UNIVERSITÀ DEGLI STUDI DI ROMA
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DOTTORATO IN NEUROSCIENZE CLINICO-SPERIMENTALI E PSICHIATRIA (XXXII Cycle)

Early detection of psychosis: findings from the "Reggio Emilia At-Risk Mental States" (ReARMS) program

Candidate
Lorenzo Pelizza

Tutor
Prof. Maurizio Pompili
Sapienza University of Rome

Advisor
Prof. Andrea Raballo
University of Perugia

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A mio padre,
medico e uomo giusto,
che mi ha insegnato ad essere quello che sono;

A Simona, Vittoria e Costanza,
unici, fondamentali motivi che non mi hanno fatto fuggire da questa "povera patria",
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SUMMARY

Primary and secondary prevention strategies have been addressed in several fields of medicine, but early detection in psychiatry still remains a grey zone, also in psychosis. Serious mental illnesses share an early presentation, with a typical beginning during adolescence for the 75% of them. The personal and societal impact of such disorders makes early detection and intervention a crucial issue, in the attempt to prevent significant consequences on individual functioning.

Staging models have been developed in order to use a preventative approach, targeted at avoiding the onset and/or progression of serious mental disorders (especially of psychosis), with treatment regimens selected according to stage and individual profile risk factors. Staging allows the introduction of effective treatment in early illness phases, by means of placing individuals on a continuum in the context of the disorder progression. This goes along with the assumption that administering treatments during early illness stages could also modify the individual risk of disease progression. Although the first models were mainly applied to psychosis, the concept of staging has been progressively applied to severe psychiatric disorders, in the attempt to define early clinical phenotypes showing an enhanced risk of progression into chronic and recurrent phases of such disorders.

In this research, our interest was focalized on early detection of psychosis (specifically, of adolescents and young adults with First Episode Psychosis [FEP] or at Ultra-High Risk [UHR] of psychosis). A 2-step identification procedure was proposed. For the first ("*screening*") step, different instruments were described and were analyzed in their psychometric characteristics. These screeners can also be used in different settings (e.g. the "Checklist per la Valutazione dell'Esordio Psicotico [CVEP] in general medical practice; the Prodromal Questionnaire-Brief version [PQ-B], the 16-item Prodromal Questionnaire [PQ-16] or the Aberrant Salience Inventory [ASI] in triage services allocated in general child/adolescent and adult mental health centers). The second step included an *in-depth assessment* using clinical interviews specifically developed for the early detection of psychosis and the psychosis risk stratification (such as the CAARMS).

BACKGROUND AND CONCEPTUAL FRAMEWORK

Early intervention in Psychosis: concepts, evidence and future directions

Psychotic disorders (particularly schizophrenia) are serious illnesses which typically emerge during the sensitive developmental period of adolescence and emerging adulthood [1]. For over a century, a corrosive blend of pessimism, stigma and neglect have confined therapeutic efforts to inconsistent and delayed palliative care [2]. Much of this can be attributed to the conceptual error underpinning the concept of schizophrenia, namely that a true disorder could be validly defined by its (poor) outcome. This error was, in turn, a legacy of the 19th century degeneration theory, which has been allowed to influence the field well beyond its use-by date [3]. Although Kraepelin himself and some of his contemporaries ultimately recognized the fallacy, his dichotomy (between "dementia praecox" and "manic-depressive insanity") has withstood several challenges and has been strongly reinforced with the advent of operational diagnostic systems [4]. This has not only hampered neurobiological research, but has caused widespread iatrogenic harm and inhibited early diagnosis because of an exaggerated fear of the expected outcome [2].

Until recently, early intervention for psychotic disorders has been the furthest thing from the minds of clinicians and researchers. Ironically, however, since the early 1990s, this hitherto barren landscape has seen the growth of an increasingly rich harvest of evidence, and widespread national and international efforts for reform in services and treatment approaches, setting the scene for more serious efforts in early intervention in other mental disorders [5-6].

Development of early intervention services

Building on seminal research on first episode psychosis from the 1980s [7, 8], front-line early psychosis clinical services were established, first in Melbourne [9] and soon after in many key locations in the UK, Europe, North America and Asia [10, 11]. There are now hundreds of early intervention programs worldwide, of varying intensity and duration, which focus on the special needs of young people and their families. International clinical practice guidelines on the topic have been published [12, 13] and clinical practice guidelines for the treatment of schizophrenia now typically have a major section on early psychosis [14, 15]. The International Early Psychosis Association (IEPA), an international organization which seeks to improve knowledge, clinical care and service reform in early psychosis, has been in existence for over fifteen years, led by a highly

collegial leadership group of clinicians and researchers. This association has over 4000 members from over 70 different countries, and by 2020 will have held eleven international conferences, stimulating and capturing a large volume of research and experience [2].

