PREVENTION OF PSYCHOSIS: ADVANCES IN DETECTION, PROGNOSIS AND INTERVENTION

Paolo Fusar-Poli[1,2,3,4], Gonzalo Salazar de Pablo[1,5], Christoph U Correll [6,7,8], Andreas Meyer-Lindenberg[9], Mark J. Millan[10], Stefan Borgwardt[11,12], Silvana Galderisi[13], Andreas Bechdolf[14,15,16,17], Andrea Pfenning[18], Lars Vedel Kessing[19], Therese van Amelsvoort[20], Dorien H. Nieman[21], Katharina Domschke[22], Marie-Odile Krebs[23,24], Nikolaos Koutsouleris[25,26], Philip McGuire[4,26], Kim Q Do[27], Celso Arango[5]

Affiliations

[1] Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK;
[2] OASIS service, South London and Maudsley NHS Foundation Trust, London, UK;
[3] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;
[4] National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK;
[5] Institute of Psychiatry and Mental Health. Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), CIBERSAM, Madrid, Spain;
[6] The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA
2 Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA;
[7] The Feinstein Institute for Medical Research, Center for Psychiatric Neuroscience, Manhasset, NY, USA;
[8] Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany;
[9] Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany;
[10] Centre for Therapeutic Innovation in Neuropsychiatry, IDR Servier, 78290 Croissy sur Seine, Paris, France;
[11] Department of Psychiatry, University of Basel, Switzerland;
[12] Department of Psychiatry, Psychosomatics and Psychotherapy, University of Lübeck, Germany;
[13] Department of Psychiatry, University of Campania L. Vanvitelli, Naples, Italy
[14] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine with Early Intervention and Recognition Centre (FRITZ), Vivantes Klinikum Am Urban, Charité-Universitätsmedizin, Berlin, Germany;
[15] Vivantes Klinikum im Friedrichshain, Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Charité-Universitätsmedizin, Berlin, Germany;
[16] Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany;
[17] ORYGEN, The National Centre of Excellence in Youth Mental Health, Melbourne, Victoria, Australia;
[18] Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Medical Faculty, Technische Universität Dresden, Germany;
[19] Copenhagen Affective Disorder Research Center (CADIC), Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark;
[20] Maastricht University Medical Center, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands;
[21] Amsterdam University Medical Centers (location AMC), Department of Psychiatry, Amsterdam, Netherlands;
[22] Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany;
[23] INSERM, IPNP UMR S1266, Laboratoire de Physiopathologie des Maladies Psychiatriques, Université Paris Descartes, Université de Paris, CNRS, GDR3557-Institut de Psychiatrie Paris, France;

[24] Faculté de Médecine Paris Descartes, GHU Paris - Sainte-Anne, Service Hospitalo-Universitaire, Paris, France;
[25] Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany;
[26] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK;
[27] Center for psychiatric neuroscience Lausanne University Hospital, Lausanne-Prilly, Switzerland.

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Correspondence to: Dr Paolo Fusar-Poli MD PhD, Department of Psychosis Studies, 5th Floor, Institute of Psychiatry, Psychology & Neuroscience, PO63, 16 De Crespigny Park, SE5 8AF London, UK. E-mail: paolo.fusar-poli@kcl.ac.uk

Key points

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

Findings: Detecting individuals at-risk for psychosis requires knowledge of their specific sociodemographic, clinical, functional, cognitive and neurobiological characteristics. Prediction of outcomes is achieved with good accuracy, provided the assessment tools are used in clinical samples. Evidence for specific effective interventions for this patient population is currently insufficient.

Meaning: Clinical research knowledge for psychosis prevention is substantial; while it is possible to detect and formulate a prognosis in individuals at-risk for psychosis, further research is needed to identify specific effective interventions in samples with sufficient risk enrichment, so that prevention of psychosis can be achieved in an efficient way.

ABSTRACT

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. To formulate updated recommendations.

Evidence Review: PRISMA/RIGHT-compliant systematic umbrella review of the Web of Science, Cochrane Central Register of Reviews, and Ovid/PsychINFO from 01/01/2013-06/31/2019 (PROSPERO CRD42019135880) to identify meta-analyses conducted in CHR-P individuals. Data included first author, year of publication, topic investigated, type of publication, study design and number, sample size of CHR-P and comparison group, type of comparison group, CHR-P age and sex, type of prognostic assessment, interventions, quality assessment (AMSTAR), and key findings with their effect sizes.

Findings: 42 meta-analyses published in the past six years and encompassing 81 outcomes were included. Detection: CHR-P individuals are young (mean age=20.6±3.2 years), more frequently male (58.0%), predominantly presenting with attenuated psychotic symptoms that have lasted for >1 year before their presentation to specialised services. CHR-P samples accumulate several sociodemographic risk factors compared to controls. Substance use, comorbid mental disorders, suicidal ideation and self-harm are also frequent in CHR-P individuals. CHR-P individuals show impairments in work/educational functioning, social functioning and quality of life. Several neurobiological and neurocognitive alterations have been confirmed in this study. Prognosis: The prognostic accuracy of CHR-P instruments is good, provided that they are used in clinical samples. Overall, risk of psychosis is 22% at 3 years; being the highest in the brief and limited intermittent psychotic symptoms subgroup. Baseline severity of attenuated psychotic and negative symptoms and low functioning are associated with an increased risk of psychosis. Controlling risk enrichment and implementing sequential risk assessments can optimise the prognostic accuracy. Intervention: Although there is not yet evidence to favour any indicated intervention over another (including needs-based interventions/control conditions) for preventing psychosis or ameliorating any other outcome in CHR-P individuals, the uncertainty of evidence is high and therefore needs-based and psychological interventions should still be offered.

Conclusions and Relevance: Over the recent years, substantial advancements in the detection and prognosis of CHR-P individuals have been confirmed, while effective indicated interventions need to be better identified. An evidence-based recommendation statement is presented.

