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SEMISTRUCTURED INTERVIEW FOR BIPOLAR AT RISK STATES (SIBARS)

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Abstract

The external prognostic accuracy of Bipolar At Risk (BAR) criteria is undetermined and no psychometric tools are available to measure them. We present here three studies that overcome these limitations. Study 1 and 2 investigated the prognostic accuracy (Harrell's C) of the original BAR and revised Bipolar At Risk States (BARS) criteria respectively for the prediction of bipolar disorders, using a retrospective cohort of individuals at Clinical High Risk for Psychosis (CHR-P). Study 3 validated externally the prognostic accuracy of a newly developed Semistructured Interview of At Risk Bipolar States (SIBARS) in an independent prospective CHR-P cohort. In study 1 ($n=205$), those meeting BAR criteria had an increased risk of developing bipolar disorders ($HR=5.30$) relative to those not meeting them, but the prognostic accuracy was poor (Harrell's $C=0.659$). In study 2 ($n=205$), those meeting the refined BARS criteria had a higher risk of developing bipolar disorders than those not meeting them ($HR=12.364$), with an adequate prognostic accuracy (Harrell's $C=0.777$). Study 3 ($n=71$) confirmed that SIBARS criteria had an adequate prognostic accuracy (Harrell's $C=0.742$) and clinical utility. Overall, these findings suggest that the SIBARS could be used for the detection of individuals at risk of developing bipolar disorders in CHR-P services.

1. INTRODUCTION

Early interventions in adolescence or young adulthood (Paus et al., 2008) have opened unprecedented opportunities for ameliorating the outcomes of serious mental disorders (McGorry, 2015). However, intervening in youths at the time of the first presentation of established mental disorders is associated with limited benefits. For example, early interventions at the time of a first episode of psychosis have no benefits on reducing the risk of relapse (Fusar-Poli et al., 2017b) or on shortening the duration of untreated psychosis (Oliver et al., 2017). Therefore it seems crucial to implement preventative strategies in youths who are at risk of developing mental disorders (Fusar-Poli, 2017). The model which has received the largest empirical support has validated indicated preventative interventions in individuals at Clinical High Risk of developing Psychosis (CHR-P hereafter) (Fusar-Poli, 2017). These individuals are detected through established psychometric interviews such as the Comprehensive Assessment of At risk Mental States (CAARMS) which was the first instrument developed to specifically assess the CHR-P group (Yung et al., 2005), and CHR-P services have been implemented worldwide (NICE, 2014; NHS England, 2016). Other semi-structured interviews have been developed and validated to assess CHR-P individuals (for a comparative analysis see (Fusar-Poli et al., 2016c)). Although these interviews have a good prognostic performance for the prediction of psychosis (Fusar-Poli et al., 2015a; Fusar-Poli and Schultze-Lutter, 2016) they can't predict the development of any non-psychotic emergent mental disorder (Webb et al., 2015; Fusar-Poli et al., 2017d). For example, CHR-P criteria are not associated with an increased risk of developing new bipolar disorders (HR=1.689, 95%CI 0.327 - 8.719 (Fusar-Poli et al., 2017d)). Therefore, new criteria and assessment instruments that can be used in CHR-P samples to detect youths at risk of developing bipolar disorders (Fusar-Poli et al., 2017d) are required. Bipolar disorder is a recurrent disorder with a lifetime prevalence between 0.1 and 4.4 percent (Merikangas et al., 2011). Its chronic course is associated with excess morbidity and mortality rates (Charlson et al., 2015), making bipolar disorder one of the main causes of disability among young and working-age people (Charlson et al., 2015). Early intervention strategies may help to modify the outcome of the illness, as early phases of bipolar disorders may be more responsive to treatment. Retrospective studies of adults with bipolar disorder indicate an onset of mood symptoms during childhood or adolescence, usually before the age of 21

(Berk et al., 2014). The progressive nature (Kapczinski et al., 2017) of bipolar disorder supports the existence of milder phases of the condition prior to its classic presentation, which early detection efforts may be able to identify. A recent review on the results of longitudinal studies assessing potential predictors of development of bipolar disorder (Vieta et al., 2018) concluded that parental bipolar disorder, especially early-onset (e.g. <21 years old) parental bipolar disorder (Hafeman et al., 2016), is the most important single risk factor for developing bipolar disorder. In addition, sub-syndromal manic symptoms, which is the most consistent prodromal factor, and ongoing mood lability or irritability, anxiety, and depression, also increase the likelihood that a young person will develop bipolar disorder (Egeland et al., 2012). In line with these observations, preliminary Bipolar At Risk (BAR) criteria for assessing those who may be at risk of developing the disorder have been suggested (Bechdolf et al., 2010) (Table 1, left column). However, the use of these criteria in standard routine to assess youths seeking help at CHR-P services is currently limited by the lack of external validation in independent CHR-P samples, and of a proper psychometric instrument to collect and rate these features.