Shift in thinking: pessimism to optimism

The advent of preventive thinking has required a shift in the way schizophrenia and other psychotic disorders are viewed. Rather than seeing them as having inevitably poor prognoses with deterioration in social and functional outcome as the norm, more recent thinking backed up by evidence from large international studies views the course of these disorders as much more fluid and malleable [16-18].

Examination of risk factors which can influence outcome has revealed that many of these may be reversible. For example, disruption of peer and family networks and vocational drop-out commonly occur around and even before the onset of a first psychotic episode. Attention to these areas as part of treatment has the potential to limit or repair the damage [2]. Comorbid depression, substance use, personality dysfunction and post-traumatic stress disorder are all factors which may influence outcome in a person with first episode psychosis. Again, early and vigorous management of these problems can result in better outcomes [19].

What is early intervention?

Early intervention is a potentially confusing term. Because there is no etiopathological basis for diagnosing psychotic disorders, they can only be diagnosed by symptoms or combinations of symptoms. In addition, we have no known causal risk factors which predict onset of psychotic disorder with any specificity [2]. Thus, it seems that primary prevention is currently out of our reach. Early intervention, therefore, means early *secondary prevention*.

In keeping with the clinical staging model [20], early intervention in psychosis can be defined as comprising three main stages: (a) ultra-high risk, (b) first episode, and (c) the recovery or critical period. The principal reason for making such distinctions relates to the underlying risk of chronicity, and specifically the timing and duration of prescription of antipsychotic medication, since psychosocial interventions are needed at all stages, though these interventions too vary by stage.

What is the target for early intervention: psychosis or schizophrenia?

Clinicians and researchers have debated whether to focus on the preventive target of schizophrenia or of psychotic disorders more broadly. There are several reasons for stepping out of the current diagnostic silos and preferring a relatively broad target.

Schizophrenia is conceived and defined, in part, as an outcome as much as a diagnosis. While it is very stable once applied [21], it is intrinsically difficult to apply until the patient has been ill for a prolonged period of time. Within a first episode psychosis sample, only 30-40% will meet criteria for schizophrenia, and this percentage will increase over time with additional diagnostic flux. Thus, some cases of first episode psychosis which do not meet criteria for schizophrenia can be seen as being at risk for this in the future [22]. Schizophrenia, therefore, is to some extent a more distal target than psychosis, which is a better and broader initial way-station for critical treatment decisions. An even earlier and broader point for intervention is the "ultra-high risk" clinical stage, where there is a need for care prior to the positive psychotic symptoms having become severe and sustained.

As a consequence of this heterogeneous group of patients, a broader range of clinical skills will be required in early psychosis programs than in narrower schizophrenia programs [2]. Indeed, provided there is a flexible attitude and a broad range of clinical expertise available, both groups of patients (i.e. those with schizophrenia and other psychotic disorders) benefit more from this broad, early, and inclusive focus on the spectrum of psychosis. It provides a good balance between specialization and addressing common needs, and also facilitates both clinical and etiological research, which increasingly needs to transcend traditional diagnostic barriers.

ENHANCING THE VALUE OF DIAGNOSIS: THE CLINICAL STAGING MODEL

Many of the problems of categorical diagnosis flow from a telescoping of syndromes which distorts the natural ebb and flow of illness, remission and progression. The notion of staging can be borrowed and adapted from mainstream medicine to assist us here. A clinical staging model provides a heuristic framework allowing the development and evaluation of broad and specific interventions as well as the study of the variables and processes underlying the evolution of psychiatric disorder [20, 23].

What is clinical staging?

Clinical staging is simply a more refined form of diagnosis [24]. Its value is recognized in the treatment of malignancies, where quality of life and survival rely on the earliest possible delivery of effective interventions. However, it also has applicability in a diverse range of diseases. Clinical staging differs from conventional diagnostic practice in that it defines the extent of progression of disease at a particular point in time, and where a person lies currently along the continuum of the course of illness [23].

The differentiation of early and milder clinical phenomena from those that accompany illness extension, progression and chronicity lies at the heart of the concept. It enables the clinician to select treatments relevant to earlier stages, and assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course.

While staging links treatment selection and prediction, its role in the former is more crucial than in the latter, particularly since early successful treatment may change the prognosis and thus prevent progression to subsequent stages. In addition to guiding treatment selection, a staging framework, which moves beyond the current diagnostic silos to encompass a broader range of clinical phenotypes, and which at the same time introduces subtypes along a longitudinal dimension, has the potential to organize endophenotypic data in a more coherent and mutually validating fashion [23].