Key words: Psychosis; Schizophrenia; CHR-P; Prevention, Evidence, Prediction, First-Episode, Meta-analysis.

INTRODUCTION

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 maximise the benefits of early interventions in psychosis[1,2]. The CHR-P paradigm originated in Australia twenty-five years ago[3] and ever since it has gained traction to the point that it has stimulated hundreds of research publications. These publications have been summarised by evidence synthesis studies spanning different topics, that eventually impacted several national[4] and international[5] clinical guidelines and diagnostic manuals (e.g., DSM-5[6]). Overall, CHR-P represents the most established preventive approach in clinical psychiatry; it is, therefore, essential to periodically review its progress and limitations. 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 the last publication in this journal about six years ago[7] . This study is produced by the European College of Neuropsychopharmacology Thematic Working Group on the Prevention of Mental Disorders and Mental Health Promotion (ECNP TWG PMD-MHP)[8]. The objective of this manuscript is to provide the first umbrella review summarising the most recent evidence in the CHR-P field. The additional objective was to provide evidence-based recommendations relating to the three core components that are necessary to implement the CHR-P paradigm in clinical practice: detection, prognosis and intervention[9].

METHODS

The protocol for this study was registered on PROSPERO (CRD42019135880). This study was conducted in accordance with the PRISMA[10] and RIGHT[11] statements (eTable 1).

Search strategy and selection criteria

A multi-step literature search was performed as detailed in eMethods 1 from 01/01/2013-06/30/2019 (this period is consistent with JAMA Psychiatry's advances in diagnosis and treatment review guidelines). Second, MEDLINE was used to search the reference lists of retrieved articles. The literature search, study selection and data extraction were conducted by two reviewers independently (GSP, PFP), and consensus was reached through discussion.

Studies included were: a) meta-analyses (pairwise or network, aggregate or individual participant data), published as original investigation, review, research letters or grey literature, without restriction on the topic investigated[12]; b) conducted in CHR-P individuals (i.e., individuals meeting Ultra-High Risk (UHR) and/or Basic Symptoms (BS) criteria) as established by validated

psychometric instruments[7] (eMethods 2), without restriction on the type of comparison group; c) published in the last 6 years.

Studies excluded were: a) original studies, study protocols, systematic reviews without quantitative analyses, and any other non-meta-analytical study; b) studies that did not formally assess and selected participants with established CHR-P instruments; c) abstracts and conference proceedings.

In order to respect the hierarchy of the evidence (eMethods 3), if two or more meta-analyses addressing the same topic were found, individual participant data meta-analyses were preferred over aggregate network meta-analyses, and this over aggregate pairwise meta-analysis. The most recent study was selected when the previous criteria did not apply. If after applying the hierarchical criteria, two studies were similar, both were included.

Outcome measures and data extraction

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

Timing and effect measures

When feasible, effect size measures were estimated through Cohen's d. Other effect size measures were converted to Cohen's d[12]. In case of meta-analyses reporting time-dependent risks or rates or descriptive data only, proportions (95%CI) or means (SD) were summarised.

Quality assessment

The quality of the included meta-analyses was assessed with the "Assessing the Methodological Quality of Systematic Reviews (AMSTAR)" tool[13] (eMethods 5).

Standards for guidelines development

To develop the recommendations, we followed the Preventive Services Task Force (USPSTF) grading system[14] (eTable 2), which is suited explicitly for preventive approaches and has already received extensive validation within the JAMA network[15-20]. Guideline development followed the JAMA Clinical Guidelines Synopsis, reaching consensus across the multidisciplinary ECNP TWG PMD-MHP; the rationale for the recommendations was also provided. Conflicts of interests were fully detailed.

RESULTS

Database

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

Detection

Characteristics of the CHR-P state

No meta-analysis focused on BS criteria. The majority (85%, 95%CI 79%-90% from[21]) of CHR-P individuals met Attenuated Psychosis Symptoms (APS) criteria, less frequently (10%, 95%CI 6%-14%[21]) Brief Limited Intermittent Psychotic Symptoms (BLIPS) criteria, and rarely (5%, 95%CI 3%-7%[21]) Genetic Risk and Deterioration syndrome criteria (GRD). The mean age of CHR-P individuals across the included studies was 20.6±3.2 years (range 12-49 years[5,21-51], several studies included underage patients[5,21-29,31-34,38-49,51-53]) and 42.0% were female [21-28,30,32,34-42,45-49,54,55], without differences across APS, BLIPS and GRD[21]. However, the mean duration of untreated attenuated psychotic symptoms tended to be shorter in the BLIPS (435.8 days) versus the GRD (783.5 days) and APS (709.5 days) subgroups (eTable 3).

Genetic and environmental risk and protective factors in the CHR-P state

Individuals meeting CHR-P criteria, compared to those not meeting them, were more likely to have olfactory dysfunction (d=0.71)[56], physical inactivity (d=0.7), obstetric complications (d=0.62), be unemployed (d=0.57) and single (d=0.27), have a low educational level (d=0.21) and be male (d=0.18)[52]. Trauma, encompassing childhood emotional abuse (d=0.98)[52], high perceived stress (d=0.85)[52], childhood physical neglect (d=0.62)[52], and bullying victimization (d=0.62)[53] (eTable 4, Figure 3), was also more frequent (86.8%)[22] and severe (d=1.38) in CHR-P individuals versus controls[53]. No meta-analysis addressed the association between genetic factors and the CHR-P state.

Substance use in the CHR-P state

There was a significant association between the CHR-P state and tobacco use (d=0.61)[52]:

Altogether, 32.6% of CHR-P individuals smoked tobacco versus 14.2% in controls[57]. CHR-P individuals were also more likely current cannabis users than controls (26.7% vs 17.1%)[54]. Current cannabis use disorder was associated with an increased risk of psychosis (d=0.31), whereas lifetime cannabis use has not[23]. Higher levels of unusual thought content (d=0.27) and suspiciousness (d=0.21) were found in CHR-P individuals using cannabis than in non-cannabis users[54], but attenuated positive or negative symptoms did not differ between these two groups[54] (eTable 5).

