the community subjects of that roughly a third must be expected to develop a mental disorder in their lifetime[39]. Consequently, if CHR criteria and symptoms would be more frequent in community subjects compared to inpatients, then they are likely pluripotential; (2) In the case of CHR criteria and symptoms representing a transdiagnostic risk factor or dimension, they would be expected to accumulate in the extreme range of persons with mental disorders. Thus, if CHR criteria and symptoms would be more frequent in the inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension; and (3) Lastly, in the case of CHR criteria and symptoms being a severity marker of psychopathology, they should be associated with illness severity and, relatedly, the degree of functional impairment. Consequently, if CHR criteria and symptoms would show a significant negative correlation with functioning, then they likely represent a severity marker of psychopathology.

MATERIALS AND METHODS

Sample description

We recruited the samples as part of the multicenter naturalistic ‘Bi-national Evaluation of At-Risk Symptoms in children and adolescents’ (BEARS-Kid) study between September 2013 and December 2017. Recruitment of inpatients took place at the Child and Adolescent Psychiatric Departments of the Universities of Bern, Switzerland, Zurich, Switzerland, and Cologne, Germany; recruitment of community subjects was exclusively carried out in Bern. General inclusion criteria were: age between 8.0 and 17.9 years, and sufficient language skills in German or English. General exclusion criteria were: past or present diagnosis of a psychotic disorder; current antipsychotic medication; a clinical indication of an IQ \leq 70; presence of disturbance due to the direct physiological effects of a general medical condition or of substance use; and clinical suspicion of an emerging psychosis and, consequently, consultation of the local early detection service. Because co-occurrence of mental disorders is rather the rule than the exception in patients with mental disorders, in clinical as well as in community samples [40,41], we did not use (co-) morbidities with mental disorders as an exclusion criterion in either the inpatient and community sample in order not to limit representativeness.

For the recruitment of a representative community sample, the Agency for Informatics and Organization of the Canton Bern randomly drew a sample (including addresses) stratified for age and sex from the population register of the city of Bern and its urban hinterland (approximately 200 000 residents). Subsequently, we searched directories and the Internet for telephone numbers. The availability of a working telephone number served as an eligibility criterion in this group. We established first contact by an information letter, personally addressing each potential participant and his/her parents. Next, we contacted parents and/or their children by telephone, informed them in detail, and asked them to give written informed consent and assent. In children below age 16.0 years, we contacted parents first. Nine hundred and eighty persons were drawn from the register, for 176 of them, we could not ascertain a working telephone number, and 41 persons were drawn twice. Of the remaining 763 persons, 234 agreed to participate, yet one person later on withdrew consent. A total of 353 did not agree to participate, mainly for lack of interest (35.6%) or time (35.9%). We excluded 52

persons because they had reached 18 years old by the time contact was made (53.9%), had moved away from the greater Bern area (32.7%), or lacked the ability to participate in the study for language or physical health reasons (13.5%). With 124 persons, all attempts (at least 40) to reach them on the telephone remained fruitless. Thus, according to the standard definitions of the American Association for Public Opinion Research[42], the contact rate was 82.7%, the cooperation rate was 39.9%, the refusal rate was 49.2%, and the response rate was 32.6%.

The inpatient sample was recruited in all three participating centers during their inpatient stay or during their subsequent day clinic stay; seven inpatients (2.3%) had been strongly advised to undergo inpatient treatment but had refused. For inclusion, the main diagnosis according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, DMS-IV[38] had to be one for which Rubino *et al* [37] had reported at least a 2.5 times increased prevalence of subsequent schizophrenia (Supplementary Table S1): attention deficit hyperactivity disorder (ADHD) (inattentive, hyperactive and impulsive subtype); anxiety disorders (social and severe specific phobia, mainly school phobia); obsessive-compulsive disorder; and eating disorder (anorexia and bulimia nervosa). Additionally, we included patients with Asperger's syndrome, which had not been considered by Rubino *et al*[37] but has been recognized explicitly as a developmental disorder with an increased risk of psychotic episodes in young adulthood in DSM-IV[38]. We recruited 539 inpatients, 97 with eating disorders, 86 with ADHD, 94 with anxiety and obsessive-compulsive disorders, and 29 with Asperger's syndrome.

We followed up 423 subjects (78.5%) after 1 year; 243 inpatients, 23 (9.5%) with a CHR criterion at baseline; and 180 community subjects, 15 (8.3%) with a CHR criterion at baseline. A total of 331 subjects (61.4%) participated in the 2-year follow-up; 189 inpatients, 16 (8.5%) with a CHR criterion at baseline, and 142 community subjects, 10 (7.0%) with a CHR criterion at baseline.

Clinical high-risk assessments

We used well-established semistructured interview assessments to assess CHR criteria and symptoms, which had demonstrated good inter-rater reliability in trained raters[43-45]. The Structured Interview for Psychosis-Risk Syndromes (SIPS)[43], including a revised version of the Global Assessment of Functioning scale, was carried out for the evaluation of the five APS and BIPS (Table 1) as well as the genetic risk and functional decline criterion of the UHR criteria in the SIPS definition of the Criteria of Psychosis-Risk Syndromes (COPS) (Table 1). The five criteria-relevant positive items of the SIPS are syndromally rated for psychopathological severity on a seven-point Likert scale, ranging from 0 (not present) to 6 (severe and psychotic). In doing so, APS are defined by any SIPS positive item with a score between 3 and 5, and BIPS by any SIPS positive item with a score of 6. We rated a SIPS-positive item as present when its score was 3-6. We calculated the sum score of the five positive items across all scores (0-6) as a severity estimate of symptomatic UHR criteria.

We used the Schizophrenia Proneness Instrument, Child and Youth version, SPI-CY[44,45] for the evaluation of the 14 basic symptoms included in COPER and COGDIS (Table 2). Basic symptoms were rated for their severity according to their frequency of occurrence on a seven-point Likert scale, ranging from 0 (not present) to 6 (present daily). We rated basic symptoms as present when their score was 1-6. We calculated the sum scores of the nine basic symptoms included in COGDIS and of the 10 basic symptoms included in COPER as a severity estimate of COGDIS and COPER, respectively.

Basic symptoms included in COPER and COGDIS differ from APS/BIPS as defined by a score of 3 on the SIPS-positive items by the more immediate insight into basic symptoms that results from the lack of externalization or of their consideration of possibly being meaningful, and from the immediate control of these[14,15,44,45]. Thus, other than in attenuated hallucinations or illusions (SIPS positive item P4), which are at least briefly perceived as true perceptions of existence, real stimuli [43], in perceptual basic symptoms, the misperceived real object or sound is not considered as a true change of the stimulus for even a split-second[44]. Rather, the insight into the pathological nature of the misperceptions of features of a real object or sound is immediate and complete, and thus, contrary to APS, perceptual basic symptoms are not puzzling to the degree that they are considered to indicate a meaningful change in the surroundings[43], apart from a change in one's own mental processes[44]. With this, perceptual basic symptoms rate 1-2 in the SIPS positive item P4, *i.e.*, as sensitivity or perceptual changes that are noticed but not considered to be significant in terms of what is going on in the world[43]. Furthermore, cognitive basic symptoms are not related to thought content and, consequently, are not rated as any unusual thought content or attenuated delusional idea on SIPS positive items P1-P3. Additionally, for their immediate recognition as unusual, commonly brief disruptions in normal thought processing[44], cognitive basic symptoms rarely impair the individual's own way of structuring and verbally presenting thoughts in terms of *conceptual disorganization* (SIPS positive item P5), *i.e.*, by talking about irrelevant topics or going off track to a degree that is unusual to the individual[43]. Moreover, the basic symptoms *derealization* and *unstable idea of reference* are only "as if" feelings with full reality testing and no (temporary) consideration as realistic ideas or of meaningfulness[44]; thus, they differ from attenuated nihilistic ideas or attenuated ideas of reference that are scored at APS-level in the SIPS positive item P1 - or in P2, if the idea of reference has a paranoid touch[43]. Finally, *impaired discrimination between ideas and perception* in terms of basic symptoms always occurs with real stimuli or memories of real events that are briefly considered as possible phantasies[44]; thus, it does not even briefly introduce unusual ideas as required for an attenuated delusion[43] and, for this reason, also rates

Table 2 Sociodemographic and clinical characteristics of the sample (n = 539)

	Inpatients (n = 306)	Community subjects (n = 233)	Statistics; effect size
Age: mean ± SD (Median)	14.4 ± 2.5 (14.9)	13.0 ± 2.9 (12.9)	U = 26032.5, ^c P < 0.001; r = 0.231
Sex: n (%) male	133 (43.5)	102 (43.8)	$\chi^2_{(1)} = 0.013$, P = 0.908; V = 0.005
Migration background ¹ : n (%)	52 (17.0)	64 (27.5)	$\chi^2_{(1)} = 8.593$, ^b P = 0.003; V = 0.126
Graduated from school: n (%)	28 (9.2)	15 (6.4)	$\chi^2_{(1)} = 1.326$, P = 0.250; V = 0.050
Current school class (n = 491): mean ± SD	7.5 ± 2.5 (8)	6.2 ± 2.6 (6)	U = 20894.5, ^c P < 0.001; r = 0.253
Family history of psychotic disorder: n (%)	4 (1.3)	1 (0.4)	$\chi^2_{(1)} = 1.105$, $P_{\text{exact}} = 0.396$, V = 0.045
Any lifetime nonpsychotic axis-I disorder ² : n (%)	306 (100)	22 (9.4)	$\chi^2_{(1)} = 455.368$, ^c P < 0.001; V = 0.919
Any present nonpsychotic axis-I disorder ² : n (%)	306 (100)	13 (5.6)	$\chi^2_{(1)} = 488.187$, ^c P < 0.001; V = 0.952
Number present axis-I disorders ² : mean ± SD (Median)	1.5 ± 0.7 (1)	0.1 ± 0.3 (0)	U = 1499.5, ^c P < 0.001; r = 0.883
Any present depressive disorder: n (%)	55 (18.0)	0	$\chi^2_{(1)} = 46.638$, ^c P < 0.001; V = 0.294
Any present manic episode ³ : n (%)	0	1 (0.4)	$\chi^2_{(1)} = 1.316$, P = 0.251; V = 0.049
Any present anxiety disorder ² : n (%)	68 (22.2)	2 (0.9)	$\chi^2_{(1)} = 53.426$, ^c P < 0.001; V = 0.315
Any present obsessive-compulsive disorder: n (%)	35 (11.4)	1 (0.4)	$\chi^2_{(1)} = 25.720$, ^c P < 0.001; V = 0.218
Any present adjustment disorder: n (%)	3 (1.0)	0	$\chi^2_{(1)} = 2.297$, P = 0.262; V = 0.065
Any present eating disorder: n (%)	98 (32.0)	0	$\chi^2_{(1)} = 91.203$, ^c P < 0.001; V = 0.411
Any present somatoform disorder: n (%)	4 (1.3)	0	$\chi^2_{(1)} = 3.069$, P = 0.137; V = 0.075
Any present substance use disorder: n (%)	4 (1.3)	2 (0.9)	$\chi^2_{(1)} = 0.242$, P = 0.623; V = 0.021
Any present tic disorder: n (%)	9 (2.9)	0	$\chi^2_{(1)} = 6.969$, ^b P = 0.008; V = 0.114
Any present attention deficit hyperactivity disorder: n (%)	103 (33.7)	7 (3.0)	$\chi^2_{(1)} = 76.532$, ^c P < 0.001; V = 0.377
Any present conduct disorder: n (%)	18 (5.9)	2 (0.9)	$\chi^2_{(1)} = 9.345$, ^b P = 0.002; V = 0.132
Any present developmental disorder: n (%)	31 (10.1)	0	$\chi^2_{(1)} = 25.045$, ^c P < 0.001; V = 0.216
Global Assessment of Functioning score (0-100): mean ± SD (Median)	52.3 ± 8.8 (53)	81.0 ± 10.0 (85)	U = 1516.0, ^c P < 0.001; r = 0.819
SOFAS (0-100): mean ± SD (Median)	60.0 ± 11.0 (60)	84.3 ± 7.9 (88)	U = 3001.5, ^c P < 0.001; r = 0.786

¹defined by first or second nationality other than the country of residence;

²does not include simple specific phobias of objects with little functional relevance but includes severe specific phobias such as school phobia;

³no participant met criteria of a bipolar disorder at baseline. SOFAS: Social and Occupational Functioning Assessment Scale[42]. V: Cramer's V; r: Rosenthal's r: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

at most 2 on the SIPS positive item P1.

Assessments of mental disorders and functioning

We used the Mini-International Neuropsychiatric Interview for Children and Adolescents, M.I.N.I. KID [46] for the assessment of past and present mental disorders according to the DSM-IV, including past and present affective or nonaffective psychotic disorders that served as exclusion criterion. The M.I.N.I. KID had demonstrated good construct validity with other interview assessments of DSM-IV disorders and expert diagnoses as well as good inter-rater and test-retest reliability[46].

We estimated symptom-independent current and highest-within-last-12-mo global levels of psychosocial functioning using the Social and Occupational Functioning Assessment Scale (SOFAS) of DSM-IV[38]. We used SOFAS scores to define functioning in the analyses of the correlation between severity of mental disorders and CHR symptoms and criteria.

