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ORIGINAL CONTRIBUTION

Clinical high risk for psychosis in childhood and adolescence: findings from the 2-year follow-up of the ReARMS project

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Abstract

The clinical significance and the prognostic value of clinical high risk (CHR) for psychosis, while substantially corroborated in adults, remains less firmly established in children and early adolescents. This follow-up study, developed within the Reggio Emilia At Risk Mental States project, is meant to contribute to the reduction of such lacuna, and has two main aims: (1) to characterize the clinical profile of help seekers [stratified in non-CHR, CHR and first episode psychosis (FEP)] referred to child–adolescent mental health services; and (2) to monitor the cumulative transition rate from CHR to FEP in adolescents at the follow-up of 12 and 24 months. 112 adolescents (aged 13–18 years) were assessed with the Comprehensive Assessment of At-Risk Mental States and the Schizophrenia Proneness Instrument, Child and Youth version. 51 subjects met CHR criteria (45.5% of the sample) and 33 subjects met FEP criteria (29.5%) at baseline. The criterial transition rate from CHR to FEP was 7% over 12 months and 13% over 24 months; higher rates of cumulative transition were detected when also functional transition (indexed by the consensual introduction of antipsychotic medication by the treating clinical staff) was considered. The identification of CHR for psychosis in help-seeking adolescents is feasible and clinically relevant. Studies conducted in real world, publicly funded components of the national health system, should take into consideration not only criterial, psychometric transition, but also functional equivalents of transition.

Keywords Clinical high risk · Ultrahigh risk · Basic symptoms · Attenuated psychosis syndrome · Criterial transition · Functional transition

Introduction

In the last 20 years, prodromal phases of psychosis have attracted a growing clinical interest, boosted by a renewed attention to the issues of early detection of at-risk subjects and of indicated prevention of potential transitions to psychosis [1]. In this context, McGorry and colleagues developed a specific subset of criteria to identify individuals with a prospective ultrahigh risk (UHR) of psychosis [2]. Framed within the clinical staging model of psychosis [3, 4], prodromal states are clinically characterized by three UHR subgroups: (1) attenuated psychotic symptoms (APS), which represent sub-threshold positive symptoms; (2) brief limited intermittent psychotic symptoms (BLIPS), which are transient psychotic symptoms that spontaneously remit within 1 week; and (3) genetic risk and functioning deterioration syndrome (GRFD), a trait/state risk condition in which the patient has a family history of psychosis (in first-degree relatives) or manifests schizotypal personality disorder

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along with low functioning sustained for at least 1 month [5]. In addition to the UHR criteria, basic symptoms (BS) criteria were developed to detect the risk for psychosis as early as possible in the development of the disorder, ideally before functional impairment and prodromes of psychotic symptoms. BS refer to subjectively experienced subclinical disturbances in drive, affect, thinking, speech, body as well as sensory perception, motor action, central vegetative functions and stress tolerance [6, 7]. Among BS, cognitive disturbances (COGDIS) have been shown to be more predictive of transition to psychosis in comparison with cognitive and perceptual symptoms [8].

The pooled transition rate to psychosis of UHR subjects increases from 15% at 1 year to 37% at the 4-year follow-up [9], with a dilution effect in more recent UHR cohorts [10]. A recent meta-analytical stratification of risk among UHR subtypes [11] showed that in a pooled sample of 33 studies and 4227 subjects, prodromal stages are mostly characterized by APS (85% of enrolled cases), with BLIPS (10%) and GRFD (5%) representing a small proportion of cases. APS and BPLIS were characterized by distinct profiles of longitudinal risk at subsequent follow-ups, at 12 months (16% vs. 22%), 24 months (19% vs. 39%), 36 months (21% vs 38%) and ≥ 48 months (24% vs. 38%). Although exploratory, given the relatively few subjects presenting BS criteria without concomitant UHR criteria [11], meta-analytical results indicate that compared with the UHR criteria alone, clinical high risk (CHR) (i.e., UHR + BS) and BS criteria alone subgroups had higher psychosis transition rate or cumulative hazard rates at 36 and 48 months, respectively [9].

UHR in children and adolescents

Despite the substantial availability of validation studies in adult samples, empirical evidence on the clinical significance and the prognostic value of UHR criteria in children and early adolescents is less robust [12, 13]. Indeed, the current European Psychiatric Association (EPA) guidance papers on early CHR detection and intervention indicate that these criteria "should only be used and communicated with outmost care in children and young adolescents" [9, 14]. This cautionary position is mainly suggested by the shortage of specific evidence in the developmental years [15] and by relatively low predictive power of psychotic experiences in childhood and adolescence with respect to the specific outcome of adult psychosis [16, 17]. Indeed, such psychotic experiences in developmental years tend to be conceptualized as a general index of broader (and unspecific) vulnerability to mental health problems in later years. An instructive indication of the current situation of the field is provided by a recent systematic review [15] which analyzed 48 studies addressing CHR in children and adolescents:

- less than half of the studies (23 out of 48) had a sample with age ≤ 18 years, whereas another half ($n = 23$) with a far more extended age range (i.e., between 12 and 25 years) were included because the pooled sample mean age was ≤ 18 years;
- almost two-thirds (30 out of 48 studies) were provided by only four clinical centers, with the possibility of partially overlapping samples between studies;
- among reviewed studies only five studies [18–22] (Table 1) reported the baseline prevalence of UHR adolescents among those assessed and only five studies [18, 19, 21, 23, 24] reported follow-up evaluations and relative transition rates to psychosis.

To account for potential developmental peculiarities and a different clustering of BS in children and adolescents, the Schizophrenia Proneness Instrument-Child and Youth version (SPI-CY) was developed [25]. It showed good discriminant validity, demonstrating to be a helpful tool for detecting and assessing BS in the psychosis spectrum in children and adolescents [26]. In COGDIS (criteria alone) child and

Table 1 Studies on UHR in help-seeking adolescents

Study (first author, year, reference)	CHR instrument (criteria)	CHR age (mean ± SD)	CHR+ Baseline (*n*)	CHR prevalence baseline (%)	Follow-up (months)	Follow-up UHR—FEP transition rate
Ziermans 2011 [23]	SIPS	15.3 ± 1.9	72	na	24	15.2% (at 2 years)
Lindgren 2014 [19]	SIPS	16.6 ± 0.9	54	33.5%	12	8.5 (at 1 year)
Welsh 2014 [18]	CAARMS	15.8 ± 1.4	30	85.71%	6	3.4% (at 6 months)
Armando 2015 [24]	SIPS	13.8 ± 2.1	35	na	12	20% (at 1-year)
Gerstenberg 2015 [20]	SIPS	15.1 ± 1.6	21	24.13%	na	na
Spada 2016 [21]	CAARMS	16.09 ± 1.02	22	44%	6	18.18% (at 6 months)
Lo Cascio 2016 [22]	SIPS	14.7 ± 1.4	22	31.9%	na	na
Pelizza 2017 [25]	CAARMS	14.76 ± 1.33	25	48%	12	10% (at 1 year)

UHR ultrahigh risk, *FEP* first episode psychosis, *CAARMS* Comprehensive Assessment of At-Risk Mental State, *SIPS* Structured Interview for Prodromal Symptoms, *na* not available

adolescent samples, a 2-year conversion rate of 17.9% was found [9].