Clinical comorbidity in the CHR-P state

Depressive (40.7%) and anxiety (15.3%) disorders are frequent in the CHR-P state[24] (see also the prognostic section). The majority of CHR-P individuals presented with suicidal ideation (66%)[25]. The prevalence of self-harm was 49% and of suicide attempts 18% in CHR-P individuals[25] (eTable 6).

Functioning and quality of life in the CHR-P state

CHR-P individuals had lower level of adolescence (d=0.96-1.03) and childhood (d=1.0) functioning than controls[52]. Functional impairments in CHR-P individuals are as severe as in other mental disorders, more severe than in controls (d=3.01)[26], but less severe than in established psychosis (d=0.34). The CHR-P status is also associated with significant social deficits (d=1.25)[52]. Quality of life is worse in CHR-P than in controls (d=1.75)[26], while there are no differences with psychotic individuals[26] (eTable 7).

Cognition in the CHR-P state

Visual learning (d=0.27), processing speed (d=0.42) and verbal learning (d=0.42)[55] are impaired in CHR-P individuals versus controls. CHR-P individuals who will later develop psychosis show poorer cognitive functioning (d=0.24-0.54)[55], versus those not converting to psychosis. However, there is no evidence for cognitive decline from baseline to follow-up in CHR-P individuals at any time-point[27]. While social cognition is impaired in CHR-P individuals versus controls (d=0.48)[29], theory of mind is less impaired than in first-episode psychosis subjects (d=0.45)[30]. CHR-P individuals show more metacognitive dysfunctions (d=0.57-1.09) than controls, but are similar to established psychosis[28] (eTable 8).

Neuroimaging and biochemistry in the CHR-P state

CHR-P individuals have decreased blood IL-1β levels[32] (d=0.66), increased salivary cortisol levels (d=0.59)[31] and blood IL-6[32] (d=0.31), versus controls.

The thalamus is smaller in CHR-P individuals versus controls (d=0.60)[35], while there are no significant differences in the pituitary volume[36]. Right hippocampal volume is also significantly smaller in CHR-P[37] versus controls (d=0.24) (unlike the left one)[37].

Levels of glutamate and glutamine (measured together) are higher in the medial frontal cortex of CHR-P individuals versus controls (d=0.26)[33].

Compared to controls, CHR-P individuals show 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[34] (eTable 9). As for neurophysiological processes, the mismatch negativity amplitude is reduced in CHR-P versus controls (d=0.4)[38] and in CHR-P individuals who develop psychosis versus those who do not develop it (d=0.71)[58]. A theoretical neurobiological model of the CHR-P state, which integrates these findings, is reported in Figure 4.

Prognosis

Overall prognosis

Currently used semi-structured interviews for psychosis prediction have an excellent overall prognostic performance (AUC=0.9)[41]. However, sensitivity is high (96%), specificity is low (47%)[41], and these interviews are not valid outside clinical samples that have undergone risk enrichment (e.g., it is not useful to screen the general population)[41] (Figure 3). The Comprehensive Assessment of At-Risk Mental States (CAARMS), has an acceptable (AUC=0.79) prognostic accuracy for predicting psychosis[42]; there are no substantial differences in prognostic accuracy versus other CHR-P instruments[41] (although the Structured Interview of Psychosis-Risk Syndromes has a slightly higher sensitivity (0.95) than the CAARMS (0.86)[42]. This lack of difference in prognostic accuracy is due to the fact that the majority of the risk for psychosis (post-test 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[40]. Pretest risk for psychosis is 15% at 3 years and it is heterogeneous, ranging from 9% to 24%. Variability in pretest risk for psychosis is modulated by the type of sampling strategies[40], increasing if samples are recruited from secondary care and decreasing if samples are recruited from the community[40] (Figure 3, eTable 10).

The proportion of CHR-P who develop a psychotic disorder (positive post-test risk, updated in 2016) is 22% at 3 years (Figure 2)[39]. Speed of transition to psychosis is greatest in the first months after CHR-P individuals present to the clinical services (median time to psychosis: 8 months)[59]. Transition to schizophrenia-spectrum psychoses is over six times more frequent (73%) than transition to

affective psychoses (11%); transition to other psychoses is 16%[39]. The transition risk to psychosis is higher in the BLIPS (38%) than in the APS (24%) than in the GRD (8%) subgroup at ≥48 months follow-up[21], while the GRD subgroup is not at higher risk than help-seeking controls (which represents the standard comparative group during CHR-P interviews)[21]. There is no prognostic difference in the risk of psychotic recurrence across different operationalizations of short-lived psychotic episodes, including Acute and Transient Psychotic Disorders (ATPD) and Brief Psychotic Disorders, but this risk is lower than in remitted first-episode schizophrenia patients[60] (eTable 10). The 2-year risk of developing schizophrenia and affective psychoses in the BLIPS group is 23% and 0%, respectively[60]. Conversely, the remission rate of the baseline CHR-P symptoms is 35.4% at 1.94 years follow-up[44]; there are no data on the remission rates across BLIPS, APS and GRD subgroups.

Prediction of outcomes in CHR-P

Within CHR-P individuals, transition to psychosis is associated with severity of negative symptoms (d=0.39), right-handedness (d=0.26), severity of attenuated positive psychotic symptoms (d=0.35), disorganised and cognitive symptoms (d=0.32), unemployment (d=0.32), severity of total symptoms (d=0.31), low functioning (d=0.29), severity of general symptoms (d=0.23), living alone (d=0.16), male sex (d=0.10) and lifetime stress/trauma (d=0.08) (eTable 11, Figure 3)[61]. However, only severity of attenuated psychotic symptoms and low functioning (highly suggestive level of evidence[12]) and negative symptoms (suggestive level of evidence[12]) are associated with psychosis onset after controlling for several biases[61]. Comorbid anxiety and depressive disorders are not significantly associated with transition to psychosis[24]. There are no data on the predictors of outcomes other than psychosis onset.