Assessment procedure and quality assurance

We conducted the baseline assessments of inpatients in the clinic, and community participants could choose between being assessed in the clinic or at their homes, mostly choosing the latter. Thus, we could not blind raters to the group assignment. Therefore, in order to avoid systematic assessment bias due to this nonblinding of groups, interviewers were restricted to the assessment of either the inpatient or the community sample. Interviewers were clinical psychologists who had received an intensive training for about 3 months, especially in the semistructured context-dependent personalized assessment of CHR symptoms and mental disorders, in order to achieve a $\geq 95\%$ concordance rate with the trainers (in all instances the first or the last author). Only when an interviewer had achieved this level of agreement with the experts, they were allowed to conduct interviews independently. We had chosen the concordance rate over Cohen's kappa, because kappa is dependent on the prevalence of an event[47] and tends to decrease when a response/event is rare or very frequent. Thus, because low prevalence rates were expected for the community sample in particular, we chose the concordance rate to define the minimum inter-rater reliability[48,49]. In the training, we paid close attention not only to the validity and reliability of positive ratings but also to those of negative ratings, *i.e.*, to not jump to a negative rating at the first negation of a symptom. Weekly supervision of symptom ratings performed by the first or last author further ensured excellent, valid and reliable data quality across centers.

At 1- and 2-year follow-ups, we interviewed participants for CHR symptoms and criteria as well as conversion to psychosis using the SPI-CY, SIPS and psychoses section of the M.I.N.I. KID. Potential conversions were also discussed in the weekly supervisions.

Data analysis

We used SPSS version 24 for all analyses that the first and last author, both trained in biostatistics, conducted. We compared frequency rates of CHR symptoms and criteria between groups by χ^2 test or Fisher's exact tests in case of expected cell frequencies below $n = 5$ in 2×2 tables. Standardized residuals were used to detect significantly deviating cell frequencies of standardized residuals $\geq |1.96|$; the effect size was calculated using Cramer's V.

We compared the severity of the ordinal CHR symptoms and criteria as well as the ordinal level of functioning as assessed with the SOFAS, which were all non-normally distributed (Kolmogorov-Smirnov test: all $P < 0.001$), between groups using Kruskal-Wallis with post-hoc Mann-Whitney U tests; the effect size of the Mann-Whitney U tests was calculated using Rosenthal's r .

We analyzed the correlations between severity of CHR symptoms and criteria, and functioning using Kendall's tau, which controls for tied pairs, and, additionally, using partial correlation analyses with group as the control variable.

To not decrease the sensitivity to detect group differences and, thus, to support one of the alternative explanatory models of the CHR state, we did not adjust for multiple testing. Although such an adjustment of the alpha level would have greatly reduced the type I error, *i.e.*, the false rejection of a true null hypothesis, the detection of meaningful small to moderate group differences would have become unlikely[50]. Thus, in light of this, the nonadjustment of alpha was regarded as a more conservative testing of the alternative models. Additionally, testing for group differences in CHR criteria and symptoms independently (weak testing criterion[50]), the power of the study, the ability to correctly reject a false null hypothesis assuming group equality, can be assumed to be independent of the multiple testing[50]. At a given alpha of 0.05, a sample size of $n = 539$ in two or five groups, and an assumed small to medium effect of 0.2, G*Power version 3.1. estimated the power of the different group comparisons of frequency or severity of CHR criteria and symptoms between 0.911 and 0.997.

RESULTS

Group characteristics

Inpatients and community subjects did not differ in distribution of sex, family history of psychotic disorder, or number of those already graduated from school (Table 2). However, inpatients were slightly older and, when still at school, attended a higher school class. Furthermore, we detected a small effect of migration background with higher frequency in the community sample. Unsurprisingly, we detected strong group effects for clinical variables, demonstrating that, compared to community subjects, inpatients suffered more frequently from mental disorders and had a lower level of functioning (Table 2).

Group differences in frequency of CHR symptoms and criteria

Neither inpatients nor community subjects reported any BIPS. Furthermore, the genetic risk and functional decline syndrome was rare and only occurred in two inpatients, without reaching a level of significance (Table 3). Also, we detected only at most weak and nonsignificant group effects with respect to all other single or combined CHR criteria, which, overall, were reported by $< 10\%$ of both samples (Table 3). In doing so, the most frequent CHR criterion was COPER (Table 3). We found similar

Table 3 Frequency of clinical high-risk criteria in the two groups (n = 539)

	Inpatients (n = 306)	Community subjects (n = 233)	χ^2 test; Cramer's V
BIPS syndrome: n (%)	0	0	--
APS syndrome: n (%)	7 (2.3)	5 (2.1)	$\chi^2_{(1)} = 0.012$; $P = 0.912$, $V = 0.005$
Genetic risk and functional decline syndrome: n (%)	2 (0.6)	0	$\chi^2_{(1)} = 1.529$; $P_{\text{exact}} = 0.508$, $V = 0.053$
COGDIS: n (%)	10 (3.3)	4 (1.7)	$\chi^2_{(1)} = 1.258$; $P = 0.262$, $V = 0.048$
COPER: n (%)	21 (6.9)	10 (4.3)	$\chi^2_{(1)} = 1.613$; $P = 0.204$, $V = 0.055$
Any 1 of 5 CHR criteria: n (%)	29 (9.5)	17 (7.3)	$\chi^2_{(1)} = 0.806$; $P = 0.369$, $V = 0.039$
Any 1 of 3 EPA criteria: n (%)	15 (4.9)	9 (3.9)	$\chi^2_{(1)} = 0.336$; $P = 0.562$, $V = 0.025$
No CHR criterion: n (%)	277 (90.5)	216 (92.7)	$\chi^2_{(7)} = 5.676$; $P = 0.578$, $V = 0.103$
Only genetic risk and functional decline: n (%)	2 (0.7)	0	
Only COPER: n (%)	12 (3.9)	8 (3.4)	
Only COGDIS: n (%)	2 (0.7)	2 (0.9)	
COPER and COGDIS: n (%)	6 (2.0)	2 (0.9)	
Only APS: n (%)	4 (1.3)	5 (2.1)	
APS and COPER: n (%)	1 (0.3)	0	
APS, COPER and COGDIS: n (%)	2 (0.7)	0	

BIPS: Brief intermittent psychotic symptoms; APS: Attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive Basic Symptoms; EPA: European Psychiatric Association. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

results when we compared frequencies of CHR criteria across the different inpatient groups and community subjects (Table 4); thus, these results did not indicate that CHR criteria were especially associated with any of the four diagnostic categories.

Between inpatients and community subjects, we detected differences of weak effect size with respect to CHR symptoms for only three basic symptoms, two of them only included in COPER (Supplementary Table 2): (1) *Pressure of thought* (8.5% in inpatients vs 3.0% in community subjects; Cramer's V = 0.113, yet, all standardized residuals < |1.96|); (2) *Derealization* (11.4% in inpatients vs 2.6% in community subjects; Cramer's V = 0.165, both standardized residuals of symptom present > |1.96|), and (3) *Visual perception disturbances* (11.4% in inpatients vs 4.7% in community subjects; Cramer's V = 0.119, standardized residuals of symptom present in community subjects > |1.96|).

When we considered the different diagnostic categories, we found some additional, yet unsystematic group differences - often only at single cell level in terms of a significant standardized residual (Tables 5 and 6). The strongest, near moderate group effect yielded for *derealization*, which showed an increased prevalence in eating disorders, and anxiety and obsessive-compulsive disorders, and a decreased prevalence in community subjects (Table 5). All other effect sizes of group comparisons with at least one significant standardized residual of any cell were only small (Tables 5 and 6). *Visual perception disturbances* were again significantly less frequent in community subjects (Table 5). *Thought pressure* and *impaired discrimination between ideas and true memories, and phantasy* were only more prevalent in anxiety and obsessive-compulsive disorders, *thought interference* and *captivation of attention* in Asperger's syndrome, and *unstable ideas of reference* in eating disorders (Table 5). With regard to APS, *unusual thought content / delusional ideas* (SIPS positive item P1) were most frequent in anxiety and obsessive-compulsive disorders (Table 6), which was mainly due to frequent report of *thought insertion* and *broadcasting* as well as *unusual, somatic and nihilistic ideas* at attenuated level. Furthermore, patients with Asperger's syndrome most frequently reported *suspiciousness/persecutory ideas* (SIPS positive item P2), mainly attenuated *ideas of being redlined or observed* (Table 6). Of all CHR symptoms, both inpatients and community subjects most frequently reported *perceptual abnormalities/hallucinations* (SIPS positive item P4) (Table 6).

Group differences in severity of CHR symptoms and criteria

The severity of CHR criteria and symptoms hardly differed between inpatients and community subjects (Table 7). Only the sum score of the ten basic symptoms of COPER, the single basic symptoms *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive item *suspiciousness/persecutory ideas* (P2) were significantly more severe in inpatients (Table 7). Again, more indications of

Table 4 Frequency of clinical high-risk criteria in the four diagnostic subsamples and the community sample (*n* = 539)

	ED (<i>n</i> = 97)	ADHD (<i>n</i> = 86)	AnxD and OCD (<i>n</i> = 94)	ASS (<i>n</i> = 29)	Community subjects (<i>n</i> = 233)	χ^2 test; Cramer's V
APS syndrome: <i>n</i> (%)	4 (4.1)	0	3 (3.2)	0	5 (2.1)	$\chi^2_{(4)} = 4.632$; <i>P</i> = 0.327, <i>V</i> = 0.093
Genetic risk and functional decline syndrome: <i>n</i> (%)	0	1 (1.2)	1 (1.1)	0	0	$\chi^2_{(4)} = 4.016$; <i>P</i> = 0.404, <i>V</i> = 0.086
COGDIS: <i>n</i> (%)	4 (4.1)	2 (2.3)	4 (4.3)	0	4 (1.7)	$\chi^2_{(4)} = 3.427$; <i>P</i> = 0.489, <i>V</i> = 0.080
COPER: <i>n</i> (%)	9 (9.3)	3 (3.5)	8 (8.5)	1 (3.4)	10 (4.3)	$\chi^2_{(4)} = 5.558$; <i>P</i> = 0.235, <i>V</i> = 0.102
Any 1 of 5 CHR criteria: <i>n</i> (%)	11 (11.3)	5 (5.8)	12 (12.8)	1 (3.4)	17 (7.3)	$\chi^2_{(4)} = 5.369$; <i>P</i> = 0.252, <i>V</i> = 0.100
Any 1 of 3 EPA criteria: <i>n</i> (%)	7 (7.2)	2 (2.3)	6 (6.4)	0	9 (3.9)	$\chi^2_{(4)} = 5.022$; <i>P</i> = 0.285, <i>V</i> = 0.097
No CHR criterion: <i>n</i> (%)	86 (88.7)	81 (94.2) ¹	82 (87.2)	28 (96.6)	216 (92.7)	$\chi^2_{(28)} = 20.675$; <i>P</i> = 0.839, <i>V</i> = 0.098
Only genetic risk and functional decline: <i>n</i> (%)	0	1 (1.2)	1 (1.1)	0	0	
Only COPER: <i>n</i> (%)	4 (4.1)	2 (2.3)	5 (5.3)	1 (3.4)	8 (3.4) ¹	
Only COGDIS: <i>n</i> (%)	0	1 (1.2) ¹	1 (1.1)	0	2 (0.9)	
COPER and COGDIS: <i>n</i> (%)	3 (3.1)	1 (1.2)	2 (2.1)	0	2 (0.9)	
Only APS: <i>n</i> (%)	2 (2.1)	0	2 (2.1)	0	5 (2.1)	
APS and COPER: <i>n</i> (%)	1 (1.0)	0	0	0	0	
APS, COPER and COGDIS: <i>n</i> (%)	1 (1.0)	0	1 (1.1) ¹	0	0	

¹Indicates that 1 subject of this category converted to psychosis within 2 years. No brief intermittent psychotic symptoms (BIPS) criteria met. ED: Eating disorder; ADHD: attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; APS: attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive Basic Symptoms; EPA: European Psychiatric Association; CHR: Clinical high-risk. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

group differences were globally indicated when diagnostic groups were analyzed separately in Kruskal-Wallis tests (Table 8). The sum scores of SIPS positive items and of the basic symptoms of COPER, the basic symptoms *captivation of attention by details of the visual field*, *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive items *unusual thought content/delusional ideas* (P1) and *suspiciousness/persecutory ideas* (P2) significantly differed between groups (Table 8). Mann-Whitney tests of these variables (Supplementary Table 3) revealed that the severity of the basic symptoms of COPER was higher in eating disorders than in both ADHD and community subjects, higher in anxiety and obsessive-compulsive disorders than in ADHD and community subjects, and more pronounced in Asperger's syndrome compared to community subjects. The severity scores of the five SIPS positive items and of *unusual thought content/delusional ideas* (P1) were significantly higher in anxiety and obsessive-compulsive disorders compared to eating disorders, ADHD and community subjects. *Captivation of attention by details of the visual field* was significantly more pronounced in Asperger's syndrome compared to eating disorders, but less pronounced in Asperger's syndrome compared to ADHD; furthermore, it was more severe in anxiety and obsessive-compulsive disorders compared to community subjects. *Thought pressure* only differed between eating disorders and community subjects, with higher score in the former. Severity ratings of *derealization* were higher in eating disorders than in community subjects, and higher in anxiety and obsessive-compulsive disorders compared to both ADHD and community subjects. *Visual perception disturbances* scored higher in eating disorders, anxiety and obsessive-compulsive disorders, and Asperger's syndrome than in community subjects. Finally, ratings of *suspiciousness/persecutory ideas* (SIPS positive item P2) were higher in eating disorders than in community subjects, higher in anxiety and obsessive-compulsive disorders compared to community subjects as well as to ADHD, in which it was higher than in Asperger's syndrome; further, they were more severe in Asperger's syndrome compared to community subjects.

