PREVENCIÓN DE LA PSICOSIS, AVANCES EN DETECCIÓN, PRONÓSTICO E INTERVENCIÓN.

Resumen

Detección, pronóstico e intervenciones indicadas en individuos con alto nivel clínico. El riesgo de psicosis (CHR-P) son componentes claves de la psiquiatría preventiva.

OBJETIVOS:

Proporcionar una evaluación sistemática integral basada en la evidencia de avances, limitaciones de detección, pronóstico e intervención en la Psicosis.

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JAMA Psychiatry | Review

Prevention of Psychosis
Advances in Detection, Prognosis, and Intervention

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IMPORTANCE Detection, prognosis, and indicated interventions in individuals at clinical high risk for psychosis (CHR-P) are key components of preventive psychiatry.

OBJECTIVE To provide a comprehensive, evidence-based systematic appraisal of the advancements and limitations of detection, prognosis, and interventions for CHR-P individuals and to formulate updated recommendations.

EVIDENCE REVIEW Web of Science, Cochrane Central Register of Reviews, and Ovid/PsychINFO were searched for articles published from January 1, 2013, to June 30, 2019, to identify meta-analyses conducted in CHR-P individuals. MEDLINE was used to search the reference lists of retrieved articles. Data obtained from each article included first author, year of publication, topic investigated, type of publication, study design and number, sample size of CHR-P population and comparison group, type of comparison group, age and sex of CHR-P individuals, type of prognostic assessment, interventions, quality assessment (using AMSTAR [Assessing the Methodological Quality of Systematic Reviews]), and key findings with their effect sizes.

FINDINGS In total, 42 meta-analyses published in the past 6 years and encompassing 81 outcomes were included. For the detection component, CHR-P individuals were young (mean [SD] age, 20.6 [3.2] years), were more frequently male (58%), and predominantly presented with attenuated psychotic symptoms lasting for more than 1 year before their presentation at specialized services. CHR-P individuals accumulated several sociodemographic risk factors compared with control participants. Substance use (33% tobacco use and 27% cannabis use), comorbid mental disorders (41% with depressive disorders and 15% with anxiety disorders), suicidal ideation (66%), and self-harm (49%) were also frequently seen in CHR-P individuals. CHR-P individuals showed impairments in work (Cohen *d* = 0.57) or educational functioning (Cohen *d* = 0.21), social functioning (Cohen *d* = 1.25), and quality of life (Cohen *d* = 1.75). Several neurobiological and neurocognitive alterations were confirmed in this study. For the prognosis component, the prognostic accuracy of CHR-P instruments was good, provided they were used in clinical samples. Overall, risk of psychosis was 22% at 3 years, and the risk was the highest in the brief and limited intermittent psychotic symptoms subgroup (38%). Baseline severity of attenuated psychotic (Cohen *d* = 0.35) and negative symptoms (Cohen *d* = 0.39) as well as low functioning (Cohen *d* = 0.29) were associated with an increased risk of psychosis. Controlling risk enrichment and implementing sequential risk assessments can optimize prognostic accuracy. For the intervention component, no robust evidence yet exists to favor any indicated intervention over another (including needs-based interventions and control conditions) for preventing psychosis or ameliorating any other outcome in CHR-P individuals. However, because the uncertainty of this evidence is high, needs-based and psychological interventions should still be offered.

CONCLUSIONS AND RELEVANCE This review confirmed recent substantial advancements in the detection and prognosis of CHR-P individuals while suggesting that effective indicated interventions need to be identified. This evidence suggests a need for specialized services to detect CHR-P individuals in primary and secondary care settings, to formulate a prognosis with validated psychometric instruments, and to offer needs-based and psychological interventions.

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Supplemental content

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Detection, assessment, and intervention before the onset of a first episode of the disorder in individuals at clinical high risk for psychosis (CHR-P) have the potential to maximize the benefits of early interventions in psychosis.[1,2] The CHR-P paradigm originated in Australia 25 years ago[3] and has since gained enough traction to stimulate hundreds of research publications. These published studies have been summarized in evidence synthesis studies spanning different topics and have influenced several national[4] and international[5] clinical guidelines and diagnostic manuals (eg, *DSM-5*[6,7]). Overall, CHR-P represents the most established preventive approach in clinical psychiatry; therefore, periodically reviewing its progress and limitations is essential.

The rapid developments of detection, prognostic, and intervention-focused knowledge in the CHR-P field have not yet been integrated into a comprehensive, evidence-based summary since a 2013 publication in *JAMA Psychiatry*.[8] Produced by the European College of Neuropsychopharmacology Network on the Prevention of Mental Disorders and Mental Health Promotion,[9] the present study aimed to provide the first umbrella review summarizing the most recent evidence in the CHR-P field. An additional objective was to provide evidence-based recommendations for the 3 core components that are necessary to implement the CHR-P paradigm in clinical practice: detection, prognosis, and intervention.[10]

Key Points

Question What is the status of current clinical knowledge in the detection, prognosis, and interventions for individuals at risk of psychosis?