The current study tackles these limitations by conducting three experiments, with the following aims: (i) to externally replicate the validity of the BAR criteria in CHR-P samples, to (ii) refine these criteria accounting for an expanded at risk phenotype (the Bipolar At Risk State, BARS), to (iii) validate the BARS criteria ascertained through a newly developed psychometric instrument that can be used to detect individuals at risk of developing bipolar disorders among those accessing CHR-P services.

2 METHODS

The current study consists of three experiments. In the first experiment (study 1) we have validated the BAR criteria, measured clinically, in a retrospective cohort of individuals under the care of a CHR-P clinic. In the second experiment (study 2) we have refined the BAR criteria by adding further symptoms which previous studies have identified as potential sub-threshold features of bipolar disorders (see 2.2 Data collection) and validated these new criteria (BARS) in the same cohort used in study 1. In the third experiment (study 3) we developed a new semi-structured instrument for the

assessment of the BARS criteria from study 2 and validated it in another independent prospective cohort of individuals accessing CHR-P services.

2.1 Sample

Ethical permission for study 1 and 2 participants to be traced, contacted and interviewed was given by the South London and Maudsley NHS Mental Health Trust (SLaM) in Dec 2010. Study 1 and 2 were based on a retrospective cohort including all of the OASIS (“Outreach and Support in South-London”) patients considered to be at CHR-P after receiving a clinical assessment between 2001 and 2011. The details of the OASIS service, including clinical care offered and pathways to care, have been presented in separated manuscripts (Fusar-Poli et al., 2013; Fusar-Poli et al., 2015b; Fusar-Poli et al., 2016e). In brief, people are offered treatment at OASIS if, following assessment with the CAARMS (Yung et al., 2005) CHR-P criteria are met. Therefore, all individuals included in study 1 and 2 met CHR-P criteria (CHR-P+ hereafter). Study 3 was approved in Sept 2017 as an audit study by the SLaM. It consisted of a new independent prospective cohort, which included patients undergoing a CHR-P assessment again at the OASIS between March 2013 and December 2015. Individuals eligible to enter in study 3 could then receive a designation of being at risk for psychosis (CHR-P+), not at risk for psychosis (CHR-P-) or already affected with an established first episode of psychosis (FEP).

Study 1, 2 and 3 were all conducted in the same group of patients accessing the OASIS. This is a clinical service located in Lambeth, Southwark, Croydon and Lewisham, South London, offering treatment to people at UHR between 14 and 35 years of age (Fusar-Poli et al., 2013). The catchment area has a large ethnic minority population and a high incidence of psychosis (Garety and Rigg, 2001). People are offered treatment at OASIS if, following assessment with the Comprehensive Assessment for the At-Risk Mental States (CAARMS (Yung et al., 2005)) by trained interviewers they met one or more of the following criteria, as objectively assessed by the clinicians of the team: a) attenuated (i.e. subthreshold) psychotic symptoms (APS) b) brief limited intermittent psychotic symptoms (a history of one or more episodes of frank psychotic symptoms that resolved spontaneously within 1 week in the past year; BLIPS) or c) a recent decline in function, together with either the presence of

schizotypal personality disorder or a family history of psychosis in a first degree relative (Genetic Risk and Deterioration Syndrome, GRD).

2.2 Data collection

For study 1 and 2, clinical notes of OASIS patients written by psychiatrists responsible for the care of the patients after their first contact (including the baseline CAARMS report) with the patient were reviewed by an experienced clinician (IF) who was blinded to longitudinal outcomes to establish whether (1) BAR criteria (Bechdolf et al., 2010) and (2) the refined criteria (BARS; Table 1) were met. Definition of BAR and BARS criteria was based on an unstructured psychopathological assessment of the clinical records, in line with the previous attempts performed to identify clinically the BAR criteria (Bechdolf et al., 2010). Furthermore, a list of specific exclusion criteria was defined (Table 1). Refinement of BARS criteria with the inclusion of new subgroups was informed by evidence indicating that sub-threshold mixed episodes (Salvatore et al., 2007; Salvatore et al., 2014) and mood swings (Ozgurdal et al., 2009) may represent prodromal features of bipolar disorders.

To ascertain the presence of mood symptoms, both sources (CAARMS and clinical notes) were consulted as, although the CAARMS scale does measure some mood symptoms, its main focus is on the assessment of sub-threshold psychotic symptoms. This procedure ensured that none of the available information on mood symptoms was missed. Information was regarded as insufficient and cases were excluded when neither the baseline CAARMS record nor the clinical notes could be retrieved or when the baseline CAARMS record could not be retrieved and the clinical notes contained no mentioning of mood symptom assessment.