In addition to these studies, we recently published the baseline characteristics and 1-year transition rate (10%) of the UHR cohort ($n = 25$) [27] selected with a dedicated tool (i.e., the Comprehensive Assessment of At-Risk Mental States—CAARMS) [5] among 79 help-seeking adolescents attending the Reggio Emilia At-Risk Mental States (ReARMS) project [28] (see Table 1). Overall, the empirical literature on the clinical significance of UHR in children and adolescents is poorer in comparison with the one on young adults and would therefore benefit from further investigation.

Starting from this background, the aim of the current study is twofold:

1. to characterize the clinical profile and the functioning level of distinct help-seeking subgroups of adolescents identified through the CHR criteria [i.e., non-CHR vs. CHR vs. first episode psychosis (FEP)];
2. to monitor the cumulative transition rate from CHR to FEP in adolescents at the follow-up of 24 months.

Methods

Participants

All the participants ($n = 112$) were help-seeking adolescents recruited through the ReARMS project between September 2012 and August 2017. ReARMS is an early detection and intervention infrastructure implemented under the aegis of the "Regional Project on Early Intervention in Psychosis" within all of adult mental health services and Child and Adolescent Mental Health Services (CAMHS) of the Reggio Emilia Department of Mental Health [28], a semi-urban catchment area of approximately 550.000 inhabitants, of whom nearly 105.000 are < 18-year-old), in northern Italy.

For the aims of the study, ReARMS inclusion criteria were: (1) specialist help seeking; (2) age between 13 and 18 years; (3) presence of "imminent" clinical high-risk status (CHR), including individuals who met UHR criteria defined by the CAARMS (i.e., APS, BLIPS, and GRFD) [5] or COGDIS criteria defined by the SPI-CY [25], or (4) duration of untreated psychosis (DUP) < 2 years in case CAARMS FEP criteria are detected at baseline assessment. Since ReARMS is a clinical project providing evidence-based intervention in CHR/FEP adolescents, we opted for a DUP of < 2 years; indeed, previous reviews and meta-analyses showed that short DUP was associated with a better outcome of FEP, whereas long DUP was associated with a poorer general symptomatic outcome, failure to achieve remission, and decreased social and daily functioning [29, 30].

For research purposes, Cornblatt and colleagues [31] distinguished CHR individuals from subjects at genetic high risk (GHR) (i.e., the first-degree relatives of an affected individual) to examine risk differences in the probabilistic nature of future psychotic disorder. In their CHR group, the authors defined two different subgroups: (1) CHR+ (i.e., people with moderate to severe APS) and (2) CHR − (i.e., subjects with only nonspecific, attenuated negative symptoms, such as social isolation and deterioration of school/role functioning). In comparison with this classification, in the present study, together with BLIPS and COGDIS subgroups, the term CHR included Cornblatt's CHR+ individuals in the APS group and Cornblatt's GHR subjects in the GRFD group.

The exclusion criteria were: (1) history of affective and non-affective psychotic disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR) [32]; (2) history of previous exposure to antipsychotics; (3) current substance dependence; (4) known intellectual disability (intelligence quotient < 70, as measured with the Wechsler Intelligence Scale for Children-IV edition [WISC-IV] [33] or the Wechsler Adult Intelligence Scale-IV edition [WAIS-IV] [34]—as appropriate); and (5) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. In the current study, we considered previous exposure to antipsychotic (i.e., before ReARMS enrollment) as an equivalent of past psychotic episode in patients without a history of psychotic disorders. Indeed, this was in line with the psychosis criteria defined by the CAARMS [5], in which the threshold of full-blown psychotic episode (defined by operationalized clear-cut levels of fully positive symptoms occurring for > 1 week, either daily or > 3 times a week with each symptom continuing for > 1 h on each occasion) is essentially that at which antipsychotic medication would probably be commenced in common clinical practice. Although antipsychotics could be prescribed in other kinds of symptoms (not only in relation to psychotic symptoms), we however preferred to exclude individuals with previous exposure to antipsychotic to avoid the inclusion of subjects with a possible past psychotic episode whose clinical expression may have been mitigated by antipsychotic medication itself.

All adolescent help seekers entering the ReARMS protocol and their parents agreed to participate in the research and gave their informed consent. All participants were Italian native speakers. Relevant ethical approvals were sought for the study. The current research was also carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments including humans.

Instruments

The psychopathological assessment for this study included the CAARMS (approved Italian translation [CAARMS-ITA] [35]) and the PANSS (approved Italian version [36]).

The *CAARMS* is a semi-structured clinical interview designed to cover different features of attenuated psychopathology, as well as functioning (via the integrated SOFAS [Social and Occupational Assessment Scale] module) [5]. It takes approximately 1–1.5 h to be administered and consists of 27 items, each one rated in terms of intensity (0–6) and frequency/duration (0–6), which can be clustered into seven subscales: (1) "Positive Symptoms" (disorders of thought content, perceptual abnormalities, disorganized speech); (2) "Cognitive Change, Attention and Concentration" (subjective experience and observed cognitive change); (3) "Emotional Disturbance" (subjective emotional disturbance, observed blunted affect, observed inappropriate affect); (4) "Negative Symptoms" (alogia, avolition/apathy, anhedonia); (5) "Behavioral Change" (social isolation, impaired role functioning, disorganizing/odd/stigmatizing behavior, aggressive/dangerous behavior); (6) "Motor/Physical Changes" (complaints of impaired motor functioning, impaired bodily sensation, impaired autonomic functioning); and (7) "General Psychopathology" (mania, depression, suicidality and self-harm, mood swings/lability, anxiety, obsessive–compulsive symptoms, dissociative symptoms, impaired tolerance to normal stress). Embedded in these subscales, the CAARMS also enlists items inspired by Huber's basic symptoms. Those are anomalous subjective experience of "cognitive change", "emotional disturbance", "avolition/apathy", "impaired motor functioning", "impaired bodily sensation", "impaired autonomic functioning", and "impaired tolerance to normal stress".

