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Course of psychotic symptoms, depression and global functioning in persons at clinical high risk of psychosis: Results of a longitudinal observation study over three years focusing on both converters and non-converters

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ABSTRACT

The aim of this study was to test the validity of the CHR state by focusing on the course of psychosis spectrum symptoms, depression and global functioning in converters and non-converters. A total of 188 CHR-positive subjects (60.2% men) aged between 13 and 35 years (mean = 20.5) at study outset were assessed five times (t0-t4) over a total observation period of 36 months. Conversion to manifest psychosis was defined according to ICD-10 criteria for schizophrenia (F20) or brief psychotic disorder (F23). Measures of positive and negative symptoms were assessed with the Structured Interview for Prodromal Syndromes (SIPS), depression with the Calgary Depression Scale (CDS), and global functioning with the Global Assessment of Functioning Scale (GAF). Converters scored higher over time on all SIPS scales apart from grandiosity (Cohen's d: 0.5–0.7; all $p < 0.001$), higher on the CDS ($d = 0.43$, $p = 0.001$) and lower on the GAF ($d = 0.69$, $p < 0.001$) than did non-converters. Positive and negative symptoms as well as depression were most severe at study outset (t0) and then declined sharply following a linear function over the three-year observation period (t1-t4) across groups (all linear contrasts $p < 0.001$). In conclusion, converters showed significantly more psychopathological symptoms and poorer functioning before crossing the diagnostic threshold for manifest psychosis. CHR-subjects who convert to manifest psychosis during follow-up appear to be recovering from illness rather than becoming ill. Major issues involve the poor discrimination of CHR state and psychosis as well as the dichotomous definition of both at-risk and disease states. Further examination in other CHR-samples is warranted.

1. Introduction

The clinical high-risk (CHR) state as a means to screen vulnerable persons at increased risk for manifest psychosis is now an established feature of modern evidence-based medicine. Thus far, most work has centred on the predictive validity of CHR criteria, related brain biomarkers and on estimates of conversion rates (for reviews see: Addington and Heinssen, 2012; Cannon, 2016; Fusar-Poli et al., 2013; Klosterkotter et al., 2011). These reviews concluded that the CHR approach is a promising prognostic tool aimed at detecting early prodromal signs in order to prevent onset of first episode psychosis. However, CHR screening in its present form has also been criticised on various grounds (Fusar-Poli et al., 2014; McGorry and Nelson, 2016; van Os and Murray, 2013). Critical issues particularly involve the discriminant and prognostic validity of CHR screening.

For instance, a study by Lin et al. (2011) over a mean observation period of 7.3 years found that among participants with the poorest functional outcome only 49% were converters. The remaining 51% of these severely impaired persons were thus non-converters. Ziermans et al. (2011) showed that youths meeting ultrahigh-risk (UHR) criteria were at least three times more likely to remit from their CHR status than to develop psychosis during a two-year follow-up. In addition, Schlosser et al. (2012) showed a conversion rate of 30% and a rate of 66% for symptomatic remission or functional recovery over a 2-year observation period, while Velthorst et al. (2011) reported a conversion rate of 26% contrasted with a rate of 56% for full remission over a

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three-year period. These findings indicate that full remission and recovery is the more likely outcome in CHR-positive subjects than a conversion to psychosis. Accordingly, over a three-year follow-up period the false-positive rate of psychosis based on a CHR-positive screening was estimated at 64%, suggesting that approximately two-thirds of CHR-positive subjects do not develop psychosis even over an extended timespan (Fusar-Poli et al., 2012). Although low conversion rates do not necessarily imply poor construct validity, they could nevertheless compromise the cost-benefit ratio of CHR screening and hence its public health significance. Moreover, a screening test's high false-positive rate compromises clinical utility when treatments carry the risk of severe side-effects and long-term consequences (Fusar-Poli and Schultze-Lutter, 2016). For instance, it is not clear whether mammography screening for breast cancer does more harm than good, as the ratio of positive (life prolonged) to negative consequences (unnecessary lumpectomy or mastectomy) is negative (Gotzsche and Nielsen, 2011).

