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Annual Research Review: Prevention of psychosis in adolescents – systematic review and meta-analysis of advances in detection, prognosis and intervention

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Background: The clinical high-risk state for psychosis (CHR-P) paradigm has facilitated the implementation of psychosis prevention into clinical practice; however, advancements in adolescent CHR-P populations are less established. **Methods:** We performed a PRISMA/MOOSE-compliant systematic review of the Web of Science database, from inception until 7 October 2019, to identify original studies conducted in CHR-P children and adolescents (mean age <18 years). Findings were systematically appraised around core themes: detection, prognosis and intervention. We performed meta-analyses (employing Q statistics and I^2 test) regarding the proportion of CHR-P subgroups, the prevalence of baseline comorbid mental disorders, the risk of psychosis onset and the type of interventions received at baseline. Quality assessment and publication bias were also analysed. **Results:** Eighty-seven articles were included ($n = 4,667$ CHR-P individuals). Quality of studies ranged from 3.5 to 8 (median 5.5) on a modified Newcastle–Ottawa scale. **Detection:** Individuals were aged 15.6 ± 1.2 years (51.5% males), mostly (83%) presenting with attenuated positive psychotic symptoms. CHR-P psychometric accuracy improved when caregivers served as additional informants. Comorbid mood (46.4%) and anxiety (31.4%) disorders were highly prevalent. Functioning and cognition were impaired. Neurobiological studies were inconclusive. **Prognosis:** Risk for psychosis was 10.4% (95%CI: 5.8%–18.1%) at 6 months, 20% (95% CI: 15%–26%) at 12 months, 23% (95%CI: 18%–29%) at 24 months and 23.3% (95%CI: 17.3%–30.7%) at ≥ 36 months. **Interventions:** There was not enough evidence to recommend one specific treatment (including cognitive behavioural therapy) over the others (including control conditions) to prevent the transition to psychosis in this population. Randomised controlled trials suggested that family interventions, cognitive remediation and fish oil supplementation may improve cognition, symptoms and functioning. At baseline, 30% of CHR-P adolescents were prescribed antipsychotics and 60% received psychotherapy. **Conclusions:** It is possible to detect and formulate a group-level prognosis in adolescents at risk for psychosis. Future interventional research is required. **Keywords:** Psychosis; schizophrenia; clinical high-risk state for psychosis; psychosis risk; prevention; evidence; prediction; first-episode; meta-analysis; childhood; adolescence.

Introduction

Psychotic disorders typically onset in adolescence and early adulthood, with the peak of risk occurring between the ages of 12 and 25 years (Radua et al., 2018). Once the disorder onsets, the opportunities to

improve its course are limited (Millan et al., 2016). Therefore, early intervention and particularly preventive approaches in young people with subtle signs and symptoms of the disorder (termed ‘primary indicated prevention’ Arango et al., 2018; Fusar-Poli, Bauer, et al., 2019) have the potential to benefit the lives of many young people. Primary indicated prevention in individuals at clinical high-risk state for psychosis (CHR-P) has grown exponentially over the past two decades and has become one of the most established preventive approaches in psychiatry (Correll et al., 2018; Fusar-Poli, McGorry, & Kane,

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2017). There is consensus that the key elements of the CHR-P paradigm encompass three concatenated steps: detection, prognosis and intervention (Fusar-Poli et al., 2020; Oliver, Radua, Reichenberg, Uher, & Fusar-Poli, 2019). The first rate-limiting step involves the detection (Fusar-Poli et al., 2020) of individuals aged 12–35 who accumulate risk factors for psychosis (Fusar-Poli, Tantardini, de Simone, Ramella-Cravaro, et al., 2017; Oliver, Reilly, et al., 2019) and functional impairment (Fusar-Poli, Rocchetti, et al., 2015), seeking help (Falkenberg et al., 2015) at specialised mental health clinics (Fusar-Poli, Estradé, et al., 2019). In the second step, these individuals are assessed with specific psychometric interviews which discriminate between those meeting CHR-P criteria (Table 1), those already psychotic (i.e. above threshold) and those not at risk (Fusar-Poli, Cappucciati, et al., 2015), thus formulating a group-level prognosis (Fusar-Poli, Hijazi, Stahl, & Steyerberg, 2018). In the final third step, CHR-P individuals are offered need-based interventions and, if available, specific indicated preventive interventions (Fusar-Poli, Davies, Solmi, et al., 2019).

The CHR-P paradigm is, therefore, ‘transitional’ in nature and ‘integrated’ (Fusar-Poli, 2019) across child and adolescent, and adult mental health services, bridging the existing gap between the traditional two-tier system. While advancements in detection, prognosis and interventions in adult CHR-P populations have recently been appraised in an umbrella review (Fusar-Poli et al., 2020), the specific advancements that pertain to child and adolescent CHR-P individuals are less clear. In fact, most of the evidence focuses on adult CHR-P samples, with relatively little research surrounding children and adolescents. Investigating the CHR-P paradigm in children and adolescents poses additional empirical challenges with respect to their detection, prognosis and interventions. Original studies in CHR-P children and adolescents report inconclusive findings across these three mainstream clinical research areas (Schlosser et al., 2012; Welsh & Tiffin, 2014).

This study addresses these gaps and advances understanding in the field of prevention of psychosis for children and adolescents at CHR-P, summarising the available evidence relating to detection, prognosis and intervention in this field. The research in these areas has substantial potential to increase the benefits of the early intervention in psychosis approach (Fusar-Poli et al., 2020). The systematic appraisal of the evidence is also complemented by meta-analytic analyses regarding each of the three core components. The results are discussed critically to advance clinical knowledge and inform future research.

Methods

This review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Table S1) (Moher, Liberati, Tetzlaff, &

Altman, 2009) and Moose checklist (Table S2) (Stroup et al., 2000), following EQUATOR Reporting Guidelines (Altman, Simera, Hoey, Moher, & Schulz, 2008).

Search strategy and selection criteria

A systematic search strategy was adopted to identify relevant articles, and three independent researchers implemented a two-step literature search (Appendix S1). Articles identified were screened as abstracts; those not meeting inclusion criteria were then excluded, and the full texts of the remaining articles were assessed for eligibility.

The following inclusion criteria were used to select the articles: (a) original studies, (b) conducted in individuals meeting CHR-P criteria as defined by the following standardised criteria (Appendix S2) and (c) conducted in children and adolescents, empirically defined through a mean age of the sample of <18 years, in line with previous systematic reviews in this population (Tor et al., 2018). Exclusion criteria were as follows: (a) reviews, clinical cases, conference proceedings and study protocols, (b) studies that did not formally assess and select participants with established CHR-P instruments and (c) studies in languages other than English.