Prognostic accuracy may be optimised by controlling pretest risk enrichment[52] and using sequential assessments that include a staged assessment based on clinical information, EEG, neuroimaging and blood markers[43] (eTable 11).

Intervention

There is no evidence to favour any indicated intervention over each other (including needs-based-interventions or control conditions) for preventing transition to psychosis[45]. There is likewise no evidence either of superior efficacy of any intervention versus another for reducing attenuated positive psychotic symptoms[46,47] (two meta-analyses on the same topic were retained after applying the hierarchical criteria) or negative symptoms[48], improving overall functioning[5] or social

functioning[49], alleviating depression[51], improving symptom-related distress or quality of life[50], or impacting acceptability[45] in CHR-P individuals (eTable 12).

DISCUSSION

This is the first comprehensive umbrella review (42 meta-analyses, 81 outcomes) focusing on detection, prognosis and intervention of CHR-P individuals. There were no meta-analyses that reported consistent results from well-designed, well-conducted studies with regards to detection, prognosis or interventions in representative primary care populations (USPSTF criteria for high level of certainty).

There is a moderate level of certainty (Grade B, Table 1) with respect to the detection of CHR-P individuals. Over recent years, research has revealed that detection of truly at-risk individuals is the key rate-limiting step towards 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, young 20.6±3.2-year old males (58%) presenting with APS who have associated impairments in global functioning (d=3.01), social functioning (d=1.25) [52] and quality of life (d=1.75)[26], suicidal ideation (66.0%[25]), self-harm (49.0 %[25]) and suicide attempts (18%[25]). Because of these problems, these individuals seek help at specialised clinics; however, on average, their problems remain undetected (and untreated) for ≥1 year. Currently, detection of CHR-P individuals is entirely based on their referral on suspicion of psychosis risk and on the promotion of help-seeking behaviours. These detection strategies appear inefficient: only about 5% (OASIS, UK)[62] to 12% (Orygen, Australia)[63] of first-episode cases are detected at the time of their CHR-P stage through standalone or youth mental health services. A further caveat is that about one-third of first-episode cases may not develop psychosis through a CHR-P stage[64,65]. Furthermore, at presentation, CHR-P individuals often have comorbid non-psychotic mental disorders (40.7% depressive disorders, 15.3% anxiety disorders[24]), and substance use (32.6% tobacco use[57], 26.7% cannabis use[54]). Because of these limitations, there is a lack of coherence in the chain of evidence (USPSTF, eTable 2) with regards to detection of CHR-P individuals. These issues could be tackled by integrated detection programmes leveraging automatic detection tools that can screen large clinical[9,62,66] and non-clinical[67] samples in a transdiagnostic[68] fashion, encompassing primary and secondary care, the community[69] and youth mental health services[70]. Furthermore, detection of CHR-P individuals is currently based on the assessment of symptoms, but symptoms may only be epiphenomena of underlying pathophysiological processes. CHR-P individuals often have several established

sociodemographic, environmental and other types of risk factors for psychosis[71]: male sex, unemployment, single status, low educational and functional level, obstetric complications, physical inactivity, olfactory dysfunction and childhood trauma (Figure 3 and eDiscussion 1). Incorporating the assessment of these multiple factors along with CHR-P symptoms resulting in a "Psychosis Polyrisk Score, (PPS)" may produce refined detection approaches[72] that better map the etiopathology of psychosis onset.

There is a moderate level of certainty (Grade B, Table 1) with respect to the prognosis of CHR-P individuals[46,73]. Converging evidence has demonstrated that CHR-P assessment instruments have good prognostic accuracy (AUC=0.9)[41] for the prediction of psychosis, comparable to that of clinical tools employed in other areas of medicine[41]. However, alternative instruments are needed to predict other non-psychotic outcomes (e.g. bipolar onset in those at risk[74,75]). There are no substantial prognostic accuracy differences across different CHR-P tools[41]**.** The CHR-P 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 3). 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[46,76]. It follows that the next generation of research should better deconstruct and control risk enrichment[77] to maximise the scalability of use of the CHR-P instruments[69]. The 3-year meta-analytic risk of psychosis onset in the entire CHR-P group has declined from 31.5% (estimated in 2012[78]) to the current 22% (Figure 2[21]), although not globally[79]. Transition risk has declined when recruitment strategies focused on the community as opposed to primary or secondary care (eDiscussion 2). Risk is the highest in BLIPS (38% at 4 years; 89% at 5 years if there are "seriously disorganising or dangerous" features as defined by the SIPS[80]), intermediate in APS (24% at 4 years) and lowest in GRD (8% at 4 years) individuals[21]. GRD individuals are not at higher risk than help-seeking controls up to 4 years follow-up[21]. A revised version of the CHR-P model, which includes stratification across these three subgroups has therefore been proposed[2,81]. The BLIPS group also overlaps substantially with ICD-10 ATPDs[80]. Therefore, current CHR-P instruments can only allow subgroup-level (i.e., BLIPS>APS>GRD) but not subject-level prognosis (inconsistent evidence, USPSTF, eTable 2). To refine prognosis at the individual subject level, future research may consider specific risk factors (e.g., sex, stress/trauma, employment, living status[61]), biomarkers (e.g., hippocampal volume[37]) or cognitive markers (e.g., processing speed, verbal and visual memory and attention[82]) in addition to the CHR-P subgroups[21] and clinical symptoms (only severity

of attenuated positive and negative symptoms and level of functioning are robust risk factors for psychosis[61]). The potential of this approach has been supported by the development and validation of individualised clinical prediction models that leverage multimodal risk profiling[62,83,84], including dynamic[85] risk prediction models[86]. Because these models tend to be more complex than standard symptomatic CHR-P assessments, they are more likely to enter clinical routine through a sequential testing framework[43] (eDiscussion 3). Finally, good outcomes in CHR-P individuals have not been fully operationalised[87], and there is lack of information on prediction of relevant clinical outcomes (USPSTF, eTable 2) such as functional level and quality of life, with only about one-third of individuals remitting from their initial CHR-P state[44].