During study 3, the BARS criteria were incorporated into the standard psychometric assessment conducted at the OASIS. This required the development of a new semi-structured psychometric interview complementing the baseline CHR-P assessment, to specifically measure the BARS criteria. The Semi-structured Interview for Bipolar At Risk States (SIBARS) included a combination of several items adapted from well-established rating scales: (CAARMS (Yung et al., 2005); Hypomania Checklist-32 (Angst et al., 2005); Altman Self-Rating Mania Scale (Altman et al., 1997); TEMPS-A questionnaire (Akiskal et al., 2005); QIDS-SR (Rush et al., 2003); Bergen Insomnia Scale (Pallesen et

al., 2008); Idiopathic hypersomnia questionnaire (Vernet et al., 2010)). The SIBARS interview was developed for youths aged 15-35 and comprehended 5 domains: 1. Subthreshold Mania, 2. Depression, 3. Cyclothymic Features, 4. Genetic Risk, 5. Mood Swings. Subthreshold Mania, Depression and Mood Swings are continuous rating scales (that include a severity and frequency anchors), while Cyclothymic Features and Genetic Risk are categorical scales (yes/no). The inclusion of items for the SIBARS was decided by the first and last authors, with revisions made based on feedback from the other co-authors. The original interview is available from the authors upon request. The patients' answers to the SIBARS are then rated according to pre-specified cutoffs and intake criteria that are detailed in Table 2. These cut-offs allow assigning the specific subgroup of the BARS criteria: 1. Subthreshold Mania, 2. Depression+Cyclothymic Features, 3. Depression+Genetic Risk, 4. Cyclothymic Features+Genetic Risk, 5. Subthreshold Mixed Episode, 6. Mood Swings. A restricted pool of experienced clinicians (ADM, MR, MC) underwent a briefing session on the use of the SIBARS and then administered the interview. The scoring of the SIBARS criteria was then discussed under the supervision of a senior clinician (PFP) to reach consensus.

2.3 Measures

2.3.1 Demographic and baseline clinical characteristics

For studies 1-3, demographic variables included age, gender, ethnicity, employment status, accommodation status, while baseline clinical characteristics included CHR-P symptom severity (attenuated positive psychotic symptoms as measured by the CAARMS (Yung et al., 2005)), and functioning (Global Assessment of Functioning GAF (Goldman et al., 1992)). Study 3 additionally included marital status and exposure to medications (antidepressants and mood stabilizers).

2.3.2 Outcomes

The main outcome variable was defined as the onset of a first episode of bipolar disorders, operationalised as in Table 2. For study 1-2 the outcome was measured through face-to-face interviews as well as phone contact with patients, as previously described (Falkenberg et al., 2015), with censoring date to August 1st 2012. For study 3 the outcomes were further assessed through the

local electronic case register. The South London and Maudsley NHS Foundation Trust is paper-free and all clinical notes are recorded on the local electronic case register (Stewart et al., 2009). Conducting follow-up through the electronic case register allowed us to minimise the risk of dropouts. The use of this electronic case register for conducting follow-up studies has already been detailed and validated by our research group in previous publications (Fusar-Poli et al., 2016d; Fusar-Poli et al., 2016e; Fusar-Poli et al., 2017d). Censoring date was on January 1st 2017. To minimise the biases associated with the use of the same scale to measure predictors (BARS+, BARS-) and outcomes (defined as in Table 2), in study 3 we used the ICD-10 diagnoses as gold standard against which to validate the SIBARS operationalization of bipolar disorders. The following ICD-10 diagnoses were considered:

[F30.0] – Hypomania lasting more than > 4days, [F30.1] - Mania without psychotic symptoms, [F30.8] - Other manic episodes, [F30.9] - Manic episode, unspecified, [F31.0] - Bipolar affective disorder, current episode hypomanic, [F31.1] - Bipolar affective disorder, current episode manic without psychotic symptoms, [F31.3] - Bipolar affective disorder, current episode mild or moderate depression, [F31.4] - Bipolar affective disorder, current episode severe depression without psychotic symptoms, [F31.6] - Bipolar affective disorder, current episode mixed, [F31.7] - Bipolar affective disorder, currently in remission, [F31.8] - Other bipolar affective disorders (including Bipolar II disorder), [F31.9] - Bipolar affective disorder, unspecified, [F30.2] - Mania with psychotic symptoms, [F31.2] - Bipolar affective disorder, current episode manic with psychotic symptoms, [F31.5] - Bipolar affective disorder, current episode severe depression with psychotic features.

2.4. Statistical analysis

Demographic and baseline clinical characteristics for the two cohorts (study 1-2 and study 3) were described using mean and SD for continuous variable, absolute and relative frequencies for categorical variables and median and interquartile range for ordinal variables. The association between risk groups and demographic and baseline clinical characteristics was assessed by one-way analysis of variance. Chi-square test and Fisher's Exact Test were employed for categorical variables and Kruskal–Wallis

test by ranks was used for ordinal variables (CAARMS severity of attenuated positive psychotic symptoms).