Findings In this review of 42 meta-analyses encompassing 81 outcomes, detecting individuals at risk for psychosis required knowledge of their specific sociodemographic, clinical, functional, cognitive, and neurobiological characteristics, and predicting outcomes was achieved with good accuracy provided that assessment tools were used in clinical samples. Evidence for specific effective interventions for this patient population is currently insufficient.

Meaning Findings of this review suggest that, although clinical research knowledge for psychosis prevention is substantial and detecting and formulating a prognosis in individuals at risk for psychosis are possible, further research is needed to identify specific effective interventions in individuals with sufficient risk enrichment.

Methods

The protocol of this study was registered in PROSPERO (registration No. CRD42019135880). This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) reporting guideline[11] and the Reporting Items for Practice Guidelines in Healthcare (RIGHT) statement[12] (eTable 1 in the Supplement).

Search Strategy and Selection Criteria

A multistep literature search was performed for articles published between January 1, 2013, and June 30, 2019 (eMethods 1 in the Supplement). Web of Science, Cochrane Central Register of Reviews, and Ovid/PsychINFO were searched for meta-analyses conducted in CHR-P individuals, and MEDLINE was used to search the reference lists of retrieved articles. The literature search, study selection, and data extraction were conducted independently by 2 of us (G.S.d.P., P.F.-P.), and consensus was reached through discussion.

Studies included were (1) meta-analyses (pairwise or network; aggregate or individual participant data) published as original investigations, reviews, research letters, or gray literature without restriction on the topic investigated[13]; (2) conducted in CHR-P individuals (ie, individuals meeting ultra-high-risk and/or basic symptoms criteria) as established by validated psychometric instruments[8] (eMethods 2 in the Supplement) without restriction on the type of comparison group; and (3) published in the past 6 years.

Studies excluded (1) were original studies, study protocols, systematic reviews without quantitative analyses, and other non-meta-analytical studies; (2) did not formally assess and selected participants with established CHR-P instruments; or (3) were abstracts and conference proceedings. Data obtained from each article included first author, year of publication, topic investigated, type of publication, study design and number, sample size of CHR-P population and comparison group, type of comparison group, age and sex of CHR-P individuals, type of prognostic assessment, interventions, quality assessment (using AMSTAR [Assessing the Methodological Quality of Systematic Reviews]), and key findings with their effect sizes.

To respect the hierarchy of the evidence (eMethods 3 in the Supplement), if 2 or more meta-analyses addressing the same topic were found, we gave preference to individual participant data meta-analyses over aggregate network meta-analyses and to network meta-analyses over pairwise meta-analyses. The most recent study was selected when the previous criteria did not apply. If, after applying the hierarchical criteria, 2 studies were similar, both were included.

Outcome Measures, Data Extraction, and Timing and Effect Measures

From each study, a predetermined set of outcome measures (eMethods 4 in the Supplement) was extracted. The results were then narratively reported in tables, clustered around 3 core domains: detection, prognosis, and intervention.

When feasible, effect size measures were estimated through Cohen *d*. Other effect size measures were converted to Cohen *d*.[13] In case of meta-analyses reporting time-dependent risks or rates or descriptive data only, proportions (95% CIs) or means (SDs) were summarized.

Quality Assessment

The quality of the included meta-analyses was assessed with the AMSTAR tool.[14] Details of the meta-analyses and items evaluated are found in eMethods 5 in the Supplement.

Standards for Guidelines Development

To develop the recommendations, we followed the US Preventive Services Task Force (USPSTF) grading system[15] (eTable 2 in the Supplement), which is suited explicitly for preventive approaches and has received extensive validation in articles published in several journals, including *JAMA*.[16-21] Guideline development followed

the *JAMA* Clinical Guidelines Synopsis, reaching consensus across the multidisciplinary European College of Neuropsychopharmacology Network on the Prevention of Mental Disorders and Mental Health Promotion.[9] The rationale for the recommendations was provided. Conflicts of interest were fully detailed.

Results

The literature search yielded 886 citations, which were screened for eligibility, and 55 of them were considered. After checking the inclusion and exclusion criteria, we included 42 meta-analyses encompassing 81 outcomes in the final analysis (**Figure 1**; eTables 3 to 11 in the Supplement).

Detection

Characteristics

No meta-analysis focused on the basic symptoms criteria. Overall, 85% (95% CI, 79%-90%) of CHR-P individuals met the attenuated psychosis symptoms (APS) criteria,[22] 10% (95% CI, 6%-14%) met the brief limited intermittent psychotic symptoms (BLIPS) criteria,[22] and 5% (95% CI, 3%-7%) met the genetic risk and deterioration (GRD) syndrome criteria.[22] The mean (SD) age of CHR-P individuals across the included studies was 20.6 (3.2) years, with a range of 12 to 49 years.[5,22-52] These individuals were predominantly male (58%)[22-29,31,33,35-43,46-50,53,54] and had attenuated psychotic symptoms lasting for more than 1 year before their presentation to specialized services. Several studies included underage patients.[5,22-30,32-35,39-50,52,55,56] No differences were observed across the APS, BLIPS, and GRD subgroups.[22] However, the mean (SD) duration of untreated attenuated psychotic symptoms tended to be shorter in the BLIPS group (435.8 [456.4] days) compared with the GRD group (783.5 [798.6] days) and APS group (709.5 [518.5] days) (eTable 3 in the Supplement).

