TITLE PAGE

Title. THE APPROVED ITALIAN VERSION OF THE COMPREHENSIVE ASSESSMENT OF AT-RISK MENTAL STATES (CAARMS-ITA): FIELD-TEST AND PSYCHOMETRIC FEATURES.

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ABSTRACT

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Aim. The “Comprehensive Assessment of At-Risk Mental States” (CAARMS) was specifically developed to assess and detect young people at “Ultra-High Risk” (UHR) of developing psychosis. The current study was undertaken to test the reliability and validity of the authorized Italian version of the CAARMS (CAARMS-ITA) in a help-seeking population. **Methods.** Psychometric properties of the CAARMS-ITA were established on a sample of 223 Italian adolescents and young adults aged between 13 and 35 years, who were divided into three groups according to the CAARMS criteria: UHR-negative individuals (UHR[-]; n=64), UHR-positive (UHR[+]; n=55), and individuals with a “first-episode psychosis” (FEP; n=104). The CAARMS-ITA reliability was tested measuring inter-rater reliability and internal consistency. Construct validity was tested comparing the “Positive and Negative Syndrome Scale” (PANSS) and CAARMS-ITA subscale scores across groups (i.e. UHR[-], UHR[+] and FEP). For concurrent validity, we studied correlations between symptoms of the CAARMS-ITA and their equivalents in the PANSS. Finally, the predictive validity was examined by following-up the UHR [+] individuals. The 12-month transition rate to psychosis was calculated. **Results.** The CAARMS-ITA showed good inter-rater reliability. The PANSS “Positive Symptoms” subscale scores in UHR [+] individuals were intermediate between FEP and UHR [-] groups. The positive and negative symptoms scores of the CAARMS-ITA significantly correlated with the corresponding scores of the PANSS. After 12 months, 4 of 41 (9.8%) UHR [+] individuals had transitioned to psychosis. **Conclusions.** The CAARMS-ITA is a reliable and valid instrument for assessing and detecting at-risk mental states in Italian clinical settings. It also appears to be helpful in prediction to psychosis transition.

Keywords. At-Risk Mental States, Ultra-High Risk, Psychosis, Early Detection, Prodrome, Assessment.

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INTRODUCTION

In the last 20 years, there has been a broadening of research interest from timely recognition and phase-specific treatment of first-episode psychosis (FEP) to the pre-onset period or prodromal phase (Schmidt et al., 2015). In this context, the notion of “At Risk Mental States” (ARMS), proposed by McGorry and colleagues to identify individuals at increased risk of psychotic disorder, has replaced the retrospective concept of “prodrome”, which conveys an implicit sense of unavoidable progression to psychosis (Yung & McGorry, 1996; McGorry et al., 2003; McGorry et al., 2006). Within the potential variety of “ARMS”, a specific subset of criteria – so called “Ultra-High Risk” (UHR) – was proven to identify three subgroups of individuals with prospectively high (but not inevitable) imminent risk of developing psychosis. Those are: (a) “Attenuated Psychotic Symptoms” (APS), which represent subthreshold, attenuated positive symptoms; (b) “Brief Limited Intermittent Psychotic Symptoms” (BLIPS), which are transient psychotic symptoms that spontaneously remit within 1 week; and (c) “Vulnerability”, a trait/state risk condition in which the patient has a family history of psychosis (in first-degree relatives) or manifests schizotypal personality disorder along with low functioning that is sustained for at least 1 month. Although over the years some slight modifications have occurred, the core of the UHR criteria remains the

combination of socio-demographic risk features (age range: 14-30 years) with state and trait factors (APS, BLIPS, vulnerability) and help-seeking behavior (Yung et al., 2008; Raballo & Larøi, 2009). The focus on help-seekers is crucial, since it mitigates the potential high number of false positives that might occur assessing large asymptomatic community samples (Ramella Cravaro & Raballo, 2014).

In the initial years of applying these criteria, approximately 40% of those identified as UHR subsequently developed a FEP within 12 to 30 months (Cannon et al., 2008; Yung et al., 2003). However, a steady decrease in transition rates of UHR clients has been observed across continents and institutions, declining to a 12-month rate of approximately 15% (Nelson et al., 2013; Hartmann et al., 2016). This decrease has also been empirically verified in a meta-analysis (Fusar-Poli et al., 2012 [a]). All the above mentioned studies used specific assessment tools to identify young people with ARMS and to determine those transition rates. One of the most common is the “Comprehensive Assessment of At-Risk Mental States” (CAARMS), which was explicitly developed at the PACE clinic in Melbourne (McGorry et al., 2003; Yung et al., 2005) to assist the timely identification, risk stratification and longitudinal monitoring of ARMS (Yung et al., 2005; Raballo et al., 2011; Schultze-Lutter et al., 2015). It has been adopted in many European, Asiatic, and Arabic countries outside Australia, including UK, France, Spain, Germany, Denmark, Sweden, Greece, Japan, China, Korea, Honk Hong and Tunisia (Braham et al., 2014).

