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The Clinical High-Risk State for Psychosis (CHR-P), Version II

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The Clinical High-Risk state for psychosis (CHR-P) paradigm was introduced about 2 decades ago. Over this period of time accumulating knowledge has been gained. Conceptual advancements involve new knowledge into risk enrichment and the impact of recruitment strategies, specificity for prediction of psychotic and nonpsychotic mental disorders and heterogeneity of psychosis risk among the different CHR-P subgroups. The current special issue advances current knowledge on deconstructing the CHR-P paradigm across its 3 subgroups: genetic risk, attenuated psychotic symptoms, and short-lived and remitting psychotic episodes. A conceptual revision of the paradigm (Version II) is suggested and supported by 3 original studies published in this special issue.

Key words: psychosis/schizophrenia/risk/UHR/ARMS/SIPS

Introduction

The original At Risk Mental State (ARMS) construct (also termed as the Clinical High-Risk state for psychosis [CHR-P]) was introduced about 2 decades ago, in 1996,[1] to enable identification of subjects at enhanced "imminent development of a first-episode psychotic disorder" (page 964 in Yung et al[2]). Since then, the explosion of interest in the literature has been remarkable to the point that the specialist CHR-P provision is currently being recognized as an important component of the clinical services for early psychosis intervention (eg, NICE guidelines[3]; NHS England Access and Waiting Time [AWT] standard[4]). After about 2 decades of research, new knowledge has been gained that may inform a revision of the CHR-P paradigm. Three substantial conceptual advancements are summarized below.

Risk Enrichment and the Impact of Recruitment Strategies

The use of CHR-P criteria is associated with high prognostic accuracy (AUC at 38 mo = 0.9) that is comparable to other paradigms of preventative medicine,[5] leading to correct 38-month disease prediction in approximately one-fourth of the cases (26%),[5] a risk that peaks in the initial 2 years and then plateaus.[6] However, the CHR-P criteria yield successful predictive results only if they are applied to selected samples of individuals.[5] Indeed, recent evidence suggests that significant psychosis risk enrichment occurs before the CHR-P assessment (15% pretest risk at 38 mo,[7] for details see Fusar-Poli and Schultze-Lutter[8]). For example, applying CHR-P criteria to samples with a lower pretest risk of psychosis[9] may substantially dilute the prognostic accuracy of the paradigm and eventually lead to negative findings in the research studies (eg, Klauser et al[10]; see also table 2 in the study[5] for more examples). Within help-seeking individuals undergoing CHR-P assessment, the pretest risk of psychosis is substantial (15 of 26 [58%])[11] and heterogeneous (95% CI 9%–24%).[7] It is thus crucial to understand the factors that may modulate it. Recent studies have highlighted that recruitment strategies[7] and outreach campaigns[7,12] may impact the pretest risk enrichment. Specifically, individuals referred by first episode and inpatient mental health services have a high pretest risk.[13] These findings advance knowledge indicating that CHR-P assessment should primarily be offered to selected samples of individuals "already distressed by mental problems and seeking help for them" (European Psychiatric Association recommendation n.4[14]). Stratification of these subgroups[11] may inform outreach campaigns, subsequent testing[13] and optimize the psychosis prediction.

Specificity for Psychosis Prediction

Whether the CHR-P indicates specifically the risk for future psychosis, or to the nonspecific deterioration in mental health, including other nonpsychotic disorders, is of paramount relevance for both clinical and research perspectives. Recent studies have confirmed that CHR-P individuals are not at risk for developing incident bipolar

disorders, nonbipolar mood disorders or anxiety disorders[15] compared to control groups and that the vast majority of comorbid disorders observed in CHR-P individuals who do not develop psychosis is already present at the baseline.[16] These findings advance knowledge indicating that the possible outcomes specifically associated with the CHR-P (which may be preferred to the acronym "CHR" to better acknowledge the specificity for psychosis prediction) designation may include the onset of psychotic disorders, remission or persistence of initial symptoms and variable functional outcomes[17] but not an increased risk of emergence of new (incident) nonpsychotic mental disorders.