Outcome measures and data extraction

We extracted the following data from each study: first author, year of publication, country, study type and design (cohort, cross-sectional, randomised controlled trial – RCT – naturalistic), sample size of CHR-P and comparison group, topic, type of comparison group, mean age (*SD* and range when available), % of male CHR-P individuals, instruments used to define the CHR-P criteria, quality assessment and key findings.

Strategy for data synthesis

We provided a narrative synthesis of the systematic review from the included studies, structured around core themes: detection (characteristics of the CHR-P state, clinical comorbidity, functioning and quality of life, cognition, neuroimaging, biochemistry, electrophysiology), prognosis (overall prognosis and prediction of outcomes) and interventions. The narrative findings were complemented by specific meta-analyses that were performed when enough studies were available within each domain. The meta-analyses addressed: (a) the proportion of individuals in each CHR-P subgroup, (b) the prevalence of comorbid nonpsychotic mental disorders at baseline, (c) the risk of psychosis onset in this population and (d) the type of indicated preventive interventions received at baseline. The proportion of individuals in each of the three CHR-P subgroups (attenuated psychotic symptoms, APS; brief-limited-intermittent psychotic symptoms, BLIPS/BIPS; and genetic risk and deterioration syndrome, GRD) was defined according to established criteria (Fusar-Poli, Cappucciati, Bonoldi, et al., 2016; Fusar-Poli, Cappucciati, Borgwardt, et al., 2016; Fusar-Poli, Cappucciati, de Micheli, et al., 2017). The prevalence of baseline comorbid nonpsychotic disorders was indexed as the proportion of CHR-P individuals with comorbid nonpsychotic ICD/DSM (any version) mental disorders. The risk of developing psychosis in CHR-P children and adolescents at 6, 12, 24 and 36 or more months was ascertained using ICD/DSM (any version) or psychometric operationalisation (i.e. CHR-P-based) of psychosis onset. The types of treatments received at baseline were analysed, including psychotherapy or psychopharmacology as reported by each individual study. For all of these meta-analyses, additional inclusion criteria were as follows: (a) nonoverlapping samples and (b) availability of ≥ 3 independent studies reporting on the same outcome. Overlapping was defined as studies that used the same sample of individuals at CHR-P.

Table 1 Core definitions of the CHR-P state, which include the ultra-high risk and basic symptoms domains (adapted from Fusar-Poli et al. 2013)

| | CHR-P subgroup (acronym); 2 years risk of psychosis (95% CI) (Fusar-Poli, Cappucciati, Borgwardt, et al., 2016) | CAARMS | SIPS/SOPS | SPI-A/SPI-CY |
|--------------------------------|--|---|---|--|
| Ultra-High-Risk (UHR) criteria | Attenuated Psychotic Symptoms (APS); 0.19 (0.15–0.23) | Subthreshold attenuated positive symptoms; for example ideas of reference, ‘magical’ thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, held with either subthreshold frequency or subthreshold intensity, and decline in functioning or sustained low functioning | Subthreshold attenuated positive symptoms; for example unusual ideas, paranoia/suspiciousness, grandiosity, perceptual disturbance, conceptual disorganisation, without psychotic conviction. | NA |
| | Brief limited Intermittent Psychotic episode (BIP/BLIP); 0.39 (0.07–0.51) | Transient psychotic symptoms: symptoms in the realm of delusions, hallucinations, disorganisation; duration of the episode less one week; spontaneous remission without antipsychotic, and decline in functioning or sustained low functioning | Transient psychotic symptoms: symptoms in the realm of delusions, hallucinations, disorganisation lasting up to 3 months if not seriously disorganising/dangerous | NA |
| | Genetic Risk and Deterioration syndrome (GRD); 0.03 (0–0.08) | First-degree relative with psychotic disorder or schizotypal personality disorder, or an individual with schizotypal personality and decline in functioning or sustained low functioning | First-degree relative with psychotic disorder or an individual with schizotypal personality and decline in functioning | NA |
| | Basic Symptoms (BS); 0.03 (0–0.11) | NA | NA | Cognitive-perceptive basic symptoms: subtle, subjectively experienced disturbances in mental processes including thinking, speech, attention, perception, drive, stress tolerance and affect (Schultze-Lutter & Theodoridou, 2017) |

Abbreviations: CAARMS, Comprehensive Assessment of the At-Risk Mental State; NA, no applicable; SIPS/SOPS, Structured Interview for Psychosis-Risk Syndromes; SPI-A, Schizophrenia Proneness Instrument, adult version; SPI-CY, Schizophrenia Proneness Instrument, child and youth version.

Since high heterogeneity was expected, random-effects meta-analyses were conducted (DerSimonian & Laird, 1986). Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index (Lipsey & Wilson, 2000). Publication bias was assessed for the risk of psychosis onset meta-analysis by inspecting meta-funnel plots and assessing Egger’s test (Egger, Davey Smith, Schneider, & Minder, 1997). For the other meta-analyses (comorbid nonpsychotic disorders, types of treatments received at baseline and the proportion of

individuals in each of the three CHR-P subgroups), we did not use the Egger test because studies included in the meta-analyses of proportions are noncomparative, thus there are no ‘negative’ or ‘undesirable’ results or study characteristics, such as significance levels, that may have biased publications (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011). We also performed sensitivity analyses for each of the meta-analyses, comparing the studies that included exclusively CHR-P participants <18 years versus those that included some participants ≥ 18 years of age. Finally, we conducted meta-analytical regressions to evaluate the association

between our outcomes and the quality of the studies. All analyses were 2-sided, with $\alpha = .05$. Comprehensive Meta-Analysis (CMA) V3 software (Borenstein, Hedges, Higgins, & Rothstein, 2013) was used.

Quality assessment

Study quality was assessed in all the included studies. A modified version of the Newcastle–Ottawa scale for cross-sectional and cohort studies, ranging from 0 to 8, was used to remain consistent with previous studies (Fusar-Poli, Tantarini, de Simone, Ramella-Cravaro, et al., 2017; Salazar de Pablo, Catalan, & Fusar-Poli, 2019) (Table S3).

Results

Of 15,577 articles identified, 87 articles were included in the systematic review ($n = 4,970$ CHR-P individuals) (Figure 1). Forty-four studies were from the United States (50.6%), 35 from Europe (40.3%), 6 from Australasia (6.8%) and 2 from Canada (2.3%). The sample size of the studies ranged from 7 to 358; the age of included participants ranged from 5 to 35 years. Ten studies included samples with only participants aged under 18 years. Only eight studies included participants under 12 years; as such, hereafter we use the term adolescents to refer to the results of our search.

