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The "Clinical High-Risk State for Psychosis" in Youth

Global Challenges and Controversies

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Abstract

Whereas identification of a "clinical high-risk state for psychosis" (CHR-P) marks a groundbreaking global advance in the treatment of youth with potential subthreshold psychotic symptoms, controversies regarding the CHR-P exist. This chapter explores three sets of challenges: validity of the CHR-P diagnosis, stigma and ethical concerns, and challenges in implementing CHR-P identification measures globally.

It critically analyzes the current knowledge regarding these challenges. Debates surrounding core validity of the CHR-P diagnosis include whether CHR-P is a distinct syndrome from other common mental disorders, decline of transition rates in studies over time, and the value of identifying an at-risk status when empirically validated treatments have not yet been developed. Ethical challenges include potential stigma of the CHR-P state, and the ethics of diagnosing an at-risk state that encompasses a period of adolescence and extends into youth. Challenges in implementing CHR-P interventions globally include questions of whether early mental health intervention shows sufficient economic return, and promotion of psychosis terms in cultural settings where such conceptions may be entirely novel. Addressing these controversies could facilitate adoption of the CHR-P identification into mental health-care systems globally, thus maximizing public health impact.

The Clinical High-Risk State for Psychosis: Core Concepts and Approach

A substantial proportion (80–90%) of individuals suffering from schizophrenia experience subacute (or "prodromal") symptoms prior to the onset of full psychosis (Addington and Heinssen 2012). Whereas those with a first episode of psychosis (FEP) already experience significant psychotic symptoms,

From "Youth Mental Health: A Paradigm for Prevention and Early Intervention," edited by Peter J. Uhlhaas and Stephen J. Wood. Strüngmann Forum Reports, vol. 28, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 978-0-262-04397-7

individuals identified at CHR-P show subthreshold psychotic signs and need for care. Significant efforts have been made to identify, evaluate, and provide treatment in this earlier high-risk stage, so that early treatment and consistent monitoring can forestall and possibly prevent the first psychotic break and the full development of psychosis (Addington and Heinssen 2012; McGorry 1993). Roughly one-third of these cases develop FEP over a three-year follow-up (Fusar-Poli et al. 2012). CHR-P services enable interventions in the earliest stages, prior to the first episode of psychosis. Implementation of CHR-P services, such as those which have taken place in the United States, Europe, and Australia, could avert significant financial and social burdens associated with psychosis (McGlashan et al. 2010).

Initiating treatment at an earlier point can reduce the duration of untreated psychosis (DUP). Longer DUP is associated with worse outcomes, including poorer overall functioning, positive symptoms, quality of life, and response to antipsychotic treatment at six months (Niendam et al. 2009). Conversely, shortened DUP is associated with better positive and general symptom outcomes, better functioning, and a greater likelihood of being referred to outpatient treatment (Addington et al. 2015). Accordingly, early interventions in CHR-P individuals could effectively lead to a much reduced or negligible DUP, even when transition to a full psychotic disorder results.

CHR-P Identification: Operationalization

As one possibility, individuals can be identified as being on the psychosis-risk spectrum if they meet the at-risk mental state, which emphasizes psychotic-like symptoms and sharp declines in functioning (initially proposed by Yung and McGorry 1996), defined as follows:

1. The ultra-high risk state for psychosis (UHR-P), identified via the comprehensive assessment of at-risk mental state (CAARMS) criteria based on Yung and McGorry's (1996) pioneering work, provides one way of identifying the high risk for psychosis state (Yung et al. 2005).
2. Alternatively, the CHR-P state, as assessed by the SIPS/SOPS (described below), is met if an individual meets at least one of the following inclusion criteria: brief intermittent psychotic syndrome (BIPS), attenuated positive symptom syndrome (APSS), or genetic risk and decline (GRD); for definitions, see Table 11.1.

It is important to note, however, that UHR-P and CHR-P samples are similar in terms of their diagnostic makeup (i.e., BIPS, APSS, and GRD cases, symptom severity, and level of functional impairment).

As an example of how the at-risk mental state is assessed, consider the Structured Interview for Prodromal Symptoms (SIPS), which represents a

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Table 11.1 Defining the three subtypes of the CHR-P syndrome (after Miller et al. 2003).

Subtype	Description
Attenuated positive symptom syndrome (APSS)	Presence of one or more positive symptoms, including but not limited to "suspiciousness/persecutory ideas," "grandiosity," or "perceptual abnormalities/hallucinations" at a prodromal rating (3–5). Symptoms developed or began to worsen over the past year and have occurred at least once per week during the previous month.
Brief intermittent psychotic syndrome (BIPS)	One or more positive symptoms experienced at a fully psychotic level. Symptoms must have started within the previous three months and occur several minutes a day at a rate of at least one time per month, up to four times per week.
Genetic risk and decline (GRD)	Includes (a) having a first-degree relative with a diagnosed psychotic disorder or meeting criteria for schizotypal personality disorder and (b) experiencing a significant decrease in functioning over the past year as measured by the GAF scale (i.e., at least a 30% drop).

significant advance in operationalizing CHR-P (Fusar-Poli et al. 2013b). SIPS includes the following measures:

- A family history questionnaire
- A scale of prodromal symptoms (SOPS)
- A schizotypal personality disorder checklist
- A global assessment of functioning (GAF) scale

All are used in combination to ascertain high-risk status using the SOPS criteria, which includes negative, positive, disorganized, and general symptoms (Miller et al. 2003). Symptoms are rated on a scale from 0–6. The 3–5 range represents mild or attenuated symptoms, with individuals experiencing prepsychotic symptoms (e.g., hearing odd noises as a perceptual abnormality) (Miller et al. 2003). In contrast to individuals who experience a full psychotic episode (i.e., who evidence total conviction in their symptoms, a rating of 6), those who experienced prodromal symptoms recognize that their symptoms may not be real (Miller et al. 2003).