Table 5 Frequency of criteria-relevant basic symptoms in the four diagnostic subsamples and the community sample (n = 539)

	ED (n = 97)	ADHD (n = 86)	AnxD and OCD (n = 94)	ASS (n = 29)	Community subjects (n = 233)	χ^2 test; Cramer's V
Inability to divide attention: n (%)	1 (1.0)	0	2 (2.1)	0	0	$\chi^2_{(4)} = 6.534$; $P = 0.163$, $V = 0.101$
Captivation of attention: n (%)	0	0	1 (1.1)	2 (6.9)	4 (1.7)	$\chi^2_{(4)} = 9.855$; $^aP = 0.043$, $V = 0.135$
Disturbance of abstract thinking ¹ : n (%)	0	0	0	0	2 (1.3)	$\chi^2_{(4)} = 3.129$; $P = 0.536$, $V = 0.088$
Disturbance of expressive speech: n (%)	5 (5.2)	3 (3.5)	5 (5.3)	2 (6.9)	15 (5.6)	$\chi^2_{(4)} = 0.752$; $P = 0.945$, $V = 0.037$
Disturbance of receptive speech: n (%)	1 (1.0)	1 (1.2)	3 (3.2)	0	1 (0.4)	$\chi^2_{(4)} = 5.013$; $P = 0.286$, $V = 0.096$
Thought interference: n (%)	2 (2.0)	1 (1.2)	3 (3.2)	3 (10.3)	5 (2.1)	$\chi^2_{(4)} = 8.009$; $P = 0.091$, $V = 0.122$
Thought blockages ¹ : n (%)	9 (10.0)	5 (11.1)	8 (9.2)	2 (9.1)	13 (8.3)	$\chi^2_{(4)} = 0.403$; $P = 0.982$, $V = 0.032$
Thought pressure: n (%)	8 (8.2)	4 (4.7)	11 (11.7)	3 (10.3)	7 (3.0)	$\chi^2_{(4)} = 11.019$; $^aP = 0.026$, $V = 0.143$
Unstable ideas of reference: n (%)	3 (3.1)	0	1 (1.1)	0	1 (0.4)	$\chi^2_{(4)} = 6.673$; $P = 0.154$, $V = 0.111$
Thought perseveration: n (%)	0	2 (2.3)	3 (3.2)	1 (3.4)	3 (1.3)	$\chi^2_{(4)} = 3.964$; $P = 0.411$, $V = 0.086$
Impaired discrimination between true memories and phantasy: n (%)	1 (1.0)	1 (1.2)	6 (6.4)	0	7 (3.0)	$\chi^2_{(4)} = 7.310$; $P = 0.120$, $V = 0.116$
Derealization: n (%)	17 (17.5)	2 (2.3)	14 (14.9)	2 (6.9)	6 (2.6)	$\chi^2_{(4)} = 32.380$; $^cP < 0.001$, $V = 0.245$
Visual perception disturbances: n (%)	13 (13.4)	7 (8.1)	10 (10.6)	5 (17.2)	11 (4.7)	$\chi^2_{(4)} = 10.652$; $^aP = 0.031$, $V = 0.141$
Acoustic perception disturbances: n (%)	12 (12.4)	6 (7.1)	10 (10.6)	2 (6.9)	17 (7.3)	$\chi^2_{(4)} = 3.063$; $P = 0.547$, $V = 0.075$

¹Assessable only from age of 13 years onwards, thus only calculated on $n = 404$. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. In **bold**, cells with standardized residuals $\geq |1.96|$. This equals significant deviation from the expected cell frequency. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

Association of functioning with CHR symptoms and criteria

In both bivariate and partial correlation analyses, correlations between functioning and severity of CHR criteria and symptoms were at most of small effect size.

In simple bivariate correlation analyses between functioning, *i.e.*, SOFAS scores, and severity of CHR criteria and symptoms, we detected few significant correlations of small effect size with the sum score of COPER ($\tau = -0.140$, $P < 0.001$), the sum score of SIPS positive items ($\tau = -0.113$, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2; $\tau = -0.172$, $P < 0.001$), *perceptual abnormalities/hallucinations* (P4; $\tau = -0.112$, $P = 0.001$), and *disorganized communication* (P5; $\tau = -0.076$, $P = 0.034$) as well as the basic symptoms *thought pressure* ($\tau = -0.078$, $P = 0.028$), *derealization* ($\tau = -0.116$, $P = 0.001$), and *visual* ($\tau = -0.096$, $P = 0.007$) and *acoustic perception disturbances* ($\tau = -0.073$, $P = 0.040$). All of these four basic symptoms are part of COPER; only *thought pressure* is also part of COGDIS. For the severity of COGDIS and other CHR symptoms, the correlations with functioning were between $\tau = -0.065$ ($P = 0.056$) for *thought interference* and $\tau = 0.018$ ($P = 0.614$) for *disturbances of abstract thinking*.

When group was controlled for in partial correlation analyses, the correlations between functioning and the sum score of COPER ($r = -0.087$, $P = 0.044$), the sum score of SIPS positive items ($r = -0.164$, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2; $r = -0.120$, $P = 0.005$), *perceptual abnormalities/hallucinations* (P4; $r = -0.165$, $P < 0.001$), and *disorganized communication* (P5; $r = -0.126$, $P = 0.003$) remained, and in the case of SIPS items, became even slightly more pronounced. Contrary to this, none of the single basic symptoms with a significant correlation with functioning in bivariate analyses was again significant when group was controlled for. Rather, *thought inference* ($r = -0.102$, $P = 0.019$) and *disturbances of expressive speech* ($r = -0.094$, $P = 0.030$) became significant. The remaining correlations with functioning were between $r = -0.078$ ($P = 0.071$) for *acoustic perception disturbances* and $r = 0.019$ ($P =$

Table 6 Frequency of brief intermittent and attenuated psychotic symptoms in the four diagnostic subsamples and the community sample (*n* = 539)

	ED (<i>n</i> = 97)	ADHD (<i>n</i> = 86)	AnxD and OCD (<i>n</i> = 94)	ASS (<i>n</i> = 29)	Community subjects (<i>n</i> = 233)	χ^2 test; Cramer's V
P1: Unusual thought content/delusional ideas: <i>n</i> (%)	6 (6.2)	4 (4.7)	14 (14.9)¹	4 (13.8)	13 (5.6)	$\chi^2_{(4)} = 11.391$; $^aP = 0.023$, $V = 0.145$
P2: Suspiciousness/persecutory ideas: <i>n</i> (%)	2 (2.1)	1 (1.2)	4 (4.3)	3 (10.3)²	4 (1.7)	$\chi^2_{(4)} = 9.425$; $P = 0.051$, $V = 0.132$
P3: Grandiose ideas: <i>n</i> (%)	0	0	0	0	1 (0.4)	$\chi^2_{(4)} = 1.316$; $P = 0.859$, $V = 0.049$
P4: Perceptual abnormalities/hallucinations: <i>n</i> (%)	14 (14.2)	20 (23.3)	22 (23.4)	8 (27.6)	54 (23.2)	$\chi^2_{(4)} = 4.150$; $P = 0.368$, $V = 0.088$
P5: Disorganized communication: <i>n</i> (%)	0	0	0	0	1 (0.4)	$\chi^2_{(4)} = 1.316$; $P = 0.859$, $V = 0.049$

¹most frequent in AnxD and OCD: thought insertion and broadcasting; unusual, somatic and nihilistic idea;

²most frequent in ASS: ideas of being redlined or observed (common rating). In **bold**, cells with standard residuals $\geq |1.96|$. This equals a significant deviation (less or more) from the expected cell frequency. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

0.666) for *thought perseveration*.

Conversion to psychosis

Altogether, four had developed a psychosis within 2 years (*i.e.*, 0.7% of the whole sample and 1.2% of the 2-year follow-up sample). Only one of the converters had not met a CHR criterion at baseline (Table 4). Three conversions had occurred in the inpatient sample, including the one without CHR criteria at baseline, and one in the community subjects (Table 4), in a female without any mental disorder at baseline. Thus, with regard to the total baseline sample (*n* = 539), the 2-year conversion rate in subjects without CHR criteria was 0.2% and the 2-year conversion rate in subjects with CHR criteria was 6.5% ($\chi^2_{(1)} = 22.807$, Fisher's exact $P = 0.002$; Cramer's $V = 0.206$). With regard to the 2-year follow-up sample (*n* = 331), these numbers were 0.3% and 11.5% ($\chi^2_{(1)} = 25.220$, Fisher's exact $P = 0.002$; Cramer's $V = 0.276$).

DISCUSSION

In light of the relevant nonconversion rates in CHR samples, in particular in UHR samples[19,20], and their various outcomes[25,26], it has been suggested that CHR criteria might better be regarded as a pluripotent syndrome, or a transdiagnostic risk or severity marker[27-30]. If either of these were true, relevant and systematic differences in the frequency and severity of CHR criteria and symptoms between patients with severe mental illness requiring inpatient treatment and community subjects should be present. We examined this in two child and adolescent samples of the BEARS-Kid study with respect to both the UHR and the basic symptom approach.

We had chosen this age group because higher nonconversion rates compared to adult samples were reported for this group[19,21], and because CHR symptoms and criteria were shown to be more prevalent and less clinically relevant in children and adolescents[22,23,51-53]. Consequently, we expected that CHR symptoms and criteria would most likely show characteristics indicative of a pluripotent syndrome, of a transdiagnostic risk factor or of a severity marker in this age group.

Age and the CHR state

Both community and clinical studies on the effect of age on CHR symptoms and criteria indicated an age threshold around age of 16 years for APS and BIPS, with perceptual APS/BIPS being more prevalent below this age and all APS/BIPS being less clinically relevant[22,23,51,53]. For perceptual and cognitive basic symptoms, the age thresholds for prevalence and clinical significance were around age of 18 and 23 years, respectively[23,52]. Thus, all participants were at an age below the threshold suggested for basic symptoms, while the suggested age threshold for APS/BIPS was within the age range of our sample. Consequently, the observed group difference in age could have biased the overall older inpatient group towards reporting a lower number of APS/BIPS compared to the younger community sample; consequently, hiding relevant group effects. Therefore, we repeated the analyses of APS/BIPS in the age group below the suggested age threshold; *i.e.*, with 8- to 15-year-old (Supplementary Tables 4-6), which led to comparable results.

Table 7 Severity of clinical high-risk criteria and symptoms (mean SD, median) in inpatients and the community sample (*n* = 539)