Detection

Characteristics of the CHR-P state. Systematic review: Sixteen studies reported on general characteristics of the CHR-P state in adolescents. The mean age of CHR-P individuals across the included studies was 15.6 ± 1.2 years, and 51.5% were males. Altogether, 72 studies employed the SIPS/SOPS, 19 the CAARMS, 6 the BSABS, 3 the SPI-CY and 4 the PANSS (10 studies used more than one instrument). The proportion of individuals meeting CHR-P criteria was 16%–36% in mental health settings (Koren et al., 2019, Lo Cascio et al., 2017), including 23.6% in adolescent inpatient settings (Gerstenberg et al., 2015) and 13% in nonhelp-seeking adolescents with disruptive behaviours (Manninen et al., 2014). From a psychometric perspective, four studies focused on the validation of CHR-P assessment scales in adolescents across different languages (Fux, Walger, Schimmelmann, & Schultze-Lutter, 2013; Kline et al., 2012; Pelizza, Azzali, et al., 2019; Thompson, Kline, Reeves, Pitts, & Schiffman, 2013). One study reported on the iPQ-16 (the Italian Version of the 16-item Prodromal Questionnaire) screening tool against the CAARMS (Pelizza, Azzali, et al., 2019). Another study compared the Prime Screen, the YPARQ-B (Youth Psychosis At-Risk Questionnaire-Brief) and the PQB (Prodromal Questionnaire-Brief) scales against the SIPS (Kline et al., 2012). Finally, two studies (Thompson et al., 2013, 2014) compared the BASC-2 (Behaviour Assessment System for Children, Second Edition) with the SIPS. All of these prescreening instruments demonstrated good discriminant validity [accuracy ranging from 61% (Kline et al., 2012) to 90%

(Fux et al., 2013)] against the gold standard CHR-P instruments in this age range (Table S4).

In adolescents, the raters' agreement on the CHR-P designation (on the SIPS) between self-report data and family reports was moderate ($\kappa = .5$) (Golembo-Smith, Bachman, Senturk, Cannon, & Bearden, 2014). The accuracy of identification of cases at risk of psychosis differed when information was collected from the CHR-P individuals themselves (sensitivity: 68%, specificity: 79% and accuracy: 73%) compared to their parents (sensitivity: 65%, specificity: 76% and accuracy: 70%), and was greatly improved upon when both informants were consulted (sensitivity: 82%, specificity: 79% and accuracy: 81%) (Thompson et al., 2014). Another study (Simeonova, Nguyen, & Walker, 2014) indicated that the Child Behaviour Checklist (CBCL) scale could differentiate CHR-P individuals from the general population. This instrument is a commonly used tool in child and adolescent psychiatry. The CBCL parent-report scale was used to assess behavioural problems and competencies of participants. The measure includes 118 items rated from 0 (not at all typical of the child) to 2 (often typical of the child) and is appropriate for use in those aged 4–18 years. The CBCL clinical scales contain the Total Problems scale, two 'broadband' dimensions (internalising problems and externalising problems) and eight cross-informant syndromes (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, delinquent behaviour and aggressive behaviour). The CBCL also yields a measure of social competencies – the total competence scale (composed of the activities, social and school subscales).

From a broader clinical perspective, CHR-P adolescents typically presented with attenuated psychotic symptoms (Lo Cascio et al., 2016), predated by negative symptoms (Meyer et al., 2005). A further study (Spada et al., 2016) sought to describe a subgroup of CHR-P individuals defined based on negative psychotic symptoms, finding that this potential category was highly prevalent (18% of adolescents meeting CHR-P criteria). Although basic symptoms were suggested to be useful in the detection of CHR-P adolescents, only one study reported on this (Lo Cascio et al., 2016).

Other studies focused on behavioural characteristics of this population and reported that CHR-P individuals experienced a more external locus of control and more social stress (Millman et al., 2017) than healthy controls (HC), associated with greater severity of APS (Millman et al., 2018). Four studies focused on the influence of family relationships in adolescents at CHR-P (O'Brien et al., 2008; Salinger, O'Brien, Miklowitz, Marvin, & Cannon, 2018; Tsai et al., 2015), indicating impairments in self-reliance and relations with their parents (Thompson et al., 2015). Lower familial warmth (measured using self-

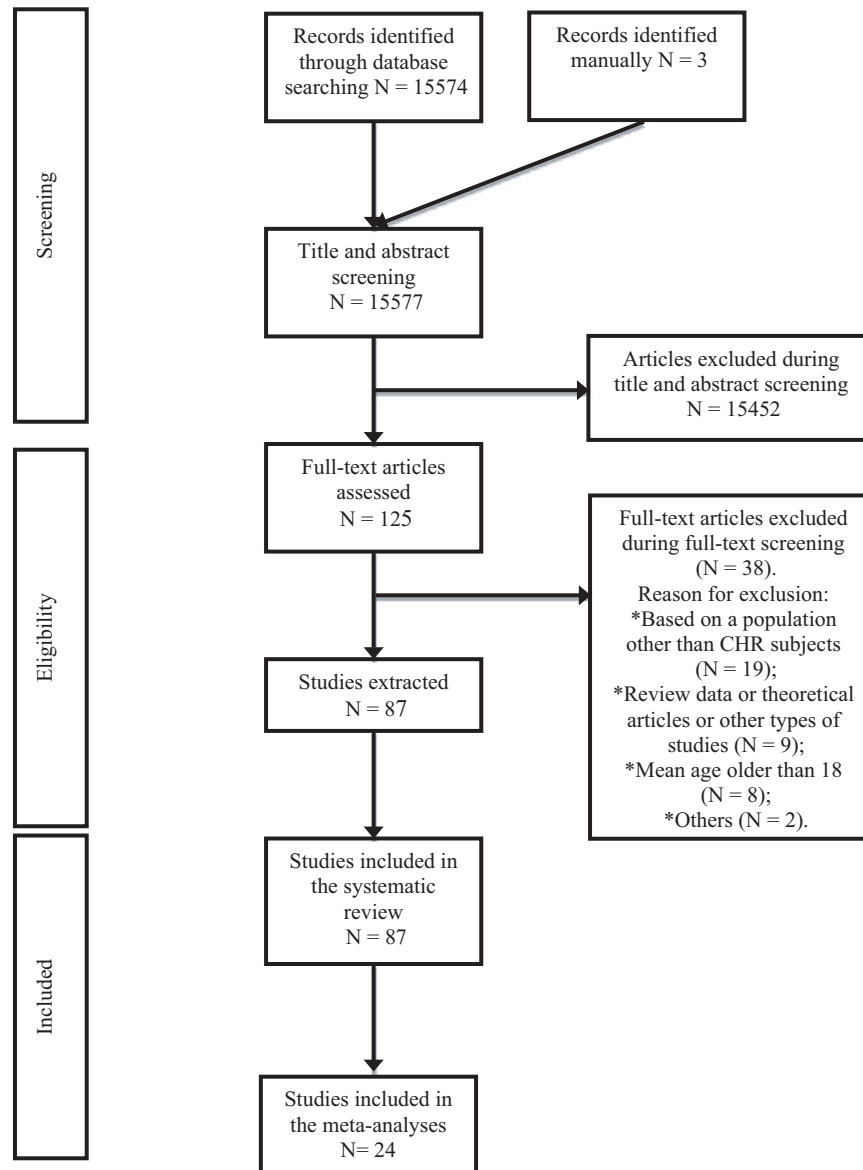


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart outlining the study selection process

report questionnaires) was associated with an increased severity of attenuated positive psychotic symptoms (Tsai et al., 2015). Behaviours and attitudes towards mental disorders were found to be more negative in parents of adolescents at CHR-P compared to parents of adolescents at risk for bipolar disorder (Salinger et al., 2018).