Heterogeneity of Psychosis Risks Within CHR-P Subgroups

Despite the immense research on reliable markers that can predict the subsequent onset of psychosis among CHR-P individuals, researchers are yet to discover such a holy grail.[18] If the CHR-P category is heterogeneous, this may hamper the ongoing efforts to identify reliable markers for clinical practice. A recent meta-analysis has elucidated the extent by which the 3 different CHR-P subgroups of Attenuated Psychotic Symptoms (APS), Brief (and Limited) Intermittent Psychotic Symptoms (BLIPS or BIPS) and Genetic Risk and Deterioration Syndrome (GRD) (for details see Fusar-Poli et al[19]) can be considered as belonging to a single CHR-P group. There was a significantly higher transition risk in the BLIPS subgroup, compared to the other CHR-P subgroups (ie, BLIPS: 39% vs APS: 19% at 24 mo).[20] These findings indicate that the BLIPS and APS subjects may represent distinct subgroups within the CHR-P category.[20] Furthermore, there was no prognostic difference between the GRD subgroup and the patients assessed but not deemed at risk for psychosis up to 4-year follow-up[20] (familiar risk may still be associated with an increased risk of psychosis[21] over longer intervals). This raised concerns about the validity of GRD as a state risk criterion for the CHR-P, suggesting more precise alternatives.[22]

Contributions of This Special Issue

The current special issue advances current knowledge on deconstructing the CHR-P paradigm across its 3 subgroups and piloting alternative approaches.

The first study[23] focuses on the diagnostic and prognostic significance of the BLIPS. Although the founders of the CHR-P have recommended comparing BLIPS with operationally-based ICD/DSM psychotic disorders (page 706 in Miller et al[24]), no studies have been published to date. The current study identified that at baseline, two-thirds (68%) of BLIPS met the criteria for ICD-10 "Acute and Transient Psychotic Disorder" (ATPD), mostly featuring schizophrenic symptoms.[23] At 5-year, about half of them developed psychosis,[23] in line with the meta-analytical prognostic outcomes observed in these groups.[25] The study further elucidated the course of the BLIPS, with recurrent episodes in 11% of cases. Recurrent episodes were associated with an increased risk of psychosis (hazard ratio [HR] 3.98).[23] Finally, the study investigated the prognostic significance of seriously disorganizing or dangerous BLIPS features that represent a distinctive operationalization between different CHR-P instruments.[26] It was shown that these features associated with an extremely high risk of psychosis (HR 89% at 5 y).[23] These findings contribute to the recent accumulating evidence pointing to the BLIPS distinctiveness.

Accordingly, the second study focused on the APS subgroup.[27] This study employed an advanced machine learning method to replicate the first predictive model that was specifically developed for APS-only individuals and included disorganized communication, suspiciousness, verbal memory, and a decline in social functioning.[28] Although the original predictive model did not replicate, both the models supported unusual thought content and suspiciousness, poor social functioning, and verbal memory and fluency, as highly consistent predictors of psychosis onset in the individuals meeting the APS subgroup of the CHR-P.[28] Inconsistencies between the 2 models were explained through the impact of recruitment strategies, in line with the above observations. In fact, the authors noted that locally developed models should only be expected to work on samples that are "recruited in the same way."[28] These findings suggest that it may be possible to develop and validate predictive models that are specific to each of the specific CHR-P subgroups.