As an alternative possibility, "basic symptoms" can be used to identify earlier prodromal symptoms (e.g., subjective experienced changes in self-perception, tolerance to stress, cognitive disturbances, and cognitive-perceptive disturbances). Here, to meet basic symptoms criteria, individuals must (a) exhibit ≥2 of 9 cognitive-perceptive symptoms (COPER), with a score of ≥3 in the past three months, and/or (b) demonstrate a disturbance in cognition (COGDIS), with a score of 3 over the past three months and a first occurrence at least one year ago, irrespective of earlier frequency or persistence. While the psychosis risk spectrum can include individuals who meet basic symptom criteria, basic symptom and CHR-P/UHR-P criteria, as well as CHR-P/UHR-P

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criteria alone, we focus on controversies associated with the psychosis risk designation using the CHR-P example.

Core Ascertainment Strategy in CHR-P

CHR-P programs mainly care for adolescents and young adults who are already showing signs and seeking help for potential mental health problems (Fusar-Poli et al. 2013b). In addition to providing comprehensive care, monitoring, and evaluation via a multidisciplinary team, CHR-P clinics engage in community outreach in an effort to increase enrollment of help-seeking individuals (Compton et al. 2008). Outreach activities include recruitment from primary schools, colleges, primary care, and other mental health services, as well as CHR-P education within the community to improve lay identification of individuals who meet CHR-P criteria (Cannon et al. 2008; McFarlane et al. 2010; McGlashan et al. 2007). The intent of ascertainment from nonmental health community sources is to identify individuals who have not yet sought tertiary mental health treatment and to improve the course of their illness while they are still in a "high-risk" state, ultimately reducing the burden of psychosis (McGorry et al. 2008a).

The Portland Identification and Early Referral (PIER) program in Portland, Maine (McFarlane et al. 2010), provides an example of a community CHR-P program. To identify CHR-P youth, PIER employed a public education campaign directed at a broad spectrum of the community (i.e., counselors at the primary and college level, clinicians in primary care, mental health, and other health-care areas). Through on-site visits as well as via a public education campaign using radio and TV ads, brochures, and customized websites (see Figure 11.1), PIER's efforts were aimed at enhancing recognition of the warning signs of early psychosis (McFarlane et al. 2010). Although there was, on average, a six-month lag

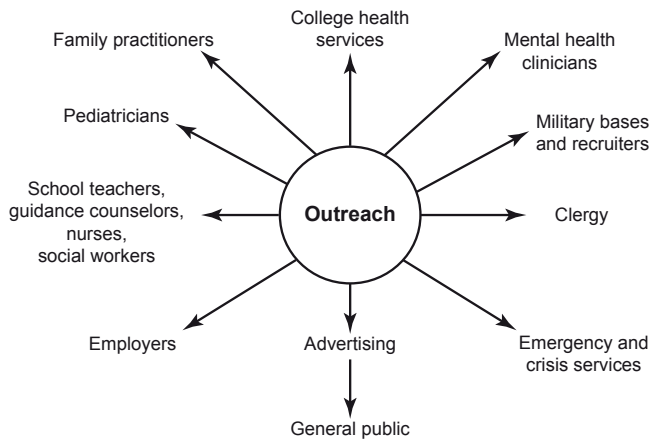

Figure 11.1 Example of community ascertainment from PIER.

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between outreach efforts and referral to PIER, this community outreach program achieved its objectives: more than 50% of CHR-P referrals came from sources outside traditional mental health agencies (McFarlane et al. 2010). Further, the presence of a community CHR-P program appeared to decrease rates of first hospitalizations for psychosis in that region. A follow-up study found that there was an 8% increase in hospitalization rates related to psychosis in a control group of comparable catchment areas in which no CHR-P programs existed, compared to a 26% decrease in the catchment area for the PIER program (i.e., the experimental group) (McFarlane et al. 2014).

The Validity of CHR-P Identification: Challenges and Controversies

In this section we explore the controversies and challenges that surround the core validity of CHR-P identification. We discuss whether the CHR-P can be considered to assess a "true" syndrome with useful predictive features across populations. Conversion rates have been reportedly decreasing over time. While some studies have examined the observed declining transition rates as a potential artifact of whether participants are ascertained earlier in the course of CHR-P, others have focused on the heterogeneity between subgroups (CHR-P, UHR-P, and basic symptoms) as a source of variance. We also discuss the inconclusive state regarding the comparative effectiveness of treatment options and current controversies regarding treatment recommendations.