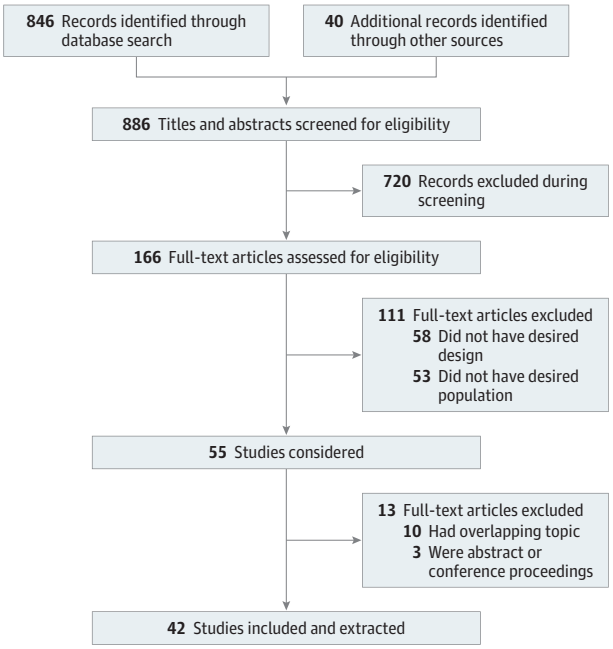
Genetic and Environmental Risk and Protective Factors

Individuals who met CHR-P criteria, compared with those who did not, were more likely to have olfactory dysfunction (Cohen *d* = 0.71),[57] be physically inactive (Cohen *d* = 0.7), have obstetric complications (Cohen *d* = 0.62), be unemployed (Cohen *d* = 0.57), be single (Cohen *d* = 0.27), have a low educational level (Cohen *d* = 0.21), and be male (Cohen *d* = 0.18).[55] Trauma, which encompassed childhood emotional abuse (Cohen *d* = 0.98),[55] high perceived stress (Cohen *d* = 0.85),[55] childhood physical neglect (Cohen *d* = 0.62),[55] and being bullied (Cohen *d* = 0.62)[56] (eTable 4 in the Supplement; **Figure 2**), was also more frequent (87% for overall trauma)[23] and severe (Cohen *d* = 1.38)[56] in CHR-P individuals compared with the control groups. No meta-analysis addressed the association between genetic factors and the CHR-P state.

Substance Use

A statistically significant association was found between the CHR-P state and tobacco use (Cohen *d* = 0.61).[55] Altogether, 33% of CHR-P individuals smoked tobacco compared with 14% in the control groups.[58] Those in the CHR-P group were also more likely to be current cannabis users than control participants (27% vs 17%).[53] Current cannabis use disorder was associated with an increased risk of psychosis (Cohen *d* = 0.31), whereas lifetime cannabis use was not.[24]

Figure 1. PRISMA Flowchart of Study Selection Process



Higher levels of unusual thought content (Cohen *d* = 0.27) and suspiciousness (Cohen *d* = 0.21) were found in CHR-P individuals who were cannabis users compared with non–cannabis users,[53] but attenuated positive or negative psychotic symptoms did not differ between these 2 groups[53] (eTable 5 in the Supplement).

Clinical Comorbidity

Depressive (41%) and anxiety (15%) disorders were frequent in the CHR-P state.[25] Most CHR-P individuals presented with suicidal ideation (66%).[26] The prevalence of self-harm was 49% and of suicide attempts was 18% in CHR-P individuals[26] (eTable 6 in the Supplement).

