Original article

Psychosis prediction in secondary mental health services. A broad, comprehensive approach to the “at risk mental state” syndrome

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A B S T R A C T

Background: Accuracy of risk algorithms for psychosis prediction in “at risk mental state” (ARMS) samples may differ according to the recruitment setting. Standardized criteria used to detect ARMS individuals may lack specificity if the recruitment setting is a secondary mental health service. The authors tested a modified strategy to predict psychosis conversion in this setting by using a systematic selection of trait-markers of the psychosis prodrome in a sample with a heterogeneous ARMS status.

Methods: 138 non-psychotic outpatients (aged 17–31) were consecutively recruited in secondary mental health services and followed-up for up to 3 years (mean follow-up time, 2.2 years; SD = 0.9). Baseline ARMS status, clinical, demographic, cognitive, and neurological soft signs measures were collected. Cox regression was used to derive a risk index.

Results: 48% individuals met ARMS criteria (ARMS-Positive, ARMS+). Conversion rate to psychosis was 21% for the overall sample, 34% for ARMS+, and 9% for ARMS-Negative (ARMS–). The final predictor model with a positive predictive validity of 80% consisted of four variables: Disorder of Thought Content, visuospatial/constructional deficits, sensory-integration, and theory-of-mind abnormalities. Removing Disorder of Thought Content from the model only slightly modified the predictive accuracy (~6.2%), but increased the sensitivity (+9.5%).

Conclusions: These results suggest that in a secondary mental health setting the use of trait-markers of the psychosis prodrome may predict psychosis conversion with great accuracy despite the heterogeneity of the ARMS status. The use of the proposed predictive algorithm may enable a selective recruitment, potentially reducing duration of untreated psychosis and improving prognostic outcomes.

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1. Introduction

Over the last two decades, one of the main goals in clinical and research psychiatry has been to develop standardized criteria to detect individuals at risk for psychotic onset (i.e., “at risk mental state”, ARMS) in order to provide early intervention and thus achieve better outcomes [1,2]. These criteria emphasize recent onset of subsyndromal psychotic symptoms (SPS), defined as attenuated psychotic symptoms (APS) or brief limited and intermittent psychotic symptoms (BLIPS) [3,4].

Using these criteria, approximately 1/3 of ARMS individuals develops a psychotic episode [5,6]. However, a large proportions of ARMS individuals do not convert to psychosis [7] or even remit from an ARMS state [8].

It has been hypothesized that this high rate of false ARMS (i.e. false positive) may be dependent on reliance on SPS as primary criterion defining risk for future onset psychosis [6,9,10].

As shown by two independent research groups, the use of risk algorithms relying on multiple risk factors in addition to meeting
SPS may indeed result in a dramatic increase in prediction accuracy compared to SPS criteria alone [10,11]. In particular, in one of these studies, when SPS were combined with verbal memory deficits and social functioning decline, it was possible to predict psychosis conversion with accuracy up to 82% [10]. These results suggest that SPS represent just one piece of the prodromal puzzle.

The prodrome, as all phases of Psychotic Spectrum Disorders (PSDs), is characterized by a combination of transient-state and enduring-trait markers [12,13], with SPS being part of the former group. These symptoms are indeed often transitory [14–16], and according to some authors “may potentially represent the phenotypic expression of other psychiatric syndromes” rather than an actual psychosis risk [9]. SPS have been reported in depressive, anxiety [17,18], and borderline personality disorders [19] without showing a specific predictive ability on future psychosis onset [9]. These considerations raise doubts on the role of SPS as the unique and primary criterion defining a real “at-risk” state when ARMS samples are characterized by high rates of comorbid psychiatric syndromes, such as those recruited in secondary mental health facilities. These individuals are indeed characterized by higher rates of comorbid depression and anxiety compared to ARMS detected with more widely used recruitment strategies [20].