Declining Conversion Rates in Samples over Time

A key meta-analysis reported that the rate of symptomatic, help-seeking CHR-P youth who transition to (i.e., meet full criteria for) a psychotic disorder within three years after first identification is approximately 36% (Fusar-Poli et al. 2012). Similarly, the North American Prodrome Longitudinal Study (NAPLS) found that 35% of individuals convert to psychosis within 2.5 years of follow-up (Cannon et al. 2008). However, one controversy concerns declining conversion rates to psychosis that have been observed over time (Yung et al. 2007). Early studies identified upward of a 40% conversion rate to full psychosis over a follow-up period of two to three years after identification (Gee and Cannon 2011). In more recent studies, reported rates declined when the essentially interchangeable UHR-P state was used as the criterion: large portions of UHR-P individuals did not convert to psychosis and even remitted from a UHR-P state (Fusar-Poli et al. 2012; Nelson et al. 2013; Simon et al. 2014). One meta-analysis reported an average conversion rate of only 24% among UHR-P patients, whereas earlier publications showed significantly lower conversion rates, especially among studies with a naturalistic (i.e., nontreatment) study design (Simon et al. 2011).

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With CHR-P, a similar decline in transition rates has been observed. In their study of 129 patients, separated into two periods of enrollment (2005–2009 and 2009–2013), Lim et al. (2016) found transition rates to be lower in the later-identified CHR-P sample. When the duration of prodromal positive symptoms was accounted for, however, this significant difference disappeared. This suggests that referral of youth who are earlier in their trajectory of illness to CHR-P clinics may be associated with decreasing transition rates, a trend that occurred in the more recently enrolled patients. A meta-analysis that examined eight studies (N = 773 CHR-P youth) conducted between 2002 and 2012 found that 73% of individuals identified with CHR-P did not convert during a two-year follow-up period and that an additional 46% fully remitted from baseline psychotic signs (Simon et al. 2013). Possible explanations include more effective treatments, comorbidity with other disorders, differences between earlier cohorts and more recent cohorts (e.g., higher proportion with trait risk factor), or lead time bias (the difference in time between initial CHR screening and when the onset of symptoms might occur in the absence of screening) (Simon et al. 2013). Here, CHR-P patients are diagnosed at an even earlier stage than they would have been without clinical involvement, giving the illusion that more time has elapsed in the CHR-P stage and that transition rates are declining. It may be that as programs continue to advance, in terms of being able to detect and treat CHR-P individuals at progressively earlier stages, transition rates may continue to decrease.

Another factor that may contribute to declining conversion rates to psychosis is that features of CHR-P closely overlap with that of other common psychiatric disorders. In their review of possible comorbid psychiatric conditions (e.g., isolated hallucinations, unusual bodily perceptions, hypochrondriatic fears and cenesthetic psychotic symptoms, depersonalization, obsessive-compulsive, overvalued, and delusional ideas), Simon et al. (2014) found that the vast majority (86%) of UHR-P patients reported ≥1 of these four clinical subgroups. Given the substantial overlap of these clinical symptoms with other common mental disorders, future studies should characterize the influence of comorbid clinical symptoms on transition (or nontransition) rates for psychosis.

Psychosis Risk Spectrum as Distinct Subsyndromes

Another possible explanation for why transition rates are declining is that subgroups of CHR-P, UHR-P, and individuals with basic symptoms have heterogeneous conversion rates; that is, the differing compositions of these subgroups across study samples may be a source of variance in the observed transition rates. In a meta-analysis that compared rates of those who met criteria for the UHR-P subgroup versus those meeting basic symptoms criteria of COGDIS, conversion rates were found to be similar for both criteria at

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two-year follow-up. This changed after two years, at which time conversion rates for COGDIS became significantly greater (Schultze-Lutter et al. 2015).

A larger meta-analysis was conducted for 33 independent studies (N = 4,227 participants) which categorized CHR-P individuals based on the presence of (a) any BIPS, APSS, and GRD, (b) APSS alone, (c) GRD alone, and (d) basic symptoms (Fusar-Poli et al. 2016). It identified a control group across studies comprised of individuals who were assessed for risk of CHR-P, but did not ultimately meet these criteria. The proportion of each subgroup having any psychotic disorder at 6, 12, 24, 36, and >48 months follow-up was then evaluated. Findings indicated that the GRD subgroup did not demonstrate a higher risk of psychosis compared with the CHR-P subgroup. The BIPS subgroup was at higher risk compared with APSS (39% vs. 19% transition rates). However, APSS demonstrated the highest proportion of CHR-P cases, comprising 85% of this meta-analytic sample. Although the BIPS subgroup demonstrated the highest conversion rates, it has been questioned whether those who meet these criteria are already psychotic (Fusar-Poli et al. 2016), which could potentially bias transition rates because those in the BIPS subcategory are more likely to transition yet they make up a relatively smaller proportion of CHR-P samples.

A more focal analysis of four distinct clinical variables—disorganized communication (from APSS), suspiciousness (from APSS), verbal memory (neuropsychological deficits), and decline in social functioning (global functioning)—was examined among 101 patients at baseline with an average three-year follow-up (Cornblatt et al. 2015). Only cases exhibiting ≥1 APSS symptoms at a moderate-to-severe level were included; cases that solely met BIPS or GRD criteria were excluded. Overall conversion rates at follow-up were 28%, and the final model had a positive predictive value of 82%. Additionally, based on data from 596 clinical high-risk participants from NAPLS-2, Cannon et al. (2016) identified predictors of conversion: unusual thought content and suspiciousness, decline in social functioning, lower performance on verbal learning and memory, slower speed of processing, and younger age at baseline. These findings, externally validated by Carrión et al. (2016) with a sample of 210 participants from the Early Detection and Intervention for the Prevention of Psychosis Program, indicate that in addition to standard prodromal criteria, domains for global functioning and neuropsychological abilities impacted psychosis conversion rates. Accordingly, identifying distinctive symptom components of CHR-P criteria offers the potential to improve predictive accuracy of conversion while also providing insight into treatment targets.

