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Checking the predictive accuracy of basic symptoms against ultra high-risk criteria and testing of a multivariable prediction model: Evidence from a prospective three-year observational study of persons at clinical high-risk for psychosis

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ABSTRACT

Background: The aim of this study was to critically examine the prognostic validity of various clinical high-risk (CHR) criteria alone and in combination with additional clinical characteristics.
Methods: A total of 188 CHR positive persons from the region of Zurich, Switzerland (mean age 20.5 years; 60.2% male), meeting ultra high-risk (UHR) and/or basic symptoms (BS) criteria, were followed over three years. The test battery included the Structured Interview for Prodromal Syndromes (SIPS), verbal IQ and many other screening tools. Conversion to psychosis was defined according to ICD-10 criteria for schizophrenia (F20) or brief psychotic disorder (F23).
Results: Altogether $n = 24$ persons developed manifest psychosis within three years and according to Kaplan–Meier survival analysis, the projected conversion rate was 17.5%. The predictive accuracy of UHR was statistically significant but poor (area under the curve [AUC] = 0.65, $P < .05$), whereas BS did not predict psychosis beyond mere chance (AUC = 0.52, $P = .730$). Sensitivity and specificity were 0.83 and 0.47 for UHR, and 0.96 and 0.09 for BS. UHR plus BS achieved an AUC = 0.66, with sensitivity and specificity of 0.75 and 0.56. In comparison, baseline antipsychotic medication yielded a predictive accuracy of AUC = 0.62 (sensitivity = 0.42; specificity = 0.82). A multivariable prediction model comprising continuous measures of positive symptoms and verbal IQ achieved a substantially improved prognostic accuracy (AUC = 0.85; sensitivity = 0.86; specificity = 0.85; positive predictive value = 0.54; negative predictive value = 0.97).
Conclusions: We showed that BS have no predictive accuracy beyond chance, while UHR criteria poorly predict conversion to psychosis. Combining BS with UHR criteria did not improve the predictive accuracy of UHR alone. In contrast, dimensional measures of both positive symptoms and verbal IQ showed excellent prognostic validity. A critical re-thinking of binary at-risk criteria is necessary in order to improve the prognosis of psychotic disorders.

1. Introduction

The clinical high-risk (CHR) state has demonstrated excellent prognostic validity when applied to the help-seeking population seen at specialized high-risk services. In this population, persons who screen positive for CHR have a substantially increased risk of developing manifest psychotic disorders compared to persons who screen negative for CHR. Specifically, Fusar-Poli et al. [1] recently came at a meta-analytic averaged sensitivity for CHR assessments of 96% (excellent), but specificity was only 47% (poor) and therefore in need of improvement. CHR criteria encompass, among others, attenuated psychotic symptoms (APS) and brief limited intermittent psychotic symptoms (BLIPS). Since both APS and

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BLIPS are widely accepted prodromal/at-risk symptoms [2,3], it stringently follows that almost all persons who later develop psychotic disorders show these early signs. Nevertheless, this does not indicate that persons who develop psychosis necessarily show APS and/or BLIPS. Since sensitivity is calculated as the number of true-positives divided by the number of true-positives and false-negatives, sensitivity of CHR is consequently excellent. The CHR screening therefore produces only few false-negatives in help-seeking samples. Because prodromal psychotic symptoms are used to predict psychotic disorders, it further needs to be acknowledged that this approach is at least in part tautological [4–6]. The downside of this liberal and rather circular psychosis prediction is that most help-seeking persons who actually do not develop psychosis were also screened as CHR positive. That is, CHR testing also produces many false-positives, which is why specificity is low, as specificity is calculated as the number of true-negatives divided by the number of true-negative plus false-positive.

Currently the false-positive rate of CHR screenings is about 78% at 1-year follow-up, 71% at 2 years, and 64% at 3 years [7]. This false-positive rate is unacceptably high, given the negative effects of stigma attributed to a diagnosis of schizophrenia [8,9]. It has further been shown that the prognostic validity of CHR is inflated due to opportunistic risk enrichment in CHR samples [10]. In a large and representative sample of secondary mental health care patients ($n = 33{,}820$), screening positive for CHR at intake accounted for only 5.2% of all conversions to psychosis over a mean observation period of 4.4 years [11]. That is, the vast majority of secondary mental health care patients who develop psychosis do not meet the common CHR criteria at baseline. Therefore, and due to its poor specificity, the CHR screening as a stand-alone test will not suffice to provide an accurate prediction of psychosis. Owing to that limitation, various research groups have started to refine the prediction of psychosis by applying additional tests to CHR positive subjects. This work showed that in particular baseline psychotic symptoms and cognitive functioning improve the prognostic validity of CHR criteria substantially [12–15].