The use of trait markers of PSDs, such as functional impairments [21], neuro- and social-cognitive disturbances [22,23], and neurological soft signs (NSS) [24,25], could be particularly useful in detecting true ARMS in secondary mental health services, where the symptom based approach may suffer from a lack of specificity. Furthermore, some of the trait markers of future psychotic onset, cut across the SPS based definitions of risk, being expressed in all phases of PSDs independently of positive symptoms [25–27]. For these reasons, in secondary mental health settings, given the potential low specificity of the SPS based approach, follow-up strategies and risk algorithms to predict future onset psychosis, should consider the use of trait markers of psychosis risk in addition to or independent of ARMS status.

Few studies have developed predictive models of psychosis transition in individuals recruited in secondary mental health settings [17,18]. However, all of these studies used an SPS-based approach, which, for the reasons stated above, could be considered “limited” given the specific setting with high rates of psychiatric comorbidity. These considerations might be of relevance since prodromal patients who are in treatment with secondary services for non-psychotic disorders may have up to seven times longer Duration of Untreated full blown Psychosis (DUP) and worse prognostic outcomes than patients who are diagnosed as psychotic at first contact [28].

Given the above, we recruited a large sample of young patients with different recent onset non-psychotic DSM diagnoses, assessed ARMS status, neuro- and social cognitive measures and neurological soft signs, with the aim of identifying key predictors of psychosis conversion using a broad trans-diagnostic approach consistent with the Research Domain Criteria (RDoC) initiative from the National Institute of Mental Health [29].

Given the specific recruitment setting, where SPS-based interviews may suffer from a lack of specificity, we hypothesize that: (1) it is possible to create a psychosis-risk algorithm independent of ARMS status; and (2) the predictive accuracy of the proposed algorithm mainly relies on trait- rather than state-markers of the psychosis prodrome.

2. Methods

All procedures were approved by the institutional review board of Sapienza, University of Rome and carried out in accordance with the latest version of the Declaration of Helsinki.

Written informed consent (with assent from participants <18) was obtained from all participants.

2.1. Participants and recruitment strategy

Subjects were recruited in three different clinics (Rome, Italy) that provide secondary general mental health care for adolescents and young adults. For 17 months (November 2011 to June 2013), the attending psychiatrists screened patients for the following exclusion criteria: current or past diagnosis of psychosis-spectrum or bipolar disorder; present or past diagnosis of a brief psychotic disorder with a duration equal to or greater than 1 week; diagnosis of mental retardation or other cognitive disorders, psychiatric disorders due to a somatic factor or related to psychotropic substances; drug abuse within the last 3 months; central nervous system disorders; and history or current use of antipsychotic medications. Patients with a substance abuse disorder (e.g., alcohol) were excluded according to previous evidence [30], since this might potentially confound results on some of the variables investigated (e.g., neurological soft signs).

After this first screening, patients aged 17–35 years old, were referred to a group of three trained interviewers. Referred individuals underwent the Structural Clinical Interview for DSM-IV Axis I (SCID-I) and II (SCID-II) [31] disorders to certify exclusion criteria and diagnoses.

2.2. Baseline assessment

Clinical information was obtained through the SCID-I and II, and the Positive and Negative Syndrome Scale (PANSS) [32]. The Comprehensive Assessment of At-Risk Mental (CAARMS) interview was used to identify ARMS-positive (ARMS+) and ARMS-negative (ARMS–) individuals [3]. The CAARMS inter-rater reliability was assessed in 34 subjects (ICC = 0.93). The ARMS+ status, as defined by the CAARMS, is a heterogeneous condition comprising different categories of psychosis-risk: Attenuated Psychotic Symptoms (APS) and/or Brief Limited Intermittent Psychotic Symptoms (BLIPS) and/or Genetic Risk and Deterioration syndrome (GRD) (more details are given in eMethods).