An emerging area of CHR-P research has been the characterization of social and functional outcomes for nonconverters; that is, individuals who exhibit significant decline in social functioning but have not yet transitioned to psychosis. Since nonconverters possess suboptimal functional outcomes, we need to know whether there is heterogeneity among nonconverters that might enhance our understanding of psychosis prediction. In a major NAPLS study that examined 300 CHR-P patients longitudinally, 71% (214) of CHR-P patients had

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not transitioned to psychosis after 2.5 years. Although there were significant declines in attenuated positive and negative symptoms for nonconverters, at least one positive symptom was present for 40% of this group at one- and two-year follow-up. When compared with their nonpsychiatric counterparts, these nonconverters had significantly poorer social and role functioning (Addington et al. 2011).

To address the issue of whether nonconverters are heterogeneous in outcome, Schlosser et al. (2012) examined 84 CHR-P participants and 58 healthy controls across a two-year period. At the two-year follow-up, 30% of their CHR-P sample had transitioned to psychosis while 20% had fully remitted; that is, they no longer exhibited prodromal symptoms at subpsychotic levels (e.g., symptomatically remitted) and demonstrated high global and social functioning (e.g., functional recovery). Of note, another 17% were symptomatically remitted but did not functionally recover; conversely, 17% did not experience symptomatic remission but functionally recovered. Those symptomatically remitted patients who did not experience a full functional recovery were more similar to healthy controls in terms of baseline and longitudinal symptoms and functioning compared with the other two groups. This can be explained by the symptomatically remitted (but functionally impaired) group also having presented initially with less severe prodromal symptoms than the other two groups; although they did not experience a full functional recovery at two-year follow-up, they did possess a more normative trajectory of psychosocial functioning over time. This suggests that the symptomatically remitted (but functionally impaired) group might more accurately represent the "false positive" cases from the perspective of risk ascertainment, whereas the functionally recovered but still symptomatic patients represent a clinical profile similar to that of their converted counterparts. Accordingly, future research should seek to follow these still symptomatic (but functionally recovered) nonconverters past the two-year follow-up period to track their continued risk for psychosis conversion.

Inconclusive Treatment Recommendations for CHR-P Status

Existing randomized controlled studies of treatment for CHR-P individuals recommend psychosocial and pharmacological interventions, in particular cognitive behavioral therapy (CBT) as effective in delaying the onset of acute psychosis (Woodberry et al. 2016). A recent review of CHR-P interventions, however, concluded that no particular treatment has demonstrated greater efficacy than any other available treatment (Woodberry et al. 2016). Partly due to overlap across different strategies, treatment recommendations are currently unable to claim whether psychosocial interventions, neuroprotective agents, or antipsychotic medications are more effective for the prevention or delay of transition to psychosis. While eight guidelines have been proposed for treating CHR-P, only two were deemed of sufficient quality, by the Canadian Treatment

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Guideline developers (Addington et al. 2017), to offer treatment recommendations: the National Institute for Health and Care Excellence and the European Psychiatric Association (EPA) guidelines. Although both propose psychotherapy (in particular, CBT) with or without family intervention and pharmacological interventions (NCCMH 2013), more rigorous evaluations of treatment efficacy are still needed.

Pharmacological Interventions

A source of substantial debate and controversy is that the most recently published guidelines, the Canadian Treatment Guidelines, have recommended short-term, low-dose, second-generation antipsychotics if CHR-P individuals are not responsive to psychological interventions, and there are severe and progressive attenuated psychotic symptoms that could signal an impending transition to psychosis (Addington et al. 2017). These recommendations are controversial due to the numerous side effects and stigma associated with antipsychotic use. For example, studies have suggested that young people are more prone to having neuroleptic side effects (Fraguas et al. 2008) and that possible brain shrinkage is associated with long-term medication use (Ziermans et al. 2010). Highlighting the unresolved nature of this controversy, two recent reviews of randomized controlled trials (RCTs) that assessed the efficacy of antipsychotics in CHR-P treatment failed to present conclusive evidence for this approach (Stafford et al. 2013; Woodberry et al. 2016). These studies did not provide sufficient evidence owing to frequent confounding of the effects of psychosocial treatment with pharmacological treatment, poor medication adherence, and high dropout rates (Becker et al. 2015; Stafford et al. 2013). The latter two factors signaled very poor tolerability of these medications in the CHR-P population. In sum, given the inconclusive evidence and the demonstrated efficacy of more tolerable psychosocial treatments (below), and because the recommendation for the selective use of antipsychotics has yet to be adopted outside of Canada, further evidence is necessary to support an evidence-based approach concerning antipsychotic use.

Psychosocial Interventions

Numerous psychosocial interventions exist for CHR-P: CBT, family-focused therapy, case management, assertive community treatment, multifamily group psychoeducation, cognitive remediation/enhancement, social skills training, supported employment/education, supportive therapy, needs-based intervention, and crisis intervention (Woodberry et al. 2016). Similar effects have been evidenced in the treatment of CHR-P across existing psychosocial treatments. Cognitive and cognitive behavioral approaches are the most studied psychosocial interventions. Stafford et al. (2013) reviewed nine CBT intervention studies

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and determined that CBT has a moderate effect on reducing the likelihood of transition at 12 and 18 months. Although European Psychiatric Association guidelines do not include a recommendation for family intervention, the most recently developed treatment guidelines, citing one RCT of a family-focused treatment, recommend CBT with or without family intervention as first treatment after evaluation (Addington et al. 2017). Additionally, one study demonstrated that family-aided assertive community treatment (FACT) is significantly more effective than community care in reducing positive symptoms and improving work and school participation among CHR-P youth at two-year follow-up (McFarlane et al. 2014). Accordingly, the family component should be considered for inclusion in future treatment recommendations.