As stated by Fusar-Poli and Schultze-Lutter [16], a test should be highly specific when treatments carry the risk of severe side effects and long-term consequences, which is possibly the case when people are diagnosed as CHR positive. The best-validated conversion risk prediction model in CHR positive subjects to date is the NAPLS-2 risk calculator. However, there are some important issues with this model. First, in the NAPLS-2 sample [17], the accuracy of this model was only 71%, which is acceptable, but not excellent. In the external validation sample [18], also from the US, the accuracy was slightly better (79%), but in this sample, none of the included six predictor variables actually reached statistical significance at $P < 0.05$, suggesting that different predictor variables might fit better in this validation sample. Of further concern is whether basic symptoms (BS), which have been introduced as CHR criteria in addition to the more broadly recognised ultra high-risk (UHR) criteria [19], can significantly contribute to an improved psychosis prediction in CHR subjects. A direct comparison of BS and UHR indicated that these alternative criteria did not differ in their predictive value and that a combination of UHR with BS was tentatively superior to UHR alone [15,20]. However, findings are inconclusive and both reports were conducted by the same research group. A direct comparison of UHR and BS criteria thus needs independent cross-validation.

The three main objectives of this exploratory study were hence, firstly, to estimate the conversion rate in this CHR positive sample, secondly, to compare the prognostic validity a various CHR criteria, including specifically UHR and BS, and thirdly, to test whether cost-efficient psychiatric assessment instruments could provide an optimized risk assessment with incremental prognostic validity over the established CHR criteria.

2. Material and methods

2.1. Participants and procedure

The "Early Recognition of High Risk of Bipolar Disorder and Psychosis" project is a part of the "The Zurich Program for Sustainable Development of Mental Health Services" (ZInEP) at the University Hospital of Psychiatry Zurich (www.zinep.ch/fez). At the beginning, an information campaign was launched in newspapers, magazines, brochures and flyers to raise awareness on early recognition of psychotic and bipolar disorders within the general public and among healthcare professionals. The majority of subjects were referred to the early recognition centre through mental health professionals, counselling services and general practitioners. There was also the possibility for participants or worried relatives to directly schedule a consultation through the ZInEP-website or helpline. All interviews and clinical assessments were carried out by trained psychiatrists and psychologists. For a detailed account of the study design, see Theodoridou et al. [21]. The study was approved by the ethics committee of the canton of Zurich and was conducted in accordance with the Declaration of Helsinki.

Participants were assigned to BS and UHR groups depending on the results of their psychopathological assessment, though note that these criteria were not mutually exclusive and often coincided. The BS group included participants fulfilling cognitive perceptive basic symptoms (COPER) or cognitive disturbances (COGDIS) criteria as assessed by the Schizophrenia Proneness Interview, Adult version (SPI-A) [22] or child and youth version (SPI-CY) [23]; whereas in the UHR group, participants fulfilled attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) or genetic risk and functional deterioration (GRD) assessed by the Structured Interview for Prodromal Syndromes (SIPS) [24]. The main outcome measure was a diagnosis of schizophrenia (F20) or brief psychotic disorder (F23) according to a thorough clinical evaluation according to ICD-10 criteria [25]. Such a stringent definition of psychosis is necessary to avoid false transitions and inflated conversion rates [26], which in turn undermine the prognostic validity of CHR assessments.

A total of 305 help-seeking persons were screened during a 28-month recruitment period (April 2010–July 2012). Out of these, 273 individuals (89.5%) were eligible for the study and gave written informed consent. For participants under the age of 18, additional parental written consent was required. Participants were excluded from the study upon fulfilling one of the following criteria:

- age under 13 or above 35 years;
- past or present manifest schizophrenic psychosis;
- current substance dependency disorder;
- drug induced or organic psychosis;
- inability to give informed consent;
- low intellectual abilities (IQ < 80).

Before completion of baseline assessments, 52 persons discontinued the study or withdrew their consent, which reduced the sample to 221 persons (72.5% of all participants initially screened for eligibility). For the present study, we focused exclusively on BS and UHR subjects, leading to a final sample size of $n = 188$.

2.2. Instruments and measures

The SIPS [24] is a structured diagnostic interview to diagnose the three risk syndromes APS, BLIPS and GRD. It also consists of a 19 items rating scale to assess the severity of psychotic symptoms.