The authorized Italian version of the CAARMS (CAARMS-ITA) was developed in 2007, through a close collaboration between the Reggio Emilia Departmental Group on Early detection of Psychosis and the Australian authors of the CAARMS, that granted the copyright to the CAARMS-ITA in 2008. The CAARMS-ITA (a copy of which is available as Appendix S1, Supporting Information)

was later published under the aegis of the “Emilia-Romagna Regional Project on Early Detection in Psychosis” (Raballo et al., 2013). To the best of our knowledge, up until to now only pilot psychometric data, derived from a limited sample (i.e. 40 UHR, 10 FEP, and 20 healthy controls) and with an unofficial, non-authorized and not publicly Italian version of the CAARMS were published (Fusar-Poli et al. 2012 [b]). In the present study, we tested the reliability and validity of the CAARMS-ITA in a sample of young Italian help-seekers. To allow comparison between different versions of the CAARMS, we followed the procedure adopted to validate the Japanese (Miyakoshi et al. 2009) and the Arabic (Braham et al. 2014) version of the CAARMS.

METHODS

Participants

All the participants (n=223) were help-seekers recruited through the “Reggio Emilia At-Risk Mental States” Project (ReARMS), an early detection infrastructure developed under the governance of the “Regional Project on Early Detection in Psychosis” in the Reggio Emilia Department of Mental Health (Raballo et al., 2014). Referrals to ReARMS were mainly performed by General Practitioners (51%), hospital emergency rooms (22%), family members (15%), school and social services (10%). All the help-seekers referred to the ReARMS protocol are assigned to a multidisciplinary team including a clinical psychologist, a psychiatrist, and a case-manager for recovery-oriented early rehabilitation generally within 2-3 weeks.

The ReARMS team is specialized in identifying young people who are at ultra-high risk of developing psychosis as measured by the CAARMS-ITA. ReARMS inclusion criteria are: (a)

young individuals seeking the help of a specialist; (b) age between 13 and 35 years (this extended age range was modeled on the procedure adopted in validation studies of the Japanese and the Arabic version of the CAARMS); and (c) presence of UHR criteria defined by the CAARMS (i.e. APS, BLIPS, and/or Vulnerability) or (d) DUP < 2 years in case FEP is detected in the assessment. The exclusion criteria were matched on the study of Miyakoshi and colleagues (2009): (a) history of frank psychotic episodes, either affective or schizophrenic, as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) (Andreoli et al., 2002), (b) history of previous exposure to antipsychotics, (c) current substance dependence, (c) known mental retardation (IQ<70), and (d) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. All help-seekers entering the ReARMS protocol who voluntarily agreed to participate to the research, gave their written informed consent to the psychopathological assessment, composed – among others (see Raballo et al., 2014) – by the CAARMS (approved Italian translation by Raballo et al., 2007) (Raballo et al., 2013) and the PANSS (approved Italian version by Bersani et al., 1995) (Conti, 1999). All individuals assessed in this research were native speakers of Italian. Relevant ethical and local NHS research and development approvals were granted for the study.

Over the course of the study, 223 individuals (128 males and 95 females; mean age $\pm$ SD = 21.46 $\pm$ 5.99) consecutively attended an intake interview within the ReARMS protocol in the Reggio Emilia Department of Mental Health. Using the CAARMS-ITA, the ReARMS team (details provided below) determined whether these individuals met the UHR criteria. The axis-I diagnosis was made according to DSM-IV-TR (Andreoli et al., 2002) on the basis of the agreement between two trained ReARMS team members. After the interview, the participants were divided into three groups on the

basis of the UHR criteria: UHR [+] group, FEP group, and UHR [-] group (table 1). Among the UHR [+] group (n=55), thirty-six participants met APS criteria, fourteen met the APS and Vulnerability criteria, two met Vulnerability criteria, two met BLIPS criteria, and one met BLIPS and Vulnerability criteria. The FEP group (n=104) consisted of patients with DSM-IV-TR schizophrenia (n=48), affective (bipolar or major depressive) psychosis (n=19), schizophreniform disorder (n=10), brief psychotic disorder (n=8), and psychotic disorder not otherwise specified (n=19). The remaining 64 participants were below the threshold for being considered at risk of developing psychosis and were included in the UHR [-] group. They were diagnosed with depressive disorders (n=42), anxiety disorders (n=12), bipolar II disorder (n=5), somatoform disorders (n=3), and adjustment disorders (n=2).