Nutrition Supplementation

Because deficits in vitamins and polyunsaturated fatty acids are associated with poorer outcomes (e.g., greater symptom severity, reduced neural integrity, and neurocognitive impairments in individuals with FEP), the value of nutrition supplementation (i.e., adjunctive vitamin or antioxidant supplementation) has been examined (Firth et al. 2018). One prominent study showed that intake of omega-3 polyunsaturated fatty acids (FA) was significantly associated with reduced positive, negative, and general symptoms as well as improved functioning (Amminger et al. 2010). Moreover, 93.8% of participants completed this study, compared with the 20% to 66% completion rates for antipsychotics (Amminger et al. 2010). A recent replication study (Cadenhead et al. 2017), however, found that while the experimental group did not significantly differ from the placebo group, there was a significant association between a baseline diet low in omega-3 FA-rich foods and increased symptoms, decreased functioning, and higher likelihood of conversion to psychosis. Because this study was underpowered to detect effects (Cadenhead et al. 2017; Markulev et al. 2017), a subsequent multisite RCT was conducted to assess the efficacy of omega-3 FAs and CBT case management (McGorry et al. 2017). Results again failed to replicate previous findings found in the original Amminger et al. (2010) study, as no significant difference was found in transition rates between the experimental group receiving omega-3 FA plus cognitive behavioral case management (CBCM) and the control group which received a placebo plus CBCM. Because both groups received CBCM as well as focal medication as needed (i.e., selective serotonin reuptake inhibitors for major depression, benzodiazepine therapy for anxiety), and good-quality psychosocial supports have been shown to decrease transition rates thus leading to symptomatic and functional improvement in both groups, conclusions about the specific role of omega-3 FAs were difficult to reach (McGorry et al. 2017). More research is thus required to clarify its role in potentially decreasing rates of transition.

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Exercise Interventions

More recently, attention has focused on the use of exercise interventions as adjunctive treatments for individuals with psychosis. In persons with schizophrenia, exercise interventions have been effective in improving physical fitness, reducing cardiometabolic risk, and decreasing psychiatric symptoms (Firth et al. 2015). For CHR-P, research has found that individuals identified as CHR-P are more likely to be physically inactive and to have higher rates of sedentary behavior than persons who did not develop psychosis (Koivukangas et al. 2010). Additionally, self-report assessment of physical activity levels in a CHR-P sample concluded that those with CHR-P exercise less frequently, less intensely, and report lower perceived fitness levels than healthy controls. Further, CHR-P participants reported more barriers to exercise and less positive reasons for exercising (Deighton and Addington 2015). While research has reported on the extent of physical activity among CHR-P individuals, limited work has been conducted to test the efficacy or effectiveness of exercise interventions. Given the evidence above regarding the efficacy of exercise interventions with FEP, these interventions might also benefit individuals with CHR-P. To our knowledge, the only published exercise intervention within the CHR-P population assessed the efficacy of a 12-week program of supervised exercise. The intervention improved positive and negative symptoms, social and role functioning, cognitive functioning, as well as functional connectivity between the hippocampus and occipital cortex (Dean et al. 2017). This research presents promise for the use of physical activity interventions in persons with CHR-P.

Future Work

CHR-P constitutes a meaningful risk syndrome for distressed, help-seeking individuals. Identifying it in individuals not only helps us predict the transition to psychosis among converters, it enables us to address impaired functioning among a substantial proportion of nonconverters. A great deal of research into both aspects has been conducted within high-income, Western European societies. As research has proliferated, a more nuanced understanding of CHR-P identification has emerged (e.g., differing transition rates between symptom subgroups), and we expect that further refinement will be needed to enhance understanding in the prediction of psychosis. Better defining the clinical subtypes may help reduce heterogeneity; identifying core characteristics that predict psychosis may result in more targeted, and ultimately effective, treatment approaches and recommendations.

A substantial gap remains however, in that most or nearly all psychosis risk studies have been conducted in Western European, high-income countries, with the exception of Hong Kong and China (see below). Currently, we do not know how well CHR-P states, including the utility of the risk calculator (Cannon et al. 2016), predict transition to psychosis in non-Western, low- and

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middle-income countries. Addressing this gap could greatly expand applicability of this meaningful risk syndrome and help symptomatic individuals in other income global contexts.

Stigma and Ethical Dimensions of CHR-P Identification

The second set of issues that we address concerns the stigmatizing effects of being identified with a severe mental health disorder. Comprehensive reviews of stigma and early psychosis among youth are available elsewhere (see Gronholm et al. 2017). Here we highlight stigma and ethical considerations of youth identified as CHR-P at an early and critical stage in their development trajectory.