The CAARMS "Positive Symptoms" subscale, which covers delusions, hallucinations and thought disorder, is used to determine both the UHR criteria and the threshold for psychosis [5]. UHR status is defined as follows: (1) GRFD group: schizotypal personality disorder in the subject or family history of psychosis in a first-degree relative combined with 30% drop in functioning for ≤ 1 month or chronic low functioning, as measured with SOFAS scale (decline in functioning is calculated subtracting current SOFAS score from the highest SOFAS score in the past year); (2) APS group: sub-threshold positive psychotic symptoms within the past 12 months; and (3) BLIPS group: criteria for psychosis met for < 7 day at a time and ceasing spontaneously (i.e., without antipsychotic medications). According to the psychosis criteria defined by the CAARMS [5], the threshold of full-blown psychotic episode is defined by operationalized clear-cut levels of fully positive symptoms occurring for > 1 week, either daily or > 3 times a week with each symptom continuing for > 1 h on each occasion.

CAARMS interviews were conducted by clinical psychologists and neuropsychiatrists trained by the main author of the approved Italian translation [35], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability of these assessments. The intra-class correlation (ICC) coefficients of each CAARMS-ITA subscales showed good to excellent inter-rater reliability [37], in line with the original version of Yung and colleagues [5]. In details, the inter-rater reliability for the overall score was 0.91 and above 0.74 for all the subscales [37].

The *PANSS* is a 30-item scale specifically designed to assess the severity of psychotic symptoms, subdivided into three major dimensions: (1) "Positive Symptoms" (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution, hostility); (2) "Negative Symptoms" (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking); and (3) "General Psychopathology" (somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance). Each item can be rated from 1 ("absent") to 7 ("extreme"). In the present study, we used the Italian version of the PANSS [36], which has been widely used to assess psychotic symptoms in adolescents, showing good psychometric properties [38].

The *COGDIS criteria* and their nine constituting "thought disturbance" basic symptoms (BS) (i.e., disturbances of abstract thinking, inability to divide attention, disturbance of expressive speech, captivation of attention by details of the visual field, thought interference, thought pressure, disturbance of receptive speech, thought perseveration, thought blockage) were assessed using the *SPI-CY*, approved Italian version [25]. Overall, the instrument consists of four subscales: "adynamia", "perception disturbances", "neuroticism", and "thought and motor disturbances". The SPI-CY showed good discriminant validity and good reliability across trained raters and different settings [25]. The ReARMS team members routinely use the SPI-CY in the initial assessment to determine whether individual meets BS criteria. They were trained in the administration of the instrument by the certified Italian trainer and main translator of the approved Italian version (E.G.) [25]. Regular SPI-CY collective supervision sessions and scoring workshops, chaired by E.G., ensured the inter-rater reliability of these assessments.

All the participants entering the ReARMS protocol underwent an extensive diagnostic assessment [28]. The axis

I diagnosis was made according to DSM-IV-TR criteria by two trained ReARMS team members, using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I) [39]. Moreover, intelligence quotient (IQ) was measured using WISC-IV [33] or WAIS-IV [34] to exclude intellectual disability.

Procedures

After SPI-CY and CAARMS interviews, participants were divided into three groups according to COGDIS and UHR/psychosis criteria: CHR+ group [i.e., COGDIS and/or UHR (APS, BLIPS and GRFD)], FEP group, and CHR − group (i.e., those individuals under the threshold of the COGDIS/CAARMS inclusion criteria). All the help seekers referred to the ReARMS protocol were assigned to a multi-professional team including a child/adolescent neuropsychiatrist, a clinical psychologist, and a case manager for early rehabilitation, generally within 2–3 weeks. According to their symptoms, CHR individuals were then provided with a comprehensive 2-year intervention package including multi-element psychosocial intervention [combining individual cognitive–behavioral therapy (CBT), psychoeducational sessions for family members, and a recovery-oriented case management] as first step and pharmacological treatment as second step, according to the current guidelines [13, 40]. The prescription of antipsychotics was avoided unless the CHR individual (1) had an imminent risk of suicide or severe violence, (2) was overwhelmed by abruptly worsening full-blown psychotic symptoms, (3) was rapidly deteriorating in daily functioning, or (4) did not respond to any other treatment. Low-dose atypical antipsychotics were used. Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia.

Functioning and psychopathology experienced by adolescent help seekers at baseline were assessed by evaluating between-group comparisons (FEP, CHR+, and CHR −) on the SOFAS, CAARMS (including Huber's basic symptoms scores), and PANSS subscale scores. Between-group comparisons on the three CAARMS empirical dimensions (i.e., "negative-interpersonal", "communicational–cognitive–behavioral disorganization", and "perceptual–affective instability") identified in a previous study [41] were also carried out.

Lastly, the predictive validity of the CHR criteria was tested by consecutively identifying CHR+ adolescents according to SPI-CY-defined COGDIS or CAARMS-defined UHR criteria. CHR+ participants were followed up for 2 years in the ReARMS protocol. In detail, after 12 and 24 months from baseline assessment, CAARMS was re-administered to detect any possible psychosis transition. During the 2-year intervention period, they were usually followed up weekly or after every 3–4 weeks, in accordance with their clinical needs. Since the definition of psychotic episode is consensually based on the presence of a clear-cut threshold level of positive symptoms at which neuroleptic medication would probably be commenced in common clinical practice [5], we calculated the rates of transition to psychosis (at 12 and 24 months from baseline) adopting a rational, context-sensitive operationalization compatible with the real-world, non-academic clinical setting of the ReARMS project. That is, we considered as equivalents of transition to psychosis the two following conditions:

1. the psychometric threshold for the diagnosis of psychosis based on the CAARMS (i.e., "criterial" equivalent of transition to psychosis according to Yung et al. [5]);

   OR

2. the consensual, clinical decisional threshold at which antipsychotic treatment was commenced under the agreement of the treating clinical staff (i.e., "functional" equivalent of transition to psychosis according to Yung et al. [5]). Indeed, for these authors, this threshold could be considered equivalent to the presence of full-blown positive psychotic symptoms.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) 15.0. Descriptive analyses included mean values and standard deviation (SD) for continuous variables, and absolute and relative frequencies for categorical variables. Cross-sectional analyses on the demographic, clinical, and psychopathological characteristics among the three groups were assessed with ANOVA, using Fisher's least significant difference (LSD) to correct for multiple comparisons involving normally distributed variables. The Kruskal–Wallis test was used for variables that were not normally distributed, and post hoc analyses were performed by using the Mann–Whitney *U* test. A Chi square test and Fisher's exact test were employed for categorical variables. Fisher's exact test was used when any expected frequency was < 1, or 20% of the expected frequency was ≤ 5.