NSS were assessed with the Neurological Evaluation Scale (NES) [31], which comprises the following subscales: “Sensory integration”, “Motor coordination dysfunction”, “Sequencing of complex motor acts”, and “Others”. Neurocognition was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status [33]. The RBANS comprises five index scores (Attention, Immediate and Delayed Memory, Language and Visuospatial indices) and a total score. Theory of Mind was assessed though The Reading the Mind in the Eye Test [34], the Faux Pas test [35], and the Theory of Mind Assessment Scale (Th.o.m.a.s.) [36]. Baseline functioning was assessed using the Global Assessment of Functioning Scale and The Life Skills Profile 39 item (LSP-39) [37]. The LSP-39 comprises 5 subscales: Self-Care, Responsibility, Communication, Non-Turbulence, and Social-contact.

2.3. Follow-up procedure and conversion to psychosis

Patients were followed-up with phone call for detection of psychotic symptoms (SCID, psychosis module) [38] every 6 months. A single follow-up face to face interview took place at a mean time of 2.2 years from the baseline assessment. Transition to psychosis was defined according to CAARMS criteria [3].

2.4. Statistical analysis

All analyses were conducted using SPSS version 21.0 (SPSS Inc.). Comparisons of baseline characteristics were performed with
ANOVA for continuous variables and Pearson $\chi^2$ tests for categorical variables (2-tailed, $P < .05$).

The cumulative incidence rates of transition to psychosis during the follow-up period were estimated with Kaplan–Meier survival analysis. Subjects with survival times exceeding the 36-month follow-up were considered censored at the end of month. We compared ARMS+ and ARMS− survival curves using the log-rank test. The effect of covariates on survival time, i.e. time to transition, was estimated with the Cox proportional hazard model.

Based on previous evidence, predictor variables were generated within the following domains: demographic [39], clinical [1], neurocognitive [40], theory of mind [23], NSS [41] and functioning at baseline [21] (eTable 1).

Predictors were selected in several steps [42]. In the first stage of variable selection, covariates were computed individually and chosen for further analyses when changes of the $-2$ log-likelihood of the model and the Wald statistic became significant ($P < .10$). Variables that remained after the initial screening procedure were entered into domain-specific regressions at a liberal level of significance ($P < .15$). A final multivariable model was built with the remaining variables using backward (stepwise, likelihood ratio method) inclusion ($P < .05$).

Bootstrap resampling with replacement (B = 10,000 bootstrap samples) was used to internally validate the prediction models [43] (eAppendix). The variables scores included in the final model were dichotomized at their respective cutoffs, which were determined by explorative receiver operating characteristic curve analyses to combine a specificity equal or greater than 0.25 with a high sensitivity [30].

After deriving a final Cox regression model, a weighted risk index was calculated by multiplying each coefficient estimate from the model by the corresponding observed value for each individual. The risk index was then converted into an estimated probability of converting to psychosis with the inverse logistic function. Model discrimination and diagnostic accuracy were determined with the C statistic (area under the curve, AUC). Model calibration was assessed with the Hosmer–Lemeshow goodness-of-fit test ($P \geq 0.10$).

The final model was adjusted for the possible confounding effects of DSM-IV diagnosis at baseline; APS, BLIPS and GRD; PANSS general subscale score at baseline; antipsychotic and psychotherapy intervention at follow-up; and drug/alcohol abuse at follow-up.

3. Results

3.1. Sample characteristics

A total of 140 participants were referred to the study. Two individuals fulfilled SCID-I criteria for substance abuse, and were excluded. The remaining 138 individuals underwent CAARMS interview. A total of 67 ARMS+ and 71 ARMS− were enrolled in the study.

A total of 116 (84.1%) individuals completed the follow-up evaluation; 22 (15.9%) were lost at follow-up, of which 9 (12.7%) were ARMS+ and 13 (19.4%) were ARMS− (Fig. 1). Patients with follow-up information did not differ significantly from those lost to follow-up in terms of any of the variables investigated.