How do we define the stages of a disorder?

In other medical conditions, clinical stages are defined by the degree of extent, progression and biological impact of illness in the patient, which in turn must correlate with prognosis. This approach usually depends upon a capacity to define pathologically as well as clinically the limits or extent of the disease process.

In clinical psychiatry, this could involve not only a cross-sectional clinical definition, but a wider biopsychosocial definition of extent or progression [2]. Therefore, in addition to the severity, persistence and recurrence of symptoms, biological changes (e.g. hippocampal volume loss), and the social impact of the disorder (e.g. the collateral damage affecting social relationships and employment), could also be drawn into the definition.

What are the potential benefits of staging?

On the clinical side, defining discrete stages according to progression of disease creates a prevention-oriented framework for the evaluation of interventions. The key positive health

outcomes are prevention of progression to more advanced stages, or regression to an earlier stage. This requires an accurate understanding of those broad social, biological and personal risk and protective factors which influence progression from one stage to the next [2].

Furthermore, we need to know the relative potency of these risk factors and which of them may be responsive to current interventions. While some factors may operate across several or all stage transitions, others may be stage-specific, for example substance abuse or stress may be especially harmful in triggering onset of the first episode of illness, yet be less toxic subsequently [25].

From an etiological perspective, over a century of research with traditional diagnostic categories of psychosis and severe mood disorders has failed to relate these flawed concepts to any discrete pathophysiology [26]. A clinical staging model, which allows the relationship of biological markers to stage of illness to be mapped, may help to validate the boundaries of current or newly defined clinical entities, distinguish core biological processes from epiphenomena and sequelae, and enable existing knowledge to be better represented and understood.

THE STAGES OF EARLY PSYCHOSIS

Stage 1: Ultra-high risk

In psychotic disorders, an early prepsychotic stage is known to exist, one in which much of the collateral psychosocial damage is known to occur [27]. This earliest stage could, in retrospect, be termed the "prodrome" (i.e. the precursor of the psychotic stage). However, since we can only apply the term "prodrome" with certainty if the definitive psychotic stage does indeed develop, terms such as the "ultra-high risk" [28] or "clinical high-risk" [29, 30] stage have been developed to indicate that psychosis is not inevitable and that false positive cases also occur. This symptomatic yet prepsychotic stage is the earliest point at which preventive interventions for psychosis can concurrently be conceived [31].

The challenge in detecting such a stage prospectively is firstly to define the clinical frontier for earliest intervention and "need for care" which represents the boundary between normal human experience and pathology. Secondly, a set of clinical and other predictors need to be defined which identify a subgroup at imminent risk for psychotic disorder. Earlier writers aspired to the diagnosis of schizophrenia in the prodromal phase [32]. At the end of the 20th century, German psychopathologists emphasized subtle changes in experience and behavior [33, 34], though their complexity meant that they had little impact on Anglophone psychiatry initially. A practical operational definition of a prepsychotic "at risk" or "ultra-high risk" mental state, which could be

shown to confer a substantially high risk of fully fledged psychosis within a 12 month period, was then developed and tested in the early 1990s [35]. This has captured the attention of the field and has been the focus of much subsequent research, focusing on prediction, treatment and neurobiological aspects.

These criteria do indeed predict an "ultra-high risk" group for early transition to psychosis [36], leading to a relative risk of 40% compared to the incident rate of psychotic disorders in the general population [37]. However, there is still a significant false positive rate of 60-80%, though they typically are or turn out to be true positives for other disorders, notably depression and anxiety disorders. As the predictive power for psychosis can be substantially sharpened post-hoc by the use of key variables such as genetic risk and functional impairment [38], this means that increasing the positive predictive value reduces the number and percentage of cases that can benefit. So, if the sample is narrowed, one is on firmer ground, but most cases that do go on to develop the disorder are missed due to the narrower focus [39]. We know already that most cases of first episode psychosis are already missed by prodrome clinics.

There have been a series of clinical trials examining both antipsychotics and/or cognitive therapy as preventive treatment strategies for ultra-high risk patients [2, 40]. These trials suggest that cognitive therapy and antipsychotics may prevent or at least delay the onset of psychotic disorder and reduce symptomatology [13]. However, treating young people in the putative prodromal phase causes some understandable concern that patients might be exposed to unnecessary and potentially harmful treatments [2].