	Inpatients (<i>n</i> = 306)	Community subjects (<i>n</i> = 233)	Mann–Whitney U; Rosenthal's <i>r</i>
Sum score of SIPS positive items	2.5 ± 2.5, 2	2.1 ± 2.3, 1	<i>Z</i> = -1.852, <i>P</i> = 0.064; <i>r</i> = 0.080
Sum score of 9 basic symptoms of COGDIS	0.8 ± 2.5, 0	0.4 ± 1.2, 0	<i>Z</i> = -1.125, <i>P</i> = 0.260, <i>r</i> = 0.048
Sum score of 10 basic symptoms of COPER	1.6 ± 3.6, 0	0.6 ± 1.7, 0	<i>Z</i> = -3.852, ^c <i>P</i> < 0.001; <i>r</i> = 0.166
P1: Unusual thought content / delusional ideas	0.9 ± 1.0, 1	0.8 ± 0.9, 1	<i>Z</i> = -1.341, <i>P</i> = 0.180; <i>r</i> = 0.058
P2: Suspiciousness / persecutory ideas	0.4 ± 0.8, 0	0.2 ± 0.6, 0	<i>Z</i> = -4.281, ^c <i>P</i> < 0.001; <i>r</i> = 0.184
P3: Grandiose ideas	0.1 ± 0.3, 0	0.1 ± 0.4, 0	<i>Z</i> = -0.426, <i>P</i> = 0.670; <i>r</i> = 0.018
P4: Perceptual abnormalities / hallucinations	1.0 ± 1.4, 0	1.0 ± 1.2, 0	<i>Z</i> = -1.119, <i>P</i> = 0.263; <i>r</i> = 0.048
P5: Disorganized communication	0.1 ± 0.3, 0	0.1 ± 0.3, 0	<i>Z</i> = -0.397, <i>P</i> = 0.691; <i>r</i> = 0.017
Inability to divide attention	0.1 ± 0.5, 0	0	<i>Z</i> = -1.514, <i>P</i> = 0.130; <i>r</i> = 0.065
Captivation of attention	0.0 ± 0.2, 0	0.0 ± 0.3, 0	<i>Z</i> = -0.757, <i>P</i> = 0.449; <i>r</i> = 0.033
Disturbance of expressive speech	0.2 ± 0.8, 0	0.1 ± 0.4, 0	<i>Z</i> = -0.268, <i>P</i> = 0.789; <i>r</i> = 0.012
Disturbance of abstract thinking ¹	0	0.0 ± 0.1, 0	<i>Z</i> = -1.622, <i>P</i> = 0.105; <i>r</i> = 0.070
Thought interference	0.1 ± 0.6, 0	0.1 ± 0.4, 0	<i>Z</i> = -0.591, <i>P</i> = 0.555; <i>r</i> = 0.025
Thought blockages ¹	0.2 ± 0.8, 0	0.1 ± 0.6, 0	<i>Z</i> = -1.044, <i>P</i> = 0.297; <i>r</i> = 0.045
Thought pressure	0.2 ± 0.9, 0	0.1 ± 0.5, 0	<i>Z</i> = -2.639, ^b <i>P</i> = 0.008; <i>r</i> = 0.114
Disturbance of receptive speech	0.0 ± 0.3, 0	0.0 ± 0.1, 0	<i>Z</i> = -1.324, <i>P</i> = 0.185; <i>r</i> = 0.057
Unstable ideas of reference	0.0 ± 0.2, 0	0.0 ± 0.2, 0	<i>Z</i> = -1.046, <i>P</i> = 0.296; <i>r</i> = 0.045
Impaired discrimination between ideas/true memories and phantasy	0.1 ± 0.6, 0	0.0 ± 0.3, 0	<i>Z</i> = -0.230, <i>P</i> = 0.818; <i>r</i> = 0.010
Thought perseveration	0.0 ± 0.3, 0	0.0 ± 0.2, 0	<i>Z</i> = -0.607, <i>P</i> = 0.544; <i>r</i> = 0.026
Derealization	0.4 ± 1.1, 0	0.0 ± 0.2, 0	<i>Z</i> = -3.924, ^c <i>P</i> < 0.001.; <i>r</i> = 0.169
Visual perception disturbances	0.3 ± 1.1, 0	0.1 ± 0.4, 0	<i>Z</i> = -2.822, ^b <i>P</i> = 0.005; <i>r</i> = 0.122
Acoustic perception disturbances	0.2 ± 0.9, 0	0.2 ± 0.8, 0	<i>Z</i> = -1.014, <i>P</i> = 0.311; <i>r</i> = 0.044

¹Assessable only from age of 13 years onwards, thus only calculated on *n* = 404.

r: Rosenthal's *r*: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

Compared to adult samples, group differences indicative of a potential pluripotent or transdiagnostic nature of CHR symptoms and criteria should be even more obvious in children and adolescents below these age thresholds. Yet, overall, our results revealed only few group differences of small effect size in frequency and severity of CHR symptoms and no group differences in frequency of CHR criteria. Additionally, at most weak associations were found between CHR symptoms or sum scores of symptoms with level of psychosocial functioning as a proxy measure of severity of mental ill health.

The CHR state as a pluripotent syndrome

Being derived from biology and commonly applied to describe a property of cells, pluripotent (from “pluri”: several, and “potent”: being able) describes the property of immature or stem cells that are capable of giving rise to several different cell types, into which they transform[31,54]. When extended to psychiatry, a pluripotent syndrome would be the first, diagnostically indistinct expression of any developing more severe psychopathology, which only later may acquire a degree of diagnostic specificity[27,28]. In doing so, similar to pluripotent cells, a pluripotent mental state would be completely absorbed in the final, manifest mental state or disorder. Thus, if they were pluripotent, CHR criteria and symptoms would no longer be detectable in patients with manifest mental disorders; *i.e.*, after their transformation into a diagnostically specific disorder. Yet, they might already be detectable in healthy persons who might be at risk of developing a mental disorder in future, such as children and adolescents of the community, of whom a third can be expected to develop a mental disorder in their lifetime[39]. Thus, from a pluripotent point of view, we expected a higher rate of CHR criteria and symptoms in community subjects compared to inpatients.

Table 8 Severity of clinical high-risk criteria and symptoms (mean \pm SD, median) in the four diagnostic subsamples and the community sample (N = 539)

	ED (n = 97)	ADHD (n = 86)	AnxD and OCD (n = 94)	ASS (n = 29)	Community subjects (n = 233)	Kruskal–Wallis (results of <i>post hoc</i> Mann–Whitney tests)
Sum score of SIPS positive items	2.1 \pm 2.4, 1	2.0 \pm 2.1, 1	3.1 \pm 2.6, 2	3.3 \pm 3.3, 2	2.1 \pm 2.3, 1	$\chi^2_{(4)} = 18.866$, $^cP = 0.001$ (AnxD and OCD > ED = ADHD = GPS)
Sum score of COGDIS	0.8 \pm 2.1, 0	0.5 \pm 1.7, 0	1.2 \pm 3.5, 0	0.7 \pm 1.7, 0	0.4 \pm 1.2, 0	$\chi^2_{(4)} = 7.692$, $P = 0.104$
Sum score of COPER	1.8 \pm 3.6, 0	1.1 \pm 3.3, 0	2.2 \pm 4.2, 0	1.1 \pm 1.7, 0	0.6 \pm 1.7, 0	$\chi^2_{(4)} = 26.988$, $^cP < 0.001$ (ED = AnxD and OCD = ASS > GPS; AnxD and OCD = ED > ADHD)
P1: Unusual thought content	0.8 \pm 0.9, 1	0.7 \pm 0.9, 1	1.2 \pm 1.1, 1	1.2 \pm 1.3, 1	0.8 \pm 0.9, 1	$\chi^2_{(4)} = 12.397$, $^aP = 0.015$ (AnxD and OCD > ED = ADHD = GPS)
P2: Suspiciousness/persecutory ideas	0.4 \pm 0.8, 0	0.2 \pm 0.6, 0	0.5 \pm 0.9, 0	0.7 \pm 1.1, 0	0.2 \pm 0.6, 0	$\chi^2_{(4)} = 30.502$, $^cP < 0.001$ (ASS = AnxD and OCD = ED > GPS; AnxD and OCD = ASS > ADHD)
P3: Grandiose ideas	0.1 \pm 0.3, 0	0.1 \pm 0.2, 0	0.2 \pm 0.5, 0	0.1 \pm 0.3, 0	0.1 \pm 0.4, 0	$\chi^2_{(4)} = 4.029$, $P = 0.402$
P4: Perceptual abnormalities	0.8 \pm 1.3, 0	1.0 \pm 1.5, 0	1.2 \pm 1.4, 1	1.3 \pm 1.6, 1	1.0 \pm 1.2, 0	$\chi^2_{(4)} = 6.391$, $P = 0.172$
P5: Disorganized communication	0.0 \pm 0.2, 0	0.0 \pm 0.2, 0	0.1 \pm 0.4, 0	0.1 \pm 0.3, 0	0.1 \pm 0.3, 0	$\chi^2_{(4)} = 3.129$, $P = 0.539$
Inability to divide attention	0.0 \pm 0.4, 0	0	0.1 \pm 0.9, 0	0	0	$\chi^2_{(4)} = 6.537$, $P = 0.163$
Captivation of attention	0	0	0.0 \pm 0.2, 0	0.1 \pm 0.4, 0	0.0 \pm 0.3, 0	$\chi^2_{(4)} = 9.749$, $^aP = 0.045$ (ASS > ED = ADHD)
Disturbance of expressive speech	0.2 \pm 0.9, 0	0.1 \pm 0.6, 0	0.2 \pm 1.0, 0	0.1 \pm 0.4, 0	0.1 \pm 0.4, 0	$\chi^2_{(4)} = 0.675$, $P = 0.954$
Disturbance of abstract thinking ¹	0	0	0	0	0.0 \pm 0.1, 0	$\chi^2_{(4)} = 2.632$, $P = 0.621$
Thought interference	0.1 \pm 0.5, 0	0.1 \pm 0.5, 0	0.1 \pm 0.6, 0	0.3 \pm 1.0, 0	0.1 \pm 0.4, 0	$\chi^2_{(4)} = 7.912$, $P = 0.095$
Thought blockages ¹	0.2 \pm 0.8, 0	0.2 \pm 0.9, 0	0.3 \pm 1.0, 0	0.1 \pm 0.4, 0	0.1 \pm 0.6, 0	$\chi^2_{(4)} = 2.048$, $P = 0.727$
Thought pressure	0.3 \pm 0.9, 0	0.1 \pm 0.6, 0	0.4 \pm 1.2, 0	0.1 \pm 0.4, 0	0.1 \pm 0.5, 0	$\chi^2_{(4)} = 10.944$, $^aP = 0.027$ (ED = AnxD and OCD > GPS)
Disturbance of receptive speech	0.0 \pm 0.1, 0	0.0 \pm 0.2, 0	0.1 \pm 0.5, 0	0	0.0 \pm 0.07, 0	$\chi^2_{(4)} = 5.047$, $P = 0.283$
Unstable ideas of reference	0.1 \pm 0.3, 0	0	0.0 \pm 0.1, 0	0	0.0 \pm 0.2, 0	$\chi^2_{(4)} = 6.643$, $P = 0.156$
Impaired discrimination between	0.0 \pm 0.3, 0	0.1 \pm 0.7, 0	0.2 \pm 0.7, 0	0	0.0 \pm 0.3, 0	$\chi^2_{(4)} = 7.344$, $P = 0.119$
Thought perseveration	0	0.1 \pm 0.4, 0	0.1 \pm 0.4, 0	0.0 \pm 0.1, 0	0.0 \pm 0.2, 0	$\chi^2_{(4)} = 3.954$, $P = 0.412$
Derealization	0.4 \pm 1.1, 0	0.1 \pm 0.7, 0	0.6 \pm 1.5, 0	0.2 \pm 0.7, 0	0.0 \pm 0.2, 0	$\chi^2_{(4)} = 32.930$, $^cP < 0.001$ (ED = AnxD and OCD > ADHD = GPS)
Visual perception disturbances	0.4 \pm 1.2, 0	0.3 \pm 1.2, 0	0.3 \pm 1.0, 0	0.3 \pm 0.7, 0	0.1 \pm 0.4, 0	$\chi^2_{(4)} = 10.764$, $^aP = 0.029$ (ED = AnxD and OCD = ASS > GPS)
Acoustic perception disturbances	0.3 \pm 1.0, 0	0.2 \pm 0.7, 0	0.3 \pm 1.0, 0	0.1 \pm 0.3, 0	0.2 \pm 0.8, 0	$\chi^2_{(4)} = 3.227$, $P = 0.521$

¹assessable only from age of 13 years onwards, thus only calculated on $n = 404$. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; GPS: community subjects.

Contrary to this expectation, we found no global pattern of differences in CHR criteria between inpatients and community subjects, and the four group differences in the prevalence of CHR symptoms; *i.e.*, in *suspiciousness/persecutory ideas*, *thought pressure*, *derealization* and *visual perception disturbances*, pointed towards a slightly higher rather than lower prevalence in inpatients. This lack of support for

assuming pluripotency of the UHR criteria specifically, is in line with results of the longitudinal data of two North American CHR studies[55]. Comparing outcome of help-seeking patients with and without UHR criteria, these studies detected no group differences in rates of new emergence of nonpsychotic disorders, thus not supporting diagnostic pluripotency of the UHR states[55]. Furthermore, the authors noted that the persistence of the generally frequent baseline comorbidities to UHR states would not qualify as support for assuming pluripotency of UHR states, even when only the UHR state is remitted at baseline[55]. Indeed, the above definition of a pluripotent state would rule out the concurrent presence of both the pluripotent state and its assumed outcome.

The missing empirical support for regarding the CHR state as a pluripotent syndrome is somewhat unsurprising in light of the frequent indistinct use of the term pluripotential for states that were equated to earliest, unspecific mental states of mental disorders[31]. Yet, in models of developing psychosis, these earliest and unspecific states are commonly distinguished from the more specific CHR states[10, 18,56]. Then again, pluripotent states or trajectories have been equated to transdiagnostic ones[30] despite their considerably differing assumptions with regard to the course of their constituting symptoms – transformation and, thus, forever vanishing of pluripotential states and symptoms *versus* maintenance or even increase of transdiagnostic symptoms.

The CHR state as a general transdiagnostic risk factor

In contrast to a pluripotent state, a transdiagnostic risk factor as well as a transdiagnostic dimension of psychopathology would still be present in various mental disorders[32], while they would be present in the community to a clearly lesser degree or not at all outside states of mental ill health. Thus, if CHR criteria and symptoms would represent a transdiagnostic risk factor or a transdiagnostic psychopathological dimension, they should accumulate in the extreme range of persons with mental disorders and, hence, should be more frequent or severe in inpatients compared to community subjects. Indeed, a large body of research indicates that so-called psychotic-like experiences, commonly assessed by self-report questionnaires or fully-standardized lay-person interviews, can be measured in the community, in which they are linked to the presence of non-psychotic disorder, particularly common mental disorder [28,57]. Thus, it was argued that psychotic-like experiences are transdiagnostic phenomena that, among others, also predict greater illness severity[57].