Table 1 presents baseline characteristics of the whole sample, ARMS+ and ARMS− individuals. There were no significant baseline differences between the two groups in terms of demographic variables, DSM-IV diagnoses and duration of illness. Compared to ARMS−, the ARMS+ group showed significantly higher scores on positive symptoms and behavioral change CAARMS subscales. The Social Contact and Communication subscales of the LSP–39 were significantly higher in the ARMS+ group, suggesting greater functional impairments. Other significant differences were found in theory of mind domain (Faux Pas test and Th.o.m.a.s.) and in the Sensory Integration subscale of the NES, with ARMS+ showing greater impairment than ARMS−.

Table 2 presents baseline and follow-up characteristics of patients who developed psychosis at follow-up (Converters) and who did not (Non-Converters). Converters and Non-Converters did not significantly differ in any demographic features, in baseline DSM-IV diagnoses, and in duration of illness. No differences were found in negative and general symptoms expression, as shown by the negative symptoms subscale of the CAARMS and the PANSS and the general symptoms subscale of the PANSS.

At baseline, Converters compared to Non-Converters showed a higher prevalence of ARMS+ status, higher levels of Positive symptoms, greater cognitive impairments in the Visuospatial, Attention and Total Score indices of the RBANS, higher levels of

![Fig. 1](image-url) Flow chart showing the different phases of the recruitment strategy and the follow-up at a mean time of 2.2 years.
### Table 1
Baseline characteristics of the whole sample, of the patients who met ARMS criteria (ARMS+) and who did not (ARMS−).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole sample (N = 138)</th>
<th>ARMS+ (N = 67)</th>
<th>ARMS− (n = 71)</th>
<th>ARMS+ vs. ARMS−</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>24.3 (3.5)</td>
<td>24.5 (3.4)</td>
<td>24.2 (3.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Education (years), mean (SD)</td>
<td>11.0 (2.9)</td>
<td>11.1 (2.9)</td>
<td>10.9 (2.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>7 (53.0)</td>
<td>37 (57.8)</td>
<td>34 (48.6)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAARMS, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disordersa</td>
<td>35 (84.6)</td>
<td>25 (73.7)</td>
<td>28 (79.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Anxiety disorderab</td>
<td>20 (13.0)</td>
<td>8 (11.9)</td>
<td>10 (14.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Personality disorderc</td>
<td>25 (18.1)</td>
<td>13 (19.4)</td>
<td>12 (19.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Comorbidity of mood and anxiety disordersd</td>
<td>42 (30.4)</td>
<td>21 (31.3)</td>
<td>21 (29.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Duration of illness (years), mean (SD)</td>
<td>2.1 (0.9)</td>
<td>2.1 (0.9)</td>
<td>2.1 (0.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Medication, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>18 (13.3)</td>
<td>8 (12.3)</td>
<td>10 (14.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>88 (65.2)</td>
<td>44 (67.7)</td>
<td>44 (62.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>63 (46.7)</td>
<td>30 (46.2)</td>
<td>33 (47.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>35 (25.9)</td>
<td>20 (30.8)</td>
<td>15 (21.4)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/not in education, N (%)</td>
<td>59 (44.4)</td>
<td>29 (44.6)</td>
<td>30 (44.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>GAF, mean (SD)</td>
<td>63.7 (9.7)</td>
<td>62.6 (10.3)</td>
<td>64.7 (9.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>LSP-39 items, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-care</td>