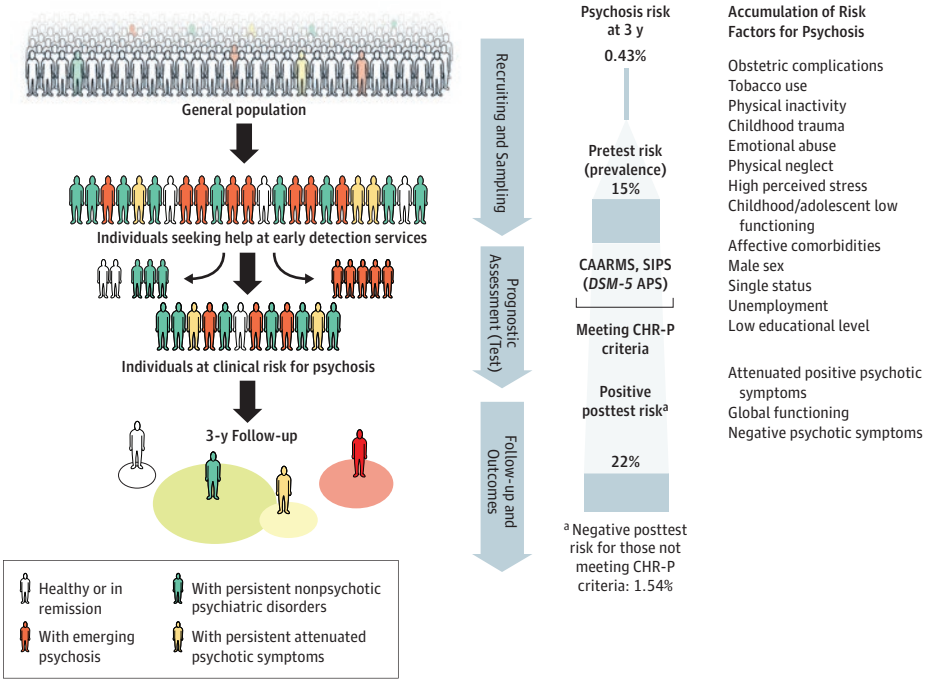
Functioning and Quality of Life

CHR-P individuals had lower levels of adolescence (Cohen *d* = 0.96-1.03) and childhood (Cohen *d* = 1.0) functioning compared with control participants.[55] Functional impairments in CHR-P individuals were as severe as impairments in other mental disorders and were more severe than in control participants (Cohen *d* = 3.01)[27] but were less severe than in established psychosis (Cohen *d* = 0.34). The CHR-P status was also associated with significant social deficits (Cohen *d* = 1.25).[55] Quality of life was worse in CHR-P individuals than in control individuals (Cohen *d* = 1.75),[27] whereas no differences from individuals with psychosis[27] were reported (eTable 7 in the Supplement).

Cognition

Visual learning (Cohen *d* = 0.27), processing speed (Cohen *d* = 0.42), and verbal learning (Cohen *d* = 0.42)[54] were impaired in CHR-P individuals compared with control participants. CHR-P individuals who later developed psychosis showed poorer cognitive functioning (Cohen *d* = 0.24-0.54)[54] compared with those who did not develop psychosis. However, no evidence of cognitive decline was

Figure 2. Recruitment and Sampling, Assessment, and Prognosis in the Clinical High Risk for Psychosis (CHR-P) State



Recruitment strategies lead to differential accumulation of risk factors for psychosis from the general population (0.43% at 3 years) to individuals undergoing CHR-P assessment (15% at 3 years; pretest risk enrichment or prevalence). Applying the CHR-P prognostic assessments (test) to these help-seeking individuals discriminates between those at risk for psychosis and those not at risk (positive posttest risk of 22% and negative posttest risk of 1.54% at 3 years). The actual transition to psychosis observed at follow-up, within a naturalistic design, largely depends on the overall level of accumulation (pretest risk) of risk factors for psychosis. CAARMS, Comprehensive Assessment of At-Risk Mental States; *DSM-5* APS, *DSM-5* Attenuated Psychosis Syndrome; and SIPS, Structured Interview for Prodromal Symptoms.

found from baseline to follow-up in CHR-P individuals at any time.[28] Although social cognition was impaired in CHR-P individuals compared with control individuals (Cohen *d* = 0.48),[30] theory of mind was less impaired than in participants with first-episode psychosis (Cohen *d* = 0.45).[31] CHR-P individuals showed more metacognitive dysfunctions (Cohen *d* = 0.57-1.09) than control participants but were similar to those with established psychosis[29] (eTable 8 in the Supplement).

Neuroimaging and Biochemistry

CHR-P individuals had decreased blood interleukin 1β (IL-1β) levels[33] (Cohen *d* = 0.66), increased salivary cortisol levels (Cohen *d* = 0.59),[32] and increased blood IL-6[33] (Cohen *d* = 0.31) compared with control groups. The thalamus was smaller in CHR-P individuals than in control participants (Cohen *d* = 0.60),[36] whereas no significant differences in the pituitary volume were found.[37] The right hippocampal volume (unlike the left one) was also significantly smaller in CHR-P individuals[38] compared with control participants (Cohen *d* = 0.24).[38] Levels of glutamate and glutamine (measured together) were higher in the medial frontal cortex of CHR-P individuals than in control participants (Cohen *d* = 0.26).[34]

Compared with control individuals, CHR-P individuals showed decreased activations in the right inferior parietal lobule and left medial frontal gyrus and increased activations in the left superior temporal gyrus and right superior frontal gyrus[35] (eTable 9 in the Supplement). As for neurophysiological processes, the mismatch negativity amplitude was reduced in CHR-P individuals compared with control participants (Cohen *d* = 0.4)[39] and in CHR-P individuals who developed psychosis compared with those who did not (Cohen *d* = 0.71).[59] A theoretical neurobiological model of the CHR-P state, which integrates these findings, is reported in **Figure 3**.[60]