Instruments

The *CAARMS* is a semi-structured clinical interview designed to cover different aspects of attenuated psychopathology as well as functioning (via the integrated *SOFAS* module). It takes approximately 1-1.5 hours to be administered and consists of 27 items (each one rated in terms of intensity [0-6] and frequency/duration [0-6]). Those items can be clustered in seven subscales, including some of Huber's basic symptoms: (a) "Positive Symptoms" (disorders of thought content, perceptual abnormalities, disorganized speech); (b) "Cognitive Change, Attention and Concentration" (subjective experience and observed cognitive change); (c) "Emotional Disturbance" (subjective emotional disturbance, observed blunted affect, observed inappropriate affect); (d) "Negative Symptoms" (alogia, avolition/apathy, anhedonia); (e) "Behavioral Change" (social isolation, impaired role functioning, disorganizing/odd/stigmatizing behavior,

aggressive/dangerous behavior); (f) “Motor/Physical Changes” (complaints of impaired motor functioning, impaired bodily sensation, and impaired autonomic functioning); and (g) “General Psychopathology” (mania, depression, suicidality and self-harm, mood swings/lability, anxiety, obsessive-compulsive symptoms, dissociative symptoms, impaired tolerance to normal stress).

The CAARMS “Positive Symptoms” subscale, which covers delusions, hallucinations and thought disorder, is used to determine both the UHR criteria and the threshold for psychosis. UHR status is defined as follows: (a) Vulnerability group: schizotypal personality disorder or family history of psychosis in a first-degree relative combined with 30% drop in functioning for at least 1 month or chronic low functioning, as measured by the “Global Assessment of Functioning” (GAF) scale (Italian version) (Andreoli et al., 2002) (the decline in functioning is calculated by subtracting of the current GAF-score from the highest GAF score in the past year; scores ranges from 1 to 100); (b) APS group: subthreshold positive psychotic symptoms within the past 12 month; and (c) BLIPS group: criteria for psychosis met for less than 7 day at a time and ceasing spontaneously (without antipsychotic medication). According to the psychosis criteria defined by the CAARMS (Yung et al., 2005), the threshold of full-blown psychotic episode is defined by operationalized clear-cut levels of fully (positive) psychotic symptoms occurring for at least 1 week, either on a daily basis or more than three times a week with each symptom continuing for more than 1 hour on each occasion.

The ReARMS team routinely used the CAARMS-ITA in the initial assessment to determine whether an individual meets UHR criteria. These assessments are conducted by specialized personnel including clinical psychologists and psychiatrists, who underwent collective supervision by the main author of the approved Italian translation (Raballo et al., 2013), who was trained at

Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS-ITA supervision sessions and scoring workshops ensure the inter-rater reliability of these assessments.

The Australian version of the CAARMS was translated into Italian by Andrea Raballo and back-checked by a team of experienced mental health professionals after obtaining permission from the original authors. This early version was then examined and judged as satisfactory by a staff member of PACE clinic in Melbourne (Magenta Simmons), who was fluent in Italian and familiar with the usage of the CAARMS.

The *PANSS* is a 30-item scale designed to assess the severity of psychotic symptomatology, subdivided into three major dimensions: (a) “Positive Symptoms” (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution, hostility); (b) “Negative Symptoms” (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking); and (c) “General Psychopathology” (somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance). Each item can be rated from 1 (“absent”) to 7 (“extreme”). In the present study, we use the Italian version of the PANSS, which showed good psychometric properties (Conti, 1999).

Procedures

The overall validation procedure was consistent with the methodological approach employed by Miyakoshi et al (2009) and Braham et al. (2014) to validate the Japanese and the Arabic versions of the CAARMS. In addition to their measures, we also assessed internal consistency.

The *inter-rater reliability* was tested by using data from consecutive joint interviews of 30 individuals who met the CAARMS defined UHR criteria at baseline (UHR [+]) (15 males and 15 females; mean age $\pm$ standard deviation [SD]: 19 ± 3.3 years). Initially, three psychologists were trained on the usage of the CAARMS through collective supervision by the main author of the approved Italian translation (Raballo et al., 2013), who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Preliminary administration of the instrument to suspected ARMS individuals were conducted before the study. Two of the three raters were paired for each interview. Inter-rater agreement was also assessed for the UHR criteria. To better assess reliability of the CAARMS-ITA, the *internal consistency* of the instrument was assessed, as were the correlations between different items of the interview measuring the same psychopathological construct (internal coherence).

We assessed *construct validity* of the CAARMS-ITA evaluating between-groups comparisons (FEP, UHR [+], UHR [-]) on the PANSS subscale scores and Huber's basic symptoms scores measured by the CAARMS. We hypothesized that the PANSS "Positive Symptoms" scores of the UHR [+] group would be intermediate between those of the FEP and UHR [-] groups. Moreover, we predicted that the scores of Huber's basic symptoms in the UHR [+] and FEP groups would be higher than those in the UHR [-] group because these self-experienced deficit symptoms are thought to be observed through the entire course of psychosis, including the prodromal phase (Maggini et al., 2003; Schultze-Lutter et al., 2016).