The third study leverages on the above 2 studies to propose a developmental clinical staging model that focuses on the BLIPS/BIPS and APS subgroups, excluding the GRD subgroup.[29] The model was based on hierarchical symptom severity across 4 groups: CHR-P with negative symptoms, CHR-P with moderately severe APS, CHR-P with severe APS, and a revised BIPS/BLIPS.[29] Of relevance, the latter group is considered to be an intermediate outcome category and no longer strictly at risk as psychotic level symptoms were already present. Accordingly, a variable outcome threshold was employed to define transitions across the different subgroups.[29] This is of great relevance because the outcome predicted from a CHR-P state (ie, psychosis development) is currently heterogeneous, including both prediction of a first episode of psychosis across APS individuals and/or prediction of psychotic recurrences given an initial BLIPS/BIPS. Accordingly, the clinical significance of the outcome predicted by recent individualized psychosis-risk calculators[30] is dependent on the initial CHR-P stage. For example, the finding that more severe patients (ie, with higher levels of unusual thought content and suspiciousness, greater decline in social functioning and some cognitive impairments[30])

Table 1. Suggested Revision of the Clinical High-Risk State for Psychosis (CHR-P)

Clinical Stage	Definition	Definition in the Clinical Staging Model	Possible Interventions
0	Asymptomatic genetic risk	Premorbid	Improved mental health literacy, family psychoeducation
1a	Negative and cognitive symptoms	CHR-P	As for 0 plus active reduction of substance misuse
1b	Attenuated Psychotic Symptoms (APS)	CHR-P	As for 1a plus individual psychological therapies
1c	Short-lived remitting psychotic episodes (BLIPS/BIPS)[a]	CHR-P	As for 1c plus close-in monitoring and prevention of psychosis recurrence
2	Full-threshold first-episode psychosis (FEP)	FEP	As for 1c plus antipsychotics and vocational rehabilitation

Note: BIPS, Brief and Intermittent Psychotic Symptoms; BLIPS, Brief and Limited Intermittent Psychotic Symptoms.
[a]Acute and Transient Psychotic Disorders (ICD) and Brief Psychotic Disorders (DSM) could also be included in this stage.

who had already suffered from a brief psychotic episode (eg, BLIPS/ATPD)[23] are at higher risk of clinical deterioration and of further psychotic recurrence is not particularly surprising. The model presented in this issue showed some promising validity because each successive subgroup (classified as different stages of the psychotic disorder) had both an incremental rise in time to conversion and also in conversion rates to a higher subgroup level.[29] Although no formal model validation for clinical practice was conducted, this pilot model holds great potential because it can overcome some of the above conceptual limitations. Altogether, these findings suggest that merging the CHR-P subgroups together into a single CHR entity is not fully justified, as they lay upon different points along the illness trajectory that are better accounted by a clinical staging approach.

Conclusions

Over the next decade, CHR-P research is likely to undergo significant challenges that may require a substantial revision of the original paradigm. The current special issue suggests main avenues for such a revision. The first step would be to fully reconsider the role of the 3 CHR-P subgroups and integrate them in new clinical staging models to better account for the observed heterogeneity, variable outcome thresholds and treatments (see table 1 for a revision proposal). This is not easy as it involves the redefinition of psychosis threshold and a new validation in clinical practice. Furthermore, it would be useful to improve the ability to predict nonpsychotic disorders for maximizing the potential of clinical staging models.[31] Since CHR-P instruments can only predict psychosis, it seems necessary to develop new psychometric instruments that can complement the CHR-P assessment. Finally, extensive research into factors modulating pretest risk enrichment is urgently required to improve the epidemiological validity of the entire paradigm and its overall reproducibility and generalizability.

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References

1. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996;22:283–303.
2. Yung A, Yuen H, McGorry P, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *ANZJP*. 2005;39:964–971.
3. NICE. Psychosis and schizophrenia in children and young people: recognition and management. 2013. https://www.nice.org.uk/guidance/cg155.
4. NHS England. Achieving better access to mental health services by 2020. 2014. https://www.gov.uk/government/publications/mental-health-services-achieving-better-access-by-2020.
5. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*. 2015;14:322–332.
6. Kempton MJ, Bonoldi I, Valmaggia L, McGuire P, Fusar-Poli P. Speed of psychosis progression in people at ultra-high clinical risk: a complementary meta-analysis. *JAMA Psychiatry*. 2015;72:622–623.
7. Fusar-Poli P, Schultze-Lutter F, Cappucciati M, et al. The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. *Schizophr Bull*. 2016;42:732–743.
8. Fusar-Poli P, Schultze-Lutter F. Predicting the onset of psychosis in patients at clinical high risk: practical guide to probabilistic prognostic reasoning. *Evid Based Ment Health*. 2016;19:10–15.
9. Lee J, Rekhi G, Mitter N, et al. The Longitudinal Youth at Risk Study (LYRIKS)--an Asian UHR perspective. *Schizophr Res*. 2013;151:279–283.
10. Klauser P, Zhou J, Lim JK, et al. Lack of evidence for regional brain volume or cortical thickness abnormalities in youths at clinical high risk for psychosis: findings from the longitudinal youth at risk study. *Schizophr Bull*. 2015;41:1285–1293.
11. Fusar-Poli P, Rutigliano G, Stahl D, et al. Deconstructing pretest risk enrichment to optimize prediction of psychosis

