Current Psychiatry Reports (2019) 21: 39
https://doi.org/10.1007/s11920-019-1027-y

PRECISION MEDICINE IN PSYCHIATRY (S KENNEDY, SECTION EDITOR)

Predictors of Transition to Psychosis in Individuals at Clinical High Risk

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Published online: 29 April 2019

Abstract

Purpose of Review Current research is examining predictors of the transition to psychosis in youth who are at clinical high risk based on attenuated psychotic symptoms (APS). Determining predictors of the development of psychosis is important for an improved understanding of mechanisms as well as the development of preventative strategies. The purpose is to review the most recent literature identifying predictors of the transition to psychosis in those who are already assessed as being at risk.

Recent Findings Multidomain models, in particular, integrated models of symptoms, social functioning, and cognition variables, achieve better predictive performance than individual factors. There are many methodological issues; however, several solutions have now been described in the literature.

Summary For youth who already have APS, predicting who may go on to later develop psychosis is possible. Several studies are underway in large consortiums that may overcome some of the methodological concerns and develop improved means of prediction.

Keywords Psychosis · Prodrome · Schizophrenia, predictors · Risk factors · Clinical high risk

Introduction

In the past two decades, researchers have attempted to identify and assess those who may be at risk for psychosis, with the hope that this could lead to substantive improvements for the outcome of psychosis. Identification of these young people is based on clinical criteria, specifically, attenuated psychotic symptoms (APS) which are suggestive of being putatively prodromal for psychosis. These individuals are considered as being at clinical high risk (CHR) of psychosis. There are well-developed criteria for identification of CHR individuals based on structured clinical interviews such as the Scale of Psychosis-Risk Syndromes (SIPS [1]), or the Comprehensive Assessment of At-Risk Mental States (CAARMS [2]). For individuals, in the age range of 12 to 35 years who have been identified as being at CHR, approximately 20 to 35% will develop psychosis within 2 years [3]. Furthermore, the risk of developing psychosis in these young people is imminent as most transitions occur within the first year after study ascertainment. Thereafter, the risk of transition is decelerating [4]. The aims of this line of research were threefold: (i) to identify early those at risk of psychosis, (ii) to determine predictors of who may ultimately make the transition to psychosis, and (iii) to determine if the prediction of transitioning to psychosis can be increased beyond 20–35%. The aim of this review is to highlight the most recent work that has been done in finding predictors that might be indicative of a later transition to full-blown psychosis in those who already meet well-established criteria for being at CHR for psychosis.

This is not a systematic review; however, a search of recently published literature from the last 3 years (January 2015–September 2018) was conducted in Pubmed. Search terms included MeSH, keywords, and related synonyms pertaining to CHR, psychosis/schizophrenia, and selected predictors of risk (cognition, social/role functioning, cannabis, trauma, migration, urbanicity, traumatic brain injury, imaging, and prediction models). Only articles published in English,

This article is part of the Topical Collection on *Precision Medicine in Psychiatry*

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regardless of study design, were included. If a relevant review article was found within the timeframe of interest, individual studies were only included if published subsequent to the review. In addition, if multiple studies concluded similar findings on the same topic, only the publication with the highest sample size and the most comprehensive and robust methods was reported. In the case of duplicate study samples represented in multiple publications, only the publication with the most up to date results or the largest sample size was included. Finally, hand searching was also undertaken to identify relevant studies for inclusion.

We first present research that focuses on individual predictors of transition to psychosis and secondly on models of prediction that encompass several factors.

Environmental Risk Factors

In the epidemiological literature, several risk factors have been proposed that may contribute to the development of schizophrenia and other psychoses. The most frequently reported factors include urban upbringing [5], migration and perceived discrimination [6, 7], a history of trauma [8], and cannabis use [9]. Many of these risk factors continue to be investigated among those at CHR for psychosis as possible predictors of later transition to psychosis.