For the calculation of the predictive validity, in addition to cumulative incidence (i.e., the number of new psychosis conversion at 1- and 2-year follow-up period by the total number of CHR+ individuals at baseline), we performed the Kaplan–Meier survival analysis to take into account the different durations of follow-ups and those who dropped out. The primary aim of survival analysis is the modeling and analysis of "time-to-event" data; that is, data that have as an end point the time when an event occurs [42]. In this respect, events are not limited to death, but may include

other "negative" events such as psychosis transition in young people at risk [11]. We specifically calculated 1- and 2-year cumulative survival and cumulative proportion of psychosis conversion (i.e., 1—cumulative survival) [42].

Results

Over the course of the study, 112 adolescents (56 males and 56 females; mean age 15.84 ± 1.68 years) consecutively attended an interview within the ReARMS protocol implemented within the CAMHS of the Department of Mental Health, Reggio Emilia. The socio-demographic variables and the mean ratings of the CAARMS subscales, PANSS subscales, and SOFAS are reported in Table 2.

Referrals to CAMHS of individuals subsequently enrolled in the ReARMS program were mainly performed by general practitioners (GPs) ($n = 43$; 38.4%), family members ($n = 18$; 16.1%), emergency room ($n = 18$; 16.1%), school and social services ($n = 16$; 14.2%), or they were self-referred ($n = 17$; 15.2%).

Among the CHR+ group ($n = 51$; 45.5% of the total sample), 39 met UHR criteria (76.5% of the CHR+ subgroup; 31 UHR + COGDIS criteria and 8 UHR criteria only) and 12 (23.5%) only COGDIS criteria (Fig. 1). Within UHR adolescents, 36 met APS criteria (92.3% of the UHR subgroup), 2 met BLIPS criteria, and 1 met GRFD criteria. In our CHR+ sample, major depression was the most frequent diagnosis ($n = 27$; 52.9%) at initial examination, followed by anxiety disorders ($n = 12$; 23.5%), schizotypal personality disorder ($n = 6$; 11.8%), obsessive–compulsive disorder ($n = 4$; 7.9%), and psychotic disorder not otherwise specified ($n = 2$: 3.9%). In our CHR+ adolescents, there is an overlap between psychotic disorder not otherwise specified and BLIPS. To disentangle these two diagnostic groups, it could be useful to focus more clinical attention on the co-occurrence of specific psychopathological features concerning the duration and the phenomenological completeness of psychotic symptomatology (indeed, BLIPS are specifically transient, full-blown, positive psychotic symptoms that spontaneously remit within 1 week) [5]. Moreover, 28 (54.9%) CHR+ individuals received individual CBT [session median = 10 (interquartile range 7–15) at 1 year and 16 [interquartile range 12–22.25] at 2 years], 22 (43.1%) received psychoeducation for family members [session median = 9 (interquartile range 5–10.50) at 1 year and 19 (interquartile range 15–32) at 2 years], and 36 (70.6%) received a case management oriented to early recovery and rehabilitation [session median = 8 (interquartile range 6–10) at 1 year and 15 (interquartile range 11–26) at 2 years]. Finally, at baseline, 12 (23.5%) CHR+ participants have been prescribed antidepressant medication [mean equivalent dose of clomipramine = 141.60 mg daily (standard deviation = ± 63.27 mg daily)] and 3 (5.9%) took benzodiazepines (mean equivalent dose of lorazepam = 2.00 mg daily (standard deviation = ± 0.87 mg daily)].

The FEP group ($n = 33$; 29.5% of the total sample) consisted of patients with DSM-IV-TR schizophrenia ($n = 15$; 45.4%), affective (bipolar or major depressive) psychosis ($n = 9$; 27.2%), psychotic disorder not otherwise specified (n = 7; 21.2%), and brief psychotic disorder ($n = 2$; 6.2%). The remaining 28 participants (25.0% of the total sample) did not meet COGDIS criteria and were below the CAARMS threshold for being considered at risk for psychosis, composing the CHR − group. They were diagnosed with DSM-IV-TR depressive disorders ($n = 11$; 39.3%), non-schizotypal personality disorder ($n = 10$; 35.7%) [i.e., borderline ($n = 5$), avoidant ($n = 3$), and narcissistic ($n = 2$) personality disorder], and anxiety disorders ($n = 7$; 25.0%).

The three subgroups showed no differences in terms of gender, ethnic group, years of education, and duration of untreated illness (DUI), defined as the interval (in weeks) between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment [43]. However, CHR+ adolescents showed significantly lower mean age than FEP patients. They also had a lower age than CHR − individuals, but the difference was not significant ($p = 0.910$).

Psychopathology and functioning

There was significant between-group difference in SOFAS scores (Table 2). As expected, SOFAS scores of the FEP and CHR+ individuals were significantly lower than those in the CHR − group, with no significant difference between FEP and CHR+ ($p = 0.323$).

PANSS "Positive Symptoms" subscale scores and all subscores of CAARMS "Positive Symptoms" dimension (i.e., "unusual thought content", "non-bizarre ideas", "perceptual abnormalities", and "disorganized speech") were different among the three groups (Table 2). Indeed, CHR+ group scores were significantly higher than those in CHR − adolescents, but significantly lower than those in FEP patients.

There were also significant differences among the three groups in the PANSS "Negative Symptoms" and "General Psychopathology" subscale scores (Table 2). In detail, PANSS "Negative Symptoms" and "General Psychopathology" subscores of FEP and CHR+ adolescents were significantly higher than those in CHR − peers. Moreover, the general psychopathology was more severe in FEP than in CHR+ individuals. However, although negative symptoms were slightly higher in the FEP group than in the CHR+ groups, the difference was not significant ($p = 0.184$). However, in comparison with CHR+, FEP adolescents showed significantly higher scores on CAARMS "observed blunted affect", "avolition/apathy", and "anhedonia" subscales.