To better gauge the utility (or possible risk) of CHR screening, it is necessary to focus on the course of symptoms in both converters and non-converters, as only a direct comparison allows for estimating what is actually at stake (hence, contrasting false-positive with true-positive diagnoses). Addington et al. (2011) examined the course of psychotic syndromes for non-converters over a 30-month follow-up period, but they did not contrast these symptom trajectories with the clinical outcome for converters. Concerning the discriminant validity of CHR screening, it has further been suggested that many conversions could be trivial and clinically irrelevant, which typically occurs when criteria for psychosis are liberal or arbitrary (Fusar-Poli et al., 2014; Yung et al., 2010). It has also been stressed that some persons assumed to be CHR are in fact already suffering some kind of first psychosis episode (Fusar-Poli et al., 2014; McGorry and Nelson, 2016). That is, specifically within converters there is possibly no clear delineation between the at-risk state and the onset of manifest psychosis. However, one can only critically address such questions when the outcomes of interest comprise the course of continuous measures of symptom severity rather than a rough distinction between psychotic and non-psychotic. To the best of our knowledge, no such test has been provided to date.

This is the first study, therefore, to focus on the course of psychotic symptoms, depression and global functioning over a three-year observation period in both converters and non-converters. The main objective was to examine whether symptom trajectories could provide evidence for discriminant validity, firstly, between converters and non-converters, and secondly, between CHR-state and manifest psychosis specifically within converters.

2. Methods

2.1. Participants and procedure

The "Early Recognition of High Risk of Bipolar Disorder and Psychosis" project is part of "The Zurich Program for Sustainable Development of Mental Health Services" (ZInEP) at the University Hospital of Psychiatry, Zurich. An information-campaign was launched in newspapers, magazines, brochures and flyers to raise awareness of 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 an opportunity 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. (2014). A total of 305 persons were screened during a 28-month recruitment period (April 2010–July 2012). 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 for fulfilling one of the following criteria: (a) age under 13 or above 35 years, (b) past or present manifest schizophrenic psychosis or bipolar disorder, (c) current substance dependency disorder, (d) drug induced or organic psychosis, (e) inability to give informed consent, (d) 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 subjects meeting basic symptom (BS) or UHR criteria, excluding participants at risk of bipolar disorder, which led to a final sample size of $n = 188$. At-risk bipolar was defined as reporting subjective distress and affective symptoms, particularly manic symptoms based on the Hypomania Checklist 32 (HCL-32; Angst et al., 2005), in the absence of BS or UHR criteria. The number of participants at each follow-up and the attrition rate (in brackets) was as follows: 148 (21.3%) at the 6-month (t1), 117 (37.8%) at the 12-month (t2), 92 (51.1%) at the 24-month (t3), and 60 (68.1%) at the 36-month follow-up (t4). In most cases dropouts were due to refusal to participate in the study, but some were also lost to follow-up due to non-response after contacting. Exact numbers cannot be given due to missing information in various participants. The study was approved by the ethics committee of the canton of Zurich and was conducted in accordance with the declaration of Helsinki of the World Medical Association.

2.2. Instruments and measures

Participants were appointed to BS and/or UHR groups for psychosis, depending on the results of their psychopathological assessment. The BS group included participants fulfilling Cognitive Perceptive Basic Symptoms (COPER) or Cognitive Disturbances (COGDIS) criteria; whereas in the UHR group, participants fulfilled criteria for either Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), or genetic risk and functional deterioration (GRD). Conversion to manifest psychosis was assessed with a diagnosis of schizophrenia (F20) or brief psychotic disorder (F23) after a thorough clinical evaluation according to ICD-10 criteria (World Health Organization, 1992). A stringent definition of psychosis was chosen to avoid false transitions and inflated conversion rates (Yung et al., 2010), which undermine the prognostic validity of CHR assessments. Conversion to psychosis was additionally assessed according to criteria based on the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002) and compared to the ICD-10 diagnoses. Individuals who converted according to SIPS fully matched with conversions based on F20/F23 diagnosis, except for one additional conversion based on the SIPS definition that was not depicted based on ICD-10 F20 or F23.

COPER and COGDIS were assessed either with the Schizophrenia Proneness Interview, Adult version (SPI-A; Schultze-Lutter et al., 2007) or child and youth version (SPI-CY; Schultze-Lutter and Koch, 2010). The UHR criteria listed above as well as positive and negative psychotic symptoms and the global assessment of functioning (GAF) score were assessed with the SIPS (Miller et al., 2002). Psychotic symptoms were additionally assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Depression was measured with the Calgary Depression Scale (CDS), which was specifically developed to assess depression in persons with schizophrenia (Addington et al., 1992). Comorbid psychiatric screening-diagnoses were assessed with the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) in adults, whereas for children and youths we applied the MINI-KID (Sheehan et al., 2010).

2.3. Statistical analysis

The longitudinal associations between conversion and repeated measures of psychotic symptoms and functioning were estimated using generalized estimating equations (GEE). These statistical models

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