Some "naturalistic" studies revealed that extensive non-evidence-based use of antipsychotic medications (i.e. used off label in a widespread and uncontrolled fashion) seems to be common in clinical settings in Europe and the US, side by side with long delayed and inadequate treatment of first episode and established psychotic disorders [41]. Therefore, clinical trial data is crucial to determining the risks and benefits of various forms of treatment in a new clinical focus and creating solid foundations for an evidence-based approach. This is the best antidote to fears on widespread and potentially harmful and unnecessary use of antipsychotic medications in particular. Indeed, in the "prodromal" or ultra-high risk field, we do not yet know which treatments will be most helpful and acceptable to patients, and crucially in which sequence or combination [2]. Moreover, prospective or naturalistic data can best be collected in the most sound and interpretable fashion in the context of a large well-funded multicenter clinical trial, with an "effectiveness" rather than efficacy design and a minimal intervention arm, to which non-consenters to randomization can be

assigned. In the meantime, the international clinical practice guidelines on early psychosis [13], which advocate a conservative approach to the use of antipsychotic medications and more liberal use of psychosocial interventions, should be followed. This rather conservative approach to treatment of ultra-high risk individuals is even more imperative, as recently it has been discovered that the rates of early transition to first episode psychosis have been falling in the more established prodromal centers [42], with a much higher rate of so-called "false positives" being accepted into these services. This may probably be due to sampling variation, earlier detection of ultra-high risk cases, or improved efficacy of interventions provided [42].

This reduction in transition rate and uncertainty over treatment in the ultra-high risk group has led to valid concerns about identification of and intervention with these individuals. Yet, help-seeking patients defined by the ultra-high risk criteria for first episode psychosis are at risk not only for schizophrenia or psychosis but for other adverse mental health outcomes [43]. We may need to define an even broader pluripotential initial clinical stage with a range of possible exit or target syndromes. Consequently, we have broadened our own clinical and research strategy [44], cross-sectionally with the development of a broader and more accessible system of clinical care for those in the peak age of risk for all types of mental disorders [45], and longitudinally with the creation of a clinical staging model for psychotic, mood and anxiety disorders [20].

Stage 2: Early detection and treatment of first episode psychosis

The second stage involves a therapeutic focus on the period after the onset of fully-fledged psychosis (often known as "first episode psychosis"). This is divided into the period before psychosis is detected and the period after detection. Unfortunately, the undetected or untreated phase can be prolonged, even in developed countries [46]. However, even when psychosis is detected, the initiation of effective treatment may still be delayed. The goal is to minimize this Duration of Untreated Psychosis (DUP). Post-detection, the intervention goals are engagement and initiation of pharmacological and psychosocial treatments. Intensive interventions aimed at maximal symptomatic and functional recovery and the prevention of relapse are ideally delivered during the early weeks and months of treatment.

The importance of DUP and treatment delay in first episode psychosis has been reported in some key systematic reviews [47, 48] and recent influential longitudinal research [2]. These studies have established that longer DUP is both a marker and independent risk factor for poor outcome. The Early Treatment and Identification of Psychosis (TIPS) study in Scandinavia has shown that

reducing DUP leads to early benefits in reducing suicidal risk and severity of illness at initial treatment and sustained benefits in terms of negative symptoms and social functioning [18, 49]. The relationship between DUP and outcome is robust, being sustained over many years of follow-up [50, 51]. However, these studies do show that, though being a relevant risk factor, DUP accounts for a relatively modest amount of outcome variance, underlining the importance of treatment access and quality during the early years of illness. There is an extensive literature attesting to the benefits of comprehensive care of the first psychotic episode. This is summarized in different current guidelines for early psychosis [12, 14], which favor the use of atypicals as first line therapy, because of better tolerability (a crucial issue in drug-naive first episode patients) and reduced risk for tardive dyskinesia. However, some atypicals have a particularly high risk of weight gain and metabolic problems, and these risks need to be carefully managed and prevented wherever possible. In this respect, a number of trials have shown that atypical antipsychotics in low dose are superior for first episode patients where tolerability and safety are at a premium [40, 52].

Psychosocial treatments in early psychosis have been extensively studied, and there are positive findings pointing to the value of cognitive therapies in accelerating and maximizing symptomatic and functional recovery [53, 54]. Increasingly there has been attention to the fact that medications, while assisting in symptomatic recovery, do not, by themselves, contribute to a return to functioning. This has led to an increased focus on the need to enhance social recovery 68 especially educational and vocational aspects [55], through the combination of effective psychosocial interventions with well-managed medication. There is also an increasing focus on targeted cognitive remediation to limit the degree of cognitive decline that is often found as illness progresses [56]. In conclusion, cognitive behavioral therapy and vocational rehabilitation are the key psychosocial interventions in early psychosis and need to be much more intensively and widely deployed. Assertive community treatment for the subset of poorly engaged patients is vital [12]. Family interventions are also an essential element of care [2].