For all studies (1 to 3), the clinical validity of the BAR/BARS assessment was investigated with Cox proportional hazards models (non-competing risk), evaluating the effects of BAR/BARS designation (BAR+ vs BAR- and BARS+ vs BARS-) on the development of incident bipolar disorders and time to development of these disorders, after checking for proportional hazards assumption (Grambsch and Therneau, 1994). In case of groups with zero events log-rank statistic was rather used. Incident bipolar disorders were defined as the emergence of bipolar disorders (see its operationalization in Table 2) from the aforementioned groups, at any time during the follow-up, when no similar diagnosis was present at baseline. We further described the cumulative incidence of the outcome of interest with Kaplan Meier failure function (1-survival) (Kaplan and Meier, 1958) along with the Greenwood 95% Cis (Greenwood, 1926). Kaplan-Meier point estimates were also reported, truncated when at least ten subjects were still at risk. Prognostic accuracy was investigated through discrimination measures. Discrimination (accurate predictions discriminate between those with and those without the outcome (Steyerberg et al., 2010)) was addressed with Harrell's C-index (Royston and Altman, 2013). Values in the range of 0.9-1 are considered outstanding, between 0.8 and 0.9 excellent, between 0.7 and 0.8 acceptable (Hosmer and Lemeshow, 1999).

Since these measures do not tell us whether the BARS designation would do more good than harm if used in clinical practice (Vickers et al., 2016), we additionally performed net benefit analyses (for conceptual and methodological details see (Vickers et al., 2016)). Such an approach includes an "exchange rate", a clinical judgment of the relative value of benefits (such as preventing psychosis in help-seeking individuals) and harms (such as unnecessary treatment) associated with the DSM-5-APS designation. However, as the answers to these kinds of questions and the exchange rates are subjective, we did not use it but rather plotted the net benefit in a decision curve analysis, as recommended (Vickers et al., 2016). Finally, the inter-rater reliability (IRR) of the SIBARS was explored in a subset of participants ($n=12$) with weighted kappa for ordinal variables, which is similar to the intra class coefficient (ICC) estimated from a two-way random effects ANOVA (Fleiss, 1973).

All analyses were conducted in STATA 14 (STATA Corp., TX, USA).

3. RESULTS

3.1 Samples characteristics

The initial cohort eligible for study 1 and 2 consisted of 290 CHR-P individuals. However, assessment reports of 85 (29.3%) patients could not be retrieved or contained insufficient information to score BAR criteria and were excluded from further analyses (eTable 1). The final database consisted of 205 CHR-P individuals aged 22.58 years (SD 4.69) on average, mostly white (55.9%) males (51.71%), employed or student (52.97%), and living alone (59.76%), with a low functional status (GAF=59.19 SD 10.85, eTable 1). There were no significant differences in terms of sociodemographic measures between the included and excluded individuals, with the exception of gender (eTable 1).

75 individuals undergoing CHR-P assessment were included in the study 3 cohort; they were aged 22.4 (SD 4.50) years on average and they were mostly males (72%) of white ethnicity (33.25%), employed or student (56.76%), single (80.56%), living in family (58.9%), never treated with antidepressants or mood stabilizers (57.14%) and with a low functional level (GAF=55.57, SD=8.59, eTable 2).

3.2 Study 1: BAR criteria in the retrospective CHR-P cohort

There were 32 (15.6%) BAR+ and 173 (84.4%) BAR- cases. There were no significant differences between the BAR+ and BAR- groups with respect to age, gender, ethnicity, accommodation status, functional status, severity of attenuated positive psychotic symptoms but BAR+ were less likely to live alone than the BAR- (eTable 3).

The median follow-up period of the cohort was of 1692 days (range 362-3902). During the follow-up period, 13 individuals developed a bipolar disorder: 5 from the BAR+ and 8 from the BAR- group. The first failure was observed at 695 days and the last one at 3852 days (median 1736 days). Compared to the BAR- those meeting BAR+ criteria were at higher risk of developing bipolar disorders (HR=5.30, SE=3.11, $Z=2.84$, $P=0.004$, 95%CI 1.679 – 16.757). However, discrimination was poor (Harrell's C= 0.659). The cumulative incidence of risk for psychosis for the BAR- was as

follows: 1-year <0.001 (95%CI <0.001-<0.001), 2-year 0.007 (95%CI 0.001-0.046), 3-year 0.02 (95%CI 0.004-0.061), 4-year 0.026 (95%CI 0.001-0.08), 5-year 0.038 (95%CI 0.014-0.101), 6-year 0.059 (0.023-0.147), 7-year 0.132 (95%CI 0.056-0.291), 8-year 0.132 (95%CI 0.056-0.291). The cumulative incidence of risk for psychosis for the BAR+ was as follows: 1-year <0.001 (95%CI <0.001-<0.001), 2-year <0.001 (95%CI <0.001-<0.001), 3-year 0.048 (95%CI 0.007-0.293), 4-year 0.127 (95%CI 0.032-0.436), 4.4-year 0.214 (95%CI 0.07-0.543, there were too few individuals to report reliable point estimates beyond this time point).

3.3 Study 2: BARS criteria in the retrospective CHR-P cohort

There were 41 (20%) BARS+ and 164 (80%) BARS- cases. Individuals in the BARS+ group were younger, with higher functional status and less likely to live alone than those in the BARS- group (eTable 4). There were no other differences in demographic and baseline characteristics (eTable 4).