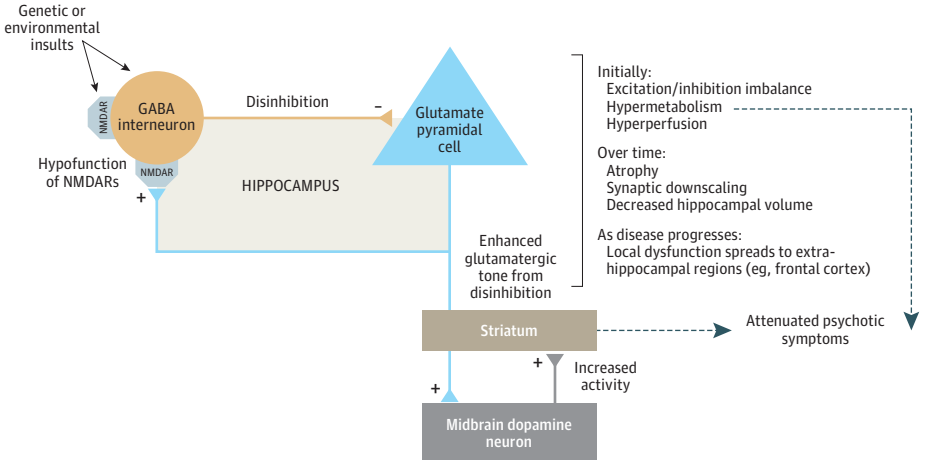
Prognosis

Overall Prognostic Performance

Currently used semistructured interviews for psychosis prediction have an excellent overall prognostic performance (area under the curve [AUC] = 0.9).[42] However, their sensitivity is high (96%) and specificity is low (47%),[42] and they are not valid outside clinical samples that have undergone risk enrichment (ie, screening the general population is not useful)[42] (Figure 2). The CAARMS (Comprehensive Assessment of At-Risk Mental States) instrument has an acceptable (AUC = 0.79) accuracy for predicting psychosis,[43] and it has no substantial differences in prognostic accuracy from other CHR-P instruments,[42] although the Structured Interview of Psychosis-Risk Syndromes has a slightly higher sensitivity (95%) than the CAARMS (86%).[43] The reason for this lack of difference in prognostic accuracy is that most of the risk for psychosis (posttest risk) is accounted for by the way these individuals are recruited and sampled (pretest risk, independent from clinically verified CHR-P status) before the CHR-P test is administered.[41] Pretest risk for psychosis is 15% at 3 years and is heterogeneous, ranging from 9% to 24%. Variability in pretest risk for psychosis is modulated by the type of sampling strategies,[41] increasing if samples are recruited from secondary care and decreasing if samples are recruited from the community[41] (Figure 2; eTable 10 in the Supplement).

The proportion of CHR-P individuals who developed a psychotic disorder (positive posttest risk, updated in 2016) was 22% at 3 years (**Figure 4**).[40] The speed of transition to psychosis was

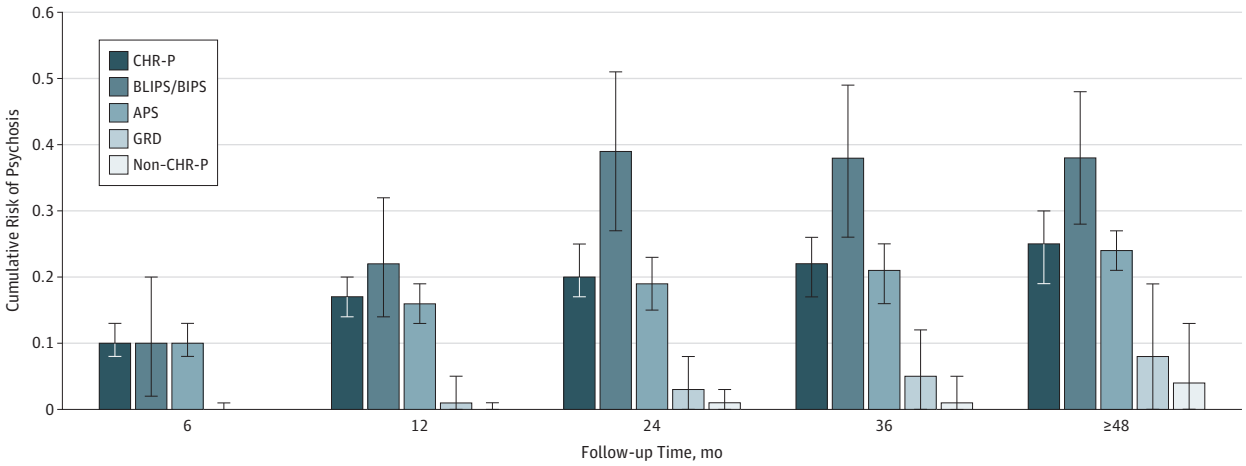
Figure 3. Simplified Schematic of Circuit Mechanisms of Neurobiological Dysfunction and Pathophysiological Processes in the Clinical High Risk State for Psychosis



Low glutamate signal/input from hypofunctioning *N*-methyl-D-aspartate class of glutamate receptor (NMDAR) (akin to faulty homeostatic sensors) leads γ-aminobutyric acid (GABA)–mediated (GABAergic) interneurons to homeostatically increase excitation by reducing inhibition (disinhibition) of glutamatergic pyramidal cells. However, by disinhibiting pyramidal cells (and thus increasing glutamate signaling) in this dysfunctional neural environment, the potential homeostatic adaptation becomes allostatic. Enhanced excitation leads to an overdrive in the responsivity of midbrain dopamine neurons, which project to the associative striatum. Completing the (simplified) circuit, the local glutamatergic tone is increased but is not detected as such by hypofunctioning NMDARs on GABAergic interneurons.