Stigma of CHR-P

Despite the many potential benefits of early CHR-P identification, those who are identified may experience stigma. Risk of stigma is especially important, given that a majority (i.e., approximately 65%) of those identified as CHR-P will not develop a full psychotic disorder, yet may be subject to negative effects from the stigma associated with this psychiatric classification (Fusar-Poli et al. 2012; Yang et al. 2015). Being identified as at-risk for a severe mental illness during critical developmental stages of adolescence and youth—when an individual's concept of "self" consolidates (Eccles et al. 1993) and when social acceptance is key to identity formation (Moses 2009)—can severely threaten a young person's sense of identity and normalcy (Wisdom and Green 2004; Yang et al. 2007). A small qualitative study showed that CHR-P youth expressed concerns about how peers would perceive them if information about their at-risk status was revealed (Welsh and Brown 2013). Recent research has delineated whether differences in stigma are associated with the CHR-P label or with symptoms (Yang et al. 2015). While stigma related to both symptoms and label mattered for CHR-P youth, stigma related to symptoms was more prominent overall and was associated with increased depression (Yang et al. 2015). In contrast, stigma related to the label was associated with anxiety (Yang et al. 2015). Further, research from a multisite study indicated that a little less than one-third of CHR-P youth endorsed their sense of self as being "most impacted" because they were at-risk for a psychotic disorder (i.e., psychosis or schizophrenia) compared to a nonpsychotic disorder such as anxiety or depression (Yang et al. 2019). In examining factors associated with sense of self, Yang et al. found that individuals who reported "being told" that they were at risk by others or who "believed themselves" to be at risk for developing psychosis experienced increased odds of psychosis risk impacting their sense of self (Yang et al. 2019). This indicates that the stigma associated with CHR-P identification is significant for some individuals and linked to negative

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psychosocial outcomes. It also suggests that interventions to mitigate stigma could further improve CHR-P outcomes. However, it is also important to consider whether stigma related to CHR-P identification may be affected by other information relayed during the process of being told one is at-risk. For example, an "at-risk" state is distinct from a FEP, and there is a relatively low risk of transition to psychosis, particularly if one is engaging in treatment. Beneficial effects of providing accurate information about the "at-risk" state have been shown to mitigate stigma toward CHR-P among community members (Yang et al. 2013) and could possibly provide similar benefits among CHR-P individuals themselves.

Ethical Challenges

The process of and procedures involved in obtaining informed consent for CHR-P youth (<18 years of age) need to be carefully considered before they participate in research or clinical interventions. Children and adolescents have altered risk perceptions, such as heightened focus on short-term risks and benefits (Scott et al. 1995). Therefore, support should be given to ensure that such participants can competently evaluate the risks and benefits of engaging in research. Additionally, because family members often play an important role in recruitment and may be subject to a particular emotional state (e.g., in distress or overly enthusiastic) when providing informed consent for their children, procedures need to incorporate steps to minimize the potential effects of these biases.

Implementing CHR-P Identification and Treatment Globally

To address the challenges and controversies associated with implementing CHR-P identification on a global scale, we begin with a discussion of how it was originally implemented in Australia. Thereafter we move to the context of Hong Kong, where CHR-P services are currently being developed, and conclude with a discussion of costs and benefits.

Implementation in Australia

The first clinic established to treat UHR-P individuals was the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, Australia (Yung et al. 1995). The establishment of PACE led to the development of other UHR-P programs in Australia, many of which are paired with FEP treatment programs (Cannon et al. 2008; Carr et al. 2000; McGorry et al. 2008a; Phillips et al. 2000; Yung et al. 2008), a model that has proliferated worldwide. In Australia, CHR-P identification and treatment is embedded within Orygen Youth Health, a public mental health program that serves young people from 15–24 years of age (Yung et al. 2004, 2008). Additionally, in 2006, the

From "Youth Mental Health: A Paradigm for Prevention and Early Intervention," edited by Peter J. Uhlhaas and Stephen J. Wood. Strüngmann Forum Reports, vol. 28, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 978-0-262-04397-7

Australian government invested in the creation of *headspace*, a nationwide policy initiative designed to decrease fragmentation of services and increase access to services for young people (ages 12–25 yr) who were experiencing a range of mental and substance abuse problems (McGorry et al. 2007b). Headspace provides no- or low-cost services, at in-person locations as well as online, and is focused on youth-oriented treatment and in minimizing the stigma associated with treatment.

Implementation in Hong Kong

Hong Kong is currently initiating a new CHR-P program within an established FEP program. Because many challenges of implementing new CHR-P services mirror the implementation of FEP services within new mental health service settings, Hong Kong serves as an appropriate case study for implementation of CHR-P services in new global contexts.

Mental Health Literacy and Identifying an Appropriate Term for CHR-P for Chinese Groups

In Chinese societies, mental health literacy (or knowledge about mental disorders, which aids in its recognition, management, and prevention), especially regarding psychosis, is poor. In a nationally representative study using hypothetical vignettes, only 8.7% of (urban) respondents correctly identified schizophrenia (vs. 38% for depression) (Huang et al. 2019). Low mental health literacy does not arise from a lack of mental health education alone, but stems from the widespread stigma toward mental illness and the presence of culturally specific idioms regarding mental conditions. In Chinese culture, preserving status as a "fully formed human being" is essential to one's ability to work as well as to achieve a marriage to perpetuate one's family lineage—accomplishments that "matter most" for many Chinese people (Yang and Kleinman 2008). Thus, individuals with a severe mental illness are perceived as "not being fully formed human beings." This diminishes one's participation in social exchange networks (known as *guanxi*), where opportunities to work and to locate marriage partners are often situated. Stigma often extends to family members. In a large study of 1,491 relatives of individuals with schizophrenia, >50% reported experiencing adverse effects of stigma (Phillips et al. 2002b).