The mean follow-up period of the cohort has been described above. Among the 13 transitions, 5 were from the BARS- and 8 from the BARS+ group. The IRR for the main BARS outcome was 0.862. Compared to the BARS- those meeting BARS+ criteria were at higher risk of developing bipolar disorders (HR=12.364, SE=7.62, Z=4.08, $P<0.001$, 95%CI 3.694 – 41.379). The discrimination was adequate (Harrell's C= 0.777).

The cumulative incidence of risk for psychosis for the BARS- was as follows: 1-year estimate <0.001 (95%CI <0.001-0.001), 2,3 and 4-year estimates 0.007 (95%CI 0.001-0.049), 5,6-year estimates 0.02 (95%CI 0.005-0.082), 7,8-year estimates 0.095 (95%CI 0.031-0.271) and for the BARS+ 1,2-year estimates <0.001 (95%CI <0.001-0.001), 3-year estimate 0.075 (95%CI 0.019-0.272), 4-year estimate 0.127 (95%CI 0.042-0.350), 4.4-year estimate 0.267 (95%CI 0.115-0.546, there were too few individuals to report reliable point estimates beyond this timepoint).

3.4 Study 3: SIBARS assessment in individuals undergoing CAARMS assessment, prospective cohort.

The median administration time for the SIBARS assessment was 25 minutes (mean=26.31, SD=6.91). The assessment revealed that four individuals were already affected with a first episode of psychosis (FEP) at baseline. These four were then excluded from further analysis. The baseline association

between the outcomes of the CAARMS assessment (CHR-P+, CHR-P-) and the outcomes of the SIBARS assessment (BARS+, BARS-, bipolar disorders) in non-psychotic cases (n=71) was non-significant ($P=0.814$, Table 3). Among those CHR-P+, 22 (49%) were BARS-, 16 (36%) were BARS+, 7 were already affected by bipolar disorders (15%); among those CHR-P- 12 (46%) were BARS-, 11 (42%) BARS+ and 3 were already affected by bipolar disorders (12%) (Table 3). No significant group differences were found between the BARS+, BARS- and bipolar disorder groups regarding demographic and baseline clinical characteristics and previous exposure to antidepressants or mood stabilizers (eTable 5). Mean duration of follow-up was of 531 days (SD: 409.13). Over the course of the follow-up period, 5 individuals developed bipolar disorders, all of them in the BARS+ group. The conversion diagnoses were further confirmed against the ICD-10: 2 patients developed bipolar disorders (F31.2) or mania (F30.2) with psychotic symptoms and 3 patients developed bipolar II disorders (F31.81). The first transition was observed at 147 days and the last one at 1132 days, with a median time to transition of 539 days. The point estimates in the BARS+ group were: at 6 months 0.048 (95%CI 0.007-0.293), at 12 months 0.098 (95%CI 0.025-0.338), at 18 months 0.167 (95%CI 0.056-0.442), at 24 months 0.234 (95%CI 0.094-0.523). The log-rank test confirmed a significant between-group difference ($P<0.05$). The discrimination was adequate (Harrell's C = 0.742).

The decision curve analysis showed that, compared to conducting no tests for bipolar risk (detect none) or considering everyone at risk (detect all), identifying individuals at risk of developing bipolar disorders on the basis of the BARS is associated with significant net benefits for a 0.038 to 0.23 range of threshold probability (individual risk of developing bipolar disorders at 3 years, Figure 3).

4. DISCUSSION

To our best knowledge this is the first study to have extended previous bipolar at-risk research (Bechdolf et al., 2010) in independent samples accessing CHR-P services. Our ultimate overarching aim was to develop a refined set of criteria to be used conjointly with a new psychometric instrument that could complement the current CHR-P interviews. Such an approach is in line with recent efforts aimed at broadening the benefits of preventative intervention to those at risk for multiple outcomes beyond psychosis onset (Fusar-Poli et al., 2017d). The findings of our three experiments taken together concur with the earlier reports indicating that it is clinically feasible to identify bipolar at-risk

individuals within CHR-P services (Bechdolf et al., 2010). Since the CHR-P paradigm has been established worldwide, it may well serve as a viable platform to develop and validate bipolar at-risk detection and interventions. Since our aim was mainly to improve the prediction of bipolar disorders in CHR-P services, prognostic accuracy was selected as the key outcome across the three experiments.