Therefore, initial skepticism regarding DUP has slowly melted in the face of evidence but also the logic of early diagnosis. If we believe we have effective interventions in psychosis, it is perverse to argue that delayed treatment is acceptable. In reducing the DUP the two key components of intervention are community awareness and mobile detection services. Both are important, as the data from TIPS and other studies have shown [57, 58]. When both are in place, it is possible to achieve very low levels of DUP (a median of a few weeks only). These strategies also result in a less risky and traumatic mode of entry into care and enable patients to be engaged without a surge

of positive symptoms or disturbed behavior being required to force entry into poorly accessible or highly defended service systems. They should be available in all developed communities and a standard feature of all mental health systems.

Stage 3: The critical period of the first 5 years after diagnosis

This third stage involves the critical early years beyond the first episode, which can be viewed as the critical period [59]. Treatment goals in this phase are the management of effective medication and the use of effective psychosocial interventions to minimize the development of disability and maximize functioning.

Beyond the first episode, we know that the first 2-5 years post-diagnosis are crucial in setting the parameters for longer term recovery and outcome. This is the period of maximum risk for disengagement, relapse and suicide, as well as coinciding with the major developmental challenges of forming a stable identity, peer network, vocational training and intimate relationships. It makes sense that a stream of care specially focused on young people and on this stage of illness is required to maximize the chances of engagement, continuity of care, appropriate lifestyle changes, adherence to treatment, family support and vocational recovery and progress. Indeed, the available evidence from naturalistic and randomized studies strongly supports the value of specialized early psychosis programs in improving outcome in the short term [60]. If these programs are only provided for 1-2 years, there is also evidence that some of the gains are eroded, suggesting that, for a substantial subset at least, specialized early psychosis care needs to be provided for a longer period, probably up to 5 years in many cases [51, 61]. At this point, persisting illness and disability may be present in a much smaller percentage of people, whose needs may subsequently be well met by more traditional mental health services for older adults.

In conclusion, the best available evidence indicates that streamed care provides superior outcomes in the short to medium term compared to generic care [17, 62]. Such evidence, combined with face validity and obvious poorly met need, has been sufficient to convince mental health policy makers and service providers in hundreds of locations worldwide to adopt, adapt and implement this model.

THE PROCESS OF REFORM

The pace of reform is typically slow in health care. While early intervention in psychosis has made great progress in recent years, dissemination remains in many ways frustratingly slow. Many

developed and most developing countries have made no progress at all, and even those countries which have made significant investments have only achieved partial coverage.

In the process of reform, there are many contextual factors involved. Firstly, we must consider perceptions of the innovation. There must be perceived benefit; the innovation should be compatible with the values and needs of those considering it. In the process of spread, it is vital that innovations be adapted and reinvented in relation to local needs. Secondly, the evidence standards demanded for innovations are rarely if ever applied to the status quo, which in mental health at least is typically less evidence-based than the new approach. This active rearguard action is aided and abetted by the tendency of systems to rapidly build inertia and re-institutionalize after periods of progress.

Despite the welcome progress in early intervention, the laggards (i.e. those apparent members of a modern day flat earth society, whose point of view is the past) have been prominent in the early intervention field [2]. They are also exposed defending the indefensible and demanding impossible and unrealistic levels of evidence before accepting change. While evidence-based medicine is the best antidote for taking wrong and potentially dangerous and wasteful turns in health care, opponents of change have been observed to misuse the paradigm to frustrate change which is overdue and in the best interests of the community. There is regrettably insufficient debate about what considerations other than evidence should influence decisions, especially where changes have high face validity, such as emergency care and indeed early intervention. It is unlikely that oncologists would debate the relative value of early diagnosis and palliative care, which is where psychiatry has got stuck repeatedly. However, Gladwell and Berwick pointed out that the dissemination of innovation has a tipping point, usually around 15-20% adoption [63, 64]. Therefore, once the early majority supporting the change has swung in behind an innovation, the late majority is certainty likely to feel comfortable to move as well [2].

In *conclusions*, many of the obstacles to early intervention are the same ones which impede progress in mental health [65]. They include stigma, pessimism, the silence that surrounds the mentally ill, and a consequent failure to invest. Developed and rapidly developing countries need to recognize the public health importance of untreated and poorly treated mental disorders. A key aspect which is beginning to be recognized is that mental disorders are the chronic diseases of the young [66]. Most adult type mental disorders − notably psychotic, mood, anxiety, substance use and personality disorders − have their onset and maximum impact in late adolescence and early adult life. A broader focus for early intervention should be more effective in mobilizing community support for investment and reform in mental health [2].