Reprinted and adapted from Davies et al.[60]

Figure 4. Cumulative Risk of Developing Psychosis in Individuals at Clinical High Risk for Psychosis (CHR-P)



CHR-P refers to the whole group comprising APS and/or BLIPS and/or GRD. APS indicates the attenuated psychosis symptoms subgroup (referring to APS only or APS plus GRD); BLIPS/BIPS, brief limited intermittent psychotic symptoms/brief intermittent psychotic symptoms (referring to BLIPS only or BLIPS plus APS or BLIPS plus GRD or BLIPS plus APS plus GRD); GRD, genetic risk and deterioration syndrome subgroup (referring to GRD only); and non–CHR-P, individuals assessed for but not meeting CHR-P criteria. Error bars indicate 95% CIs.

Data are from Fusar-Poli et al.[22]

greatest in the first months after CHR-P individuals presented to clinical services (median time to psychosis = 8 months).[61] Transition to schizophrenia-spectrum psychoses was more than 6 times more frequent (73%) than transition to affective psychoses (11%), whereas transition to other psychoses was 16%.[40] The transition risk to psychosis was higher in the BLIPS subgroup (38%) than in the APS (24%) and GRD (8%) subgroups at the 48-month follow-up or later,[22] whereas the GRD subgroup was not at higher risk compared with the help-seeking control participants (which represents the standard comparative group during CHR-P interviews).[22] No prognostic difference in the risk of psychotic recurrence was found across different operationalizations of short-lived psychotic episodes, including acute and transient psychotic disorders and brief psychotic disorders, but this risk was lower than in patients with remitted first-episode schizophrenia[62] (eTable 10 in the Supplement). In the BLIPS group, the 2-year risk of developing schizophrenia was 23% and

Table. Executive Summary: Relevant Recommendations for Detection, Prognosis, and Intervention in Individuals at Clinical High Risk for Psychosis (CHR-P)[a]

Core Component	Recommendation
Detection	Identify help-seeking persons at increased risk of psychosis primarily in primary and secondary health care settings, and refer persons at increased risk of psychosis to specialized clinical services for further evaluation and, possibly, care. Grade B.[a]
Prognosis	Assess persons seeking help at specialized clinical services using validated psychometric instruments; do not use these instruments in the general population. Grade B.[a]
Intervention	Offer indicated primary prevention of psychosis using needs-based interventions and psychological interventions (cognitive behavioral therapy or integrated psychological interventions) first, titrating the intervention according to the characteristics and risk profile (CHR-P subgroups BLIPS>APS>GRD, severity of attenuated positive and negative symptoms, and level of functioning) as well as the values and preferences of the CHR-P individuals. Treat other comorbid psychiatric conditions according to available guidelines, and aim for improving recovery, functional status, and quality of life beyond prevention. Grade C/I.[a]

Abbreviations: APS, attenuated psychosis symptoms; BLIPS, brief limited intermittent psychotic symptoms; GRD, genetic risk and deterioration syndrome.

[a] Grade-level evidence based on US Preventive Services Task Force criteria (eTable 2 in the Supplement).

affective psychoses was null.[62] Conversely, the remission rate of the baseline CHR-P symptoms was 35% at 1.94 years' follow-up.[45] No data were available on the remission rates across the BLIPS, APS, and GRD subgroups.

Prediction of Outcomes

Among CHR-P individuals, transition to psychosis was associated with severity of negative symptoms (Cohen *d* = 0.39), right-handedness (Cohen *d* = 0.26), severity of attenuated positive psychotic symptoms (Cohen *d* = 0.35), disorganized and cognitive symptoms (Cohen *d* = 0.32), unemployment (Cohen *d* = 0.32), severity of total symptoms (Cohen *d* = 0.31), low functioning (Cohen *d* = 0.29), severity of general symptoms (Cohen *d* = 0.23), living alone (Cohen *d* = 0.16), male sex (Cohen *d* = 0.10), and lifetime stress or trauma (Cohen *d* = 0.08) (eTable 11 in the Supplement; Figure 2).[63] However, only severity of attenuated psychotic symptoms and low functioning (highly suggestive level of evidence[13]) and negative symptoms (suggestive level of evidence[13]) were associated with psychosis onset after controlling for several biases.[63] Comorbid anxiety and depressive disorders were not significantly associated with transition to psychosis.[25] No data were available on the predictors of outcomes other than psychosis onset.

Prognostic accuracy may be optimized by controlling pretest risk enrichment[55] and using sequential assessments that include a staged assessment based on clinical information, electroencephalogram, neuroimaging, and blood markers[44] (eTable 11 in the Supplement).

Interventions

No evidence was found that favored any indicated intervention over another (including needs-based interventions or control conditions) for preventing the transition to psychosis.[46] Likewise, no evidence supported the superior efficacy of any intervention over another for reducing attenuated positive psychotic symptoms[47,48] (2 meta-analyses on the same topic were retained after the hierarchical criteria were applied) or negative symptoms,[49] improving overall functioning[5] or social functioning,[50] alleviating depression,[52] improving symptom-related distress or quality of life,[51] or affecting acceptability[46] in CHR-P individuals (eTable 12 in the Supplement).