Migration, Ethnic Status, and Perceived Discrimination

Very little research of CHR individuals has been performed to date regarding migration, ethnic status, and perceived discrimination. However, in one study, it was reported that CHR individuals endorsed more items of perceived discrimination compared with controls that could not be accounted for by APS, in particular, suspiciousness [10]. Furthermore, these CHR individuals who endorsed more items of perceived discrimination had a greater chance of transition to psychosis [11]. A recent suggestion for the association between migration status and risk for psychosis was presented by Egerton and colleagues [12] who found that in independent CHR samples from both the UK and Canada, striatal dopamine function is elevated in immigrants compared with non-immigrants.

Urbanicity

To date, little research has addressed urban density in CHR individuals. In one study, Stain and colleagues [13] reported that functional impairment was significantly poorer for rural CHR youth compared with urban youth. However, contrary to what has been shown in the literature on established psychosis, a recent study found that although there was a trend for CHR individuals living in more deprived areas, there were no associations between the rate of identification of CHR migrants and neighborhood ethnic density [14], and that migration was not a significant predictor of later transition to psychosis [15].

Cannabis

Several studies have demonstrated that youth at CHR for psychosis present with increased cannabis use compared with healthy controls. A recent review and meta-analysis of 30 studies examining cannabis use in CHR reported that CHR participants are more than five times more likely to have a current cannabis use disorder compared with healthy controls and that among CHR individuals, cannabis users experience more severe unusual thought content and suspiciousness compared with non-cannabis users [16]. However, studies examining the role of cannabis use in later transition to psychosis are mixed. The review by Kraan and colleagues [17•] reported that in seven studies examining lifetime cannabis use, cannabis use was not associated with later transition to psychosis. However, a second meta-analysis including five studies suggested a dose-response relationship between cannabis use and psychosis, and that among CHR individuals, only cannabis abuse and dependence were predictors of transition to psychosis [17•].

Trauma

It has been a consistent finding in the literature that CHR individuals experience significantly more trauma compared to control samples, with evidence from one meta-analysis providing mean prevalence rates of 86.8% [18]. Longitudinal data has reported that trauma often occurs prior to the age of 12, and prior to the onset of CHR symptoms [19]. However, the literature is inconsistent regarding whether trauma history is a significant predictor of transition in CHR individuals. Interestingly, a recent systematic review suggested that CHR individuals who have experienced sexual trauma are at a heightened risk of transition to psychosis [20]. This is in contrast to many other recent studies which found that although CHR individuals experience more trauma than their healthy control peers, which can be associated with increased symptomatology and poorer functional outcome, there is no support for trauma as a significant predictor of transition to psychosis [11, 21–23].

Summary of Environmental Risk Factors

Although a range of environmental risk factors has been associated with CHR status, a history of trauma in childhood and cannabis use seem to be the most consistent factors related to transition to psychosis. However, these findings should be interpreted with caution given the contradictory evidence, as

well as the limited amount of literature on the impact of other factors such as migration, urbanicity, and perceived discrimination. Some authors have suggested that regardless of the specific environmental factor, a common feature underlying all these experiences is social stress [24]. The exact mechanisms on how this relationship impacts the brain, and the eventual transition to psychosis continues to be investigated.

Cognition

CHR individuals present with robust deficits in almost all cognitive domains and their level of cognitive functioning is often intermediate between healthy controls and first-episode psychosis patients [25, 26]. While most longitudinal studies have suggested that deficits in cognition predict transition to psychosis, there is a little consensus on which specific cognitive domains are involved. The most common cognitive deficits currently observed in CHR individuals who transition to psychosis when compared with those who do not, include verbal memory and processing speed, verbal learning, verbal fluency, working memory, and attention [27•, 28–31]. Even though the specific cognitive functions implicated in transition differed across studies, almost all studies found a role for cognition in the prediction of transition to psychosis. The only study that did not find a difference between those who transitioned to psychosis versus not [32] was likely underpowered due to a small number of CHR individuals who transitioned to psychosis. Furthermore, some of the discrepancies in identifying specific cognitive domains as predictors of transition may result from methodological differences, such as the use of different cognitive measures. Hauser et al. found that some measures, such as the Rey-Osterrieth Complex Figure Test, the verbal fluency test, and California Verbal Learning Test better discriminate CHR individuals who have transitioned to psychosis compared with other measures of the same construct [33•].