In our analyses, these assumptions were not supported for CHR criteria. The prevalence rates of CHR criteria did not differ between the community subjects (7.3%) and the inpatient sample (8.2%). Yet, both rates were higher than the 2.4% rate of clinician-assessed CHR criteria in young adults of the community aged 16–40 years[58]. In line with earlier findings[22,23], this indicates an effect of age across broader age ranges but not within children and adolescents. This lack of support for a transdiagnostic model of CHR criteria is likely related to the differences in assessments and definition. Studies on psychotic-like experiences commonly do not use CHR instruments for the assessment of APS/BIPS by trained clinicians in semi-structured interviews, which makes such psychotic-like experiences a poor and invalid proxy of APS that overestimates the presence of APS by far[59-62]. Furthermore, studies on psychotic-like experiences commonly disregard the onset/worsening and frequency requirements of CHR criteria[62] (Table 1).

With regard to CHR symptoms and irrespective of these additional requirements, we found some group differences in frequency and severity, in particular with respect to the severity of some single CHR symptoms. Yet, these findings were mostly unsystematically and randomly distributed, except for the UHR-relevant APS *suspiciousness/persecutory ideas*, the two COPER-relevant basic symptoms *derealization* and *visual perception disturbances*, and the COPER- and COGDIS-relevant basic symptom *thought pressure*. These four CHR symptoms were more frequent and severe in inpatients, in particular in eating disorders, and anxiety and obsessive-compulsive disorders; additionally, the paranoid APS was more frequent and severe in autism-spectrum disorder. Thus, they may be the most likely candidates of all CHR symptoms for transdiagnostic risk factors or a transdiagnostic psychopathological dimension.

Suspiciousness/persecutory ideas (P2) of the SIPS in terms of APS/BIPS include symptoms ranging from a general lack of trust in and suspiciousness of others, as well as vague ideas of threat or that others do not mean well to more concrete ideas of being followed, observed or in danger and paranoid ideas of reference[43]. Their severity can range from ideas still being doubted to various degrees and not significantly impeding behavior, to holding these ideas with absolute conviction, resulting in significant impact on behavior[43]. Social fears related to one's own possibly inadequate or embarrassing behavior (but not to the negative intentions of others) were not scored here. In adolescents, ideas of reference that exclusively involved peers and the idea that they might think or talk badly about the patient/subject were also not rated, as the critical comparison with peers is a common phenomenon in adolescents' identity formation and, consequently, as these ideas are possibly related to lower levels of self-esteem [63,64].

In our study, the paranoid APS was most frequent and severe in anxiety, obsessive-compulsive, and in autism-spectrum disorders. This is in line with reports that paranoia is not specific to psychosis but occurs in a wide range of disorders[65] and also frequently in community samples of adolescents[65, 66]. In particular, paranoia was significantly positively associated with anxiety but not autistic symptoms, and negatively associated with symptoms of ADHD[63]. The latter is also in line with our finding that none of the ADHD patients reported paranoid APS. Other studies have linked autistic traits

and psychotic-like experiences, including paranoia, in the adult community[67] and reported similarly high levels of paranoia in psychotic and autism-spectrum disorders[68]. In contrast to psychotic disorders in which paranoia was based upon victimization, suspicion, and threat of harm, in autism-spectrum disorders, paranoia was based less upon these but more so upon social cynicism[68]. Yet, certain (developing) personality accentuations or disorders that involve paranoia and suspiciousness, in particular paranoid, schizotypal and borderline personality[69,70], might have contributed our findings. However, for the ongoing personality development in this age group, we had not assessed these in our study on children and adolescents.

Of the basic symptoms, *thought pressure* that is part of both COPER and COGDIS was more frequent and severe in inpatients, particularly in anxiety and obsessive-compulsive disorders. *Thought pressure* involves the subjective occurrence of a great number of thematically unrelated and often unrecognized, fragmented thoughts whose (dis)appearance is hard to control[44]. Thereby, *thought pressure* is distinct from intrusive thoughts of obsessive-compulsive disorder that involve a certain topic. Furthermore, in their assessment, the occurrence within states of extreme emotional arousal, such as in panic attacks, has to be excluded[44]. Thus, this finding is not explained by phenomenological similarities between *thought pressure* and cognitive symptoms in anxiety and obsessive-compulsive disorders. Yet, these similar cognitive symptoms might signal a general liability to difficulties in suppressing irrelevant or inadequate thoughts that, as suggested for intrusive thoughts, might be related to altered functional connectivity in the temporal gyri[71]. More qualitative and basic research into the link between *thought pressure* and anxiety and obsessive-compulsive disorders is clearly needed.

Visual perception disturbances include various, often fleeting misperceptions of real visible objects including oneself and other persons that are immediately recognized as false perceptions, and are not even for a split-second considered as changes in the outside world[44]. As with all basic symptoms, they have to have started at a certain point in life[44] and thus, contrary to schizotypy-related perceptual aberrations, have no trait characteristic[15,72,73]. Furthermore, they must be unrelated to a somatic condition or substance use[44]. As outlined above in the section “Assessments”, they rate on the SIPS below the APS-relevant range with a score of 2[43,44,73]. Examples of *visual perception disturbances* include changes in the perception of the color or color intensity of objects, in the perception and estimation of the size of, or distance to objects, and in the shape of objects, as well as perceptions that resemble floaters or flashes of light in the vision as known, for example, from auras of migraine, retinal detachment or optic neuritis[44]. Therefore, they are different from unformed attenuated or frank visual hallucinations that are not perceived as “in the eye” but are located – at least initially – in the outside world[43,73]. Despite being a part of COPER, *visual perception disturbances* were found to be on the periphery of a network of symptoms of psychosis in an adult patient sample[74]. Such a peripheral position was also found for the depression items of the SIPS and of the Positive And Negative Syndrome Scale[75], though at the opposite side of the network, likely indicating that these symptoms are less specific to psychosis. Thus, *visual perception disturbances* that longitudinally had been significantly linked to the development of psychosis in adults[14] might be a more general expression of severe mental problems in childhood and early adolescence. This view is supported by reports that visual hallucinations were more frequent in children and adolescents with psychosis compared to adult psychosis patients[76], and that attenuated and transient hallucinations as well as perceptual disturbances were more frequent and less clinically relevant in children and adolescents[22,23], who likely grow out of them over time due to progressing neurocognitive and brain maturation[52].

Derealization is defined by an alienation from the surrounding and/or the experience of the external environment as unfamiliar, with other people appearing as if only acting a role and the world appearing as if being two-dimensional or a stage set in the presence of knowledge of its reality[44]. It often co-occurs with more frequent depersonalization experiences; and together, they might form a syndrome in itself[77-79]. Both are part of the definition of panic disorders[77,78] and are therefore not rated as basic symptoms when exclusively occurring within a panic attack. Thus, as in *thought pressure*, our finding of increased *derealization* in anxiety and obsessive-compulsive disorders is not explained by this phenomenological overlap. Yet, as personality disorders had not been assessed in this study, we did not exclude their possible occurrence as part of a developing Borderline or schizotypal personality accentuation or disorder[78]. *Depersonalization* and, to a lesser degree, *derealization* are frequent phenomena in the general population with higher rates in psychiatric patients, in particular those with affective and anxiety disorders[77,78]. *Derealization* and *depersonalization* might have partly different neurobiological underpinnings[80]; and only *derealization* was found to be predictive of future psychosis and, thus included into COPER[14]. However, in line with our current findings, studies reported that both *derealization* and *depersonalization* might be responses to strong emotions, such as embarrassment, or might be attempts at coping, in particular in affective and anxiety disorders[81]. Additionally, one study on bulimia reported a link between threatening stimuli and dissociative states, in particular *derealization*, in which it was assumed to fulfill a similar function as binge eating itself; *i.e.*, lowering awareness of generalized threat and negative self-esteem[82]. Thus, the increased prevalence and severity of *derealization* in patients with eating disorders, and anxiety and obsessive-compulsive disorders might be related to their propensity to perceive high emotional arousal, especially threat.

Derealization and *visual perception disturbances* are only part of the basic symptom criterion COPER (Table 1) that is likely less specific but more sensitive compared to COGDIS[15]. Although not more frequent, our analyses revealed that COPER was more severe in inpatients, in particular those with eating disorders, and anxiety and obsessive-compulsive disorders. Therefore, the inclusion of *derealization* and *visual perception disturbances* in COPER in addition to that of *thought pressure* might have conveyed the higher severity, though not frequency of COPER in inpatients, in particular in eating, autism-spectrum, and anxiety and obsessive-compulsive disorders.

The CHR state as a general transdiagnostic severity marker

A transdiagnostic severity marker of psychopathology would be expected to be generally present in mental disorders and to be most pronounced in those with severe mental disorders and, relatedly, in those with most severe functional impairment due to their mental problems. Thus, the severity and likelihood of presence of CHR criteria and symptoms would be expected to significantly increase with decreasing psychosocial functioning as a proxy measure of illness severity. As already discussed, CHR symptoms and criteria differed only to a minimal degree in their prevalence between inpatients and community subjects, in whom they were also rare. They hardly exceeded 10% in inpatients, except for *derealization* and *visual perception disturbances* (both 11.4%) and *perceptual abnormalities/hallucinations* (P4) that were present in 20.9% of inpatients but also in 23.4% of community subjects. Furthermore, CHR symptoms and criteria demonstrated an association with psychosocial functioning, the proxy severity measure. However, this association was, at most, of small effect size even when becoming significant. This finding indicates that CHR criteria and symptoms would be poor transdiagnostic severity markers of mental problems; at least when psychosocial functioning is used as a proxy measure.

With regard to basic symptoms, only COPER became significant in both bivariate and partial group-controlled correlation analyses, showing a small maximum effect of $\text{Tau} = -0.140$. Significant single basic symptoms differed between the two types of analyses. In doing so, *thought pressure*, *derealization*, and *visual* and *acoustic perception disturbances* became significant in bivariate, and *thought inference* and *disturbances of expressive speech* became significant in partial analyses, in no case exceeding $\text{tau} = -0.116$. Of these six symptoms, all but *disturbances of expressive speech* are part of COPER, while only *thought pressure* and *interference* as well as *disturbances of expressive speech* are part of COGDIS. Since *thought pressure*, *derealization*, and *visual perception disturbances* showed significant group differences, this strong group effect may mostly explain their association with functioning in bivariate correlation that, consequently, was strongly reduced in partial correlations.

Results on the APS syndrome and single APS were more consistent. In both bivariate and partial correlation analyses, the sum score of SIPS positive items as well as the single SIPS positive items *suspiciousness/persecutory ideas* (P2), *perceptual abnormalities/hallucinations* (P4), and *disorganized communication* (P5) were significantly negatively correlated with psychosocial functioning. Yet, as in basic symptoms, these correlations were only of weak effect size and did not exceed $r = -0.165$ (respectively $r = -0.201$ in 8–15-year-olds) in *perceptual abnormalities/hallucinations* (P4). This is in line with a recent community study, whose $n = 211$ participants had been 11–13 years old at baseline[84]. Authors reported an association between psychotic experiences assessed with the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS[83]) and poorer functioning[84]. Furthermore, $n = 86$ (40.8%) and $n = 56$ (26.5%) participated in the first and second follow-up at age 14–16 years and 17–21 years, respectively[84]. Participants with psychotic experiences at baseline had persistently poorer global functioning throughout adolescence and into early adulthood. As in our cross-sectional results, this effect was above and beyond what was explained by presence of a mental disorder, suggesting an underlying vulnerability which extends beyond diagnosable mental disorder [84]. Unfortunately, the authors did not report effect sizes and did not distinguish between the different psychotic experiences. Therefore, it remains unclear if these associations were also of only small effect size and if they were mainly driven by similar (attenuated) psychotic symptoms.

In our study, only the comparably frequent and, (regarding content) heterogeneous SIPS positive item *unusual thought content/delusional ideas* and the extremely rare SIPS positive item *grandiose ideas* were not significantly related to functioning. *Unusual thought content/delusional ideas* (P1) includes all but paranoid and grandiose ideas[43]. Thus, it is probable that the included unusual ideas differ in their association with functioning; e.g., that attenuated *Ich-Störungen* may more strongly impair functioning than magical thinking. For this reason, future studies should examine single attenuated delusional ideas differentially to further determine which APS might or might not have the potential of a transdiagnostic severity marker. Similarly, a more differential examination is needed for *perceptual abnormalities/hallucinations* (P4) that involves different sensory modalities, as these were differentially, though inconsistently related to conversion to psychosis in UHR samples[85–87].

The lack of strong correlations between CHR symptoms and criteria, and functioning might be perceived as challenging the notion that these possess clinical relevance. However, symptoms are generally defined by a departure from normal function – not necessarily psychosocial function – or feeling, which is apparent to the patient, reflecting the presence of an unusual state or of a disease[38]. Thus, functional impairment is not always a prerequisite even for some psychotic disorders, such as delusional disorders that, according to the DSM[38], do not have to lead to functional impairment *per se*. Moreover, in ICD-10 (and the future ICD-11), functional impairment is not a requirement for any

psychotic disorder[88]. Furthermore, in the SIPS and their anchor points for severity ratings of the positive items[43], a rating of 3 (or lower) does not require an impact on functioning, while a rating of 4 requires only potential and partial impact on functioning; a significant impact on functioning is only required for severe APS of score 5 or BIPS score of 6. Yet, ratings of 5 were rare, occurring in only 13 instances, and ratings of 6 never occurred. Rather, ratings of 3 dominated in those with APS: 68.3% scored 3 on P1, 85.7% on P2 and 66.1% on P4; and the single case of APS on P3 and P5, respectively, had a rating of 3 each. Additionally, other than in the current version of Comprehensive Assessment of At-Risk Mental States, the APS syndrome of the SIPS does not require a significant functional decline or impairment[19]. Thus, the lack of an association with functional impairment does not limit the qualification of CHR symptoms and criteria as symptoms or syndromes.