Our first experiment (study 1) represents the first independent validation of the original BAR criteria. In a large retrospective cohort representative of CHR-P samples, we found that individuals meeting the BAR criteria were indistinguishable from those not meeting them on several sociodemographic and clinical characteristics, including attenuated psychotic symptoms. The lack of baseline features distinguishing individuals at risk for bipolar disorders has been previously observed in these samples (Bechdolf et al., 2014). Similarly, the proportion of individuals meeting the BAR criteria is close to that observed in the original report (11% (Bechdolf et al., 2014)). We confirmed that the BAR criteria were associated with an increased risk of developing bipolar disorders ($HR=5.30$). Our study advances knowledge by conducting a longer follow-up compared to the 12-month previously reported (Bechdolf et al., 2014). We found that the between-group differences were significant only in the longer term, after about four years of follow-up, with the BAR+ reaching a 0.127 risk and the BAR- 0.026. Contrary to previous reports (Bechdolf et al., 2014), our results suggest that to detect conversions longer follow-up times may be required for bipolar risk compared to psychosis risk. These findings are of clinical relevance because external replication of BAR criteria in CHR-P samples is problematic, given the profound sampling biases associated with idiosyncratic recruitment strategies that are adopted in CHR-P services (Fusar-Poli et al., 2016e; Fusar-Poli et al., 2016g). Despite these positive results we also reported for the first time the prognostic accuracy of the BAR criteria, which proved to be poor (Harrell's $C=0.659$). This indicated the need for refining them and improving their prognostic accuracy. Therefore, in our second experiment (study 2) we refined the BAR intake criteria including new subgroups (BARS) and rechecked them in the same retrospective cohort. Individuals meeting BARS criteria were typically younger and with a high functional status and had an increased risk of developing bipolar disorders ($HR=12.364$) in the longer term (after 4-years). This was also confirmed by an improved and prognostic accuracy, which was of adequate level (Harrell's $C=0.777$).

The next step was then to implement these criteria into a psychometric questionnaire (the SIBARS) and test their prognostic accuracy prospectively in our third experiment (study 3). The SIBARS interview was feasible in the context of a standard CHR-P assessment, taking about 25' in addition to the standard CAARMS interview. We also found that about one third of CHR-P individuals (36%) tested positive for being at risk of bipolar disorders according to the SIBARS. This indicates that detection of bipolar risk stages within individuals accessing CHR-P services may be important for a substantial proportion of individuals. Transition risks for individuals meeting the baseline SIBARS criteria were already high at 18 months (0.167) and increased at 24 months (0.234). These transition risks are consistent to those previously observed at 12 months (Bechdorf et al., 2014). More importantly, the adequate prognostic accuracy of the SIBARS criteria which was observed in study 2 was then replicated in this independent prospective sample (Harrell's $C = 0.742$). We further showed that the SIBARS criteria are associated with some potential clinical utility for a range of predicted 3-year risk probabilities spanning from 0.038 to 0.23. Although such a range is clinically meaningful, longer follow-ups would be required to better estimate the upper level of this range. These initial results support some practical advantage associated with the use of the SIBARS in clinical research settings. Future research should confirm the possibility to predict outcomes other than psychosis by using the SIBARS interview conjointly with the CAARMS or other CHR-P psychometric tools in individuals accessing early detection services such as the OASIS. This would represent the first step towards the implementation of preventive interventions for psychosis. Effective treatments are not available yet but some trials in individuals at risk for bipolar disorders are underway (Pfennig et al., 2014).

There are some important limitations. First, since study 1 and 2 were based on a retrospective cohort, the BAR designation was assigned on the basis of information available in the clinical records, as for the original BAR studies (Bechdorf et al., 2010). To mitigate for major inaccuracies, we have excluded cases where the quality of information available was not sufficient to check the BAR criteria. Second, the review of case reports in studies 1 and 2 was performed by a single rater instead of having two

independent raters perform the reviews and then reach an agreement. Third, study 3 was based on a relatively small sample, with a few events (transitions to bipolar disorders) only. As a consequence, the prognostic performance of the SIBARS should be considered as a preliminary finding in need of further independent validation. However, our sample size is similar to that previously used to develop the BAR criteria (Bechdolf et al., 2010). Similarly, our number of events ($n=5$) matches that reported by the original BAR study ($n=5$) (Bechdolf et al., 2010). A large prospective study recruiting 1500 subjects to further evaluate these criteria is currently underway (www.bipolife.org) in Germany. This multicentre, prospective, naturalistic cohort study with a follow-up of ≥ 24 months per individual studies three risk groups: (a) Help-seeking youth and young adults aged 15–35 without a diagnosis of bipolar disorder but with at least one proposed risk factor (e.g. family history of bipolar disorder) consulting early detection centers and specialized services; (b) In-/outpatients aged 15–35 with a depressive episode; (c) In-/outpatients aged 15–35 with ADHD. Given that subclinical manic symptoms are relatively common in the general population and may fluctuate over time (Kaymaz et al., 2007), additional objective indicators of imminent mania such as sleep and circadian alteration (measured for example by sleep actigraphy (Melo et al., 2016)) or increases in activity levels (which may be tracked by smartphone applications (Kessing et al., 2017)) may also help to better characterize the bipolar risk-state. Fourth, the psychometric properties of the SIBARS should be fully addressed through detailed reliability (internal consistency) and validity (construct validity, concurrent validity) measures beyond IRR and predictive validity, which are reported here. Fifth, our findings cannot be generalised to individuals at risk for bipolar disorders recruited outside individuals accessing CHR-P services. This means that the SIBARS is affected by the same conceptual limitations that have recently been observed for the CHR-P paradigm. These include substantial and idiosyncratic risk enrichment during the recruitment phases of individuals undergoing a CHR-P assessment (Fusar-Poli et al., 2015a; Fusar-Poli et al., 2016a; Fusar-Poli et al., 2016e; Fusar-Poli and Schultze-Lutter, 2016; Fusar-Poli et al., 2016f; Fusar-Poli et al., 2016g), clinical heterogeneity of the CHR-P subgroups (Fusar-Poli et al., 2016a; Fusar-Poli et al., 2016b; Fusar-Poli et al., 2017a), poor penetrance of the detection strategies for identifying individuals at risk (Fusar-Poli et al., 2017c) and low specificity of current prognostic tools (Oliver et al., 2018). These problems have been detailed in specific publications by our research