The *concurrent validity* of the CAARMS-ITA was examined by correlating the positive and negative subscales of the CAARMS with the corresponding domains of the PANSS.

The *predictive validity* of the CAARMS-ITA was tested by consecutively identifying UHR [+] people according to CAARMS-defined UHR criteria. Forty-one individuals were followed up for at least 1 year in the ReARMS protocol implemented in the Reggio Emilia Department of Mental Health: twenty-four subjects met the APS criteria, twelve met the APS and Vulnerability criteria, two met the Vulnerability criteria, two met the BLIPS criteria, and one met the BLIPS and Vulnerability criteria. All participants were provided with a comprehensive two-year intervention package which included a multi-element psychosocial intervention (combining individual Cognitive-Behavioral Therapy [CBT], psychoeducational sessions for family members, and recovery-oriented case management). The prescription of antipsychotics was avoided unless the individual (a) had an imminent risk of suicide or severe violence, (b) was overwhelmed by psychotic symptoms, (c) was rapidly deteriorating, or (d) did not respond to any other treatment. Low-dose atypical antipsychotics were used. Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia. During the first year of treatment, the participants were usually followed-up weekly or after every 2-3 weeks, in accordance with their clinical need. We calculated the rate of transition to psychosis at 12 months from baseline. Frank psychosis was defined according to the established CAARMS psychosis criteria. We predicted the transition rate at 12 months would be comparable to that in other studies in which putatively effective treatments were provided.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) 15.0 for Windows (SPSS; Chicago, IL, USA). Intra-Class Correlation (ICC) coefficients were calculated to estimate inter-rater reliability, and the kappa coefficient was calculated to evaluate the inter-rater agreement on the diagnosis. We also used Cronbach's alpha coefficient to assess the internal consistency. Between-groups comparisons were examined by using the Kruskal-Wallis test, and post-hoc analyses were performed by using the Mann-Whitney U test with Bonferroni correction. Finally, Spearman's coefficients were used to determine the correlation between PANSS and CAARMS scores.

RESULTS

The socio-demographic variables and the mean ratings of the CAARMS-ITA subscales, PANSS subscales and GAF are reported in table 1. The three groups showed no differences on gender, age, years of education, and duration of untreated illness (DUI, meant as the interval between the onset of a psychiatric clinically relevant symptom and the administration of the first pharmacological treatment). The groups were well matched with regards to socio-demographic variables.

Reliability

The *inter-rater reliability* of the CAARMS-ITA total score was 0.91. Similarly, inter-rater reliability ranged from very-good to excellent for all the seven subscales and the three positive symptoms items. The individual ICC coefficients are reported in table 2. The kappa coefficient for the agreement on the UHR criteria among the three raters was 0.85 ($p < 0.001$).

As regards the *internal consistency*, the Cronbach's alpha coefficient was 0.89, with an alpha level of 0.83 for the "Thought content" item, 0.88 for the "Perceptual abnormalities" item, and 0.79 for the "Disorganized speech" item.

Validity

In line with our expectations on the *construct validity*, the PANSS "Positive Symptoms" subscale scores were different among the three groups (table 1). In particular, the scores of UHR [+] group were significantly higher than those of UHR [-] individuals. Moreover, the PANSS "Positive Symptoms" scores were significantly more severe in the FEP group than in the UHR [+] participants.

There were significant differences among the three groups in the PANSS "Negative Symptoms" and "General Psychopathology" subscales scores (table 1). The PANSS "Negative Symptoms" subscale score of the FEP and UHR [+] individuals were significantly higher than those in the UHR [-] participants. However, although negative symptoms were more severe in the FEP group than in the UHR [+] individuals, the differences were not significant ($p=3.07$). Furthermore, the "General Psychopathology" subscale scores of UHR [+] individuals were significantly higher than those of UHR [-] participants and significantly lower than those in the FEP group.

In the assessment of the Huber's basic symptoms, five of the seven subscales adopted in the CAARMS (i.e. the subscales relating to subjective experience of cognitive change, emotional disturbance, avolition/apathy, impaired motor functioning, and impaired tolerance to normal stress) showed significant differences among the three groups (table 1). In detail, the scores of these five subscales in the FEP group were significantly higher than those in the UHR [-] group. Moreover,

UHR [+] individuals had significantly higher scores than those of UHR [-] participants in terms of subjective experience of cognitive change, emotional disturbance, and avolition/apathy. Finally, FEP patients experienced subjectively higher cognitive change, emotional disturbance, and avolition/apathy than those in the UHR [+] group; however, only the difference relating to subjective experience of cognitive change was statistically significant.