<td>18.8 (5.2)</td>
<td>19.4 (5.5)</td>
<td>18.2 (5.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Non turbulence</td>
<td>23.4 (5.2)</td>
<td>23.6 (5.8)</td>
<td>23.3 (4.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Social contact</td>
<td>11.1 (2.9)</td>
<td>11.9 (3.2)</td>
<td>10.3 (2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Communication</td>
<td>10.6 (2.6)</td>
<td>11.2 (2.8)</td>
<td>10.0 (2.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Responsibility</td>
<td>9.8 (2.1)</td>
<td>9.5 (2.4)</td>
<td>10.1 (1.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Total score</td>
<td>73.8 (11.7)</td>
<td>75.8 (14.2)</td>
<td>72.0 (8.5)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Neurocognition</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Immediate Memory Index</td>
<td>95.1 (9.8)</td>
<td>95.2 (9.2)</td>
<td>95.0 (10.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Language Index</td>
<td>89.9 (8.5)</td>
<td>89.8 (7.4)</td>
<td>90.0 (9.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Visuospatial Index</td>
<td>92.1 (8.3)</td>
<td>92.6 (7.0)</td>
<td>91.6 (9.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Attention Index</td>
<td>84.3 (8.7)</td>
<td>84.0 (8.3)</td>
<td>84.6 (9.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Delayed Memory Index</td>
<td>91.4 (8.2)</td>
<td>92.0 (7.6)</td>
<td>90.8 (8.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Total score</td>
<td>84.2 (6.6)</td>
<td>83.7 (6.8)</td>
<td>84.7 (10.1)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Theory of mind</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faux Pas, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faux Pas questions</td>
<td>17.5 (1.6)</td>
<td>17.2 (1.7)</td>
<td>17.8 (1.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>RMET, mean (SD)</td>
<td>38.7 (1.0)</td>
<td>38.8 (1.1)</td>
<td>38.7 (1.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Th.o.m.a.s. A</td>
<td>33.1 (7.2)</td>
<td>31.5 (7.7)</td>
<td>34.6 (6.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Th.o.m.a.s. B</td>
<td>28.7 (8.0)</td>
<td>26.5 (8.4)</td>
<td>30.9 (6.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Th.o.m.a.s. C</td>
<td>26.5 (6.8)</td>
<td>24.9 (7.1)</td>
<td>28.3 (6.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Th.o.m.a.s. D</td>
<td>28.1 (7.7)</td>
<td>26.2 (7.9)</td>
<td>29.9 (7.0)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Neurological soft signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NES, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor coordination</td>
<td>1.5 (1.3)</td>
<td>1.49 (1.4)</td>
<td>1.6 (1.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Sensory integration</td>
<td>1.3 (1.0)</td>
<td>1.5 (1.2)</td>
<td>1.1 (0.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sequencing of complex motor acts</td>
<td>1.3 (1.3)</td>
<td>1.3 (1.3)</td>
<td>1.4 (1.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Others</td>
<td>1.6 (1.4)</td>
<td>1.6 (1.3)</td>
<td>1.6 (1.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>Total score</td>
<td>5.9 (3.7)</td>
<td>6.0 (4.1)</td>
<td>5.8 (3.2)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Additional notes:
P-values < 0.05 are reported in bold. ARMS+, Positive to At Risk Mental State criteria; ARMS−, Negative to At Risk Mental State criteria; CAARMS, Comprehensive Assessment of At Risk Mental State; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; LSP-39, Life Skill Profile 39 item; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RMET, Reading the Mind Eyes in the Test; Th.o.m.a.s., Theory of Mind Assessment Scale; NES, Neurological Evaluation Scale.