Because of these factors, particular care has been given to identifying the appropriate term for psychosis diagnoses. The current Chinese term for schizophrenia, *jing-shen-fen-lie*, translates literally to "mind-split disease" (Chiu et al. 2010)—a term that may perpetuate stigma without offering much insight into the disorder's characteristics (Tang et al. 2010). Public awareness campaigns surrounding psychosis in Hong Kong have sought to rename the term for psychosis based on feedback from health professionals to *si-jue-shi-tiao*, which translates to "thought and perceptual dysregulation." Similar efforts to

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find an appropriate term for the "clinical high risk for psychosis" designation have been made in Hong Kong. A recent study, which used vignettes describing the at-risk CHR-P condition to 149 community members and 51 healthcare professionals, found that many (45%) preferred the Chinese diagnostic term of *yun-niang-qi*, meaning "developing period"—a term that does not connote certainty regarding development of a psychotic illness. While a promising first step, it remains to be determined whether this term is recognizable to the general public, is acceptable to CHR-P youth, and to what extent it protects participants from stigma.

FEP Services and Implementing CHR-P Services Globally

The Early Assessment Service for Young People with Early Psychosis (EASY) program, established in 2001, represents efforts by the Hong Kong government to integrate FEP services into broader mental health-care services. EASY targets 15- to 25-year-olds who present with psychotic symptoms and aims to reduce DUP while optimizing treatment in the first two years after FEP (Tang et al. 2010; Wong et al. 2008). EASY[1] includes three components:

1. *Raising public awareness*: As noted above, an educational campaign, conducted through multiple media streams (Wong et al. 2008), made use of the new term for schizophrenia to reduce stigma and encourage public acceptance of psychosis (Wong et al. 2008). A study of 1,217 local newspaper articles found an overall increase in the use of the new term (*si-jue-shi-tiao*) and a decrease in the original "split-mind disease" term (*jing-shen-fen-lie*) from 2002 to 2012 (Chan et al. 2017). However, findings regarding public acceptance for the new psychosis term have been mixed and have yet to focus on the effectiveness of this new terminology in patients' actual experiences (Chan et al. 2017; Yamaguchi et al. 2017). Additional psychoeducation efforts are thus needed before the full benefits of this new terminology are likely to be observed.
2. *Accessibility to FEP services*: To remove barriers to care, a two-stage assessment system was established: a telephone-based initial screening and a diagnostic assessment with an early psychosis clinician within one week (Wong et al. 2008). Referrals from a broad range of sources were accepted, including (but not limited to) hotlines, email, walk-ins, nongovernmental organizations, school social workers, outpatient departments, and non-EASY psychiatrists (Wong et al. 2008). While effective for FEP referrals, these channels would require further expansion for CHR-P programs to detect psychosis before it develops to its full state. This would include incorporating even more extensive contacts with

[1] For further information, see https://www3.ha.org.hk/easy/eng/service.html.

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nonclinical settings to implement community outreach to detect individuals when they are still in a high-risk state, as described earlier.

3. *Phase-specific intervention*: FEP services in Hong Kong follow a phase-specific outpatient treatment model that includes the use of multidisciplinary teams. Care is provided according to patients' needs and consists of enhancing psychological adjustment to early psychosis, intervention for secondary morbidity, and CBT for drug-resistant psychotic symptoms (Wong et al. 2008). This standardized intervention package provides in-depth engagement, comprehensive psychoeducation, support for medication adherence, coping and stress management, and relapse prevention (Chang et al. 2017). The FEP phase-specific intervention lasts for two years; in year three, patients enter a transitional step-down clinic, with psychiatric treatment but no case management (Chang et al. 2017; Tang et al. 2010). Many elements of the FEP program (e.g., the multidisciplinary team, standardized treatment protocol, and focus on functional recovery) might be applicable to implementing earlier-phase CHR-P treatment.

FEP Program Efficacy

The EASY program, when compared with standard care, showed changes in key clinical and functional outcomes. Regarding functional outcomes, patients enrolled in EASY achieved longer durations of full-time employment (15.2 months) when compared with matched historical controls (10.5 months), and a greater proportion were engaged in full-time positions for ≥6 months (Chen et al. 2011). EASY also improved clinical outcomes and service utilization. EASY participants had fewer positive and negative symptoms than historical controls, and more EASY patients achieved at least a brief period of recovery within three years (Chen et al. 2011). Finally, EASY patients had significantly better outpatient attendance as well as shorter and fewer hospitalizations than historical controls (Chen et al. 2011).

Despite these improvements, EASY did not appear to reduce DUP for participants compared with historical controls; these groups experienced DUP of 239.8 and 232.0 days, respectively (Chen et al. 2011). Accordingly, the program's impact was attributed not to reduced DUP but to the phase-specific intervention (Tang et al. 2010). This may be due to insufficient time for the public awareness program to have influenced public perceptions and care-seeking before the evaluation was conducted (Chen et al. 2011). These findings are relevant to the implementation of CHR-P programs, which are predicated on the capacity to identify the earliest psychotic signs among community members. Taking the example of Hong Kong, an area of emphasis likely lies in public education for psychosis risk and outreach to the nonclinically based community agencies, so that individuals with psychotic

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signs can be successfully identified prior to FEP in this and similar global contexts.