The available evidence is insufficient (grade C, Table 1) to assess the effects of preventive interventions on health outcomes in CHR-P groups. Although earlier meta-analyses found advantages of cognitive behavioural therapy[88], which is currently recommended by clinical guidelines[4], the inclusion of new trials in recent meta-analyses has indicated no clear benefits to favour any available intervention versus another or versus any control condition such as needs-based-interventions. An independent pairwise meta-analysis published by the Cochrane group after completion of this study concluded that there is no convincing, unbiased, high-quality evidence to favour any type of intervention[89]. Evidence is insufficient because these studies tended to report large confidence intervals and therefore high uncertainty (USPSTF, eTable 2) in the meta-analytic estimates, and significant effects of interventions in specific subgroups may not have been detected. For example, it is possible that the needs-based-interventions that are typically used as control conditions may have diluted the comparative efficacy of experimental interventions. This non-differential outcome could also be an effect of the sampling biases leading to too few CHR-P individuals in the intervention studies who are at true risk for psychosis, diluting the statistical power (USPSTF, eTable 2)[90]. However, this lack of demonstrable benefits of specific interventions could also be the consequence of one-size-fits-all-approaches in managing CHR-P individuals that go against the clinical, neurobiological, prognostic heterogeneity of this group and against the recent calls for precision medicine. For example, CHR-P interventions to date have largely been developed for APS individuals, at the expenses of BLIPS, who are often unwilling to receive the recommended interventions. Another explanation for the lack of comparative effectiveness of preventive interventions is that they have largely targeted symptoms, as opposed to key neurobiological processes related to the onset of psychosis (gaps in the chain of evidence, USPSTF eTable 2; Figure 4), or risk factors that could be modified (e.g., physical inactivity, Figure 3). Future

experimental interventions should also better target relevant outcomes (USPSTF, eTable 2) other than psychosis onset, including functioning, given the poor remission rates and low functioning of this population[91]. As acknowledged by the USPSTF criteria (eTable 2) in the case of uncertainty, new trials published over the near future may allow a more accurate estimation of preventive effects on health outcomes.

Grading the recent meta-analytic evidence summarised above, the ECNP TWG PMD-MHP recommends (Table 1) implementing specialised services to detect CHR-P individuals in primary and secondary care and to formulate a prognosis with the validated psychometric instruments. Due to insufficient evidence favouring any particular preventive intervention over another (including control conditions) and considering the uncertainty of the current evidence, no firm conclusions can be made[89] and a cautious approach is required. This involves offering the least onerous feasible primary indicated prevention, based on needs-based interventions and psychotherapy (cognitive behavioural therapy or integrated psychological interventions), titrating it in accordance with the characteristics and risk profile (CHR-P subgroups BLIPS>APS>GRD, severity of attenuated positive and negative symptoms and level of functioning), values and preferences of the CHR-P individuals[92,93]. Additionally, other comorbid psychiatric conditions should be treated as per available guidelines aiming for improving recovery, functional status and quality of life beyond preventive aims.

The main limitations of this study are that the meta-analyses had heterogeneous quality (eResults 1) and that the literature search approach may favour the selection of more commonly and readily studied domains that are more likely to be included in a meta-analysis (eLimitations).

CONCLUSIONS

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

SUPPLEMENTARY MATERIAL

Supplementary data will be available online.

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The authors declare that there are no conflicts of interest in relation to the subject of this study. PFP and GSP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

Dr. CA. has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr. PFP has been a consultant to and received research funds from Lundbeck and received honoraria from Menarini. Dr. CC has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. A M.-L acknowledges support from the Ministry of Science, Research and the Arts of the State of Baden-Wuerttemberg, Germany (MWK, grant 42-04HV.MED(16)/16/1), the European Union's Seventh Framework Programme (FP7, grants 602805, 602450, 115300 and HEALTH-F2-2010-241909), the Innovative Medicines Initiative Joint Undertaking (IMI, grant 115008), the German Federal Ministry of Education and Research (BMBF, grants 01ZX1314G, 01GS08147, 01GQ1003B, Collaborative Research Center 636 01GQ1102 subproject B7 and Collaborative Research Center 1158 subproject B09), and the German Research Foundation (DFG, ME 1591/4-1). SB acknowledges support from the University of Basel, the European Union's Seventh Framework Programme, the Swiss National Science Foundation and the ERA-NET. SB

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart outlining study selection process.