Finally, there were more severe behavioural disturbances in CHR-P adolescents with a family history of psychiatric disorders compared to those without such a family history (Simeonova, Lee, & Walker, 2015) (Table S4).

Meta-analysis: The meta-analysis on the type of CHR-P subgroup identified 20 independent studies, showing that the vast majority of young CHR-P patients fulfilled APS criteria (82.6%, 95%CI: 75.0%–88.3%), followed by GRD criteria (8.5%, 95%CI: 4.8%–14.4%), and then BLIPS criteria

(6.7%, 95%CI: 4.2%–10.5%, Table S5, Figures S1–S3). Heterogeneity across the studies included was statistically significant (I^2 : 34.0–92.0, $p < .001$) in all the primary analyses and sensitivity analyses, except for the BLIPS sensitivity analysis ($I^2 = 22.6$, $p = .25$). The sensitivity analyses comparing the studies that included exclusively underage CHR-P participants versus those that included individuals ≥ 18 years did not find differences across these subgroups, except for the GRD subgroup, in which a higher proportion of GRD was found in studies including only individuals < 18 years of age (15%) vs those including individuals aged ≥ 18 (7%) (Table S6).

Clinical comorbidity in the CHR-P state. Systematic review: Six studies had a primary focus on the investigation of comorbidities in CHR-P (Gerstenberg et al., 2015; Kline et al., 2016; Morelli et al., 2019;

Pelizza, Poletti, et al., 2019; Pitzianti et al., 2019; Stain et al., 2018). Comorbidity was frequent (from 46.4% to 7%) in adolescents at CHR-P (Table S7).

16 (76.2%) studies used structured instruments, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children scale (K-SADS) (11 studies, 52.4%) and the SCID (7 studies, 33.3%). Five studies (23.8%) used clinical criteria, including DSM-IV criteria (3 studies, 14.3%) and ICD-10 criteria (3 studies, 14.3%).

Some studies revealed that substance use was associated with higher levels of depression (Stain et al., 2018). Young people with substance use living in rural areas were more likely to seek help from community mental health services rather than from primary health care and were more likely to be prescribed antidepressants than youths living in an urban environment (Stain et al., 2018). Neurological soft signs were also more frequently present in CHR-P versus HC group (Pitzianti et al., 2019). The prevalence of previous traumatic events was high (ranging from 63.2% to 85.0%) in adolescents at CHR-P (Kline et al., 2016; Morelli et al., 2019). Other studies indicated that adolescents at CHR-P presented with elevated rates of suicidal attempts compared to HC (17.5% vs. 2.5%) (D'Angelo et al., 2017; Pelizza, Poletti, et al., 2019) (Table S7).

Meta-analysis: Mood disorders were the most frequent comorbidity in the sample (46%, 95%CI: 39%–53%), followed by anxiety disorders (31%, 95%CI: 24%–40%) and behavioural disorders (24%, 95%CI: 16%–34%). Heterogeneity across the included studies was statistically significant for mood disorders, bipolar disorders, anxiety disorders, ADHD, pervasive developmental disorder (PDD) and other comorbid conditions (I^2 : 72.4–84.8) (Table 2). Sensitivity analyses (Table S8) comparing the studies that included exclusively underage participants at CHR-P versus those that were ≥ 18 years of age showed a higher prevalence of bipolar disorder (BD) ($p = .012$), and PDD ($p = .004$) but a lower prevalence of anxiety disorders ($p < .001$) in studies including only individuals < 18 years of age.

Functioning and quality of life in the CHR-P state. Systematic review: Seven studies investigated functioning and quality of life in CHR-P adolescents. The CHR-P group presented poorer functioning scores (Carrion et al., 2013; Dolz, Tor, Portoles, et al., 2018; Velthorst et al., 2018) and health-related quality of life (Nitka, Richter, Parzer, Resch, & Henze, 2016) compared with HC. An older presentation of CHR-P (15–18 years) (Ribolsi et al., 2017), higher levels of emotional involvement, positive remarks and warmth from caregivers were associated with better social functioning (O'Brien et al., 2006). Conversely, dyskinesia was associated with greater impairments in psychosocial functioning (Mittal et al., 2011) (Table S9). Adolescents at CHR-P showed higher anhedonia scores and anhedonia were correlated with impaired role functioning and negative symptoms (Pelizza, Poletti, et al., 2019).

Cognition in the CHR-P state. Systematic review: Eight studies investigated cognition. The CHR-P state in adolescents was related to impairments in neurocognitive performance compared with HC (D'Angelo et al., 2019; Koren et al., 2019; Woodberry et al., 2010), including poor visual form perception (Ilonen, Heinimaa, Korkeila, Svirskis, & Salokangas, 2010), mild-to-moderate executive impairments (Ilonen et al., 2010) in working memory (Smith, Park, & Cornblatt, 2006), labelling of facial expressions (van Rijn et al., 2011a), and ability to recognise facial identity (van Rijn et al., 2011a). CHR-P adolescents experienced more maladaptive beliefs (Welsh, Cartwright-Hatton, Wells, Snow, & Tiffin, 2014) and difficulties in verbalising their own emotions (van Rijn, Schothorst, Wout, Sprong, Ziermans, et al., 2011). Learning deficits were associated with more symptoms and poorer functioning (Waltz et al., 2015) (Table S10).