a DSM-IV diagnoses: Major Depressive Disorder (MDD), Adjustment Disorder with Depressed Mood.
b DSM-IV diagnoses: Generalized Anxiety Disorder (GAD), Panic Disorder, Obsessive Compulsive Disorder (OCD), Adjustment Disorder with Anxiety.
c DSM-IV diagnoses: Borderline Personality Disorder.
d DSM-IV diagnoses: MDD and GAD, MDD and OCD, Adjustment Disorder with Depressed Mood and Anxiety.
Sensory Integration signs, and greater functional impairments, as revealed by the Non-Turbo-chi and Communication subscale of the LSP-39.

3.2. Treatment

At baseline, no significant differences were found between ARMS+ and ARMS− (Table 1), Converters and Non-Converters (Table 2).

During the follow-up period the percentage of patients who received antipsychotics was significantly higher than at baseline in Converters (100%; \(X^2 = 42.0, P < 0.001\)), in Non Converters (22.1%, \(X^2 = 23.6, P < 0.001\)), in ARMS+ (48.1%, \(X^2 = 34.2, P < 0.001\)) and in ARMS− (25.8%, \(X^2 = 18.37, P < 0.001\)) groups as well as for psychotherapeutic interventions (Converters, 19%, \(X^2 = 4.4, P < 0.05\); Non-Converters, 28.4%, \(X^2 = 31.4, P < 0.001\); ARMS+, 29.6%, \(X^2 = 18.7, P < 0.001\); ARMS− 24.2%, \(X^2 = 17.1, P < 0.001\)), indicating active treatment during the follow-up period.

At follow-up, Converters received more antipsychotics (\(P < 0.01\)), mood stabilizers (\(P < 0.05\)) and antidepressants (\(P < 0.01\)) than Non Converters. In contrast, Non-Converters received more antipsychotics (\(P < 0.01\)) than Converters and No differences were found between these two groups in terms of psychotherapeutic intervention at follow-up (Table 2).

Finally, 13.8% individuals developed a drug abuse at follow-up (Converters 14.3%, \(X^2 = 3.2, P = 0.07\); Non-Converters 13.7%, \(X^2 = 13.9, P < 0.001\)). No significant differences were found between Converters and Non-Converters groups.

3.3. Conversion rates

Twenty-one of the 138 patients experienced conversion to psychosis, with a mean ± SD time to conversion of 18.8 ± 6.7 months. The cumulative incidence rate of conversion was 2% for year 1 (SE = 0.01), 14% for year 2 (SE = 0.03) and 21% for year 3 (SE = 0.04), resulting in a cumulative rate of 21% (SE = 0.04). The non-converted cases were followed up for a mean ± SD of 27.9 ± 11.5 months since the baseline assessment.

**Fig. 2** presents the Kaplan–Meier estimate of the survival functions for time to onset of psychosis in the ARMS+ and ARMS− groups, who were significantly different (Log Rank test = 12.048;
We then removed Disorder of Thought Content from the model with the aim of evaluating the predictive accuracy of a multidimensional risk algorithm only relying on trait markers of the psychosis prodrome. The three remaining variables resulted in an AUC of 85.6% (95% CI: 74.6–96.5, P < 0.001), indicating a great discriminative ability, with a sensitivity of 71.4%, a specificity of 95.7%, and a PPV of 75% (see also eFigure 2). The Hosmer–Lemeshow statistic was 4.13 (P = 0.12), suggesting a well-calibrated predictive model.

Compared to the SPS-based multivariable model, the trait-marker algorithm resulted in a 2.5% drop in AUC (88.1% vs. 85.6%, respectively), a 6.2% drop in PPV (81.2% vs. 75%, respectively), and a 1.7% in specificity; in contrast, it gained a 9.5% in sensitivity (57.1% vs. 71.4%, respectively) (see also Table 3).

Both models continued to predict transition to psychosis after adjusting for potential confounding variables (see also eTable 2).

The CAARMS criteria alone resulted in an area under the curve of 69.1% (95% CI: 57.6–80.6, P = 0.05), with a sensitivity of 81% and a specificity of 57.3% and a PPV of 25.37% (eFigure 3).

Table 3 summarizes the predictive properties on future psychotic onset of (i) the CAARMS criteria alone; (ii) the SPS-based multidimensional model; (iii) and the trait-marker-based risk algorithm.

A multivariable model for psychosis prediction was also run separately for ARMS+ only (n = 67). This model consisted of three variables: Avolition ≥ 3, Faux Pas ≤ 16, and NES Sensory Integration subscale ≥ 2. These three variables resulted in an AUC of 86.8% (95% CI: 75.1–98.4, P < 0.001), indicating a great discriminative ability, with a sensitivity of 76.5%, a specificity of 92.0%, and a positive predictive value (PPV) of 81.2%. Due to lack of space, more details are given in the Supplementary material (eModel).

A correlation matrix among the variables included in the final predictive models can be found in the Supplementary material (eMatrix).