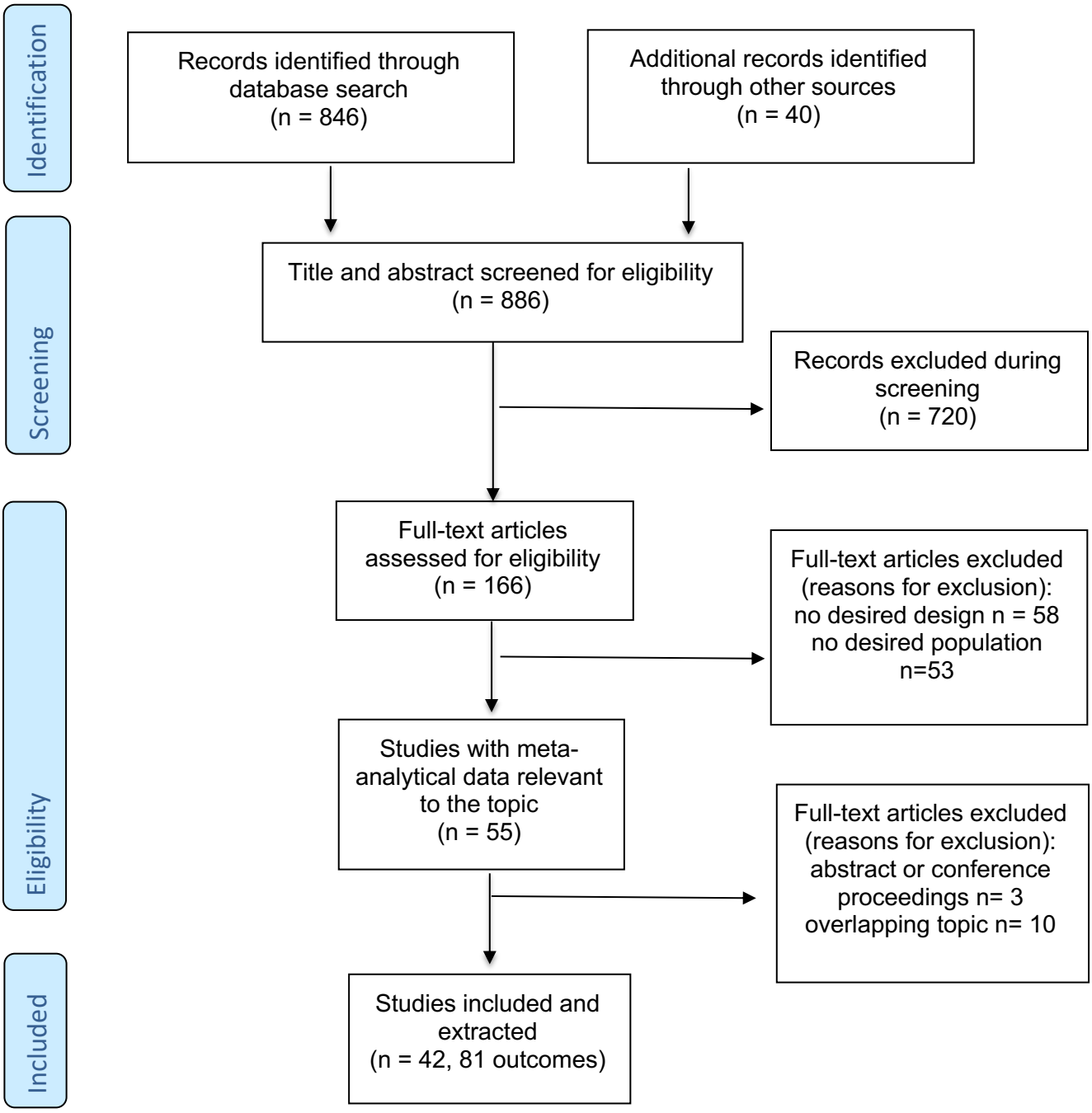

Figure 2. Proportion of CHR-P subgroups at initial presentation -on the left- and cumulative risk of developing psychosis at follow-up time -on the right-. CHR-P, Clinical High Risk for Psychosis; not CHR-P, assessed but not meeting CHR-P criteria; BLIPS/BIPS, Brief Limited Intermittent Psychotic Symptoms/ Brief Intermittent Psychotic Symptoms; GRD, Genetic Risk and Deterioration Syndrome. BLIPS: BLIPS alone or BLIPS plus APS or BLIPS plus APS plus GRD; APS: APS only or APS; GRD: GRD only. Data from[21].