Neuroimaging, biochemistry and electrophysiology in the CHR-P state. Systematic review: Thirteen studies investigated neuroimaging, biochemistry or electrophysiology in CHR-P adolescents, finding a

Table 2 Meta-analytical proportion of CHR-P adolescents with DSM/ICD comorbid mental disorders

| Comorbid disorder | N of studies | Total sample | Proportion of comorbid disorder | 95% CI | Q | df | I^2 | p |
|-----------------------|--------------|--------------|---------------------------------|-----------|--------|----|--------|-------|
| MDD/ mood disorder | 20 | 980 | 0.46 | 0.39 0.53 | 77.13 | 19 | 75.37 | <.001 |
| BD | 4 | 172 | 0.19 | 0.08 0.39 | 15.74 | 3 | 80.94 | .001 |
| Anxiety disorders | 18 | 952 | 0.31 | 0.24 0.40 | 111.55 | 17 | 84.76 | <.001 |
| OCD | 4 | 204 | 0.13 | 0.07 0.22 | 5.15 | 3 | 41.81 | .161 |
| Personality disorders | 5 | 225 | 0.11 | 0.08 0.16 | 0.75 | 4 | 0.00 | .945 |
| ADHD | 10 | 444 | 0.22 | 0.13 0.36 | 57 | 9 | 84.3 | <.001 |
| PDD | 5 | 207 | 0.14 | 0.05 0.34 | 23.04 | 4 | 82.64 | <.001 |
| Behavioural disorder | 7 | 210 | 0.24 | 0.16 0.34 | 11.55 | 6 | 48.0 | .073 |
| SUD | 5 | 270 | 0.07 | 0.05 0.11 | 2.63 | 4 | <0.001 | .621 |
| Other | 12 | 550 | 0.17 | 0.12 0.26 | 39.83 | 11 | 72.38 | <.001 |

Abbreviations: ADHD, attention deficit hyperactivity disorder; BD, Bipolar disorder; MDD, Major depressive disorder; OCD, Obsessive compulsive disorder; PDD, Pervasive developmental disorder; SUD, Substance use disorder.

higher number of biochemical alterations compared to HC, including polyunsaturated fatty acids (PUFA) deficits (Rice et al., 2015), lower testosterone levels (van Rijn et al., 2011b) and increased cortisol secretion (Moskow et al., 2016). Salivary cortisol secretion was not associated with the severity of overall positive symptoms but was related to higher levels of suspiciousness, anxiety and impaired stress tolerance (Corcoran et al., 2012).

Structural neuroimaging in this population yielded inconclusive findings. One study found no differences between CHR-P adolescents and HC in terms of brain volume or white matter density (Ziermans et al., 2009). Another study investigated subcortical volumes to distinguish between CHR-P and HC individuals, but the imaging biomarker had low sensitivity (59%) and specificity (68%) (de Wit et al., 2017). A significant association was found between subcortical volumes and poorer levels of functioning (de Wit et al., 2017) and higher significant symptoms (Bartholomeusz et al., 2014; Demro et al., 2017; de Wit et al., 2016, 2017).

Amygdala volume was positively correlated with sadness recognition in CHR-P populations (Bartholomeusz et al., 2014), while greater cortical thickness in the frontal and insular cortex was associated with higher levels of self-reflectiveness and theory of mind ability (Buchy, Stowkowy, Macmaster, Nyman, & Addington, 2015).

Only a few electrophysiological studies were found, indicating changes in prepulse inhibition (Ziermans et al., 2012) and smaller N100 amplitudes in CHR-P individuals compared with HC (Gonzalez-Heydrich et al., 2015, 2016) (Table S11).

Prognosis

Overall prognosis/risk of psychosis. Systematic review: Between 36% (Schlosser et al., 2012) and 49.1% (Ziermans, Schothorst, Sprong, & van Engeland, 2011) of adolescents at CHR-P remitted from their initial CHR-P state after 2 years, and only 40% did so after 6 years (de Wit et al., 2014). Lower levels of baseline negative and mood symptoms were associated with higher chances of recovery at 2 years (Schlosser et al., 2012). The most significant reduction in attenuated positive symptoms occurred within the first two years after the CHR-P diagnosis (Armando et al., 2015) (Table S12). The intensity of the distress associated with anxiety and substance use was also related to an increased risk of psychosis (Rapado-Castro, McGorry, Yung, Calvo, & Nelson, 2015).

The CHR-P population had a greater deviation of predicted age from the individuals' chronological age (brain age–chronological age; brain age gap) than HC (Chung et al., 2018). A higher brain age gap between the brain age and the chronological age was associated with a higher risk of developing psychosis in adolescents at CHR-P (Chung et al., 2018).

Furthermore, a smaller putamen volume was associated with higher levels of dyskinesia, while baseline caudate and putamen volumes distinguished CHR-P individuals who converted to psychosis from those who did not (Mittal et al., 2010).

Meta-analysis: Altogether, 23 independent studies reported on the risk of psychosis onset at follow-up (mean duration: 27 months \pm 24.1). The meta-analytical risk of psychosis was 10.4% (95%CI: 5.8%–18.1%) at 6 months, 20% (95%CI: 15%–26%) at 12 months, 23.0% (95%CI: 18.0%–29.0%) at 24 months and 23.3% (95%CI: 17.3%–30.7%) at 36 months of follow-up (Figure 2). Egger's test did not reveal significant publication bias at any time point (Figures S4–S11). Heterogeneity was significant at 6-month follow-up ($Q = 9.284$, $p = .026$) but not at 12-, 24-, or 36-month follow-up (all $p > .05$). Sensitivity analyses found no statistically significant differences between studies that included only individuals <18 years old and those that also included individuals \geq 18 years old (all $p > .05$) (Table S13).

Prediction of outcomes in CHR-P. Systematic review: Positive remarks and warmth within families predicted longitudinal improvement for young individuals at CHR-P (O'Brien et al., 2008). Conversely, conflictual communications between individuals at CHR-P and their families were related to an increase in positive attenuated psychotic symptoms (O'Brien et al., 2009). The individuals at CHR-P who converted to psychosis had higher baseline severity of attenuated psychotic symptoms (Simeonova, Attalla, Trotman, Esterberg, & Walker, 2011) compared with those not developing psychosis. The clinical improvement over time in this CHR-P population was associated with increased prepulse inhibition (Ziermans, Schothorst, Magnee, van Engeland, & Kemner, 2011) (Table S14). Self-reported internalising and thought content problems were associated with more frequent hospital treatments for mood and conduct disorders in a cohort of young offenders at CHR-P (Manninen et al., 2014).

The social and role functioning, which was impaired early (12 years), remained stable in those who developed psychosis but improved in those not developing psychosis (Velthorst et al., 2018). Neurocognitive impairments were also more severe in CHR-P individuals who converted to psychosis than those who did not (Woodberry et al., 2013), with a significant impairment in olfactory identification (Woodberry et al., 2010). Some studies described a positive relationship between functional activation during working memory in the frontal lobe and age in CHR-P, while the inverse was observed in the HC (Karlsgodt, van Erp, Bearden, & Cannon, 2014). Finally, low (1–4 times) to moderate (\geq 20 times) lifetime cannabis use was not associated with poorer functioning (Auther et al., 2012).