CHR individuals often present with social cognitive deficits [34], which refer to thought processes involved in understanding others' mental states. A recent meta-analysis reported that social cognition was not associated with transition to psychosis in most studies after controlling for IQ, education, and baseline symptoms [35]. While other studies have suggested that baseline theory of mind [36] and emotion recognition [37] may predict psychosis, studies that assessed multiple domains of social cognition found no difference on these measures between CHR individuals who transitioned to psychosis versus those who did not [34].

Thus, cognitive functions in isolation are unlikely to be significant predictors of psychosis development. Cognitive deficits present in several neuropsychiatric conditions and thus they lack specificity [31]. Finally, cognitive function has lower predictive power when compared with other predictors such as symptoms [38•].

Functioning

Poor functioning is the hallmark of schizophrenia and other psychotic disorders [39]. Difficulties in both social and role functioning have been observed in CHR individuals regardless of whether they transition to psychosis [40•]. However, there are many indications in the literature that social and role functioning may be important factors related to later transition to psychosis.

Several studies have examined global functioning using the Global Assessment of Functioning Scale (GAF). A recent meta-analysis of longitudinal studies reported that among CHR individuals, those who transitioned to psychosis had significantly poorer baseline global functioning than those who did not [41]. In addition, recent studies [42–46] generally demonstrated that regardless of whether functioning was examined at baseline, follow-up or over time, those who transitioned to psychosis experienced poorer functioning.

Premorbid social and role functioning, that is, before the onset of the CHR state, has been examined at different developmental periods most commonly with the Premorbid Assessment Scale (PAS) [47]. Results to date have suggested that, although premorbid functioning in childhood, early adolescence and overall premorbid functioning are not associated with transition to psychosis [48–50], poor premorbid functioning at late adolescence (16–18 years) has been found to be associated with a later transition [50]. Moreover, regression models identified poor premorbid social functioning at early adolescence (age 12–15) [51] and late adolescence (age 16–18) [48] as predictors of transition specifically to schizophrenia, while poor premorbid role functioning was not associated with transition to psychosis.

Among CHR individuals, poor social functioning has been associated with a high risk of transition to psychosis [52], with recent studies showing that baseline social functioning [27•, 53] and change in social functioning [27•] significantly differentiated those who transitioned from those who did not. Survival regression analyses identified baseline social functioning as an individual predictor for transition although with a lower positive predictive value (PPV) than global functioning [44]. Most recent studies have reported that role functioning is not associated with transition to psychosis in CHR samples [27•, 44, 45].

The timing and domain of functional difficulties may have a markedly different association with transition to psychosis in CHR individuals, and therefore predictive value. Role functioning does not appear to contribute independently to transition to psychosis. However, there is evidence that poor premorbid social functioning at early and late adolescence is

associated with transition. Moreover, difficulties in social functioning in CHR individuals at baseline and further decline over time seem to be robustly associated with transition to psychosis in both cross-sectional and survival analyses. Although one study did not identify social functioning decline as an individual predictor of transition in their model [54•], prediction models of psychosis that include deficits in social functioning seem to have the highest PPV and sensitivity [52], suggesting an independent contribution to the prediction of transition beyond other variables.