Table 2 Demographic, clinical, and psychopathological characteristics of the total sample and the three subgroups

Variable	Total sample ($n=112$)	CHR [−] ($n=28$)	CHR [+] ($n=51$)	FEP ($n=33$)	Statistics (F/X^2)	Post hoc test
Gender (males)	56 (50.0%)	17 (60.7%)	21 (41.2%)	18 (54.5%)	3.15	–
Ethnic group (Caucasian)	94 (83.9%)	24 (85.7%)	44 (86.3%)	26 (78.8%)	0.92	–
Age	15.84 ± 1.68	16.07 ± 1.86	15.41 ± 1.56	16.30 ± 1.57	3.31[c]	FEP > CHR[+]
Education (in years)	10.45 ± 1.56	10.50 ± 1.50	10.33 ± 1.61	10.58 ± 1.56	0.26	–
DUI (in weeks)	74.21 ± 51.78	69.11 ± 51.23	63.73 ± 41.80	94.73 ± 61.04	3.98	–
SOFAS	50.65 ± 11.50	59.07 ± 11.09	49.50 ± 9.11	46.94 ± 8.66	23.00[a]	CHR[-] > CHR[+]=FEP
PANSS						
Positive symptoms	14.88 ± 5.98	10.57 ± 2.78	13.24 ± 3.57	21.06 ± 6.12	52.08[a]	FEP > CHR[+]>CHR[-]
Negative symptoms	16.80 ± 7.45	11.86 ± 4.43	17.47 ± 7.47	19.97 ± 7.51	19.96[a]	FEP = CHR[+]=CHR[-]
General psychopathology	36.61 ± 10.73	30.11 ± 8.36	36.18 ± 9.16	42.79 ± 11.51	21.38[a]	FEP > CHR[+]=CHR[-]
CAARMS						
Positive symptoms						
Unusual thought content	2.66 ± 2.10	0.82 ± 1.23	2.53 ± 1.46	4.47 ± 2.09	44.03[a]	FEP > CHR[+]>CHR[-]
Non-bizarre ideas	2.93 ± 2.00	1.61 ± 1.20	2.41 ± 1.50	4.91 ± 1.82	45.18[a]	FEP > CHR[+]>CHR[-]
Perceptual abnormalities	2.28 ± 2.02	0.64 ± 1.16	2.29 ± 1.45	3.69 ± 2.33	32.77[a]	FEP > CHR[+]>CHR[-]
Disorganized speech	1.97 ± 1.81	0.89 ± 1.26	2.00 ± 1.56	2.88 ± 2.09	18.03[a]	FEP > CHR[+]>CHR[-]
Cognitive change						
Subjective cognitive change*	3.19 ± 1.60	2.04 ± 1.55	3.04 ± 1.25	4.28 ± 1.49	27.54[a]	FEP > CHR[+]>CHR[-]
Observed cognitive change	1.51 ± 1.65	0.64 ± 1.10	1.55 ± 1.50	2.00 ± 2.03.	9.54[b]	FEP = CHR[+]>CHR[-]
Emotional disturbance						
Subjective emotional disturbance*	2.05 ± 1.99	0.82 ± 1.44	2.16 ± 1.86	2.94 ± 2.12	17.11[a]	FEP = CHR[+]>CHR[-]
Observed blunted affect	2.04 ± 1.93	1.00 ± 1.44	1.92 ± 1.79	3.13 ± 2.00	17.65[a]	FEP > CHR[+]>CHR[-]
Observed inappropriate affect	0.90 ± 1.48	0.39 ± 0.92	0.78 ± 1.33	1.53 ± 1.87	6.92[c]	FEP > CHR[-]
Negative symptoms						
Alogia	1.60 ± 1.74	0.93 ± 1.27	1.71 ± 1.72	2.03 ± 1.99	6.09[c]	FEP > CHR[-]
Avolition/apathy*	2.41 ± 1.86	1.29 ± 1.67	2.45 ± 1.79	3.34 ± 1.62	18.27[a]	FEP > CHR[+]>CHR[-]
Anhedonia	2.51 ± 1.98	1.00 ± 1.76	2.73 ± 1.72	3.50 ± 1.81	23.59[a]	FEP > CHR[+]>CHR[-]
Behavioral change						
Social isolation	3.31 ± 1.69	2.57 ± 1.81	3.45 ± 1.59	3.72 ± 1.59	6.04[c]	FEP = CHR[+]>CHR[-]
Impaired role functioning	2.81 ± 2.06	1.75 ± 2.17	2.96 ± 1.84	3.50 ± 2.00	10.38[b]	FEP = CHR[+]>CHR[-]
Disorganizing/odd/stigmatizing behavior	1.86 ± 1.86	1.11 ± 1.52	1.69 ± 1.76	2.81 ± 1.92	13.35[b]	FEP > CHR[+]=CHR[-]
Aggressive/dangerous behavior	1.95 ± 1.85	1.57 ± 2.08	2.14 ± 1.81	2.00 ± 1.68	2.24	–
Motor/physical change						
Subjective impaired motor functioning*	0.59 ± 1.26	0.11 ± 0.57	0.41 ± 1.06	1.28 ± 1.67	16.18[a]	FEP > CHR[+]=CHR[-]

Table 2 (continued)

Variable	Total sample ($n=112$)	CHR [−] ($n=28$)	CHR [+] ($n=51$)	FEP ($n=33$)	Statistics (F/X^2)	Post hoc test
Objective impaired motor functioning	0.45 ± 1.05	0.18 ± 0.55	0.33 ± 1.07	0.88 ± 1.24	10.13[b]	FEP > CHR[+]=CHR[-]
Subjective impaired bodily sensation*	0.86 ± 1.51	0.32 ± 0.94	0.78 ± 1.49	1.44 ± 1.76	93.86[b]	FEP > CHR[+]=CHR[-]
Subjective impaired autonomic functioning*	1.02 ± 1.58	0.61 ± 1.31	1.18 ± 1.49	1.13 ± 1.90	3.14	–
General psychopathology						
Mania	0.54 ± 1.20	0.50 ± 1.07	0.51 ± 1.19	0.63 ± 1.36	0.81	–
Depression	2.77 ± 1.67	2.14 ± 1.63	3.06 ± 1.69	2.84 ± 1.59	6.80[c]	CHR[+]>CHR[-]
Suicidality/self-harm	1.59 ± 1.81	1.07 ± 1.36	1.75 ± 1.81	1.78 ± 2.11	2.54	–
Mood swings/lability	1.68 ± 1.74	1.50 ± 1.84	1.61 ± 1.69	1.97 ± 1.75	1.64	–
Anxiety	3.23 ± 1.73	2.86 ± 1.84	3.08 ± 1.81	3.81 ± 1.38	5.63	–
Obsessive–compulsive symptoms	0.98 ± 1.65	0.54 ± 1.14	1.16 ± 1.84	1.09 ± 1.69	2.47	–
Dissociative symptoms	1.19 ± 1.70	0.39 ± 1.13	1.37 ± 1.64	1.59 ± 2.01	9.74[b]	FEP = CHR[+]>CHR[-]
Subjective impaired tolerance to normal* stress	2.61 ± 1.91	2.18 ± 1.81	2.39 ± 2.00	3.34 ± 1.68	6.75[c]	FEP > CHR[+]=CHR[-]
CAARMS Factor1						
Negative-interpersonal dimension	20.68 ± 9.92	14.39 ± 8.86	21.29 ± 9.68	25.19 ± 8.50	19.28[a]	FEP = CHR[+]>CHR[-]
CAARMS Factor2						
Communicational–cognitive–behavioral disorganization	11.48 ± 7.31	6.50 ± 4.56	11.27 ± 5.92	16.16 ± 8.35	27.53[a]	FEP > CHR[+]>CHR[-]
CAARMS Factor3						
Perceptual–affective instability	7.50 ± 4.23	4.79 ± 3.45	7.78 ± 3.56	9.44 ± 4.71	17.40[a]	FEP = CHR[+]>CHR[-]