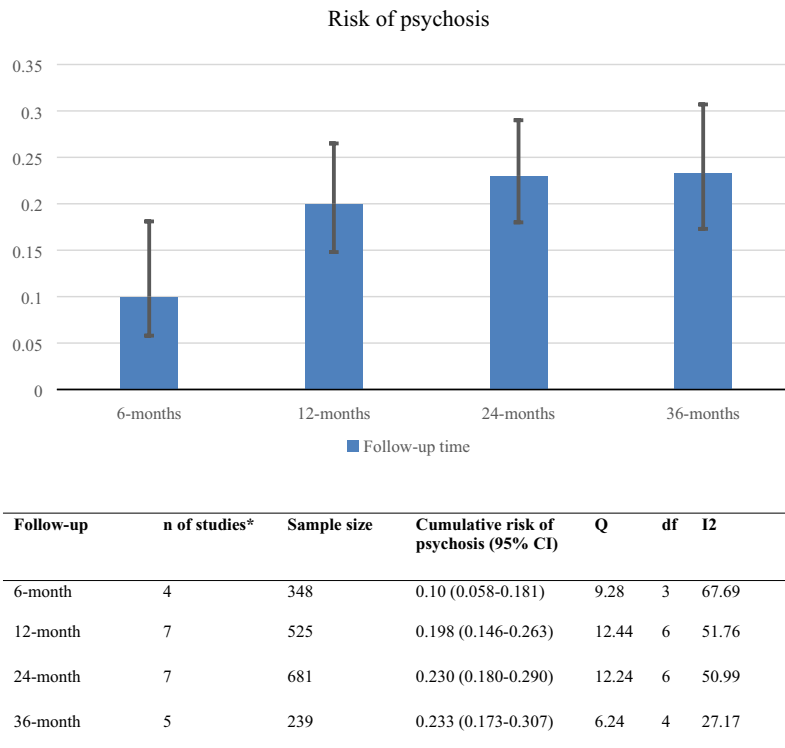


Figure 2 Meta-analytical cumulative risk of psychosis onset in adolescents meeting a CHR-P state over time [Colour figure can be viewed at wileyonlinelibrary.com]

Interventions

Systematic review. Thirteen studies investigated interventions (any design) in this subgroup: five were naturalistic, and eight were RCT.

Among the naturalistic studies, family therapy was associated with an improvement in CHR-P symptoms and functional outcomes (O'Brien et al., 2007), as well as levels of self-reported depression and hopelessness at 18 months (Grano et al., 2016). A further naturalistic study showed an improvement in the level of dysphoric mood and tolerance to normal stress after 4 weeks of biofeedback therapy (McAusland & Addington, 2018). Only two psychopharmacologic naturalistic studies were found in this population (Bowie, McLaughlin, Carrion, Auther, & Cornblatt, 2012; Cornblatt et al., 2007). One study suggested that antidepressants were more effective than second-generation antipsychotics on neurocognition, verbal learning and attention after 6 months (Bowie et al., 2012). Another study found higher levels of disorganisation symptoms in individuals treated with antipsychotics compared with those taking antidepressants (Cornblatt et al., 2007). Antidepressants were also better tolerated than antipsychotics. Transition to psychosis occurred mostly >6 months after stopping antipsychotics against medical advice (Cornblatt et al., 2007).

Among the identified RCTs, two tested the efficacy for preventing psychosis (Stain et al., 2016). One compared cognitive behavioural therapy versus

nondirective reflective listening therapy in a group of youths at CHR-P (Stain et al., 2016). The transition risk was 5% in the experimental group, without any conversion in the HC group. The second RCT found that omega-3 fatty acid supplementation reduced the risk of transitioning to psychosis (Amminger et al., 2010), alternative psychopathology and poor functioning (Amminger et al., 2010, 2013; Mossaheb et al., 2013) at 12 weeks with no substantial side effects or impact on the levels of triglycerides (Mossaheb et al., 2018) (Table S15).

Other RCTs investigated family therapy, which was associated with decreased levels of criticism from mothers (Tsai et al., 2015) at 12 months, and decreased severity of attenuated psychotic symptoms (Miklowitz et al., 2014) at 6 months. Another RCT employed computer-assisted cognitive remediation, showing improved attention, immediate and delayed memory, and general psychopathology, as well as social-occupational functioning, compared with computer games at 8 weeks (Holzer et al., 2014).

Meta-analysis. The meta-analytical results revealed that 30.4% of the adolescents at CHR-P were prescribed antipsychotics at baseline (95%CI: 22%–40%), 27.1% antidepressants (95%CI: 22%–33%), 11.0% benzodiazepines (95%CI: 3%–32%) and 15.1% other psychotropic medication (95%CI: 8%–27%); 60.4% received some type of psychotherapy (95%CI: 26%–87%). Heterogeneity (I^2) across the

included studies was statistically significant ($p < .001$) and ranged from 67.8 (antidepressants) to 94.0 (benzodiazepines) (Table 3). The sensitivity analyses comparing the studies that included exclusively underage CHR-P participants versus those that also included individuals ≥ 18 did not reveal differences (Table S16).

Meta-regressions

A higher quality of the included studies ($\beta = .378$, $p = .044$) was associated with a higher prevalence of anxiety disorders. Lower quality of the included studies ($\beta = -.861$, $p = .023$) was associated with a higher prevalence of bipolar disorders. There was no significant association between the quality of the included studies and any other DSM/ICD comorbid mental disorder. There was no significant association between the quality of the included studies and the presence of any CHR-P subgroup, the transition to psychosis in any time period or any intervention outcome (all $p > .05$) (Table S17).

Quality assessment. The quality rating of the studies ranged from 3 to 8 for the cohort studies (median = 6) (Table S18) and from 3.5 to 8 for the cross-sectional studies (median = 5.5) on a modified version of the Newcastle–Ottawa scale (Table S19).

Discussion

We systematically reviewed 87 studies, expanding the knowledge obtained from the 48 studies previously described in the only other systematic review on this topic (Tor et al., 2018).