With regard to the *concurrent validity*, the results of the Spearman correlation coefficient analysis between the CAARMS-ITA and the PANSS subscales are reported in table 3. Each subscale of the CAARMS “Positive Symptoms” dimension correlated with the corresponding PANSS “Positive Symptoms” item. Furthermore, there were significant correlations between the general psychopathology and the negative domains of the CAARMS-ITA and those of the PANSS.

The *predictive validity* of the CAARMS-ITA was the core endpoint measure of the current study. Fourteen of the 55 UHR [+] participants did not complete the 12-month follow-up period. Ten of these individuals had a follow-up period of less than 1 year. The other 4 participants moved out of the ReARMS protocol catchment area and they could not be contacted for the follow-up assessment. After 12 months of follow-up, 4 of the 41 remaining UHR [+] participants (9.8%) had transitioned to full-blown psychosis, and all four had been prescribed antipsychotics during the follow-up period. Two of these individuals had received specific psychological support (individual CBT and psychoeducational sessions for family members) in addition to recovery-oriented case management prior to their transition to psychosis.

Antipsychotics were prescribed to 18 (43.9%) UHR [+] participants during the follow-up period. Seven of the 14 UHR individuals who did not develop psychosis were still being prescribed

antipsychotics at 12 months (although not consistently with clinical practice guidelines, such as those of the European Psychiatry Association [Schmidt et al., 2015]). Twenty-four (58.5%) of people at UHR who did not convert to full-blown psychosis were still satisfying inclusion criteria for ARMS at the end of the follow-up. No UHR [-] participants developed a psychotic episode over the follow-up time.

DISCUSSION

The aim of the present study was to test the psychometric features of the approved Italian version of the CAARMS (CAARMS-ITA) (Raballo et al., 2013). The results indicate that the CAARMS-ITA has good psychometric properties and is a reliable and valid instrument for evaluating ARMS in the Italian population, allowing for comparison of results across research groups in different countries. Therefore, the concept of ARMS seems to exhibit generalizability across different cultures (Miyakoshi et al., 2009; Braham et al., 2014).

Reliability of the Italian version of the CAARMS was assessed with respect to inter-rater reliability and internal consistency. The ICC coefficients of each CAARMS subscale showed good to excellent reliability, in line with the original validation study of Yung and colleagues (2005). The inter-rater reliability for the overall score was 0.91 and above 0.74 for all the subscales. These findings demonstrate that the instrument can be clinically used to assess the broad spectrum of symptoms presented by help-seeking youths referred to mental health services. Furthermore, the inter-rater reliability of the UHR inclusion criteria defined by CAARMS-ITA was also confirmed to be satisfactory, as observed in the original validation study (Yung et al., 2005). With regards to

internal consistency, the Cronbach's alpha coefficient for the CAARMS-ITA total score was 0.89. The values for thought content, perceptual abnormalities and disorganized speech subscales were overall good (0.83, 0.88, and 0.79, respectively).

The validity of the CAARMS-ITA was assessed with respect to construct validity, concurrent validity, and predictive validity. With regards to the first point, in line with our main hypothesis, we found that the PANSS "Positive Symptoms" subscale scores of the UHR [+] individuals were intermediate between those of the FEP and UHR [-] groups. A similar pattern was observed in some studies evaluating the neurocognitive profile of people with ARMS and showing that the magnitude of their positive symptoms is generally of moderate severity but less marked than in first-episode schizophrenia (Seidman et al., 2010).

The severity of the PANSS "Negative Symptoms" subscale in the FEP and UHR [+] groups was significantly higher than that in the UHR [-] participants. It has been reported that the severity of negative symptoms in first-episode schizophrenia is usually greater compared to ARMS individuals (Haefner et al., 2004). In the present study, the PANSS negative symptoms were more severe in the FEP group than in the UHR [+] individuals, but the difference was not significant. Such a result confirms that the people with ARMS present a negative symptomatology profile that shares similarities in severity with that of FEP patients and that significantly limits their psychosocial functioning. Indeed, high levels of negative symptoms, significant impairments of academic performance and occupational functioning, and difficulties with interpersonal relationships are often observed together both in FEP and UHR individuals (Velthorst et al., 2010). Furthermore, we found that the PANSS "General Psychopathology" subscale scores of UHR [+] individuals were significantly higher than those of UHR [-] participants and significantly lower than those in the FEP

group. It has been suggested that in addition to prodromal symptoms, people who meet criteria for ARMS usually present with other clinical concerns, in particular anxiety and depression, associated with a marked impairment in psychosocial functioning (Fusar-Poli et al., 2012 [b]).