Early detection of psychosis: a clinical-psychopathological dissection of the Ultra-High Risk approach

In the last 25 years, the research focus has moved from timely recognition and phase-specific treatment of First-Episode Psychosis (FEP) to the pre-onset period (prodromal phase) [67]. This shift has revealed a critical "blind spot" in our mainstream classificatory systems that also affect the way to call and define early phases of psychotic disorders [68]. In an interesting paper, Schultze-Lutter and colleagues talk about "a near Babylonian speech confusion" [69].

Terminological issue

In this regards, the term "prodromal" has been criticized because of its sense of unavoidable transition to a psychotic disorder [70]. In fact, in medicine, the prodromes are the first signs or symptoms of a disease before it becomes clinically manifest. Thus, the retrospective concept of prodrome is unsuitable to capture prospective psychotic conditions [71]. In the 1990s, McGorry and co-workers coined the definition of "at-risk mental state" (ARMS) to identify individuals with clinical features suggesting an impending disorder, but without the certainty of onset [34]. The concept of "risk state" is borrowed from medicine (e.g. a patient suffering from angina is at risk of developing an acute myocardial infarction). Similar or derived from the ARMS concept are terms such as UHR, Clinical High Risk (CHR) and early/late at risk state. Other terms commonly used are prepsychotic state, subthreshold psychotic symptoms, and early psychosis. These terms are more descriptive than operational. Moreover, the so-called x-like experiences (psychotic, delusional, hallucination, schizophrenia - like experiences) refer to the experience of psychotic symptoms in the absence of psychotic disorder [68]. Nowadays, these experiences are assessed by self-rating scales raising doubts about the real psychotic nature of the experience itself [72]. As Schultze-Lutter and colleagues hoped for, to resolve the current confusion and to ensure the comparability between studies from different research groups, an international consensus catalog of terms and their definition shall be developed [69].

Conceptual issue

In the field of early detection of psychosis, the definitional problem echoes a conceptual one. If there is not a univocal answer to the question "how to define prepsychotic experiences?", the same happens when trying to answer what to look for in individuals at risk for developing a psychotic

disorder. There are a variety of symptoms that are assessed and called in different ways, and the principal ones are summarized below:

- *Attenuated Psychotic Symptoms* (APS): subthreshold attenuated positive symptoms (e.g. unusual ideas, perceptual disturbances, paranoia/suspiciousness, thought disorders);
- *Brief Limited Intermittent Psychotic Symptoms* (BLIPS): transient psychotic symptoms with spontaneous remission;
- *Basic Symptoms* (BS): subjective experienced disturbances of different domains including perception, thought processing, language and attention (with an intact insight);
- *Anomalous self-experiences* (ASE): non-psychotic disturbances of the person's subjective experience of his own identity or "self".

The focus on the above-mentioned symptoms and subjective experiences in people considered at CHR of developing a psychotic episode/disorder led to the development of three main approaches: UHR approach, BS approach and self-disturbance approach [68].

UHR approach

To date, the UHR approach has been widely applied in different research and clinical settings worldwide [2]. Over the years, some modifications of UHR criteria have been made both within the same research group and between different ones, but the concomitant presence of state and trait risk factors plus a sociodemographic criterion (young person aged 14-30 years referred for healthcare) has always been maintained [68]. The state risk is defined by the presence of APS or BLIPS, while the trait risk factors include genetic risk (i.e. first degree relative with a psychotic disorder) or schizotypal personality disorder in the patients, associated with a decline in psychosocial functioning or sustained low functioning.

The focus on help-seekers applies a filter reducing the high number of false positives that could necessitate assessing large asymptomatic community samples. Indeed, before the development of the UHR concept, many studies focused on genetic risk (i.e. called "high risk approach") by longitudinally monitoring individuals with a positive family history for a psychotic disorder. The recruitment of individuals on the basis of familiarity led to not only a high number of false positives, but also the loss of all those patients developing a psychotic disorder without familial risk. In 1992, Bell developed an alternative strategy to identify individuals at high risk of developing a psychotic disorder based on the concepts of "multiple-gate screening", namely the satisfaction of more than a unique criterion to define the risk state in order to obtain a selected

sample, and “close-in follow up”, namely a shorter time monitoring the onset of sign and symptoms coincident with the period of maximum incidence [73]. These acute intuitions were operationalized for the first time by the Australian group of Yung and McGorry in the middle 1990s [34]. This led to the development of the UHR approach that was widely applied in the subsequent years by many research and clinical groups worldwide [74].