Frequencies (percentages), mean ± standard deviation, one-way Anova test (F), Kruskal–Wallis test (χ^2), and Chi squared test (χ^2) values are reported

[a] $p<0.001$

[b] $p<0.01$

[c] $p<0.05$

*CAARMS Huber's basic symptoms

Furthermore, CHR+ participants had significantly higher CAARMS "depression" subscale scores than those in CHR − peers. They also had higher depression subscores than those in FEP patients, but the difference was not significant ($p=0.483$). With regard to Huber's basic symptoms, six of the seven subscales measured in the CAARMS (i.e., subjective experience of "cognitive change", "emotional disturbance", "avolition/apathy", "impaired motor functioning", "impaired bodily sensation", and "impaired tolerance to normal stress") showed significant differences among the three groups (Table 2). In detail, the scores of these six subscales in the FEP group were significantly higher than those in CHR − adolescents. Moreover, CHR+ individuals had significantly higher scores than CHR − in terms of cognitive

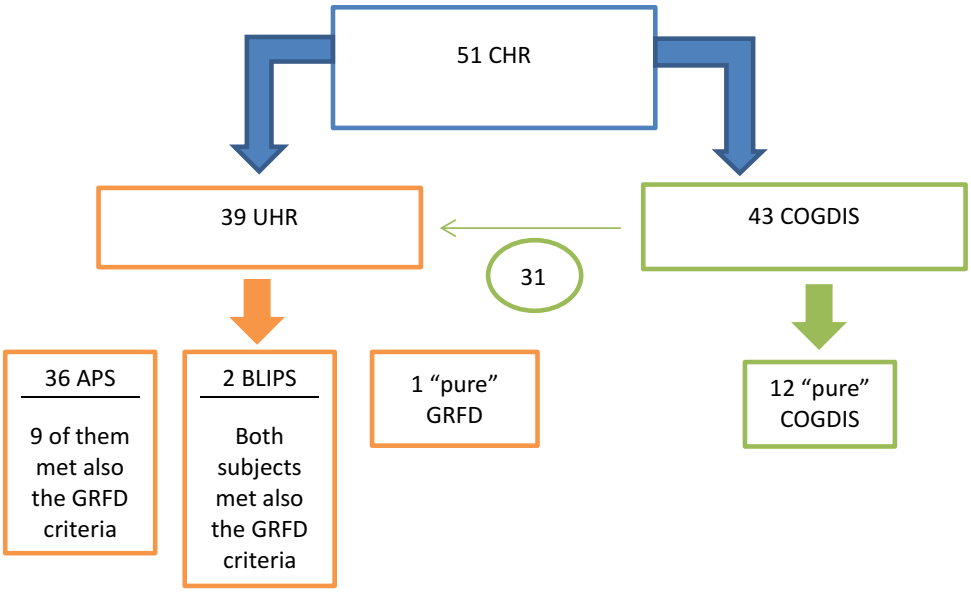

Fig. 1 Composition of CHR+ subgroup ($n=51$). *CHR+* clinical high-risk adolescents, *UHR* individuals meeting CAARMS Ultra-High Risk criteria, *COGDIS* individuals meeting SPI-CY COGDIS ("cognitive disturbances") criteria, *APS* attenuated psychotic symptoms, *BLIPS* Brief Limited Intermittent Psychotic Criteria, *GRFD* genetic risk and functioning deterioration syndrome, *CAARMS* Comprehensive Assessment of At-Risk Mental States; *SPI-CY* Schizophrenia Proneness Instrument-Child and Youth version

change and emotional disturbance, as well as avolition/apathy. Finally, in addition to avolition/apathy, FEP patients also experienced subjectively higher cognitive change, impaired motor functioning, impaired bodily sensation, and impaired tolerance to normal stress than CHR+ adolescents. However, no difference (between FEP and CHR +) was found in terms of emotional disturbance ($p=0.077$), as well as CAARMS "observed cognitive change" ($p=0.411$).

Within the CHR+ group, the highest mean values were found in CAARMS "social isolation", "anxiety", "depression", and "subjective experience of cognitive change" subscale scores, followed by "impaired role functioning" and "anhedonia" subscores (Table 2).

Finally, there were significant differences among the three groups in all of three CAARMS factor scores (Table 2). In detail, CAARMS "negative-interpersonal dimension" (factor 1), "communicational–cognitive–behavioral disorganization" (factor 2), and "perceptual–affective instability" (factor 3) subscores of FEP and CHR+ adolescents were significantly higher than those in CHR − peers. Moreover, CAARMS factor 2, as well as CAARMS "disorganizing/odd/stigmatizing behavior" subscores, was significantly higher in the FEP group than in CHR+ individuals. However, although CAARMS factor 1 and factor 3 in the FEP group were significantly more severe than in CHR+ adolescents, the differences were not significant (respectively, $p=0.073$ and $p=0.097$).

Predictive validity

Ten of the 51 CHR+ adolescents had a follow-up period of < 1 year (i.e., they did not achieve the 12-month assessment time) (Fig. 2). After 12 months of follow-up, 2 of the remaining 41 CHR+ individuals had transitioned to full-blown psychosis from a previous APS (CAARMS "criterial" transition), with the cumulative proportion of psychosis conversion equal to 7% (Table 3). One of them has been prescribed antipsychotics during the follow-up period. Moreover, antipsychotic medications were prescribed to the other 13 of the 41 CHR+ adolescents during the 12-month follow-up period ("functional" equivalent of transition to psychosis). Therefore, after 1 year of follow-up, we found a cumulative incidence of psychosis conversion equal to 29.4% ($n=15/51$ CHR+ individuals), with a cumulative proportion of psychosis transition equal to 33% (Table 3).

In addition, the other 20 CHR+ participants did not complete the 24-month follow-up (Fig. 2). Thirteen of them had a follow-up period < 2 years (i.e., they did not achieve the 24-month assessment time), four dropped out of the protocol, and the remaining three adolescents moved out of the ReARMS catchment area and could not be contacted for the follow-up assessment. After 24 months of follow-up, two new "criterial" transitions to psychosis were found (one of them was already a functional transition at 1-year assessment time), with a 2-year cumulative proportion of psychosis transition equal to 13% (Table 3). However, although antipsychotic medications were prescribed to six CHR+ adolescents after the 24-month follow-up period, no new functional equivalent to psychosis conversion has been reported. Therefore, after 2 years of follow-up, the cumulative incidence of psychosis transition increased up to 31.4% ($n=16/51$ CHR+ individuals), with a cumulative proportion of psychosis conversion equal to 37% (Table 3).