We have provided the first meta-analytical evidence of the three key components of CHR-P research: detection, prognosis and intervention. Transition risk was 10.4% at 6 months, 20% at 12 months, 23% at 24 months and 22% at ≥ 36 months. When sensitivity analyses were restricted to samples including only underage participants, the transition risk was 20% at 12 months, 23% at 24 months and 25% at ≥ 36 months. Overall, we found a similar transition risk in adolescents at CHR-P (22% after 36 months) to that observed in adult samples (22%) (Fusar-Poli et al., 2020). Interestingly, a recent meta-analysis focusing on the DSM-5 APS designation found a comparable 23%

transition risk at 36 months (Salazar de Pablo et al., 2019). It could be that the relatively lower incidence of psychosis risk observed in adolescents at CHR-P is counterbalanced by more effective risk enrichment strategies (Fusar-Poli, Rutigliano, et al., 2016; Fusar-Poli, Schultze-Lutter, et al., 2016). For example, most adolescent samples included in the current study were recruited through inpatient or outpatient mental health units or programmes, which are well known to be associated with a higher level of risk enrichment (Fusar-Poli, Rutigliano, et al., 2016; Fusar-Poli, Schultze-Lutter, et al., 2016). Furthermore, the transition to psychosis may increase in the long-term, given that adolescents may experience an extended period of risk compared with adult populations (Dominguez et al., 2013). Beyond the risk for the development of psychosis, 60% of adolescents at CHR-P did not recover and remained symptomatic after six-year follow-up (de Wit et al., 2014) with negative consequences in terms of functioning and comorbidities. In particular, lower levels of negative and mood symptoms were linked to higher possibilities of recovery (Schlosser et al., 2012), suggesting that negative and mood symptoms should become targets of future interventions in this area. Furthermore, an early presentation before the age of 15 was associated with worse social functioning (Ribolsi et al., 2017). In adults at CHR-P, the unfavourable trajectories (any recurrence, relapse, no-remission and transition to psychosis) represent 57.1% (Polari et al., 2018).

Most studies retrieved (59.3%) focused mainly on aspects related to the detection of CHR-P individuals. Several psychometric instruments are currently available to detect these individuals such as the SIPS (Millman et al., 2017; Salinger et al., 2018) or the CAARMS (Yung, Yuen, Phillips, Francey, & McGorry, 2003). However, additional psychometric instruments have been developed for this particular group under 18 years, such as the SPI-CY (Fux et al., 2013; Pelizza, Azzali, et al., 2019). The prognostic accuracy of SPI-CY and i-PQ16 (16-item prodromal questionnaire) in adolescents was good (sensitivity: 0.7–0.83, specificity: 0.73–0.86) (Fux et al., 2013; Pelizza, Azzali, et al., 2019), which is comparable to findings in adult populations (Fusar-Poli, Cappucciati, et al., 2015). Regarding the different CHR-P subgroups, our meta-analysis showed that most (82.6%) CHR-P individuals fulfilled APS criteria, concordant with the

Table 3 Meta-analysis of proportion of CHR-P adolescents receiving treatments at baseline

| Treatment | N of studies | Total sample | Proportion of treatment used | 95% CI | | Q | df | I ² | p | Egger test |
|--------------------|--------------|--------------|------------------------------|--------|------|--------|----|----------------|-------|------------|
| Antipsychotics | 15 | 737 | 0.30 | 0.22 | 0.40 | 76.85 | 14 | 81.78 | <.001 | 0.32 |
| Antidepressants | 17 | 858 | 0.27 | 0.22 | 0.33 | 48.69 | 16 | 67.80 | <.001 | 0.02 |
| Benzodiazepines | 11 | 592 | 0.11 | 0.03 | 0.32 | 166.65 | 10 | 94.0 | <.001 | 0.13 |
| Other psychotropic | 9 | 521 | 0.15 | 0.08 | 0.27 | 54.27 | 8 | 85.26 | <.001 | 0.21 |
| Psychotherapy | 6 | 270 | 0.60 | 0.26 | 0.87 | 71.72 | 5 | 93.03 | <.001 | 0.34 |

previous meta-analysis including adults (85%) (Fusar-Poli, Cappucciati, Borgwardt, et al., 2016). However, the proportion of GRD appeared higher in youth at CHR-P (8%) compared to the previous meta-analysis, including an adult population (5%) (Fusar-Poli, Cappucciati, Borgwardt, et al., 2016). This difference may be due to the fact that screening families where a parent is affected with a psychotic disorder is relatively more frequent in paediatric settings, hence increasing the proportion of those meeting this familial risk CHR-P subgroup. However, the proportion of BLIPS (6.7%) appeared lower than that reported in the adult CHR-P population (10%) (Fusar-Poli, Cappucciati, Borgwardt, et al., 2016). This difference may be due to the lower incidence of psychotic disorders in younger populations (Fusar-Poli, Davies, Rutigliano, et al., 2019). Some studies suggested that refined CHR-P subgroups may be specifically needed in this young population (Spada et al., 2016), for example, an attenuated negative symptom subgroup (Fusar-Poli & Borgwardt, 2007). Another core theme was the implication of the family for the detection of the CHR-P paediatric population. Several authors described a better recognition of the CHR-P state when the caregiver was involved in assessment procedures (Golembo-Smith et al., 2014; Thompson et al., 2014), highlighting the importance of family as a source of clinical information in this age group.

We also confirmed, at a meta-analytical level, that comorbid mental disorders were frequent in adolescents at CHR-P, particularly mood and anxiety disorders. The prevalence of mood disorders was similar to those from a previous meta-analysis conducted in CHR-P adults (41%) (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). Conversely, the proportion of comorbid anxiety disorders seemed to be higher in adolescents (31.4%) compared to rates found in the previous meta-analysis of adult patients (15%) (Fusar-Poli et al., 2014). Anxiety disorders are the most prevalent mental health concern in the adolescent population (Siegel & Dickstein, 2012), and findings suggest that the onset of the first anxiety disorder is clearly in childhood (Kessler et al., 2005).

Overall, these findings suggest that psychopathology in adolescents meeting CHR-P criteria is characterised by transdiagnostic features that cut across different mental disorders (Fusar-Poli et al., 2020). Furthermore, adolescents with CHR-P features reported more social stress (Millman et al., 2018), previous traumatic events (Kline et al., 2016; Morelli et al., 2019) and a higher risk of suicidal attempts (Pelizza, Poletti, et al., 2019) compared to matched HC. The presence of these features, if coupled with comorbid mental disorders, may trigger an increased risk of psychosis (Rapado-Castro et al., 2015). Consistent with these findings, CHR-P adolescents presented with poorer functioning (Carrion et al., 2013; Dolz, Tor, de la Serna, et al., 2018; Velthorst et al.,

2018), quality of life (Nitka et al., 2016) and moderate impairments in neurocognitive performance compared to HC (D'Angelo et al., 2019; Koren et al., 2019; Woodberry et al., 2010), similar to observations in adult CHR-P populations (Fusar-Poli et al., 2012).

Few studies explored neurobiological correlates of the CHR-P state in adolescents. Paediatric CHR-P participants showed lower testosterone (van Rijn et al., 2011b) and increased morning salivary cortisol level (Moskow et al., 2016) compared to HC. Contrary to brain morphological abnormalities observed in adults at CHR-P (Harrisberger et al., 2016; Walter et al., 2016), structural alterations have not been robustly confirmed in adolescents at CHR-P (Ziermans et al., 2009). These differences may reflect different maturational ages of the brain across these two populations or may alternatively be due to a lower true-positive rate for psychosis in paediatric CHR-P samples due to more nonspecific and overlapping phenomenologies of concurrently emerging psychiatric disorders (Gerstenberg et al., 2015, 2016; Kelleher et al., 2012; Schimmelmann, Michel, Martz-Irngartinger, Linder, & Schultze-Lutter, 2015).