Over the years, many instruments have been developed for in-depth UHR assessment. The main ones are: CAARMS, SIPS/SOPS and ERIraos. The Comprehensive Assessment of At-Risk Mental States (CAARMS) was developed by Yung and co-workers and is now widely used mainly in Australia, Asia and Europe [38]. The two main purposes of this instrument are to identify the imminent development of a psychotic episode and to determine if UHR criteria are satisfied. Indeed, all the three main UHR criteria (APS, BLIPS and supposed vulnerability) are investigated. The CAARMS is a semi-structured interview with several subscales: disorders of thought content, perceptual abnormalities, conceptual disorganization, motor changes, cognitive change (attention and concentration), emotional disturbances, negative symptoms, subjectively impairment of energy and impaired tolerance to normal stress. Functioning is also assessed with the integrated “Social and Occupational Functioning Assessment Scale” (SOFAS) module.

The Structured Interview for Prodromal Symptoms (SIPS) and the Scale of Prodromal Symptoms (SOPS) were both developed by Miller, McGlashan and colleagues at PRIME Research Clinic at Yale University and are mostly used in North America and Europe [75]. These two instruments are conjointly used to provide a systematic measure of the presence/absence of prodromal states, to measure the severity of prodromal symptoms and to define an operational threshold for psychosis. The SIPS consists of several measures: SOPS, Schizotypal Personality Disorder checklist (DSM-IV), family history questionnaire and Global Assessment of Functioning Scale (GAF). The SOPS includes different subscales: positive symptoms (unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication); negative symptoms (social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning); disorganization symptoms (odd behavior and appearance, bizarre thinking, trouble with focus and attention, personal hygiene); general symptoms (sleep disturbance, dysphoric mood, motor disturbances, impaired tolerance to normal stress).

The Early Recognition Inventory (ERIraos) was developed in the Central Institute of Mental Health (CIMH, Mannheim) in association with the University of Heidelberg and is mainly used in Europe.

The peculiarity of this instrument is that it permits the investigation of both UHR criteria and basic symptoms. It is a two-step procedure: a 17-item screening instrument is used to identify potential ARMS individuals and is administered by a general practitioner or other professional contact person; if the defined cut-off is reached, the individual should be referred to an early psychosis recognition center for a more detailed risk assessment with the ERIraos complete symptoms list (110 items). This is divided in 12 sections: introductory questions; changes in mood, interest and drive; disturbance of sleep and appetite; changes in personality; dysfunctional behavior; anxiety and obsessive-compulsive symptoms; thought disorders; disorders of self and delusions; impaired bodily sensations; abnormal perceptions; motor disorder and observed behavior [76].

BS approach

Basic symptoms are phenomenally different from APS/BLIPS. Indeed, BS are subtle, subjectively experienced subclinical disturbances in drive, affect, thinking, speech, (body) perception, motor action, central vegetative functions, and stress tolerance [77]. BS can occur not only in prodromal, but also in the residual phases of psychotic disorder and during psychotic episodes [78].

The subjective feature of BS makes these symptoms accessible only to the suffering individual, differentiating BS from negative symptoms that are functional deficits visible from the outside [79]. Indeed, avoidance or social withdrawal can represent BS coping strategies. Another feature of BS is insight: the patient realizes that something new, strange and barely understandable and explicable is happening [78].

Although Chapman [80] and Varsamis [81] firstly studied similar kind of experiences during 1960-1970, it was Gerd Huber and his research group to propose their first systematic exploration coining the notion of "Basic Symptoms" [78]. The choice of the term "basic" reflects the idea of such symptoms as the first, immediate experiential expression of the presumed neurobiological substrate of vulnerability to schizophrenia [79]. According to the BS approach, in the early phases of psychotic disorders, especially schizophrenia, symptoms occur in three developmental levels: the first consists of uncharacteristic BS (subthreshold alterations in drive, volition, affect, concentration and memory) that could spontaneously remit or gradually increase in number and severity reaching the second level of BS with more typical alterations in thinking, speech, motor action and body perception. In the absence of remission, the second level BS can evolve into third level BS represented by outright psychotic symptoms [82]. The symptomatic rise to real psychotic experiences is often the consequence of a burn-out, an exhaustion of personal resources and coping

strategies closely related to external factors such as familiar environments, social relationships, working/studying functioning, coping skills, and resilience [83].

The first instruments developed for BS assessment were the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [84] and the Frankfurt complaint Questionnaire (FBF) [85]. More recently, the Schizophrenia Proneness Instrument (available in both Adult [SPI-A] and Child-Youth [(SPI-CY] version) was developed [86, 87]. To date, SPI-A/-CY are commonly used to assess BS in Europe.