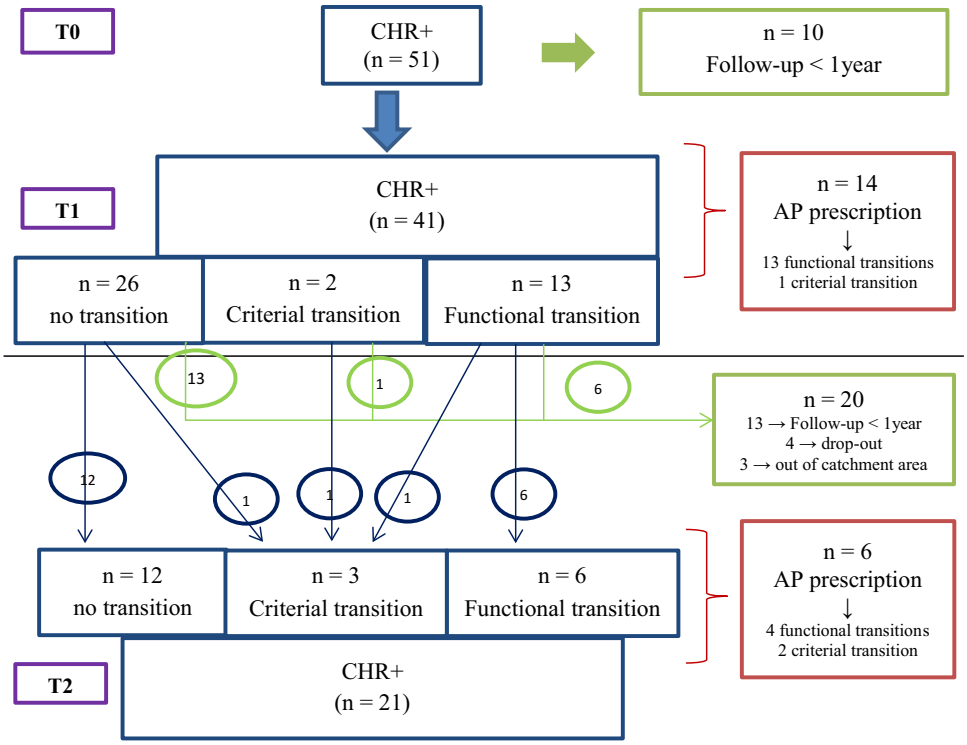

Fig. 2 Predictive validity of CHR criteria. *CHR+* clinical high-risk participants, *T0* baseline assessment time, *T1* 1-year assessment time, *T2* 2-year assessment time, Criterial transition: psychosis transition according to CAARMS psychosis criteria; *functional transition* the decision threshold at which antipsychotic medication was commenced under agreement of the treating clinical staff, *AP* antipsychotic medication, *green arrows* CHR+ participants out of follow-up period, *red arrows* CHR+ participants under antipsychotic medication, *red arrows* CHR+ participants under antipsychotic medication, *blue arrows* CHR+ participant's status at T2 assessment time, *green arrows* CHR+ participants excluded from follow-up assessments

Discussion

This study extends the results of a previous one [27] on CHR in children and adolescents attending CAMHS, supporting the feasibility of an early detection program for help-seeking adolescents, based on CHR criteria (i.e., CAARMS UHR and SPI-CY COGDIS). The baseline prevalence of CHR diagnosis among adolescents entering the ReARMS protocol was 45.5%, similar to what reported in comparable studies (48% [27]; 44% [21]) and slightly higher than the prevalence reported by other studies (see Table 1). Such differences, however, are likely to reflect different recruitment strategies as suggested by Welsh and Tiffin [18].

Psychopathology and functioning

At baseline, CHR and FEP adolescents had similar levels of functional impairment, and functioning of both groups was significantly lower than their CHR – peers. This finding further confirms that CHR mental states are clinical conditions characterized by marked psychosocial impairment and CHR adolescents are often already functionally impaired at baseline, as reported in young adults [44].

PANSS "Positive Symptoms" subscale scores of CHR+ adolescents were intermediate between FEP and CHR – groups, confirming that—according to the very definition of CHR—the magnitude of positive symptoms experienced by CHR individuals is usually of moderate severity but less marked than in first episode psychosis [45].

Our findings confirm that CHR subjects present a negative symptomatology profile that shares similarities in severity with that of FEP patients and significantly limits their psychosocial functioning. Elevated levels of negative symptoms, significant impairments of academic performance and occupational functioning, and difficulties in interpersonal relations are often jointly observed in both FEP and CHR individuals [46, 47]. Therefore, despite the small sample size, this study suggests that negative symptoms often represent earlier features which mark the prodromal phase also in adolescence [48, 49]; this is also supported by a recent study reporting that schizophrenia polygenic risk score in adolescence is associated with negative symptoms (rather than with positive symptoms) [50]. Overall, this fits in the clinical staging model in which the first prodromal phase 1a is characterized by negative and cognitive symptoms, while positive symptoms characterize subsequent 1b (attenuated psychotic symptoms) and 1c (short-lived remitting psychotic episodes) phases [3, 51]. Furthermore, our results are substantially in line with reported by Fux et al. [27] on the importance of "adynamia" section of BS in younger CHR individuals as main early features.

However, at the same time, recent research has highlighted the importance of negative symptoms not only for the increased risk of psychosis, but also in relation to a wide variety of non-psychotic mental health disorders [52, 53]. In line with previous findings [54], in our CHR+ sample, major depression was the most frequent diagnosis at initial examination and depression was higher in CHR+ adolescents than

Table 3 Cumulative survival in 51 CHR+ individuals

Time (in months)	CHR+ individuals (*n*)	Psychosis transition (*n*)	Censured individuals (*n*)	Proportion surviving	Cumulative survival	Cumulative psychosis transition
0–4	51	3	2	0.94	0.94	0.06
4–5	46	3	1	0.93	0.87	0.13
5–7	42	1	1	0.98	0.85	0.15
7–8	40	3	2	0.92	0.78	0.22
8–9	35	3	1	0.91	0.72	0.28
9–10	31	1	1	0.97	0.69	0.31
10–11	29	1	2	0.96	0.67	0.33
11–15	26	0	3	1	0.67	0.33
15–18	23	0	5	1	0.67	0.33
18–20	18	1	5	0.94	0.63	0.37
20–24	12	0	12	1	0.63	0.37
Time (in months)	CHR+ individuals (*n*)	CAARMS criterial transition (*n*)	Censured individuals (*n*)	Proportion surviving	Cumulative survival	Cumulative psychosis transition
0–4	51	0	2	1	1	0
4–5	46	0	1	1	1	0
5–7	42	0	1	1	1	0
7–8	40	0	2	1	1	0
8–9	35	0	1	1	1	0
9–10	31	1	1	0.97	0.97	0.03
10–11	29	1	2	0.96	0.93	0.07
11–15	26	0	3	1	0.93	0.07
15–18	23	0	5	1	0.93	0.07
18–20	18	1	5	0.94	0.87	0.13
20–24	12	0	12	1	0.87	0.13