4. Discussion

To the best of our knowledge this is the first study (i) to develop multidimensional predictive models of psychosis transition in a sample of young psychiatric patients consecutively recruited in secondary mental health facilities independent of their ARMS status; (ii) to compare multidimensional risk algorithms relying on trait- and state-markers of the psychosis prodrome; and (iii) to demonstrate that a multidimensional model not including...
SPS-based criteria may predict psychosis conversion with great accuracy in young help-seeking adolescents and young adults treated in secondary mental health services for non-psychotic disorders, despite the heterogeneity of the ARMS status and the DSM diagnosis. Taken together, these results suggest that in a secondary mental health setting, trait-markers of the psychosis prodrome may be as relevant as the most widely used SPS-based criteria to predict psychotic conversion. In this context, state-markers may not work as well as in primary prevention ARMS+ sample, because of the higher level of general psychopathology in a secondary mental health setting.

At 36 months, the rate of conversion was 21% for the overall sample, 34% for ARMS+, and 9% for ARMS−. These transition rates highlight the relevant contribution of CAARMS criteria to detect those individuals who will develop a future psychotic disorders despite the high clinical heterogeneity; however, the small but significant percentage of ARMS− (9%) that developed psychosis at follow-up suggests that a more comprehensive approach is needed to define psychosis risk in patients who are in treatment with secondary services for non-psychotic disorders.

Accordingly, and in line with the hypotheses stated in the introduction, we found that (1) it was possible to create an accurate psychosis-risk algorithm in patients with heterogeneous ARMS+ status; and (2) the predictive accuracy of the psychosis prediction mainly relied on trait- rather than state-markers of the psychosis prodrome. Indeed, when SPS were removed from the final multidimensional predictive model the predictive accuracy, there was a drop of only 6.2% and there was a gain in sensitivity (+9.5%) compared to a SPS-based model. Of relevance, the trait-marker algorithm resulted in a dramatic increase of predictive accuracy (75%) compared to CAARMS criteria alone (25%).

Neurocognitive abilities were significantly impaired in converters relative to non-converters, with the former group showing greater dysfunctions in the Attention, Visuospatial and Total Indices of the RBANS. Among these domains, visuospatial/constructural abilities significantly predicted psychosis transition, a result in line with previous evidence [44,45].

In contrast, no differences were found between ARMS+ and ARMS− in any of the neurocognitive domains investigated. Consistent with this finding, it has been hypothesized that some of the baseline neurocognitive impairments described in ARMS+ literature may represent a consequence of general psychopathology and distress rather than a specific characteristic of the ARMS+ status [46,47]. Meta-analytic evidence suggests that the ARMS+ status is associated with widespread neurocognitive impairments [48]; however, this evidence relies on differences between ARMS+ and healthy subjects that may not be detected when ARMS+ are compared with individuals with comparable levels of general psychopathology, as our ARMS− group.

Of relevance, ARMS+ and ARMS− showed similar visuospatial abilities, suggesting that some core neurocognitive predictors of future psychotic onset may not be detected if only ARMS+ are screened for psychotic risk. These results further highlights the limits of an SPS-based approach as the only criteria in defining risk of future onset psychosis in patients recruited in secondary mental health facilities.

Different from general neurocognition, greater ToM impairments were found not only in converters but also in ARMS+. Furthermore, problems in Faux pas recognition were independent predictors of psychosis transition at follow-up, in line with the only longitudinal study investigating ToM impairments in ARMS individuals [49].

In contrast, RMET was not a significant predictor of future psychotic onset in our sample. This result is consistent with prior studies showing that among a number of different ToM tests, RMET did not distinguish between clinical (i.e., patients with PSDs) and non-clinical groups [50]. Different from RMET, mentalizing tasks like the Faux Pas test involve rich linguistic processing in order to extract explicit mental state information conveyed by sentences [35]. It is possible that this cognitive component of ToM, not detected by the RMET, might be responsible for this discrepancy.