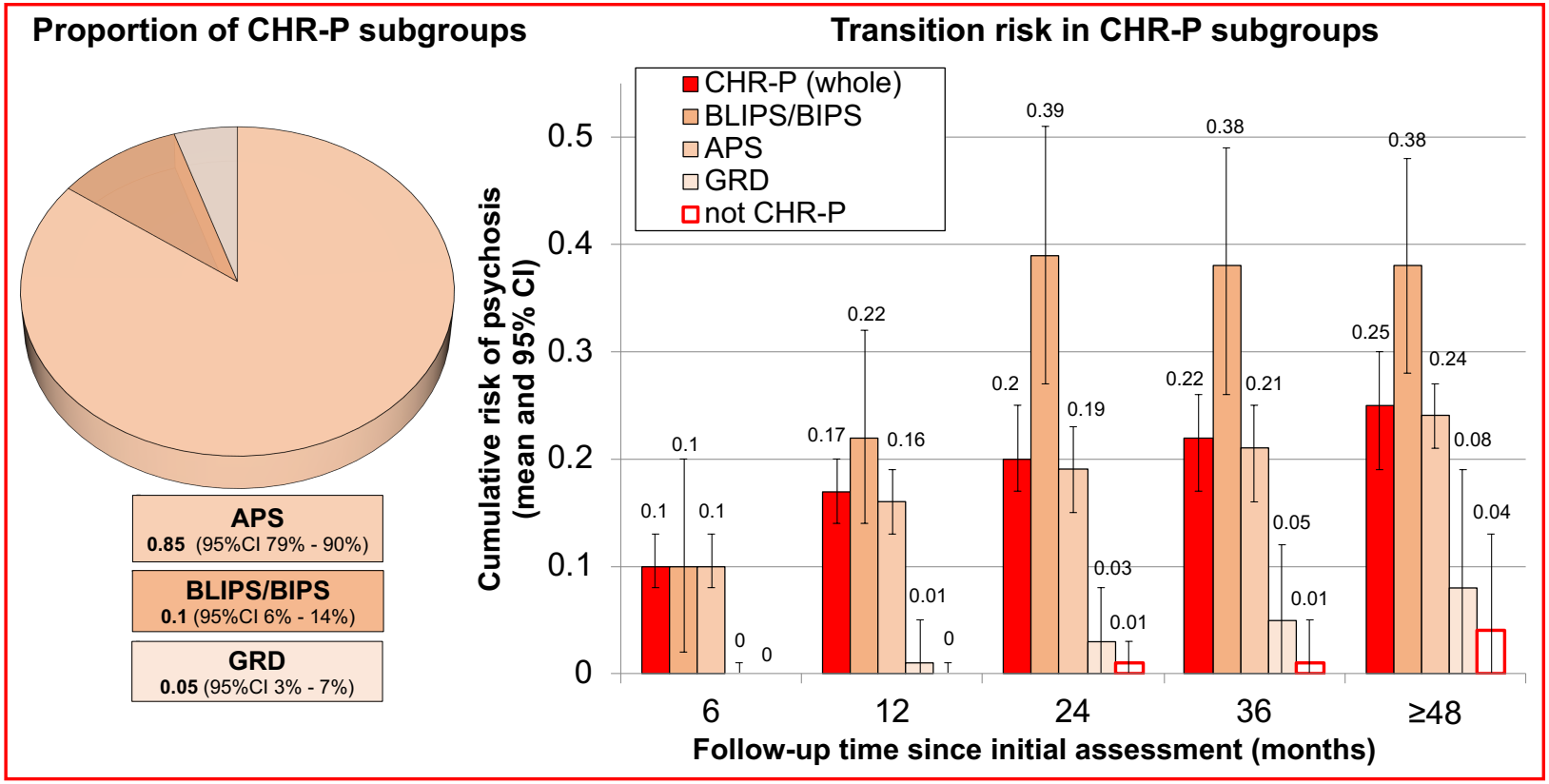

Figure 3. Prognostic assessment in the CHR-P state. Recruitment strategies lead to differential accumulation of risk factors for psychosis from the general population (0.43% at 3-year) to samples undergoing CHR-P assessment (15% at 3-year, pretest risk enrichment). Applying the CHR-P interviews to these help-seeking samples discriminates between those at-risk for psychosis and those not at-risk (positive post-test risk of 22% and negative post-test risk of 1.54% at 3-year). The actual transition to psychosis that is observed at follow-up largely depends on the overall level of accumulation of risk factors for psychosis.