As for the basic symptoms, affected persons can commonly cope with these mostly fleeting experiences (e.g., by increased willpower or concentration) for as long as their number or frequency does not exceed their coping capacities, and for as long as the employed coping strategies are not maladaptive (such as social withdrawal or other avoidance strategies)[44,52,89]. Thus, for their subjective perception as not normal, basic symptoms may induce distress and worries about one's own mental health[52,89] but not necessarily impairment in psychosocial functioning. Consequently, functional impairment is not a general prerequisite for symptoms or syndromes, in particular in the prevention of disorders that, within psychiatry, also aims for the prevention of functional impairment [90]. In light of this, making functional impairment an obligatory requirement of CHR criteria was explicitly discouraged in recent recommendations for diagnosing a CHR state within the framework of the EPA Guidance project[19].

The CHR state as a precursor state of psychoses

Four subjects developed psychosis within 2 years; *i.e.*, 0.7% of the whole sample ($n = 539$) and 1.2% of the 2-year follow-up sample ($n = 331$). These numbers are higher than the reported annual incidence rate in the community of this age of 0.1%[91]. Conversions to psychosis mainly occurred in inpatients, of whom 1.0% converted to psychosis compared to just 0.4% in the community sample. Three quarters of the few conversion-to-psychoses cases occurred in the inpatient sample, in which also the non-CHR-related conversion occurred, and three quarters of converters had met CHR criteria at baseline. Thus, with conversion rates between 6.5% across all CHR subjects at baseline, and 11.5% for CHR subjects with a 2-year follow-up, the 2-year conversion rates within CHR subjects were within the range of pooled conversions rates reported for child and adolescent CHR samples of early detection services of 9.5%[19]. At this, our conversion rates were slightly higher than the 3-year conversion rates reported for 16–40-year-olds of the community that were 4.7% for all five CHR criteria and 11.1% for the three EPA criteria[92].

Of note, the effect sizes of the association of CHR criteria at baseline with subsequent conversion to psychosis were the highest of all reported effect sizes, approaching a moderate effect size in case of the two-year follow-up sample (Cramer's $V = 0.276$).

Strengths and limitations

Our study has several strengths and limitations. Clear strengths include the large sample size, the CHR assessment with well-established instruments, and the thorough training in and supervision of the assessment of CHR symptoms and criteria in order to minimize rater and center effects, and to maximize interrater reliability. Furthermore, in order to reduce a potential systematic assessment bias due to the impossible blinding of raters to groups, the inpatient and community sample was assessed by different interviewers. Another strength is the inclusion of a severely ill inpatient sample with main disorders that had been reported to be related to an increased prevalence of schizophrenia in adulthood [37] (Supplementary Table 1). Thus, our inpatient sample – in theory – was biased towards reporting increased rates of CHR symptoms and, consequently, towards revealing any transdiagnostic nature of CHR criteria and symptoms.

Limitations to our study are the mainly cross-sectional nature and the nonassessment of nonpsychotic mental disorders at follow-up. This would have allowed us to compare conversion rates to psychosis with conversion to, or persistence of other mental disorders, and would have allowed us to study the relationship of different mental disorders to the course of CHR criteria and symptoms.

The conduction of multiple analyses and the related nonadjustment for multiple testing might have been another possible limitation. Yet, as discussed already in the section "Data analysis", because all of our hypotheses assumed group differences, the type I error (alpha), *i.e.*, the rejection of a true null hypothesis, would have become less likely, if we had corrected the alpha-level for multiple comparisons. However, even without correction for multiple testing, the null hypothesis was rarely rejected; this resulted in the main conclusion of a lack of a general group difference. This main conclusion would not have changed, had we corrected the alpha-level for multiple comparison and, consequently, had detected even fewer (and likely no) group differences. In light of this, the nonadjustment of the type I error can be regarded as the more conservative testing of the overall hypotheses assuming group differences. Additionally, the high power of the study, the ability to correctly reject a false null hypothesis assuming group equality, must be assumed to be uncompromised by the current nonadjusted analyses[50]. Thus, any adjustment for multiple testing would not have led

to a different conclusion. Furthermore, the conduction of multiple analyses had offered the advantage to detect any possibly robust pattern indicative of any one of the three examined alternative explanatory models of CHR states and symptoms.

CONCLUSION

Overall, our results did not support the general predications that CHR criteria and symptoms would represent a pluripotent syndrome[27,28], a transdiagnostic risk factor[33], a transdiagnostic dimension of psychopathology[30], or even merely a marker for the severity of nonpsychotic states[30]. To that end, our data gave no support for a general diagnostic pluripotency of CHR symptoms and criteria that exceeds their undoubted and frequently demonstrated pluripotency for psychosis outcomes[55]. Furthermore, for lack of any clinically relevant, *i.e.*, at least moderate correlation with functioning, there was also no sufficient support for CHR symptoms and criteria as general severity markers of psychopathology. Indications of some transdiagnostic risk factors or dimension status with respect to eating, autism-spectrum, and anxiety and obsessive-compulsive disorders, however, were found for four CHR symptoms, two of them exclusive to COPER: *suspiciousness/persecutory ideas* (P2), *thought pressure, derealization* and *visual perception disturbances*. The fact that these indications did not extend to any CHR criterion highlights the importance of the additional requirements of CHR criteria on onset/worsening and occurrence for their potential specificity for the psychosis-spectrum. Indeed, with regard to the CHR criteria, we found the strongest, nearly moderate effect for their association with subsequent psychosis. This association, however, seems not strong enough to conclusively explain their role in children and adolescents by their psychosis-predictive potential.

Overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than *what* they are. Our results may support the view that CHR criteria should be regarded as a self-contained disorder or syndrome, similar to the proposition of the attenuated psychosis syndrome in DSM-5[93]. To evaluate this assumption, future community studies evaluating the effect of CHR criteria on help seeking and mental wellbeing are needed. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, then CHR criteria would fulfil general criteria for mental disorders (defined as a clinically significant behavioral or psychological syndrome associated with disability and/or severe distress); and consequently, the assumption of a CHR Syndrome would be supported. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to detect factors that convey their higher clinical relevance in adulthood.

ARTICLE HIGHLIGHTS

Research background

Many patients with clinical high-risk of psychosis (CHR) criteria do not develop psychosis, in particular if they are still in their childhood and adolescence. Therefore, CHR criteria were suggested to be not a risk indicator of psychosis development but (1) A pluripotential syndrome that will transform itself into all kinds of mental disorder; (2) A transdiagnostic risk factor from that all kind of different disorders develop; or (3) Simply a severity marker of mental disorders.

Research motivation

The simple nonconversion to psychosis and the persistence or new-occurrence rate of nonpsychotic mental disorders in CHR samples, however, do not allow for the conclusion of any of the three alternative explanatory models, which might explain why they are often proposed interchangeably. Thus, to gain more insight into the nature of CHR symptoms and criteria, we examined the differential implications that each of these models has on the occurrence of CHR criteria and symptoms and their association with a proxy measure of illness severity in patients with severe mental disorders; *i.e.*, inpatients and community subjects. We expected that any pattern of group differences indicative of one of the alternative explanatory models should become particularly apparent in a child and adolescent sample, as CHR symptoms and criteria were reported to be more frequent but less clinically relevant and less associated with psychosis in children and adolescents compared to adults.

Research objectives

Following a propositional logic approach, we examined which of the three alternative explanatory models of CHR criteria and symptoms would best fit our data. The three alternative explanatory models were associated with the following differential premises with respect to the data: (1) If CHR criteria and symptoms are more frequent in community subjects compared to inpatients, then they are likely

pluripotential. This has been assumed because a pluripotent syndrome would have transformed into a mental disorder and, thus, not be present in inpatients, but in a community sample wherein a proportion can be expected to develop a mental disorder in future; (2) If CHR criteria and symptoms are more frequent in inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension. This has been assumed because they would aggregate in persons with mental illness; and (3) If CHR criteria and symptoms show a clinically relevant, significant negative correlation with functioning as a proxy measure of illness severity, then they likely represent a severity marker of psychopathology.

Research methods

As part of the Bi-national Evaluation of At-Risk Symptoms in children and adolescents (BEARS-Kid) study, we cross-sectionally examined the frequency and severity of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community ($n = 233$) and in 8–17-year-old inpatients ($n = 306$) whose main diagnosis was a disorder that, earlier, had been associated with an elevated risk for psychosis in adulthood (obsessive compulsive and anxiety, attention deficit, eating, and autism-spectrum disorder) using χ^2 and nonparametric analyses. Furthermore, the associations between psychosocial functioning, and CHR criteria and symptoms were analyzed with bivariate and partial correlation analyses, the latter controlling for group membership. CHR criteria and symptoms according to the ultra-high risk and the basic symptom approach were assessed in clinical interviews by trained psychologists using the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY). Furthermore, we followed up 78.5% of the participants after 1 year, and 61.4% after 2 years past baseline for a conversion to psychosis.

Research results

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups. The frequency and severity of CHR symptoms differed between the community and the four inpatient groups only in four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS as well as *thought pressure*, *derealization* and *visual perception disturbances* of the SPI-CY. The persistent pattern of these differences was consistent with a transdiagnostic risk factor or dimension; *i.e.*, these symptoms were more frequent and severe in inpatients, in particular in those with eating, anxiety/obsessive-compulsive and autism-spectrum disorders. Furthermore, low functioning was – if at all – at most weakly related to the severity of CHR criteria and symptoms; the highest, yet weak correlation was for *suspiciousness/persecutory ideas*. Four participants had developed a psychotic disorder within two years past baseline. In doing so, the 2-year conversion rate in participants with CHR criteria was 11.5% and, the comparison of the conversion rate in participants with and without CHR criteria at baseline exhibited the highest, near moderate effect size of all comparisons.

Research conclusions

This study was the first to systematically study alternative explanatory models for current CHR states, which propose that CHR criteria and symptoms would represent a pluripotent syndrome, a transdiagnostic risk factor or dimension, or even merely a marker for the severity of any mental disorder. The general lack of systematic differences in the frequency and severity of CHR criteria and symptoms between inpatients and community subjects, and the lack of a sufficiently strong association between functioning, and CHR criteria and symptoms did not support any of these alternative explanatory models. Rather, the strongest, though still only moderate effect was found for the association of CHR criteria and the subsequent development of a psychotic disorder within two years. This association, however, appears not strong enough to conclusively explain the role of CHR criteria and symptoms in children and adolescents by their psychosis-predictive potential. Thus, overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than indicating *what* they are.

Only four CHR symptoms – *suspiciousness/persecutory ideas* of the SIPS, and *thought pressure*, *derealization* and *visual perception disturbances* of the SPI-CY – exhibited a pattern of group differences indicative of a transdiagnostic risk factor, in particular with respect to eating, autism-spectrum, and anxiety and obsessive-compulsive disorders. Thus, their inclusion and definition in current CHR criteria should be critically examined in future studies.

Research perspectives

Our results add to the growing support of the view that CHR criteria should be regarded as a self-contained disorder or syndrome. To more fully test this assumption, future community studies should evaluate the effect of CHR criteria on help seeking and mental wellbeing. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, CHR criteria would fulfil general criteria for mental disorders in terms of a CHR Syndrome. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to

detect factors that convey their higher clinical relevance in adulthood.

ACKNOWLEDGEMENTS

The authors thank their Australian colleague, Mrs. Madelyn Thomson, for her careful language assistance.

FOOTNOTES

Author contributions: Schultze-Lutter F and Schimmelmann BG designed the study; Walger P, Franscini M, Traber-Walker N, Flückiger R and Michel C were involved in the acquisition of data; Schultze-Lutter F and Michel C analyzed and interpreted the data for the work and drafted the first version of this work; all authors revised the article critically for important intellectual content, and agreed to the submitted version.

Supported by the conjoint research grant of the Swiss National Science Foundation, SNSF, No. 144100; and the German Research Foundation, DFG, No. 231563730, within the Lead Agency Process (SNSF as exclusive evaluating and approving lead agency).

Institutional review board statement: The study was reviewed and approved by the Kantonale Ethikkommission Bern, the Institutional Review Board of the University of Bern (No. 174/10), the Kantonale Ethik-Kommission Zürich, the Institutional Review Board of the University of Zurich (No. 2010-0415/3), and the Ethikkommission Köln, the Institutional Review Board of the Medical Faculty of the University of Cologne (No. 11-071).

Informed consent statement: All study participants, and their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Schimmelmann BG received honoraria for presentations by Takeda and InfectoPharm outside the reported work. All other authors reported no conflict of interest.

Data sharing statement: Data is available upon reasonable request for clearly defined scientific purposes from the corresponding author at frauke.schultze-lutter@ivr.de. Participants of the BEARS-Kid study gave informed consent for sharing of anonymized data.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Germany

ORCID number: Frauke Schultze-Lutter 0000-0003-1956-9574; Petra Walger 0000-0003-1150-1145; Maurizia Franscini 0000-0002-0231-8368; Nina Traber-Walker 0000-0001-7164-9550; Naweed Osman 0000-0001-9761-0099; Helene Walger 0000-0002-4060-4146; Benno G Schimmelmann 0000-0002-8980-1466; Rahel Flückiger 0000-0003-1228-7267; Chantal Michel 0000-0003-1165-6681.