in individuals at clinical high risk [published online ahead of print October 26, 2016]. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2016.2707.

12. Fusar-Poli P, Schultze-Lutter F, Addington J. Intensive community outreach for those at ultra high risk of psychosis: dilution, not solution. *Lancet Psychiatry*. 2016; 3:18.
13. Schmidt A, Cappucciati M, Radua J, et al. Improving prognostic accuracy in subjects at clinical high risk for psychosis: systematic review of predictive models and meta-analytical sequential testing simulation [published online ahead of print August 17, 2016]. *Schizophr Bull*.
14. Schultze-Lutter F, Michel C, Schmidt SJ, et al. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry*. 2015;30:405–416.
15. Webb JR, Addington J, Perkins DO, et al. Specificity of incident diagnostic outcomes in patients at clinical high risk for psychosis. *Schizophr Bull*. 2015;41:1066–1075.
16. Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *Am J Psychiatry*. 2015;172: 249–258.
17. Rutigliano G, Valmaggia L, Landi P, et al. Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. *J Affect Disord*. 2016;203: 101–110.
18. Fusar Poli P. The enduring search for Koplik spots of psychosis. *JAMA Psychiatry*. 2015;72:863–864.
19. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70:107–120.
20. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of risk for psychosis within subjects at clinical high risk: meta-analytical stratification. *JAMA Psychiatry*. 2016;73: 113–120.
21. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull*. 2014;40:28–38.
22. Cornblatt BA, Carrion RE. Deconstructing the psychosis risk syndrome: moving the field of prevention forward. *JAMA Psychiatry*. 2016;73:105–106.
23. Fusar-Poli P, Cappucciati M, De Micheli A, et al. Diagnostic and prognostic significance of Brief Limited Intermittent Psychotic Symptoms in subjects at Ultra High Risk. *Schizophr Bull*. 2016;42:1395–1406.
24. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29:703–715.
25. Fusar-Poli P, Cappucciati M, Bonoldi I, et al. Prognosis of brief psychotic episodes: a meta-analysis. *JAMA Psychiatry*. 2016;73:211–220.
26. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. *Psychiatry J*. 2016;2016:7146341.
27. Addington J, Liu L, Perkins D, Carrion RE, Keefe R, Woods SW. The role of cognition and social functioning as predictors in the transition to psychosis for youth with attenuated psychotic symptoms. *Schizophr Bull*. 2017;43:57–63.
28. Cornblatt BA, Carrion RE, Auther A, et al. Psychosis prevention: a modified clinical high risk perspective from the Recognition and Prevention (RAP) Program [published online ahead of print June 5, 2015]. *Am J Psychiatry*.
29. Carrion R, Correll C, Auther A, Cornblatt B. A severity-based clinical staging model for the psychosis prodrome: longitudinal findings from New York RAP study. *Schizophr Bull*. 2017;43:64–74.
30. Cannon TD, Yu C, Addington J, et al. An individualized risk calculator for research in prodromal psychosis [published online ahead of print July 1, 2016]. *Am J Psychiatry*.
31. Nieman DH, McGorry PD. Detection and treatment of at-risk mental state for developing a first psychosis: making up the balance. *Lancet Psychiatry*. 2015;2:825–834.