team (Fusar-Poli, 2017, 2018). Overall, these limitations indicate that additional studies are required to investigate the predictive validity of SIBARS criteria in the whole secondary and primary mental health care as well as in the general youth population (e.g. schools and colleges).

5. CONCLUSIONS

This study validates the proposed BAR criteria, refines them into BARS criteria and provides preliminary prognostic accuracy data for the use of a newly developed semi-structured interview (SIBARS) for the detection of individuals at risk of developing bipolar disorders in CHR-P services.

Table 1 Original Bipolar At Risk criteria and refined Bipolar At Risk State criteria

BAR criteria (Bechdolf et al., 2010)	BARS criteria
<p><i>Inclusion criteria:</i> Aged between 15 and 25 years and fulfill criteria of at least one of three groups within the last 12 months:</p> <p><u>Group 1: Sub-threshold mania:</u> For at least 2 consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood + at least two criteria from the list: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thoughts are racing, (5) distractibility, (6) increased goal-directed activity (either socially, at work, or sexually) or psychomotor agitation.</p> <p><u>Group 2: Depression + Cyclothymic features</u></p> <p>Depression For at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation + Cyclothymic features Numerous episodes with sub-threshold manic symptoms not meeting group 1 criteria and numerous episodes with depressive symptoms. E g. sub-threshold mania as defined in group 1 only for 4 h within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria</p> <p><u>Group 3: Depression + Genetic risk</u> Depression Defined as in the group 2 + Genetic Risk: First degree relative with bipolar disorder</p>	<p><i>Inclusion criteria:</i> Aged between 15 and 35 and fulfill criteria of at least one of six groups within the last 12 months:</p> <p><u>Group 1: Sub-threshold mania:</u> For at least 2 consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood + at least two criteria from the list: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thoughts are racing, (5) distractibility, (6) increased goal-directed activity (either socially, at work, or sexually) or psychomotor agitation.</p> <p><u>Group 2: Depression + Cyclothymic features</u></p> <p>Depression For at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation + Cyclothymic features Numerous episodes with sub-threshold manic symptoms not meeting group 1 criteria and numerous episodes with depressive symptoms. E g. sub-threshold mania as defined in group 1 only for 4 h within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria</p> <p><u>Group 3: Depression + Genetic risk</u> Depression Defined as in the group 2 + Genetic Risk: First degree relative with bipolar disorder</p> <p><u>Group 4: Cyclothymic features and Genetic risk</u></p> <p>Cyclothymic features Numerous episodes with sub-threshold manic symptoms not meeting group 1 criteria and numerous episodes with depressive symptoms. E g. sub-threshold mania as defined in group 1 only for 4 h within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria + Genetic Risk: First degree relative with bipolar disorder</p> <p><u>Group 5: Sub-threshold mixed Episode</u></p>

<p>Exclusion criteria:</p> <p>(a) Past history of a treated or untreated manic episode of 4 days duration or longer.</p> <p>(b) Past history of a treated or untreated psychosis of 7 days duration or longer.</p> <p>(c) Past treatment with a mood stabilizer for longer than 6 weeks.</p> <p>(d) Past treatment with an antipsychotic for 3 weeks (equals 15 mg per week of haloperidol or equivalent).</p> <p>(e) Evidence from medical records for an IQ below the normal range.</p> <p>(f) Organic brain disorder.</p> <p>Conversion criteria:</p> <p>Hypomania/mania related additions or alterations to existing treatments, or initiation of new treatment (psychopharmacological medication, admission) by the treating physician</p>	<p>Sub-threshold mania AND depressed mood nearly every day but less than 5 consecutive days</p> <p><u>Group 6: Mood swings</u></p> <p>Recent onset mood instability</p> <p>Exclusion criteria:</p> <p>(a) Past history of a treated or untreated CAARMS-defined psychosis of 7 days duration or longer.</p> <p>(b) Past treatment with a mood stabilizer for longer than 6 weeks.</p> <p>(c) Past treatment with an antipsychotic for 3 weeks.</p> <p>(d) Evidence from medical records for an IQ below the normal range.</p> <p>(e) Organic brain disorder.</p> <p>(f) Past history of bipolar disorders (including bipolar-II-disorder and hypomania lasting more than 4 days)</p> <p>Transition criteria:</p> <p>Development of any bipolar disorder –defined in table 2-</p>
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Table 2. Intake criteria of the Semistructured Interview for Bipolar At Risk States, SIBARS.