Corresponding Author's Membership in Professional Societies: International Early Psychosis Association (IEPA), Schizophrenia International Research Society (SIRS), European Scientific Association for Schizophrenia and other Psychosis (ESAS), European Psychiatric Association (EPA, Section Prevention), World Psychiatric Association (WPA), Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), European Society of Child and Adolescent Psychiatry (ESCAP), International Consortium for Schizotypy Research (ICSR).

S-Editor: Wang LL

L-Editor: Kerr C

P-Editor: Yu HG

REFERENCES

- 1 Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L,

- Gannon B, Jones DH, Jennum P, Jordanova A, Jönsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador-Carulla L, Schlehofer B, Simon R, Steinhausen HC, Stovner LJ, Vallat JM, Van den Bergh P, van Os J, Vos P, Xu W, Wittchen HU, Jönsson B, Olesen J; CDBE2010Study Group. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**: 718-779 [PMID: 21924589 DOI: 10.1016/j.euroneuro.2011.08.008]
- 2 **Wittchen HU**, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**: 655-679 [PMID: 21896369 DOI: 10.1016/j.euroneuro.2011.07.018]
 - 3 **Whiteford HA**, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1575-1586 [PMID: 23993280]
 - 4 **Gore FM**, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM, Mathers CD. Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet* 2011; **377**: 2093-2102 [PMID: 21652063]
 - 5 **Stentebjerg-Olesen M**, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. *J Child Adolesc Psychopharmacol* 2016; **26**: 410-427 [PMID: 27136403 DOI: 10.1089/cap.2015.0097]
 - 6 **Penttilä M**, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2014; **205**: 88-94 [PMID: 25252316 DOI: 10.1192/bjp.bp.113.127753]
 - 7 **Farooq S**, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. *Schizophr Res* 2009; **109**: 15-23 [PMID: 19233621 DOI: 10.1016/j.schres.2009.01.008]
 - 8 **Dell'osso B**, Altamura AC. Duration of untreated psychosis and duration of untreated illness: new vistas. *CNS Spectr* 2010; **15**: 238-246 [PMID: 20414173 DOI: 10.1017/s1092852900000079]
 - 9 **Köhn D**, Pukrop R, Niedersteberg A, Schultze-Lutter F, Ruhrmann S, Bechdolf A, Berning J, Maier W, Klosterkötter J. [Pathways to care: help-seeking behavior in first-episode psychosis]. *Fortschr Neurol Psychiatr* 2004; **72**: 635-642 [PMID: 15529235 DOI: 10.1055/s-2004-818418]
 - 10 **Schultze-Lutter F**, Rahman J, Ruhrmann S, Michel C, Schimmelmann BG, Maier W, Klosterkötter J. Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 1831-1841 [PMID: 26155901 DOI: 10.1007/s00127-015-1093-3]
 - 11 **Schimmelmann 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**: 1-8 [PMID: 17628441 DOI: 10.1016/j.schres.2007.06.004]
 - 12 **Schimmelmann BG**, Walger P, Schultze-Lutter F. The significance of at-risk symptoms for psychosis in children and adolescents. *Can J Psychiatry* 2013; **58**: 32-40 [PMID: 23327754 DOI: 10.1177/070674371305800107]
 - 13 **Schimmelmann BG**, Schultze-Lutter F. Early detection and intervention of psychosis in children and adolescents: urgent need for studies. *Eur Child Adolesc Psychiatry* 2012; **21**: 239-241 [PMID: 22526975 DOI: 10.1007/s00787-012-0271-z]
 - 14 **Klosterkötter J**, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158-164 [PMID: 11177117 DOI: 10.1001/archpsyc.58.2.158]
 - 15 **Schultze-Lutter F**, Debbané M, Theodoridou A, Wood SJ, Raballo A, Michel C, Schmidt SJ, Kindler J, Ruhrmann S, Uhlhaas PJ. Revisiting the Basic Symptom Concept: Toward Translating Risk Symptoms for Psychosis into Neurobiological Targets. *Front Psychiatry* 2016; **7**: 9 [PMID: 26858660 DOI: 10.3389/fpsy.2016.00009]
 - 16 **Yung AR**, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl* 1998; **172**: 14-20 [PMID: 9764121 DOI: 10.1192/S0007125000297602]
 - 17 **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: S164-S169 [PMID: 11129303 DOI: 10.1080/000486700239]
 - 18 **Klosterkötter J**, Schultze-Lutter F, Ruhrmann S. Kraepelin and psychotic prodromal conditions. *Eur Arch Psychiatry Clin Neurosci* 2008; **258** Suppl 2: 74-84 [PMID: 18516519 DOI: 10.1007/s00406-008-2010-5]
 - 19 **Schultze-Lutter F**, Michel C, Schmidt SJ, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rössler A, van der Gaag M, Nordentoft M, Raballo A, Meneghelli A, Marshall M, Morrison A, Ruhrmann S, Klosterkötter J. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry* 2015; **30**: 405-416 [PMID: 25735810 DOI: 10.1016/j.eurpsy.2015.01.010]
 - 20 **Fusar-Poli P**, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, Nieman DH, Stahl DR, Rutigliano G, Riecher-Rössler A, Simon AE, Mizuno M, Lee TY, Kwon JS, Lam MM, Perez J, Keri S, Amminger P, Metzler S, Kawohl W, Rössler W, Lee J, Labad J, Ziermans T, An SK, Liu CC, Woodberry KA, Braham A, Corcoran C, McGorry P, Yung AR, McGuire PK. Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk: A Meta-analytical Stratification. *JAMA Psychiatry* 2016; **73**: 113-120 [PMID: 26719911 DOI: 10.1001/jamapsychiatry.2015.2324]
 - 21 **Cornblatt BA**, Carrión RE, Auther A, McLaughlin D, Olsen RH, John M, Correll CU. Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. *Am J Psychiatry* 2015; **172**: 986-994 [PMID: 26046336 DOI: 10.1176/appi.ajp.2015.13121686]
 - 22 **Schimmelmann BG**, Michel C, Martz-Irngartinger A, Linder C, Schultze-Lutter F. Age matters in the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in the general population: Findings from the BEAR and BEARS-kid studies. *World Psychiatry* 2015; **14**: 189-197 [PMID: 26043337 DOI: 10.1002/wps.20216]
 - 23 **Schultze-Lutter F**, Schimmelmann BG, Flückiger R, Michel C. Effects of age and sex on clinical high-risk for psychosis in the community. *World J Psychiatry* 2020; **10**: 101-124 [PMID: 32477906 DOI: 10.5498/wjp.v10.i5.101]

- 24 **Schmidt A**, Cappucciati M, Radua J, Rutigliano G, Rocchetti M, Dell'Osso L, Politi P, Borgwardt S, Reilly T, Valmaggia L, McGuire P, Fusar-Poli P. Improving Prognostic Accuracy in Subjects at Clinical High Risk for Psychosis: Systematic Review of Predictive Models and Meta-analytical Sequential Testing Simulation. *Schizophr Bull* 2017; **43**: 375-388 [PMID: 27535081 DOI: 10.1093/schbul/sbw098]
- 25 **Michel C**, Ruhrmann S, Schimmelmann BG, Klosterkötter J, Schultze-Lutter F. Course of clinical high-risk states for psychosis beyond conversion. *Eur Arch Psychiatry Clin Neurosci* 2018; **268**: 39-48 [PMID: 28054132 DOI: 10.1007/s00406-016-0764-8]
- 26 **Beck K**, Andreou C, Studerus E, Heitz U, Ittig S, Leanza L, Riecher-Rössler A. Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: A systematic review. *Schizophr Res* 2019; **210**: 39-47 [PMID: 30651204 DOI: 10.1016/j.schres.2018.12.047]
- 27 **McGorry P**, van Os J. Redeeming diagnosis in psychiatry: timing vs specificity. *Lancet* 2013; **381**: 343-345 [PMID: 23351805]
- 28 **Fusar-Poli P**, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychol Med* 2014; **44**: 17-24 [PMID: 23414600 DOI: 10.1017/S0033291713000184]
- 29 **McGorry PD**, Hartmann JA, Spooner R, Nelson B. Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* 2018; **17**: 133-142 [PMID: 29856558 DOI: 10.1002/wps.20514]
- 30 **van Os J**, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 2017; **16**: 200-206 [PMID: 28498576 DOI: 10.1002/wps.20423]
- 31 **Evans MJ**, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature* 1981; **292**: 154-156 [PMID: 7242681 DOI: 10.1038/292154a0]
- 32 **Krueger RF**, Eaton NR. Transdiagnostic factors of mental disorders. *World Psychiatry* 2015; **14**: 27-29 [PMID: 25655146 DOI: 10.1002/wps.20175]
- 33 **Zarrella I**, Russolillo LA, Caviglia G, Perrella R. Continuity and discontinuity between psychopathology of childhood and adulthood: a review on retrospective and prospective studies. *Res Psychother* 2017; **20**: 248 [PMID: 32913738 DOI: 10.4081/ripppo.2017.248]
- 34 **Sterba S**, Egger HL, Angold A. Diagnostic specificity and nonspecificity in the dimensions of preschool psychopathology. *J Child Psychol Psychiatry* 2007; **48**: 1005-1013 [PMID: 17915001 DOI: 10.1111/j.1469-7610.2007.01770.x]
- 35 **Kircanski K**, Zhang S, Stringaris A, Wiggins JL, Towbin KE, Pine DS, Leibenluft E, Brotman MA. Empirically derived patterns of psychiatric symptoms in youth: A latent profile analysis. *J Affect Disord* 2017; **216**: 109-116 [PMID: 27692699 DOI: 10.1016/j.jad.2016.09.016]
- 36 **Mennigen E**, Bearden CE. Psychosis Risk and Development: What Do We Know From Population-Based Studies? *Biol Psychiatry* 2020; **88**: 315-325 [PMID: 32061373 DOI: 10.1016/j.biopsych.2019.12.014]
- 37 **Rubino IA**, Frank E, Croce Nanni R, Pozzi D, Lanza di Scalea T, Siracusano A. A comparative study of axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology* 2009; **42**: 325-332 [PMID: 19672135 DOI: 10.1159/000232975]
- 38 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington: American Psychiatric Association, 1994
- 39 **Steel Z**, Marmare C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol* 2014; **43**: 476-493 [PMID: 24648481 DOI: 10.1093/ije/dyu038]
- 40 **Noterdaeme M**, Schlamp D, Linder M, Kischel KH. [Analysis of comorbid psychiatric disorders in child and adolescent psychiatry using the standardised basic documentation]. *Psychiatr Prax* 2004; **31** Suppl 1: S126-S128 [PMID: 15570527 DOI: 10.1055/s-2004-828452]
- 41 **Alonso J**, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lépine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martínez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004; **28-37** [PMID: 15128385 DOI: 10.1111/j.1600-0047.2004.00328.x]
- 42 **American Association for Public Opinion Research**. Standard Definitions Final Dispositions of Case Codes and Outcome Rates for Surveys. 2016. [cited 20 February 2021]. Available from: http://www.aapor.org/AAPOR_Main/media/publications/Standard-Definitions2016theditionfinal.pdf. Cited 6 February 2019
- 43 **McGlashan TH**, Walsh BC, Woods SW. The psychosis-risk syndrome. Handbook for diagnosis and follow-up. New York: Oxford University, 2010
- 44 **Schultze-Lutter F**, Marshall M, Koch E. Schizophrenia Proneness Instrument, Child and Youth version; Extended English Translation (SPI-CY EET). Rome, Italy: Giovanni Fioriti Editore s.r.l., 2012
- 45 **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**: 69-78 [PMID: 23473813 DOI: 10.1016/j.schres.2013.02.014]
- 46 **Sheehan DV**, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, Milo KM, Stock SL, Wilkinson B. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *J Clin Psychiatry* 2010; **71**: 313-326 [PMID: 20331933 DOI: 10.4088/JCP.09m05305whi]
- 47 **Byrt T**, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993; **46**: 423-429 [PMID: 8501467 DOI: 10.1016/0895-4356]
- 48 **Burn CC**, Pritchard J, Whay H. Observer reliability for working equine welfare assessment: Problems with high