Finally, the CAARMS contains several items that assess Huber's basic symptoms, which are thought to be prominent in ARMS individuals and patients with schizophrenia (Maggini et al., 2003; Schultze-Lutter et al., 2015; Schultze-Lutter et al., 2016). In line with our hypothesis, the severity of five of the seven basic symptoms subscales adopted in the CAARMS-ITA was different across the three groups. In particular, the scores of the subscales relating to subjective experience of cognitive change, emotional disturbance, and avolition/apathy in the UHR [+] and FEP groups were significantly higher than those in the UHR [-] participants. These findings may be indicative of the sensitivity of the "cognitive change", "emotional disturbance" and "avolition/apathy" items in signalling the imminent risk of psychosis. However, specific instruments - such as "Schizophrenia Proneness Instrument", available in adult and child-youth version (Schultze-Lutter et al., 2007; Schultze-Lutter et al., 2012) – are certainly more suitable for assessing basic symptoms in ARMS individuals, particularly in view of detecting COPER and COGDIS criteria for further risk stratification (Schultze-Lutter et al., 2015; Schultze-Lutter et al., 2016).

As regards concurrent validity, the present study showed that the positive, negative and general psychopathology domains measured by the CAARMS-ITA correlated with those assessed by the PANSS. These findings demonstrated that the Italian version of the CAARMS has good concurrent validity in measuring psychopathology of the ARMS.

Finally, we followed up our UHR [+] sample for 1 year and measured the predictive validity of the CAARMS-ITA. We found a risk of developing psychosis of 9.8% over 12 months, which is consistent with the 10.7% transition rate reported in the validation study of the Japanese CAARMS (Miyakoshi et al., 2009). Our results are also in line with the steady decrease in transition rate of UHR individuals observed across continents and institutions, declining to a 12-month rate of approximately 15% (Hartmann et al., 2016). Nelson et al. (2016) argued that the reducing transition rate in UHR samples seems to be a complex phenomenon not reducible to a single cause. Contributing, and possibly interacting and overlapping, factors identified to date include: (a) lead-time bias (i.e. this refers to patients in more recent cohorts possibly being referred to treatment earlier in the course of their symptoms and therefore requiring a longer observation or follow-up period to register transitioned cases); (b) earlier intervention (i.e. a shorter duration of symptoms prior to entry in more recent cohorts may have allowed intervention to be more effective in delaying or preventing transition to psychosis); (c) change in sample characteristics (i.e. more recent cohorts may inherently be at lower risk of psychosis due to differences in clinical characteristics of UHR cohorts over the years [e.g., symptom dimensions, neurocognitive functioning, etc.]) (Fusar-Poli et al., 2016); and (d) treatment changes (i.e. it also possible that standard treatment for UHR patients has become more effective over the years in delaying or preventing transition to psychosis).

Decrease in transition rate of UHR populations has also been empirically verified in a recent meta-analysis which indicated that, independent of the psychometric instruments used, risk for psychosis was 21,7% after one year (Fusar-Poli et al., 2012 [a]). This result is slightly higher than our findings. However, in their meta-analysis, the authors considered both the UHR and the basic symptoms criteria to define high risk features in help-seeking patients.

Some methodological peculiarities of the current study shall be considered when comparing the results of the 12-month follow-up in our UHR [+] group with those of other studies. Indeed, ReARMS is a clinically project providing evidence-based interventions that are supposed to be effective in reducing the transition rates in UHR individuals (i.e. intensive case-management, family psycho-education, CBT within the framework of assertive community treatment). Precisely because providing the optimal treatment for the help-seekers was the main ethical mandate in our clinical setting, our interventions were not controlled (e.g. against a placebo group or other treatments), but uniformly delivered to all UHR. However, results are comparable with ones of similar studies adopting active interventions. For example, McGorry et al. (2009) performed a randomized control study in which they compared the transition rate of ARMS individuals who were treated with specific prevention intervention (SPI) (which combined cognitive-behavioral therapy and low-dose antipsychotic medication) with that of ARMS individuals who were treated only with need-based intervention (NBI). The transition rate of the SPI group was 10% at the end of the 6-month treatment phase and 19% at the 12-month follow-up. Otherwise, the transition rate of the NBI group was 36% at the end of the treatment phase and the 12-month follow-up. Similarly, Morrison et al. (2004) conducted a randomized controlled trial and reported that the transition rate at 12-month follow-up was 6% for ARMS individuals who received cognitive therapy for 6 months and 26% for those who did not receive the treatment. Considering these results together, it can be assumed that the CAARMS-ITA can reliably detect ARMS individuals.