Neuroimaging

Changes in brain structure, particularly in the gray matter, have long been associated with the transition to psychosis [55]. Recent findings from longitudinal structural magnetic resonance imaging (MRI) studies have replicated these results and suggest that an increased rate of gray matter loss, particularly in the frontal lobes, is a predictor of transition to psychosis in CHR individuals [56]; however, it is primarily observed in those 18 or older [57•]. Furthermore, in younger CHR individuals (age 12–17), deviations between brain age, as calculated by the method introduced by Brown et al. [58], and chronological age were linked to the development of psychosis [57•]. In this study, the chronological age of those who transitioned was overestimated by their brain age. Other longitudinal studies employing machine learning suggest that gray matter changes throughout the brain can be used to identify CHR individuals who will transition to psychosis [59, 60]. Although the regions contributing to the classification were found throughout the brain, the most relevant were the cerebellum, lateral and medial temporal lobes, medial frontal lobes, and striatum. The classification became more accurate when schizotypy scales and declarative memory tests were included in the model [60]. Abnormalities in gyrification, measured using the structural covariance connectome, have also been found to predict transition [61], suggesting that the structural changes that underlie transition are present early in life.

In functional MRI (fMRI) studies, hyperconnectivity in a cerebello-thalamo-cortical circuit at baseline was found to predict time to transition to psychosis in a large CHR cohort, and this pattern of hyperconnectivity was also found in an independent sample of schizophrenia patients [62]. Cerebello-thalamo-cortical hyperconnectivity has been described by other groups and has been associated with the development of APS [63]. However, there are also reports of bi-directional changes in thalamic connectivity in CHR individuals who transition to psychosis [64], with increased connectivity between the thalamus and sensorimotor regions, and decreased connectivity between thalamus, prefrontal cortex, and cerebellum, suggesting that more work is needed to characterize these changes. In a task-based fMRI analysis, increased activity in the prefrontal, parietal, and bilateral temporal cortices during the retrieval portion of a paired-associate memory task at baseline predicted later transition to psychosis in CHR individuals [65].

Although many changes in brain structure and function have been found to be predictive of the transition to psychosis, at present, none of the neuroimaging findings can be used to identify CHR individuals who will transition. This suggests that the neural changes involved are subtle, but it is also likely a consequence of the vastness of the decision space in neuroimaging studies. Differences in imaging modalities, scanning parameters, experimental paradigms, analysis strategies, and modeling approaches make it difficult to generalize results across studies.

Neurophysiology (EEG)

The review by Riecher-Rossler and Studerus [38•] describe that a 2015 review and meta-analysis [66] concluded that the most promising EEG parameter for predicting transition is mismatch negativity. Disturbances in the gamma band have been reported in chronic psychotic disorders; however, a recent systematic review found that evidence for gamma band abnormalities in the CHR sample was mixed [67]. In resting state electroencephalogram (EEG) studies, current source density (CSD) in the beta and gamma band have been used to predict transition to psychosis in CHR individuals, with the strongest differences in CSD being found in left superior temporal gyrus, the left inferior parietal lobule, and the precuneus [68, 69]. These cortical areas are similar to those that might be important for generating the P300 event-related potential component that has also been reported as a possible predictor of psychosis [70].

Other Biomarkers

Studies examining biomarkers such as blood biomarkers, neuroinflammation, and stress hormones are relatively few. These have recently been reviewed in Riecher-Rossler and Studerus [38•]. In summary, there is early evidence that elevated baseline plasma levels of particular inflammation markers, oxidative stress, and dysregulation of the hypothalamic-pituitary-adrenal axis might be associated with transition to psychosis. Furthermore, although CHR individuals may have elevated cortisol, it does not appear to be predictive of transition. Finally, there is very early evidence implicating prolactin and the hypothalamic-pituitary-gonadal axis [71].

A summary of the considered individual predictors is presented in Table 1.