Discussion

To our knowledge, this study is the first comprehensive review (42 meta-analyses with 81 outcomes) focusing on detection, prognosis, and intervention of CHR-P individuals. No meta-analyses had reported consistent results from well-designed, well-conducted studies related to detection, prognosis, or interventions in representative primary care populations (USPSTF criteria for high level of certainty).

The detection of CHR-P individuals has a moderate level of certainty (grade B; **Table**). Research in the past 6 years has revealed that detection of truly at-risk individuals may be the key rate-limiting step toward a successful implementation of the CHR-P paradigm at scale. Although the CHR-P group is heterogeneous, its baseline sociodemographic characteristics are now clearer; typically, these individuals were young (mean [SD] age, 20.6 [3.2] years) men (58%) who presented with APS and had associated impairments in global functioning (Cohen *d* = 3.01), social functioning (Cohen *d* = 1.25),[55] and quality of life (Cohen *d* = 1.75)[27]; suicidal ideation (66%[26]); self-harm (49%[26]); and suicide attempts (18%[26]). Because of these problems, these individuals sought help at specialized clinics; however, typically, these problems remained undetected (and untreated) for 1 year or more.

Currently, detection of CHR-P individuals is entirely based on their referral on suspicion of psychosis risk and on the promotion of help-seeking behaviors. These detection strategies appear inefficient: only about 5%[64] to 12%[65] of first-episode cases were detected at the time of their CHR-P stage through stand-alone or youth mental health services. A further caveat is that approximately one-third of first-episode cases may not lead to the development of psychosis through a CHR-P stage.[66,67] Furthermore, at presentation, CHR-P individuals often had comorbid nonpsychotic mental disorders (41% depressive disorders and 15% anxiety disorders[25]) and substance use (33% tobacco use[58] and 27% cannabis use[53]). Because of these limitations, the chain of evidence lacked coherence (per USPSTF grading system; eTable 2 in the Supplement). These issues could be addressed by integrated detection programs that leverage automatic detection tools for screening large clinical[10,64,68] and nonclinical[69] samples in a transdiagnostic[70] fashion, encompassing primary and secondary care, the community,[71] and youth mental health services.[72] In addition, the detection of CHR-P individuals is currently based on the assessment of symptoms, but symptoms may be only the epiphenomena of underlying pathophysiological processes. CHR-P individuals often have several established sociodemographic, environmental, and other types of risk factors for psychosis,[73] including male sex, unemployment, single status, low educational and functional level, obstetric complications, physical inactivity, olfactory dysfunction, and childhood trauma (Figure 2; eDiscussion 1 in the Supplement). Incorporating the assessment of these multiple factors with CHR-P symptoms, resulting in a Psychosis Polyrisk Score, may produce refined detection approaches[74] that better map the etiopathological path of psychosis onset.

The prognosis of CHR-P individuals has a moderate level of certainty (grade B; Table).[47,75] Converging evidence has demonstrated that CHR-P assessment instruments have good prognostic accuracy (AUC = 0.9)[42] for the prediction of psychosis, comparable to the accuracy of clinical tools used in other areas of medicine.[42] However, alternative instruments are needed to predict other nonpsychotic outcomes (eg, bipolar onset in those at risk[76,77]). No substantial prognostic accuracy differences were found across different CHR-P tools.[42] The current CHR-P prediction instruments have high sensitivity (96%) but low specificity (47%) and are valid only if applied to clinical samples that have accumulated the above risk factors and have therefore already undergone substantial risk enrichment (Figure 2). In fact, it is not only CHR-P criteria that determine the probability of transition to psychosis but also the recruitment and selection of samples, which modulate enrichment in risk.[47,78] The next generation of research should better deconstruct and control risk enrichment[79] to maximize the scalability of the use of the CHR-P prediction instruments.[71] The 3-year meta-analytic risk of psychosis onset in the entire CHR-P group has declined from 31.5% (estimated in 2012[80]) to the current 22% (Figure 4), although not globally.[81]

Transition risk has decreased when recruitment strategies focused on the community as opposed to primary or secondary care (eDiscussion 2 in the Supplement). Risk was the highest in the BLIPS subgroup (38% at 4 years; 89% at 5 years if there were "seriously disorganising or dangerous"[82] features), intermediate in the APS subgroup (24% at 4 years), and lowest in the GRD subgroup (8% at 4 years).[22] Those in the GRD subgroup were not at higher risk than the help-seeking control individuals at up to 4 years of follow-up.[22] A revised version of the CHR-P paradigm, which includes stratification across these 3 subgroups, has therefore been proposed.[2,83] The BLIPS group also overlapped substantially with the acute and transient psychotic disorders in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*.[82] Therefore, current CHR-P instruments can allow only subgroup-level (ie, BLIPS>APS>GRD) but not participant-level prognosis (inconsistent evidence, USPSTF grading; eTable 2 in the Supplement).