Age 15-35, not meeting any of the exclusion criteria and meeting at least one of the following:
GROUP 1: SUB THRESHOLD MANIA <i>Subthreshold intensity of the Subthreshold Mania scale (SIBARS 1):</i> Severity score of 3 – 4 PLUS Frequency score of 3 – 6 <i>Subthreshold frequency of the Subthreshold Mania scale (SIBARS 1):</i> Severity score of 5 - 6 PLUS Frequency score of ≤ 3 PLUS Symptoms should not have been present for more than 4 days
Group 2: DEPRESSION+CYCLOTHYMIC FEATURES <u>Depression:</u> <i>Subthreshold intensity of the Depression scale (SIBARS 2):</i> Severity score of 3 – 5 PLUS Frequency score of 3 – 6 <i>Subthreshold frequency of the Depression scale (SIBARS 2):</i> Severity score of 6 PLUS Frequency score of ≤ 3 <u>Cyclothymic features:</u> <i>Total score on the Cyclothymic Features rating (SIBARS 3):</i> Score ≥ 11
Group 3: DEPRESSION+GENETIC RISK <u>Genetic Risk:</u> First degree relative with bipolar disorder (SIBARS 4) PLUS <u>Depression:</u> <i>Subthreshold intensity of the Depression scale (SIBARS 2):</i> Severity score of 3 – 5 PLUS Frequency score of 3 – 6 <i>Subthreshold frequency of the Depression scale (SIBARS 2):</i> Severity score of 6 PLUS Frequency score of ≤ 3
Group 4: CYCLOTHYMIC FEATURES + GENETIC RISK <u>Genetic Risk:</u> First degree relative with bipolar disorder (SIBARS 4) PLUS <u>Cyclothymic features:</u> <i>Total score on the Cyclothymic Features rating (SIBARS 3):</i> Score ≥ 11
Group 5 : SUBTHRESHOLD MIXED EPISODE: <u>Subthreshold mania:</u> <i>Subthreshold intensity of the Subthreshold Mania scale (SIBARS 1):</i> Severity score of 3 – 4 PLUS Frequency score of 3 – 6 <i>Subthreshold frequency of the Subthreshold Mania scale (SIBARS 1):</i> Severity score of 5 - 6 PLUS Frequency score of ≤ 3 PLUS <u>Depression:</u> <i>Subthreshold intensity of the depression scale (SIBARS 2):</i> Severity score of 3 – 5 PLUS Frequency score of 3 – 6 <i>Subthreshold frequency of the depression scale (SIBARS 2):</i> Severity score of 6 PLUS Frequency score of ≤ 3 PLUS Symptoms should not have been present for more than 4 days
Group 6: MOOD SWINGS: Severity score of 3 – 6 of the mood swings scale (SIBARS 5) PLUS Frequency score of 3 – 6 of the mood swings scale (SIBARS 5)
Bipolar I THRESHOLD Severity score of 5 or 6 on the <i>Subthreshold Mania scale (SIBARS 1)</i> PLUS Frequency score of greater than or equal to 4 on the <i>Subthreshold Mania (SIBARS 1)</i> PLUS Symptoms present for more than 4 days Bipolar II THRESHOLD Severity score of the <i>Depression scale (SIBARS 2)</i> less than 6 PLUS Severity and frequency scores of the <i>Subthreshold Mania scale (SIBARS 2)</i> of 4 PLUS Symptoms present for more than 4 days

Figure 1. Kaplan-Meier failure estimates for the SIBARS interview in individuals accessing CHR-P services ($n=71$). There were 18 individuals at risk at 6 months, 17 at 12 months, and 11 at 24 months in the BARS- group and 21 individuals at risk at 6 months, 19 at 12 months, and 12 at 24 months in the BARS+ group. Estimates beyond this timepoint are plotted but should be considered cautiously.

Table 3. Association between the CAARMS and SIBARS baseline assessments (n=71).

		CHR-P+	CHR-P-	Total
BARS-	<i>n</i>	22	12	34
	<i>frequency</i>	21.5	12.5	34
	<i>column percentage</i>	48.89	46.16	47.89
BARS+	<i>n</i>	16	11	27
	<i>frequency</i>	17.1	9.9	27
	<i>column percentage</i>	35.56	42.31	38.03
Bipolar Disorders	<i>n</i>	7	3	10
	<i>frequency</i>	6.3	3.7	10
	<i>column percentage</i>	15.56	11.54	14.8
Total	<i>n</i>	45	26	71
	<i>frequency</i>	45	26	71
	<i>column percentage</i>	100	100	100

$\chi^2=0.421$, $P=0.814$

Figure 2. Decision Curve Analysis indicating the clinical utility (net benefits) associated with the use of the SIBARS for the detection of individuals at risk of developing bipolar disorders amongst those accessing CHR-P services.

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