Table 1 Summary of individual predictors

Factors that have been considered possible predictors of psychosis	Amount of available research	Research outcome supporting prediction
Migration, ethnicity, perceived discrimination	Very few studies	Minimal
Urbanicity	Very few studies	None
Trauma	Few studies	Minimal but only for sexual abuse
Cannabis	Moderate number of studies	Mixed results, but a few studies suggest a dose-response, i.e., having a DSM diagnosis may be predictive
Cognition	High number of studies	There is support for cognition as a predictor, but there is limited evidence to support specific cognitive domains.
Social cognition	Low number of studies	Unlikely
Functioning	High number of studies	Social functioning, and a decline over time in social functioning are strong predictors. Role functioning unlikely to predict. Mixed results for premorbid functioning.
Imaging	High number of studies	Changes in brain structure especially increased rate of loss of gray matter may predict. Changes in thalamic connectivity may also be related to transition
Neurophysiology	Moderate number of studies	Some are possible
Blood biomarkers, neuroinflammation, stress hormones	Very few but this is the newest area to be addressed in the literature.	Possibly elevated plasma levels of certain inflammation markers, oxidative stress and dysregulation of the hypothalamic-pituitary-adrenal axis might be associated with transition.

Models of Prediction

More recently, studies have focused on examining several variables to develop prediction models. One study [44] developed what they considered a practical and clinically useful model to predict the risk of psychosis based only on clinical characteristics from the SIPS and demographics. The concordance index was 0.73 using a least absolute shrinkage and selection operator (LASSO) logistic fitting procedure. Predictors included unusual thought content, disorganized communication, and visual perceptual abnormalities plus violent behavior and ideation. As reported above, the most commonly occurring predictors tend to be poor social functioning and certain cognitive domains. Thus, adding cognition and social functioning to APS may be one way to increase predictive value. Hengartner and colleagues [46] demonstrated that using both continuous ratings on APS and verbal memory provided improved prognostic accuracy including an area under the curve (AUC) of 0.85, a sensitivity of 0.86, specificity of 0.85, and a PPV of 0.54. Ising and colleagues [72] showed that a model that included negative symptoms (subjective complaints of poor motor function, flat affect), social functioning, and distress associated with suspiciousness had a PPV of 80%, while Meltzer [30] demonstrated that a combination of positive and negative symptoms in combination with IQ were the best predictors of transition to psychosis.

However, there has been little attempt to replicate algorithms. A recent study by Cornblatt et al. [52] reported that for youth who met CHR criteria based on APS, high ratings on disorganized communication and suspiciousness, poor verbal memory, and a decline in social functioning were the best predictors of later transition to a full-blown psychotic illness. This model (the Recognition and Prevention (RAP) model) was then tested with the Prospective Prediction of Psychosis (PREDICT) sample [27•] but unfortunately did not perform well. However, when other variables from the PREDICT sample were used to examine predictors of transition to psychosis, unusual thought content, disorganized communication, baseline social functioning, verbal fluency and memory, processing speed, and age were significant. Interestingly, both models did support disorganized communication, poor social functioning, and verbal memory as predictors of transition [27•].

One of the largest CHR projects is the North American Prodrome Longitudinal Study (NAPLS). This group developed an individualized risk calculator that is comparable in accuracy with those used for cancer and cardiovascular disease [73•]. The predictors used in the calculator were limited to those that were supported by earlier studies and were clinical variables that could be readily accessible in a clinical setting. Higher levels of unusual thought content and suspiciousness, an increased decline in social functioning, poorer verbal learning, memory and speed of processing, and younger age all

contributed to the individual risk of transitioning to psychosis. Interestingly, stressful life events, trauma, and a family history of schizophrenia were not significant predictors. This model had a concordance index of 0.71 [73•]. A further study with a different sample provided external validation of the calculator [54•]. This study demonstrated an external validation model demonstrating good discrimination with an AUC of 79%, a sensitivity of 91%, and a specificity of 37% compared with 94.1% and 23.6% in the NAPLS sample. The calculator is available as a web-based tool (http://riskcalc.org:3838/napls/). However, it must be noted that this risk calculator is only valid for predicting psychosis risk in those who meet criteria for being at CHR based on the SIPS. Since the SIPS require trained raters, it may be that this risk calculator will be of best use in research including clinical trials.