The area of discovery of effective preventive treatments for adolescents at CHR-P has received less empirical evidence. The relevance of effective prevention in this population is unquestionable because a FEP at an earlier age may translate into a worse long-term prognosis (Diaz-Caneja et al., 2015) and reduced cost-effectiveness (Fusar-Poli, Frascarelli, et al., 2015; Mihalopoulos, Harris, Henry, Harrigan, & McGorry, 2009). Unfortunately, there are only two RCTs specifically investigating the efficacy of preventive psychotherapeutic interventions (cognitive behavioural therapy vs. nondirective reflective listening therapy) for adolescents at CHR-P (Stain et al., 2016). There is no evidence that this treatment is effective. Another RCT found promising results for omega-3 fatty acid supplementation (Amminger et al., 2010), but this finding was likely a false positive as it was not replicated in a subsequent confirmatory larger RCT in the adult population (McGorry et al., 2017). Overall, there is insufficient evidence to recommend one specific treatment over the others to prevent the transition to psychosis in this population, in line with current evidence in this field (Davies et al., 2018; Devoe, Farris, Townes, & Addington, 2019; Fusar-Poli et al., 2020). Other RCTs suggest that family interventions may be particularly effective in the paediatric CHR-P population improving attenuated prepsychotic symptoms (Miklowitz et al., 2014; Tsai et al., 2015). However, these promising findings have not been replicated, and future interventional research is urgently needed to confirm their robustness and address this gap in knowledge.

This study has several limitations. First, the mean age of the included samples was 15.6 but ranged from 11.7 to 17.9 years, which was highly variable,

and some studies included adult participants. However, since the CHR-P paradigm is essentially transitional, the 18 years age threshold does not work well. Differences in terms of neurodevelopment between younger children and older adolescents could exist, and this could complicate interpretation of the results. We have mitigated this issue by conducting sensitivity analyses restricted in under-age populations. Second, the included studies were very heterogeneous not only in their design and methodology but also in their quality. We have, therefore, carefully reported the study quality. Third, the number of participants per study was modest, with only five studies including >100 CHR-P individuals (Auther et al., 2012; Chung et al., 2018; Miklowitz et al., 2014; Moskow et al., 2016; Velthorst et al., 2018). To overcome this problem, we performed meta-analyses whenever possible. Finally, most of the studies were performed in specific psychiatric services and therefore represent a help-seeking clinical sample; this is well known to increase comorbidities, the necessity of treatment and risk enrichment (Fusar-Poli, Rutigliano, et al., 2016; Fusar-Poli, Schultze-Lutter, et al., 2016). Young individuals without comorbid disorders, functional impairments and help-seeking behaviour are less likely to be referred for CHR-P assessments (Fusar-Poli, Sullivan, Shah, & Uhlhaas, 2019).

Overall, this study described the core clinical characteristics of CHR-P adolescents and summarised the available instruments that can be used by clinicians to detect them. This review highlights the core outcomes presented by this vulnerable population and the limited evidence for effective interventions. The evidence appraised here should be used as a benchmark to conduct future research in children and adolescents at risk for psychosis.

Conclusions

The CHR-P paradigm in adolescents has shown to be useful and widely accepted. Although it is currently possible to detect and formulate a group-level prognosis in adolescents at risk for psychosis, effective intervention for this subgroup should be better identified.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. PRISMA statement and checklist.

Table S2. Moose checklist.

Table S3. Risk of bias (quality) assessment using modified Newcastle Ottawa Scale for cross-sectional and cohort studies.

Table S4. Detection: Characteristics of CHR-P state.

Table S5. Detection. Types of CHR-P subgroups in adolescents.

Table S6. Sensitivity analyses for the subgroups in adolescents CHR-P individuals.

Table S7. Detection: Clinical comorbidity in the CHR-P state.

Table S8. Sensitivity analyses for proportion of CHR-P adolescents with DSM/ICD comorbid mental disorders.

Table S9. Detection: Functioning and quality of life in CHR-P state.

Table S10. Detection: Cognition in CHR-P state.

Table S11. Detection: Neuroimaging, biochemistry, and electrophysiology in CHR-P state.

Table S12. Prognosis: Overall prognosis/risk of psychosis in CHR-P state.

Table S13. Sensitivity analyses for transition to psychosis in CHR-P adolescents.

Table S14. Prognosis: Prediction of outcomes in CHR-P state.

Table S15. Intervention: Interventions in CHR-P state.

Table S16. Sensitivity analysis proportion of CHR-P adolescents with treatment.

Table S17. Meta-regressions between quality of the included studies and detection, prognosis and intervention outcomes.

Table S18. Risk of bias (quality assessment) using modified Newcastle Ottawa Scale for cohort studies.

Table S19. Risk of bias (quality assessment) using modified Newcastle Ottawa Scale for cross-sectional studies.

Figure S1. Meta-analysis of the proportion of individuals with attenuated psychotic symptoms in CHR-P adolescents.

Figure S2. Meta-analysis of the proportion of individuals with Brief Limited Intermittent Psychosis Syndrome in CHR-P adolescents.

Figure S3. Meta-analysis of the proportion of individuals with Genetic Risk Deterioration in CHR-P adolescents.

Figure S4. Meta-analysis of the cumulative risk of psychosis in CHR-P adolescents at 6-months.

Figure S5. Meta-funnel and Egger's test results for the cumulative risk of psychosis in CHR-P individuals at 6-months.

Figure S6. Meta-analysis of the cumulative risk of psychosis in CHR-P adolescents at 12-months.

Figure S7. Meta-funnel and Egger's test results for the cumulative risk of psychosis in CHR-P individuals at 12-months.

Figure S8. Meta-analysis of the cumulative risk of psychosis in CHR-P adolescents at 24-months.

Figure S9. Meta-funnel and Egger's test results for the cumulative risk of psychosis in CHR-P individuals at 24-months.

Figure S10. Meta-analysis of the cumulative risk of psychosis in CHR-P adolescent at 36-months.

Figure S11. Meta-funnel and Egger's test results for the cumulative risk of psychosis in CHR-P individuals at 36-months.

Appendix S1. Search strategy.

Appendix S2. Valid psychometric instruments to diagnose CHR-P criteria.

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Key points

- The clinical high risk for psychosis paradigm involves detecting, formulating a prognosis and offering interventions to those aged 12–18.
- This study demonstrates that it is feasible to detect and formulate a prognosis in the subgroup of adolescents at risk for psychosis aged 12–18.
- Evidence of effective interventions to prevent the onset of psychosis in adolescents aged 12–18 is lacking.

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