ToM abilities, i.e. the capacity to infer other’s thought and beliefs, have been associated with the activity of a complex neural network including the medial prefrontal cortex (mPFC), bilateral temporal-parietal junction (TPJ), and posterior cingulate cortex [50]. Consistent with the ToM domain, sensory integration deficits were detected in both ARMS+ and in Converters. In particular, the sensory integration score of the NES was a key predictor of psychosis conversion at follow-up. A recent meta-analysis shows that sensory integration deficits, as those investigated by the NES, are associated with smaller volumes of the Brodmann area 6 [51], which is associated with visuospatial/structural abilities as well [52]. Area 6 is part of a wide neural network receiving information from cognitive association areas, such as the TPJ and the DLFP [51]; that, as previously mentioned, have shown functional and structural abnormalities associated with ToM impairments observed in first episode of psychosis [53,54].

These findings suggest that a common brain network may be responsible for visuospatial, sensory integration and ToM deficits characterizing those individuals that will develop a psychotic disorder at follow-up. Young patients exhibiting these characteristics may benefit from specific interventions based on plasticity-based trainings or non-invasive brain modulation techniques targeting this network and from cognitive remediation training, targeting both ToM and neurocognitive abilities, such as the Integrated Psychological Therapy or the Cognitive Behavioral Social Skill Training (CBSST). However, only future studies integrating neuroimaging, clinical, neurological and cognitive measures will be able to draw definitive conclusions.

Negative symptoms were not predictive of psychosis onset in the whole group of participants (ARMS+ and ARMS−) in contrast with previous evidence on other prodromal samples [40]. It is possible to hypothesize that this could be a consequence of ascertainment from a secondary mental health setting, where probably patients expressed more externalizing behaviors compared to other recruitment settings. However, it has to be noted that, in line with this prior evidence [40], severity of negative symptoms (i.e., avolition) was significantly associated with psychotic onset when only ARMS+ individuals were taken into account.

Finally, it is interesting to note that converters received more antipsychotics, and mood stabilizers and anxiolytics, whereas non-converters received more antidepressants (see also Section 3.2 and Table 2). This is consistent with a previous study by Cornblatt et al. [55] and suggests the possibility that antidepressants might prevent psychosis onset. However, these considerations are only speculative and further studies should clarify this issue.

4.1. Conclusion and limitations

Developing site-specific predictor profiles, as proposed here, has a number of limitations, the need for cross-validation being a primary one. More longitudinal studies, with comprehensive clinical, neuroimaging and genetic markers are needed in order to identify those markers that define the “at risk mental state” syndrome in patients seeking secondary mental health services for non-psychotic disorders. Also, our ARMS+ detection rate is higher compared to those reported by previous studies. However, it is still consistent with evidence suggesting that: (i) a consecutive screening in a secondary mental health facility detects more ARMS+ than a referral at suspicion strategy [20]; and (ii) greater
and more stable general psychopathology is associated higher ARMS+ detection rate. Similarly, the rate of psychotic conversion in the identified ARMS sample (25.4%) is consistent with previously published rates of conversion over a 1–2.5 year time period [40]. The higher ARMS+ detection rate, if confirmed by future studies, suggests that secondary mental health services could represent key sources of recruitment for prodromal patients. This finding assumes particular relevance if we consider the low ARMS+ detection rates typically associated with more widely used recruitment strategies [40]. Finally, the exclusion of patients with a substance abuse raise issues on the generalizability of our findings. Further studies are needed to evaluate the impact of this variable on the psychosis outcome in secondary mental health services.

In conclusion, our results suggest that young people seeking help for mental health problems in secondary mental health facilities should be specifically screened for neurological, neuro- and social-cognitive abnormalities, given their relevance in terms of future psychotic onset. In this context, SPS-based criteria may not be as relevant as in primary prevention ARMS+ centers, because of the higher level of general psychopathology. Increasing the accuracy of prediction in this specific setting may result in a dramatic improvement of prognostic outcomes, given the long DUP that characterizes prodromal patients who are in treatment with secondary services for non-psychotic disorders.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2016.09.002

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