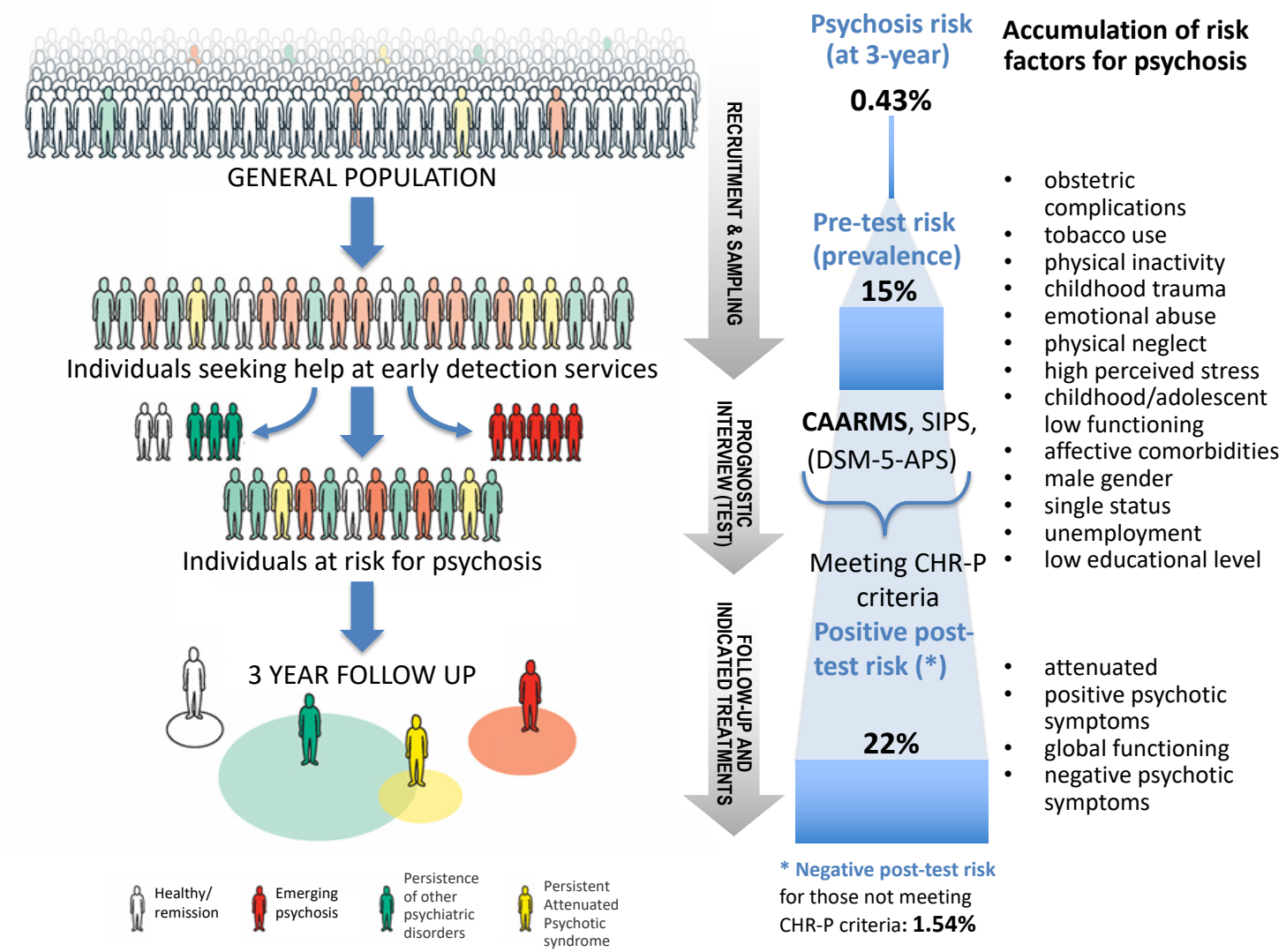

Figure 4. Simplified schematic of circuit mechanisms of neurobiological dysfunction and CHR-P pathophysiology. In (1), low glutamate signal/input from hypofunctioning NMDARs (akin to 'faulty homeostatic sensors') leads GABAergic interneurons to homeostatically increase excitation by reducing inhibition (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 (2). In (3), 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 in (4) but is not detected as such by hypofunctioning NMDARs on GABAergic interneurons. Figure reproduced and adapted from[94]. Glu, glutamate; NMDAR, N-methyl-D-aspartate receptor.

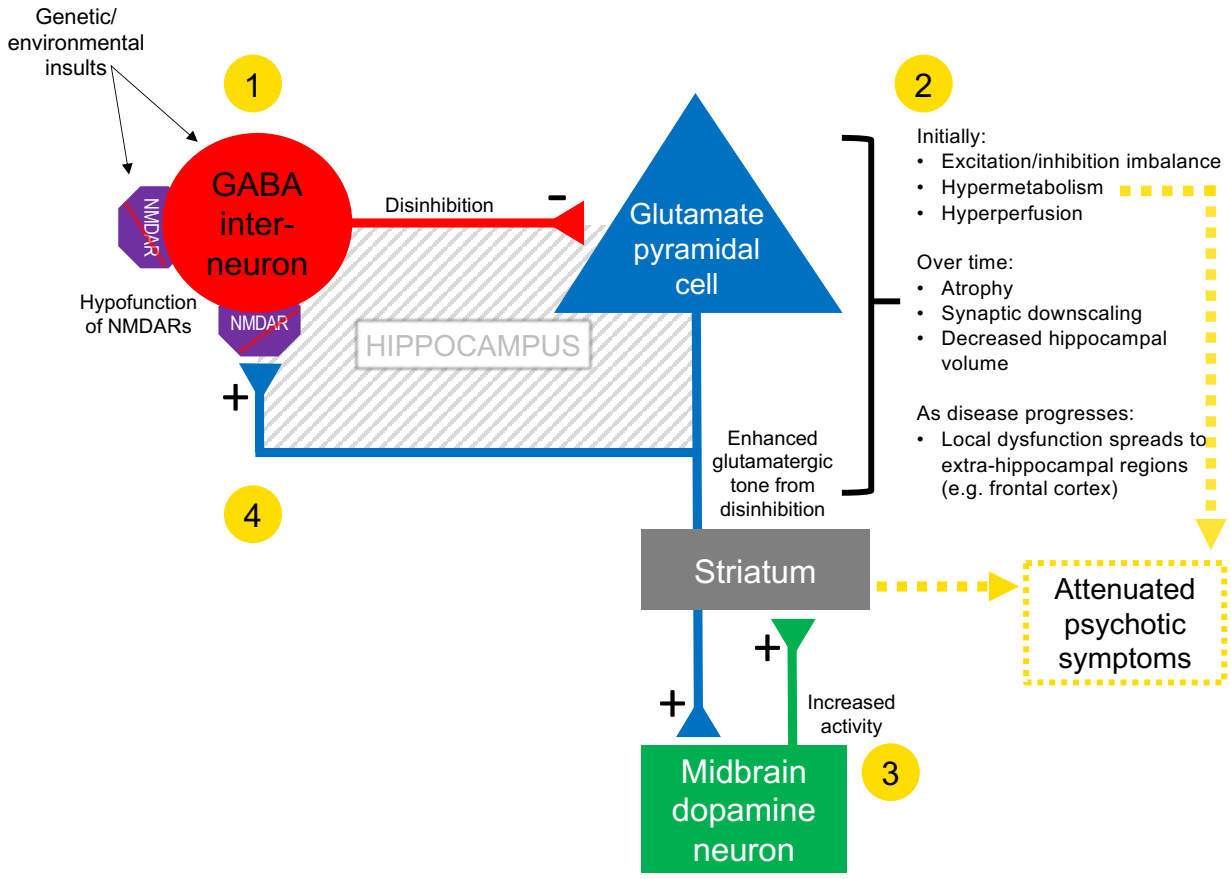

Table 1. Executive summary: Relevant ECNP TWG PMD-MHP recommendations for the detection, prognosis and prevention of psychosis in individuals at clinical high-risk for psychosis

Population	**Individuals at Clinical High Risk for Psychosis (CHR-P)**
Detection	Identify help-seeking persons at increased risk of psychosis primarily in primary and secondary healthcare settings and refer persons at increased risk of psychosis to specialized clinical services for further evaluation and, possibly, care. Grade B
Prognosis	Assess persons seeking help at specialised clinical services with validated psychometric instruments; do not use these instruments in the general population. Grade B
Intervention	Offer indicated primary prevention of psychosis utilizing needs-based interventions and psychological interventions (cognitive behavioural therapy or integrated psychological interventions) first, titrating the intervention in accordance with the characteristics and risk profile (CHR-P subgroups BLIPS>APS>GRD, severity of attenuated positive and negative symptoms and level of functioning), values and preferences of the CHR-P individuals. Treat other comorbid psychiatric conditions as per available guidelines and aim for improving recovery, functional status and quality of life beyond preventive aims. Grade I
CHR-P Grade level evidence based on USPSTF criteria, eTable 2; BLIPS, Brief and Limited Intermittent Psychotic Symptoms; APS, Attenuated Psychotic Symptoms; GRD, Genetic Risk and Deterioration Syndrome.	