In the current research, the antipsychotic prescription rate (43.9%) was almost similar to those reported in the study on validation of the Japanese version of the CAARMS (39.2%) (Miyakoshi et al., 2009) and in a North American longitudinal study conducted on 291 subjects across eight

clinical research centers (35.1%) (Cannon et al., 2008). Our high prescription rate appears to be inconsistent with clinical practice guidelines, according to which psychological intervention (in particular CBT) should be offered as first choice and be complemented by low-dose second-generation antipsychotics where they have proved ineffective and in adult patients if severe and progressive UHR symptomatology is present (Schmidt et al., 2015). However, our UHR group consisted of a significant proportion of subjects probably overwhelmed by psychotic symptoms (e.g. BLIPS in higher or increasing frequency, APS with only minimal or clearly declining insight) and rapidly deteriorating in daily functioning. Therefore, for these individuals, a prescription of antipsychotics (even up to 12 months) appeared to be necessary to achieve a degree of symptomatic stabilization that was required for psychological intervention to be really effective (Schmidt et al., 2015). In this context, we found that 14 of 18 UHR [+] participants who received antipsychotics did not progress to psychosis during the follow-up period. On the contrary, the remaining four UHR [+] individuals developed psychosis in spite of receiving antipsychotic medications. Therefore, as implicit in their pharmacological effect, antipsychotics could have delayed or avoided the conversion to psychosis in some of those UHR [+] participants. However, only half (i.e. 7), of the 14 UHR [+] participants who completed the 12-month follow-up period without developing psychosis, were still being prescribed antipsychotics. This might suggest that a long-term (up to 1 year) prescription of antipsychotics to people with ARMS is not always necessary, especially if multi-element psychosocial intervention is provided.

Limitations

There are several methodological limitations of the study. First, our results were obtained by a small group of raters who had considerable clinical experience of assessing individuals with prodromal

symptoms and were familiar with CAARMS-ITA. The clinical expertise of our raters prevented any generalizability of our findings to primary care setting with no experience in the UHR assessment. Therefore, the generalizability of the results should be studied in the future.

Second, because of the limited UHR [+] sample size, the statistical power to detect “true positives” (i.e. those individuals who were identified correctly as being in the prodromal period as they did indeed go on to develop a psychotic disorder) was not yet strong enough. Indeed, the major factor in determining the predicted power of the CAARMS-ITA depends on the source of participants being studied. To date, transition estimates in people with ARMS have largely been made in samples of help-seeking individuals who were engaged by specialized early intervention services. Our UHR [+] participants were referred to the ReARMS protocol because they were regarded as potentially at risk for psychosis, and thus would be expected to have a higher risk of psychosis than those in the general population. Therefore, the predictive value of the CAARMS-ITA in the Italian community may be lower than those reported in our research. Moreover, our UHR [+] participants were also receiving some specific psychological and pharmacological treatments in addition to traditional case management. There is evidence indicating that psychological treatment can significantly affect the transition rate to psychosis of people with ARMS (Fusar-Poli et al., 2012 [a]).

Finally, our follow-up was limited to one year. Longer term follow-up is recommended to fully detect all the people who will later develop a psychotic episode (McGorry et al., 2009; Nelson et al., 2013; Schultze-Lutter et al., 2015).

Conclusions

Despite these limitations, CAARMS-ITA demonstrated to be a reliable and valid tool for assessing and detecting ARMS in Italian clinical setting and appears to be helpful in predicting transition to psychosis.

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Table 1. Demographic and clinical characteristics of the three groups.

Variable	UHR [+] (n=55)	FEP (n=104)	UHR [-] (n=64)	Statistical test (χ^2)	Post hoc test
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Gender (males)	31 (50.8%)	60 (57.6%)	34 (58.6%)	1.07	-
Age	18.35 (4.89)	21.42 (5.51)	20.13 (6.48)	1.31	-
Education (in years)	11.15 (2.34)	11.75 (2.37)	11.23 (2.45)	1.53	-
DUI (in weeks)	47.97 (5.01)	48.87 (5.66)	49.15 (7.58)	1.45	-
<i>PANSS</i>					
Positive symptoms	13.60 (3.69)	21.96 (7.30)	9.96 (2.99)	45.56*	FEP>UHR[+]>UHR[-]
Negative symptoms	19.34 (7.17)	21.39 (8.64)	11.53 (5.45)	35.42*	FEP=UHR[+]>UHR[-]
General psychopathology	38.76 (9.35)	45.74 (14.05)	31.03 (5.82)	34.99*	FEP>UHR[+]>UHR[-]
<i>CAARMS</i>					
Positive symptoms					
<i>Thought content</i>	7.78 (4.54)	15.85 (5.75)	2.28 (2.02)	133.15*	FEP>UHR[+]>UHR[-]
<i>Perceptual abnormalities</i>	4.24 (3.07)	5.30 (5.72)	1.47 (2.29)	29.46*	FEP=UHR[+]>UHR[-]
<i>Disorganized speech</i>	3.16 (2.48)	4.86 (3.86)	1.17 (1.76)	43.49*	FEP>UHR[+]>UHR[-]
Huber's basic symptoms					
<i>Cognitive Change</i>	9.80 (6.17)	13.62 (7.23)	4.34 (3.31)	64.43*	FEP>UHR[+]>UHR[-]
<i>Emotional disturbance</i>	4.64 (2.79)	4.99 (3.49)	1.86 (2.24)	37.67*	FEP=UHR[+]>UHR[-]
<i>Avolition/Apathy</i>	3.15 (1.56)	3.33 (1.83)	1.42 (1.48)	45.40*	FEP=UHR[+]>UHR[-]
<i>Impaired motor functioning</i>	0.64 (1.21)	1.10 (1.46)	0.28 (0.83)	17.17*	FEP>UHR[-]
<i>Impaired bodily sensation</i>	1.02 (1.56)	1.09 (1.73)	0.95 (1.34)	0.01	-
<i>Impaired autonomic functioning</i>	1.22 (1.52)	1.42 (1.82)	1.28 (1.39)	0.24	-
<i>Impaired tolerance to normal stress</i>	2.91 (1.78)	3.01 (1.87)	2.20 (1.63)	11.04**	FEP>UHR[-]