Methodological Issues

There are methodological issues in many of the prediction studies described in this review. Often, different studies use different methods of ascertainment which can impact transition [74], or different criteria for CHR are used and different assessment batteries. Sample sizes tended to be small and if studies are amalgamated, then there are issues with the use of different measures. There are clear guidelines with respect to sample size and the number of predictors being considered [75] and thus, studies with smaller samples run the risk that the prediction model may possibly be overfitting and then not performing well in independent data sets. The problem with overfitting can be made worse if data-driven variable selection methods (e.g., univariate tests and/or stepwise variable selection) are used [38•, 76]. Both internal and external validation methods of a prediction model should be conducted, although is rarely done [27•, 54•]. However, differences in inclusion and transition criteria and test batteries make external validation difficult.

However, some of these issues are beginning to be addressed in the literature. Studerus et al. [76] suggest one good approach is to rely first on external knowledge for selecting candidate predictors, that is, selecting variables based on the literature versus using variables that were part of the study's battery. Secondly, to use more recent statistical regression methods that perform variable selection and regularization to enhance prediction accuracy such as the LASSO, ridge regression, or elastic net techniques. These methods have the advantage that they not only perform shrinkage of regression coefficients but also the variable selection that is often more accurate and interpretable than achieved estimates produced by univariate or stepwise methods.

Most of the prediction algorithms described in this review only employed baseline predictors, that is, data collected at the baseline assessment even though longitudinal data may be available. Dynamic prediction which involves longitudinal data collection of the predictors at subsequent assessment(s) has to date, not been used in CHR. Yuen and colleagues [77] used an emerging statistical methodology, joint modeling, to implement dynamic prediction of transition to psychosis [78, 79]. In this paper [77], compared with the conventional approach of using only baseline predictors, a dynamic prediction approach incorporating time-dependent predictors jointly modeled with a survival analysis (time to transition to psychosis) resulted in significantly better sensitivity, specificity, and likelihood ratios, and thus, a better method for prediction of transition to psychosis in CHR.

Conclusion

We have presented recent research examining predictors of transition to psychosis for those who are already deemed to be at risk. In general, from this and other reviews [38•], the prediction of psychosis is possible. Models that include several different variables appear to offer improved prediction. Research reviewed here supports an integrated model including symptoms, social functioning, and cognition variables, thus achieving better predictive performance compared with a model based only on clinical variables. It is possible that prediction will be further improved by adding not just other clinical variables but also domains that might contribute to a greater understanding of the interaction between clinical, environmental, and neurobiological factors [38•]. These include neuroimaging, neurophysiology, and blood biomarkers.

Several methodological issues have been reviewed here and supported by the recent meta-analysis by Studerus and colleagues [80•]. Thus, future goals should be to continue to increase the quality of prediction by utilizing multivariable models and advanced statistical techniques. In addition, improved standardization of ascertainment and assessment of CHR individuals occurring through ongoing research in large consortiums such as NAPLS [81], European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) [82], PSYSCAN (https://www.psyscan.eu/), and Promoting Resilience Outcome and Novel Integrated Approaches to psychosis and depression (PRONIA) (https://www.pronia.eu/) will lead to further improvement of prediction in this field. In fact, a very recent project, the National Institute of Mental Health's Harmonization of At-Risk Multisite Observational Networks for Youth (HARMONY), which is a consortium of several of the above consortiums, will allow cross-validation of predictive data analytic methods. Finally, what will need to be addressed is the use of prediction models that will serve clinicians versus prediction models that are used in research often to further understand mechanisms for transition to psychosis in CHR.

Acknowledgments Preparation of this article was supported by National Institute of Mental Health Grant MH081984 to Jean Addington. Paul Metzak and Olga Santesteban-Echarri are supported by Canadian Institutes of Health Research post-doctoral scholarships.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines). This article does not contain any studies with animal subjects performed by any of the authors.

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