CHR+ clinical high-risk participants, censured individuals, CHR+ participants lost to follow-up without psychosis transition; "proportion surviving" on a specific month interval = 1 − (number of psychosis transition/number of CHR+ individuals in this time interval); "cumulative survival" = proportion surviving in a defined month interval multiplied by cumulative survival from the previous step; "cumulative proportion of psychosis transition" = 1 − cumulative survival

in CHR − adolescents: these findings confirm that attenuated (negative and positive) CHR symptoms might also be important markers of concurrent psychopathology, especially characterized by affective dysregulation, outside the psychotic domain [15, 21, 55].

CAARMS predictive validity

In the current study, the cumulative proportion of CAARMS criterial transition rate from CHR to FEP was 7% over 12 months and 13% over 24 months. As shown in Table 1, transition rates at different follow-up durations are heterogeneous among published studies on CHR detection in help-seeking adolescents [15]: transition rates ranged from 3.4 to 18.18% at 6 months, from 8.5 to 20% at 12 months and from 7.1 to 15.5% at 24 months. Interestingly, the 6-year follow-up of the CHR sample described by Ziermans and colleagues was 22.7% [56]. Overall, the heterogeneity of transition rates may reflect methodological differences (e.g., in referral pathways, enrollment, assessment, dropouts and follow-up strategies) across the studies; however as an overall trend—replicated also in young adults—the peak of transition rates seems to intervene in the first 2 years [11, 15]. However, higher rates of psychosis conversion were detected when also functional transition was considered (33% and 37%, respectively).

Pharmacological treatment

In the current study, the 1-year antipsychotic prescription rate (29%) was lower than those (45.5%) reported by Spada et al. (2016) [21]. Eight of nine CHR+ adolescents who received antipsychotics did not progress to psychosis during the 1-year follow-up period, while the remaining CHR+ adolescent developed psychosis even when receiving antipsychotic medications. Three of the eight CHR+ individuals, who completed the 12-month follow-up period without developing psychosis, were still being prescribed

antipsychotics. This might suggest that the continuous prescription of antipsychotics to CHR people is not always necessary, especially if multi-element psychosocial intervention is provided, as indicated by the current guidelines [13, 14, 40]. Overall, even if this study contained a low proportion of patients under pharmacological treatment, our findings suggest that antipsychotic medication in CHR may delay rather than prevent transition to psychosis, in agreement with current preliminary empirical evidence on possible prevention of CHR transition [57].

Limitations

The major methodological limitations of the present study are well acknowledged. First, because of the limited CHR+ sample size ($n = 51$), the statistical power to detect true prodromal individuals who later developed psychosis was not strong enough. Indeed, the major factor in determining the predicted power of the CAARMS depends on the source of participants being studied [58]. However, when considering the prescription of antipsychotic medication by the independent treating clinician as a severity equivalent of transition to psychosis [5], the cumulative transition rate increases, especially in a real-world, non-academic settings such as the one in which we performed this study. To date, transition estimates in CHR people have largely been made in samples of help-seeking individuals who were engaged by specialized early intervention services. CHR adolescents enrolled in this study were referred to the ReARMS protocol, because they were regarded as potentially at risk for psychosis, and thus would be expected to have a higher risk of psychosis than those in the general population [59].

Our CHR individuals were also receiving some specific psychological treatments in addition to traditional case management. There is evidence indicating that psychological treatment can significantly affect the transition rate to psychosis of CHR people [57]. ReARMS is a clinical project providing evidence-based interventions that are supposed to be effective in CHR adolescents (i.e., intensive case management, family psychoeducation, and individual CBT within the framework of assertive community treatment). Precisely because providing the optimal treatment for adolescent help seekers was the main ethical mandate in our clinical setting, our interventions were not controlled (e.g., against placebo group or other treatment), but uniformly delivered. Finally, our follow-up was limited to 2 years. Longer-term follow-up is recommended to fully detect all the people who will later develop a psychotic episode.

Conclusions

Despite these limitations, the identification of adolescents at CHR for psychosis in CAMHS is feasible and clinically relevant. In this context, the approved Italian version of the CAARMS (CAARMS-ITA) was demonstrated to be a valid tool for detecting CHR mental states and predict psychosis transition. Studies conducted in clinical settings should take into consideration not only criterial transition based on instruments of CHR assessment, but also functional transition based on the clinical need of antipsychotic medication or, more generally, of greater intensity of treatment. Moreover, taking into account the results of this research, in relation to the criterial transition, the definition of CHR should also consider other symptoms in addition to positive ones (such as social functioning, negative and/or cognitive symptoms). Indeed, according to Cornblatt et al. [31], the current CHR criteria could not allow determination of the real incidence rates of risk of psychosis and should include other subclinical symptoms to avoid identification biases. Furthermore, the current CHR approach could also contribute to the results of the present research, suggesting more evidence of continuity of the psychotic experiences over time and, thus, may require a more critical, theoretical revision. Focusing on cumulative (criterial plus functional) transition rates may offer a vantage point presumably more adherent to the complexity of clinical practice.

The evidence that CHR adolescents (just as CHR young adults) present an impaired functioning and substantial negative symptoms encourages the shift of the early detection focus from prodromal to early premorbid stages (i.e., when initial functional decline and negative symptoms appear). In this perspective, early unspecific low-threshold interventions at various levels (e.g., cognitive, behavioral, social) in at-risk children and adolescents during premorbid phases may have potentially exponential positive cascading effects on long quality of life and socioemotional functioning. These early unspecific interventions could be probably more effective than specific interventions for CHR subjects in prodromal stages that nonetheless plausibly represent rather advanced/late stages from a neurodevelopmental perspective [60]. Finally, we regard our findings as promising in terms of the feasibility of integrating specific CHR-oriented early detection and intervention programs for adolescents into the standard mental health-care system (such as the ReARMS outpatient infrastructure implemented within the CAMHS of the Reggio Emilia Department of Mental Health). This is even more important in the light of recent surveys indicating substantial heterogeneity in dedicated service implementation across countries [61, 62]. Indeed, early interventions in psychosis programs could be an important driving factor for the organizational reform of CAMH services [63].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors declare that relevant ethical approvals were sought for the study and the current research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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