To refine prognosis at the individual participant level, future research may consider specific risk factors (eg, sex, stress and trauma, employment, and living status[63]), biomarkers (eg, hippocampal volume[38]), or cognitive markers (eg, processing speed, verbal and visual memory, and attention[84]) in addition to the CHR-P subgroups[22] and clinical symptoms (only severity of attenuated positive and negative symptoms and level of functioning are robust risk factors for psychosis[63]). The potential of this approach has been supported by the development and validation of individualized clinical prediction models that leverage multimodal risk profiling,[64,85,86] including dynamic[87] risk prediction models.[88] Because these models tend to be more complex compared with standard symptomatic CHR-P assessments, they are more likely to enter clinical routine through a sequential testing framework[44] (eDiscussion 3 in the Supplement). Good outcomes in CHR-P individuals have not been fully operationalized,[89] and information is lacking on prediction of relevant clinical outcomes (USPSTF; eTable 2 in the Supplement), such as functional level and quality of life, with only approximately one-third of individuals remitting from their initial CHR-P state.[45]

The available evidence is insufficient (grade C/I; Table) to assess the effects of preventive interventions on health outcomes in CHR-P groups. Although earlier meta-analyses found advantages to cognitive behavioral therapy,[90] which is currently recommended by clinical guidelines,[4] the inclusion of new trials in recent meta-analyses has indicated no clear benefits to favor any available intervention over another intervention or any control condition, such as needs-based interventions. An independent pairwise meta-analysis published by the Cochrane Group after completion of the present study concluded that no convincing, unbiased, high-quality evidence exists that favors any type of intervention.[91] Evidence is insufficient because these studies tended to report large CIs and therefore high uncertainty (USPSTF; eTable 2 in the Supplement) in the meta-analytic estimates, and significant implications of the interventions for specific subgroups may not have been detected. For example, the needs-based interventions that are typically used as control conditions may have diluted the comparative efficacy of experimental interventions. This nondifferential outcome could also be an effect of the sampling biases leading to too few CHR-P individuals in the intervention studies who were at true risk for psychosis, diluting the statistical power of current trials that may have not been able to detect small to modest effect sizes (USPSTF; eTable 2 in the Supplement).[92] This lack of demonstrable advantages of specific interventions could also be the consequence of one-size-fits-all approaches in treating CHR-P individuals that go against the clinical, neurobiological, and prognostic heterogeneity of this group and against the recent calls for precision medicine. For example, CHR-P interventions to date have been developed largely for individuals with APS at the expense of those with BLIPS, who are often unwilling to receive the recommended interventions. Another explanation for the lack of comparative efficacy of preventive interventions is that they have largely targeted symptoms, as opposed to key neurobiological processes associated with the onset of psychosis (gaps in the chain of evidence, USPSTF; eTable 2 in the Supplement; Figure 3) or risk factors that could be modified (eg, physical inactivity; Figure 2). We believe that future experimental interventions should also better target relevant outcomes (USPSTF; eTable 2 in the Supplement) other than psychosis onset, including functioning, given the poor remission rates and low functioning of this population.[93] As acknowledged by the USPSTF criteria (eTable 2 in the Supplement), in the case of uncertainty, new trials published in the near future may allow a more accurate estimation of the preventive implications for health outcomes.

Grading the recent meta-analytic evidence described in this review, the European College of Neuropsychopharmacology Network on the Prevention of Mental Disorders and Mental Health Promotion has recommended (Table) implementing specialized services to detect CHR-P individuals in primary and secondary care settings and to formulate a prognosis with the validated psychometric instruments.[9] Owing to insufficient evidence that favored any particular preventive intervention over another (including control conditions) and considering the uncertainty of the current evidence, no firm conclusions can be made,[91] and a cautious approach is required. This approach should involve offering the least onerous feasible primary indicated prevention based on needs-based interventions and psychotherapy (cognitive behavioral therapy or integrated psychological interventions), titrated in accordance with the patient characteristics and risk profile (CHR-P subgroup levels

BLIPS>APS>GRD, severity of attenuated positive and negative symptoms, and level of functioning), values, and preferences of the individual.[94,95] In addition, other comorbid psychiatric conditions should be treated according to available guidelines, aiming for improving recovery, functional status, and quality of life beyond preventive aims.

Limitations

The main limitations of this study were that the meta-analyses had heterogeneous quality (eResults in the Supplement) and that the literature search approach may have favored the selection of more commonly and readily studied domains that are more likely to be included in a meta-analysis. We cannot exclude the possibility that some promising advancements in the CHR-P field, despite having sufficient data, do not (yet) have a corresponding eligible meta-analysis, such as polygenic risk scores.[96] However, in the current era, this possibility is becoming increasingly less likely, with meta-analyses being performed frequently, to the point that multiple meta-analyses are available for the same topic.[97-99] In any case, for most putative domains that are difficult to study (or uncommonly studied), the current grade of evidence is unlikely to be remarkable, given the limited data.

Conclusions

Over recent years, substantial advancements in the detection and prognosis of CHR-P individuals have been confirmed in several meta-analyses. However, further research is needed to optimize risk enrichment and stratification and to identify effective interventions that target quantitative individualized risk signatures for both poor and good outcomes.

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