- prevalences of certain results. *Anim Welf* 2009; **18**: 177-187
- 49 **Burn CC**, Weir AA. Using prevalence indices to aid interpretation and comparison of agreement ratings between two or more observers. *Vet J* 2011; **188**: 166-170 [PMID: 20570535 DOI: 10.1016/j.tvjl.2010.04.021]
- 50 **Hager W**. Basics of planning experiments for testing empirical hypotheses in Psychology. In: Lüer G. [General Experimental Psychology]. Stuttgart: Fischer, 1987, 43-264
- 51 **Schultze-Lutter F**, Hubl D, Schimmelmann BG, Michel C. Age effect on prevalence of ultra-high risk for psychosis symptoms: replication in a clinical sample of an early detection of psychosis service. *Eur Child Adolesc Psychiatry* 2017; **26**: 1401-1405 [PMID: 28456857 DOI: 10.1007/s00787-017-0994-y]
- 52 **Walger H**, Antonucci LA, Pigioli A, Upthegrove R, Salokangas RKR, Lencer R, Chisholm K, Riecher-Rössler A, Haidl T, Meisenzahl E, Rosen M, Ruhrmann S, Kambertz J, Kambertz-Ilankovic L, Falkai P, Ruef A, Hietala J, Pantelis C, Wood SJ, Brambilla P, Bertolino A, Borgwardt S, Koutsouleris N, Schultze-Lutter F. Basic Symptoms Are Associated With Age in Patients With a Clinical High-Risk State for Psychosis: Results From the PRONIA Study. *Front Psychiatry* 2020; **11**: 552175 [PMID: 33312133 DOI: 10.3389/fpsy.2020.552175]
- 53 **Theodoridou A**, Hengartner MP, Heekeren K, Dvorsky D, Schultze-Lutter F, Gerstenberg M, Walitza S, Rössler W. Influence of demographic characteristics on attenuated positive psychotic symptoms in a young, help-seeking, at-risk population. *Early Interv Psychiatry* 2019; **13**: 53-56 [PMID: 28417595 DOI: 10.1111/eip.12444]
- 54 **Orlic D**, Bodine DM. What defines a pluripotent hematopoietic stem cell (PHSC): will the real PHSC please stand up! *Blood* 1994; **84**: 3991-3994 [PMID: 7994018 DOI: 10.1182/blood.V84.12.3991.bloodjournal84123991]
- 55 **Woods SW**, Powers AR 3rd, Taylor JH, Davidson CA, Johannesen JK, Addington J, Perkins DO, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Lack of Diagnostic Pluripotentiality in Patients at Clinical High Risk for Psychosis: Specificity of Comorbidity Persistence and Search for Pluripotential Subgroups. *Schizophr Bull* 2018; **44**: 254-263 [PMID: 29036402 DOI: 10.1093/schbul/sbx138]
- 56 **McGorry PD**, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007; **187**: S40-S42 [PMID: 17908024 DOI: 10.5694/j.1326-5377.2007.tb01335.x]
- 57 **van Os J**, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 2016; **15**: 118-124 [PMID: 27265696 DOI: 10.1002/wps.20310]
- 58 **Schultze-Lutter F**, Michel C, Ruhrmann S, Schimmelmann BG. Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychol Med* 2018; **48**: 1167-1178 [PMID: 28889802 DOI: 10.1017/S0033291717002586]
- 59 **Michel C**, Kutschal C, Schimmelmann B, Schultze-Lutter F. Convergent and concurrent validity of the Frankfurt Complaint Questionnaire as a screener for psychosis risk. *J Risk Res* 2016; **20**: 1-17 [DOI: 10.1080/13669877.2016.1179209]
- 60 **Schultze-Lutter F**, Renner F, Paruch J, Julkowski D, Klosterkötter J, Ruhrmann S. Self-reported psychotic-like experiences are a poor estimate of clinician-rated attenuated and frank delusions and hallucinations. *Psychopathology* 2014; **47**: 194-201 [PMID: 24192655 DOI: 10.1159/000355554]
- 61 **Moriyama TS**, van Os J, Gadelha A, Pan PM, Salum GA, Manfro GG, Mari JJ, Miguel EC, Rohde LA, Polanczyk GV, McGuire P, Bressan RA, Drukker M. Differences Between Self-Reported Psychotic Experiences, Clinically Relevant Psychotic Experiences, and Attenuated Psychotic Symptoms in the General Population. *Front Psychiatry* 2019; **10**: 782 [PMID: 31736802 DOI: 10.3389/fpsy.2019.00782]
- 62 **Schultze-Lutter F**, Klosterkötter J, Gaebel W, Schmidt SJ. Psychosis-risk criteria in the general population: frequent misinterpretations and current evidence. *World Psychiatry* 2018; **17**: 107-108 [PMID: 29352561 DOI: 10.1002/wps.20498]
- 63 **Wong KK**, Raine A. Developmental Aspects of Schizotypy and Suspiciousness: a Review. *Curr Behav Neurosci Rep* 2018; **5**: 94-101 [PMID: 29577010 DOI: 10.1007/s40473-018-0144-y]
- 64 **Wong KK**, Raine A. Peer Problems and Low Self-esteem Mediate the Suspicious and Non-suspicious Schizotypy-Reactive Aggression Relationship in Children and Adolescents. *J Youth Adolesc* 2019; **48**: 2241-2254 [PMID: 31520236 DOI: 10.1007/s10964-019-01125-9]
- 65 **Bird JC**, Evans R, Waite F, Loe BS, Freeman D. Adolescent Paranoia: Prevalence, Structure, and Causal Mechanisms. *Schizophr Bull* 2019; **45**: 1134-1142 [PMID: 30534970 DOI: 10.1093/schbul/sby180]
- 66 **Bird JC**, Fergusson EC, Kirkham M, Shearn C, Teale AL, Carr L, Stratford HJ, James AC, Waite F, Freeman D. Paranoia in patients attending child and adolescent mental health services. *Aust N Z J Psychiatry* 2021; 4867420981416 [PMID: 33423520 DOI: 10.1177/0004867420981416]
- 67 **Martinez AP**, Wickham S, Rowse G, Milne E, Bentall RP. Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychol Med* 2020; 1-7 [PMID: 32441234 DOI: 10.1017/S0033291720001373]
- 68 **Pinkham AE**, Sasson NJ, Beaton D, Abdi H, Kohler CG, Penn DL. Qualitatively distinct factors contribute to elevated rates of paranoia in autism and schizophrenia. *J Abnorm Psychol* 2012; **121**: 767-777 [PMID: 22686868 DOI: 10.1037/a0028510]
- 69 **Muñoz-Negro JE**, Prudent C, Gutiérrez B, Cervilla JA. Paranoia and risk of personality disorder in the general population. *Personal Ment Health* 2019; **13**: 107-116 [PMID: 30989831 DOI: 10.1002/pmh.1443]
- 70 **Lee R**. Mistrustful and Misunderstood: A Review of Paranoid Personality Disorder. *Curr Behav Neurosci Rep* 2017; **4**: 151-165 [PMID: 29399432 DOI: 10.1007/s40473-017-0116-7]
- 71 **Shi TC**, Pagliaccio D, Cyr M, Simpson HB, Marsh R. Network-based functional connectivity predicts response to exposure therapy in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology* 2021; **46**: 1035-1044 [PMID: 33446895 DOI: 10.1038/s41386-020-00929-9]
- 72 **Michel C**, Flückiger R, Kindler J, Hubl D, Kaess M, Schultze-Lutter F. The trait-state distinction between schizotypy and clinical high risk: results from a one-year follow-up. *World Psychiatry* 2019; **18**: 108-109 [PMID: 30600631 DOI: 10.1002/wps.20595]
- 73 **Flückiger R**, Michel C, Grant P, Ruhrmann S, Vogeley K, Hubl D, Schimmelmann BG, Klosterkötter J, Schmidt SJ, Schultze-Lutter F. The interrelationship between schizotypy, clinical high risk for psychosis and related symptoms:

- Cognitive disturbances matter. *Schizophr Res* 2019; **210**: 188-196 [PMID: 30683524 DOI: 10.1016/j.schres.2018.12.039]
- 74 **Jimeno N**, Gomez-Pilar J, Poza J, Hornero R, Vogeley K, Meisenzahl E, Haidl T, Rosen M, Klosterkötter J, Schultze-Lutter F. Main Symptomatic Treatment Targets in Suspected and Early Psychosis: New Insights From Network Analysis. *Schizophr Bull* 2020; **46**: 884-895 [PMID: 32010940 DOI: 10.1093/schbul/sbz140]
- 75 **Kay SR**, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261-276 [PMID: 3616518 DOI: 10.1093/schbul/13.2.261]
- 76 **Driver DI**, Thomas S, Gogtay N, Rapoport JL. Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: An Update. *Child Adolesc Psychiatr Clin N Am* 2020; **29**: 71-90 [PMID: 31708054 DOI: 10.1016/j.chc.2019.08.017]
- 77 **Hunter EC**, Sierra M, David AS. The epidemiology of depersonalisation and derealisation. A systematic review. *Soc Psychiatry Psychiatr Epidemiol* 2004; **39**: 9-18 [PMID: 15022041 DOI: 10.1007/s00127-004-0701-4]
- 78 **Michal M**, Beutel ME. [Depersonalisation/derealization - clinical picture, diagnostics and therapy]. *Z Psychosom Med Psychother* 2009; **55**: 113-140 [PMID: 19402018 DOI: 10.13109/zptm.2009.55.2.113]
- 79 **Büetiger JR**, Hubl D, Kupferschmid S, Schultze-Lutter F, Schimmelmann BG, Federspiel A, Hauf M, Walther S, Kaess M, Michel C, Kindler J. Trapped in a Glass Bell Jar: Neural Correlates of Depersonalization and Derealization in Subjects at Clinical High-Risk of Psychosis and Depersonalization-Derealization Disorder. *Front Psychiatry* 2020; **11**: 535652 [PMID: 33024435 DOI: 10.3389/fpsy.2020.535652]
- 80 **Dewe H**, Watson DG, Kessler K, Braithwaite JJ. The depersonalized brain: New evidence supporting a distinction between depersonalization and derealization from discrete patterns of autonomic suppression observed in a non-clinical sample. *Conscious Cogn* 2018; **63**: 29-46 [PMID: 29929064 DOI: 10.1016/j.concog.2018.06.008]
- 81 **Čolić J**, Bassett TR, Latysheva A, Imboden C, Bader K, Hatzinger M, Mikoteit T, Lieb R, Gloster AT, Hoyer J. Depersonalization and derealization in embarrassing social interactions: an experience sampling study in social phobia, major depression and controls. *J Anxiety Disord* 2020; **70**: 102189 [PMID: 32070861 DOI: 10.1016/j.janxdis.2020.102189]
- 82 **Hallings-Pott C**, Waller G, Watson D, Scragg P. State dissociation in bulimic eating disorders: an experimental study. *Int J Eat Disord* 2005; **38**: 37-41 [PMID: 15971242 DOI: 10.1002/eat.20146]
- 83 **Kaufman J**, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 980-988 [PMID: 9204677 DOI: 10.1097/00004583-199707000-00021]
- 84 **Healy C**, Campbell D, Coughlan H, Clarke M, Kelleher I, Cannon M. Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood. *Acta Psychiatr Scand* 2018; **138**: 26-34 [PMID: 29855047 DOI: 10.1111/acps.12907]
- 85 **Niles HF**, Walsh BC, Woods SW, Powers AR 3rd. Does hallucination perceptual modality impact psychosis risk? *Acta Psychiatr Scand* 2019; **140**: 360-370 [PMID: 31355420 DOI: 10.1111/acps.13078]
- 86 **Lehembre-Shiah E**, Leong W, Brucato G, Abi-Dargham A, Lieberman JA, Horga G, Girgis RR. Distinct Relationships Between Visual and Auditory Perceptual Abnormalities and Conversion to Psychosis in a Clinical High-Risk Population. *JAMA Psychiatry* 2017; **74**: 104-106 [PMID: 27851840 DOI: 10.1001/jamapsychiatry.2016.3055]
- 87 **Ciarleglio AJ**, Brucato G, Masucci MD, Altschuler R, Colibazzi T, Corcoran CM, Crump FM, Horga G, Lehembre-Shiah E, Leong W, Schobel SA, Wall MM, Yang LH, Lieberman JA, Girgis RR. A predictive model for conversion to psychosis in clinical high-risk patients. *Psychol Med* 2019; **49**: 1128-1137 [PMID: 29950184 DOI: 10.1017/S003329171800171X]
- 88 **Zielasek J**, Gaebel W. [Schizophrenia and other primary psychotic disorders in ICD-11]. *Fortschr Neurol Psychiatr* 2018; **86**: 178-183 [PMID: 29621821 DOI: 10.1055/s-0044-101832]
- 89 **Klosterkötter J**. The meaning of basic symptoms for the genesis of the schizophrenic nuclear syndrome. *Jpn J Psychiatry Neurol* 1992; **46**: 609-630 [PMID: 1487845 DOI: 10.1111/j.1440-1819.1992.tb00535.x]
- 90 **Campion J**, Bhui K, Bhugra D; European Psychiatric Association. European Psychiatric Association (EPA) guidance on prevention of mental disorders. *Eur Psychiatry* 2012; **27**: 68-80 [PMID: 22285092 DOI: 10.1016/j.eurpsy.2011.10.004]
- 91 **Kirkbride JB**, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Arch Gen Psychiatry* 2006; **63**: 250-258 [PMID: 16520429 DOI: 10.1001/archpsyc.63.3.250]
- 92 **Schultze-Lutter F**, Schimmelmann BG, Michel C. Clinical high-risk of and conversion to psychosis in the community: A 3-year follow-up of a cohort study. *Schizophr Res* 2021; **228**: 616-618 [PMID: 33234428 DOI: 10.1016/j.schres.2020.11.032]
- 93 **Carpenter WT**. Attenuated psychosis syndrome: need for debate on a new disorder. *Psychopathology* 2014; **47**: 287-291 [PMID: 25060627 DOI: 10.1159/000365221]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