Legend. *p<0.001; **p<0.01. Frequencies and percentages, mean (standard deviation), and statistic test (X²) values are reported.

Table 2. Intra-Class Correlation (ICC) coefficients of the main CAARMS-ITA subscales (n=30).

CAARMS subscale	ICC
Positive Symptoms	0.93
<i>Thought content</i>	0.92
<i>Perceptual abnormalities</i>	0.96
<i>Disorganized speech</i>	0.86
Cognitive change, concentration/attention	0.75
Emotional disturbance	0.74
Negative symptoms	0.88
Behavioral change	0.75
Motor/physical changes	0.85
General psychopathology	0.93
Overall	0.91

Table 3. Spearman correlations between CAARMS-ITA and PANSS (n=223).

CAARMS	PANSS	$\hat{A}$
Positive symptoms	Positive symptoms	.754*
<i>Thought content</i>	<i>Delusions</i>	.792*
<i>Perceptual abnormalities</i>	<i>Hallucinatory behavior</i>	.640*
<i>Disorganized speech</i>	<i>Conceptual disorganization</i>	.667*
Negative symptoms	Negative symptoms	.644*
<i>Emotional disturbance</i>	Negative symptoms	.653*
General psychopathology	General psychopathology	.649*

Legend. * $p < 0.001$. Spearman $\hat{A}$ correlation coefficient values are reported.

TITLE PAGE

Title. THE APPROVED ITALIAN VERSION OF THE COMPREHENSIVE ASSESSMENT OF AT-RISK MENTAL STATES (CAARMS-ITA): FIELD-TEST AND PSYCHOMETRIC FEATURES.

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ABSTRACT

Aim. The “Comprehensive Assessment of At-Risk Mental States” (CAARMS) was specifically developed to assess and detect young people at “Ultra-High Risk” (UHR) of developing psychosis. The current study was undertaken to test the reliability and validity of the authorized Italian version of the CAARMS (CAARMS-ITA) in a help-seeking population. **Methods.** Psychometric properties of the CAARMS-ITA were established on a sample of 223 Italian adolescents and young adults aged between 13 and 35 years, who were divided into three groups according to the CAARMS criteria: UHR-negative individuals (UHR[-]; n=64), UHR-positive (UHR[+]; n=55), and individuals with a “first-episode psychosis” (FEP; n=104). The CAARMS-ITA reliability was tested measuring inter-rater reliability and internal consistency. Construct validity was tested comparing the “Positive and Negative Syndrome Scale” (PANSS) and CAARMS-ITA subscale scores across groups (i.e. UHR[-], UHR[+] and FEP). For concurrent validity, we studied correlations between symptoms of the CAARMS-ITA and their equivalents in the PANSS. Finally, the predictive validity was examined by following-up the UHR [+] individuals. The 12-month transition rate to psychosis was calculated. **Results.** The CAARMS-ITA showed good inter-rater reliability. The PANSS “Positive Symptoms” subscale scores in UHR [+] individuals were intermediate between FEP and UHR [-] groups. The positive and negative symptoms scores of the CAARMS-ITA significantly correlated with the corresponding scores of the PANSS. After 12 months, 4 of 41 (9.8%) UHR [+] individuals had transitioned to psychosis. **Conclusions.** The CAARMS-ITA is a reliable and valid instrument for assessing and detecting at-risk mental states in Italian clinical settings. It also appears to be helpful in prediction to psychosis transition.

Keywords. At-Risk Mental States, Ultra-High Risk, Psychosis, Early Detection, Prodrome, Assessment.

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Title:

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