Implications for Implementing CHR-P Programs

Based on the Hong Kong implementation experience, there are a number of principles that could be further evaluated as other global settings attempt to adopt CHR-P (and FEP) services. Like the EASY program, programs in other settings should assess the impact of adopting an appropriate term for psychosis and CHR-P, for the setting to improve understanding, increase community detection, and reduce stigma. Additionally, as was conducted in EASY, other programs should target youth in the particular age range during which there is the most heightened risk. Following from the EASY program's inability to reduce DUP, despite more accessible referral and assessment channels, other settings should conduct systematic studies of the factors that shorten or lengthen DUP for this group, particularly through community outreach. Because the EASY program involved only hospital-based care, future outreach efforts for CHR-P individuals will likely require extensive contact with nonclinical, community-based agencies (e.g., schools, youth agencies) to locate CHR-P youth before they enter formal mental health services.

Cost-Effectiveness for Early Intervention for Psychosis Globally

An additional controversy arises when the economic benefits of establishing early intervention services for psychosis are considered or when the feasibility of implementing such services is considered in the context of political and structural barriers embedded within health-care systems in various high-income countries.

Globally, studies find that FEP intervention services are not only more effective than standard care, but that they show cost-effectiveness. In addition to the EASY program in Hong Kong, which demonstrated cost-effectiveness in improving outcomes (26.1% savings on average per patient; Wong et al. 2011), studies elsewhere (e.g., Italy, U.K., Denmark, and Australia) have demonstrated similar effects (Bertelsen et al. 2008; Cocchi et al. 2011; Hastrup et al. 2013; Knapp et al. 2014; Mihalopoulos et al. 2009; Serretti et al. 2009). A study of the Recovery After an Initial Schizophrenia Episode-Early Treatment Program and Navigate Intervention Package (NAV) showed mostly consistent results (Rosenheck et al. 2016). This study compared the cost-effectiveness of NAV (a multidisciplinary, team-based treatment approach for FEP) to community treatment. Compared with community treatment, NAV was somewhat more expensive (due to increased outpatient and medication costs), but it produced better clinical and quality of life outcomes, making it a better value particularly

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among patients with shorter DUP, who showed lowest costs, greatest improvements in quality of life, and greatest cost-effectiveness.

Regarding CHR-P, existing studies find that while early identification services for CHR-P individuals are initially more costly than standard care, over time the costs averted by early detection ultimately result in cost savings (Knapp et al. 2014). An investigation of the Outreach and Support in South London (OASIS) program in the United Kingdom, a service for people with an at-risk mental state with a high-risk of developing psychosis, found that at 24 months, expected service costs were £4313 and £3285 for OASIS and standard care, respectively (Valmaggia et al. 2009). However, when costs related to lost employment were included, total estimated costs per person were £961 less for OASIS than standard care (Valmaggia et al. 2009). Using a model that extends potential cost savings to criminal justice services, suicide, homicide, and lost employment, a study estimated potential savings of £47.6 million associated with U.K. early detection services within 2–5 years and £41.0 million in years 6–10; per person savings were £3,022 and £2,604 in years 2–5 and 6–10, respectively (McCrone et al. 2010).

In addition to cost, substantial political and structural barriers may exist that can impede implementation of early intervention services. Barriers related to a lack of political will include a lack of interest in preventive measures and a lack of recognition of the needs of patients with early psychosis (Csillag et al. 2017). Ineffective coordination among important stakeholder groups is also an obstacle, as treatment is fragmented, with little communication between mental health specialists, primary care providers, welfare services, and educational institutions (Csillag et al. 2017). Structural and administrative barriers include insufficient funding and constraints in public resources (Csillag et al. 2017). The physical spaces themselves may not be integrated into the medical system in a way that minimizes stigma (Arango et al. 2017). In many contexts, the structure of the mental health system itself (e.g., in countries where institutionalization forms a primary treatment) is not conducive to successful implementation of early intervention services and may be poorly adapted to young peoples' needs (Csillag et al. 2017). For example, programs do not commonly use mobile phones and social networks to communicate with the young adult population (Arango et al. 2017). CHR-P programs face many of the same implementation challenges as these early intervention programs.

Conclusion

While the CHR-P status signifies a crucial advance in the identification and treatment of youth experiencing subthreshold signs of psychosis, unresolved controversies remain regarding the early detection state as it is implemented globally. Here we have reviewed the scope of these challenges and controversies, which range from core issues regarding validity of the CHR-P

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identification state itself, to topics of stigma and ethics as well as the economic, structural, and cultural issues concerning implementation of this early detection state within novel mental health settings. In tandem with the movement toward earlier treatment for psychosis worldwide, the continuing shift toward CHR-P identification will only make resolving these complex challenges more important. In the future, earliest intervention efforts may benefit from a concerted effort to resolve those controversies most salient to that particular setting (e.g., in countries where the CHR-P identification is established, to resolve controversies around its core validity). While CHR-P identification approaches are now primarily situated within Western European, high-income contexts, as the CHR-P identification expands to novel global and cultural settings, new implementation challenges will be identified which will require resolution. Future research to address these controversies will facilitate adoption of the CHR-P identification into mainstream mental health-care systems globally, thus maximizing public health impact.

Acknowledgments

Preparation of this chapter was supported in part by an award from the National Institutes of Mental Health (NIMH R01-MH096027; PI:Yang). We dedicate this chapter to the memory of Shane Columbo, whose presence graced our lives and who left us too soon.

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