By analyzing data from the Cologne Early Recognition (CER) study [88], two BS subgroups were identified for the definition of the prodromal phase: the first, known as *COPER*, includes 10 cognitive-perceptive BS (thought interference, thought perseveration, thought pressure, thought blockages, disturbance of receptive speech, decreased ability to discriminate between ideas/perceptions and fantasy/true memories, unstable ideas of reference, derealization, visual perception disturbances and acoustic perception disturbances); the second, known as *COGDIS*, includes 9 cognitive disturbances (inability to divide attention, thought interference, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, unstable ideas of reference, disturbances of abstract thinking and captivation of attention by details of the visual field). According to the results of German Research Network of Schizophrenia, the COPER BS group has good predictive accuracy. On the other hand, the COGDIS BS group has been used as a set of high risk criteria as an alternative to UHR [88]. The combination of BS and UHR criteria may identify the highest risk of transition to psychosis in the next 18 months [89]. However, the average period between COGDIS/COPER assessment and onset of psychosis is longer than the one between UHR evaluation and first episode of psychosis, suggesting that BS are more appropriate for early detection of distal prodromal states (compared to more proximal ones indexed by UHR APS and BLIPS criteria).

Self-disturbance approach

From a phenomenological point of view, a core marker of psychotic vulnerability (and above all of schizophrenia spectrum disorders) is the concept of self-disturbance. Indeed, in early descriptions of schizophrenia the disturbances of the self always had a central role. Bleuler described “Ich-Spaltung” and “Autism”, both involving an affliction of the self, as the two basic features of schizophrenia [90]. Kraepelin metaphorically depicted the disunity of consciousness typical of schizophrenia as an “orchestra without a conductor” [91]. Jaspers sustained the possible affliction

of the self in different aspects such as activity, unity, vitality, identity and demarcation [92]. Furthermore, he described the "delusional mood", that is the first experiential, qualitative crisis that precedes the delusional manifestation. A similar construct has been labelled "trema" by Conrad [93]. Along a convergent line, Minkowsy coined the expression "le trouble generateur" [94] to describe the loss of vital contact with reality and the interrogative attitude typical of the early phases of schizophrenia, whereas Blankenburg talked about the loss of natural self-evidence, the non-specific specificity of being unable to grasp everyday mundane significations [95].

Nowadays, phenomenologically-oriented psychopathology still emphasizes the importance of examining subjective experiences rather than focusing on behavioral symptomatic manifestations to grasp the real psychotic vulnerability. This conceptual lacuna in the current behavioristic and neurobiological psychiatry is also evident in the field of early detection of psychotic disorders. The UHR assessment of state and trait factors surely has substantial pragmatic value in identifying individuals at risk for imminent onset of a psychotic episode, but partly neglects the subjective and unique psychopathological core of self-experienced vulnerability. Thus, it is important not to equate UHR criteria and psychotic vulnerability. The BS, developed by Huber and largely studied in Germany during the last decades, partly overlap with the self-disturbances described by Parnas (e.g. disturbances of consciousness and action, alterations in bodily experiences) [96], although self-disturbance tend to emphasize a global, gestaltic change of subjecthood [97].

According to the model developed by Parnas [96], self-disorders represent psychopathological trait markers of psychotic vulnerability and especially of schizophrenia spectrum disorders. Indeed, the fact that prodromal and psychotic symptomatology is not restricted to any particular modality of consciousness (i.e. it can appear as a cognitive, perception or sensory disturbance) suggests that a more basic and essential feature exists [97]. As Minkowsky said, "…it is not this or that function which is disturbed, but much more their cohesion, their harmonious interplay in its globality" [94]. As the self can be described as the first personal givenness of experience, self-disturbance may be defined as pervasive or frequently recurrent experience in which one's first-person experiential perspective or one's status as a subject of experience or action is somehow distorted [98]. These anomalous experiences are not yet of psychotic intensity, and the patient is able to keep a distance from them [99].

The instrument to assess these disturbances is the Examination of Anomalous Self-Experience (EASE) [100]. It is a symptom checklist for semi-structured phenomenological exploration of experiential subjective anomalies that appear to reflect disorders of basic self-awareness. It has been

developed on the basis of self-descriptions obtained from patients suffering from schizophrenia spectrum disorders. It consists of five domains: cognition and stream of consciousness, self-awareness and presence, bodily experiences, demarcation and transitivism, and existential reorientation. The exploration of ASE can be complex because of the difficulty for the patient to communicate these uncanny and often ineffable subjective experiences (they often need to draw upon metaphors to describe them). It is also difficult for the interviewer who needs substantial familiarity with the experiences described, as well as the ability to create an intimate but neutral interview climate, since the patient has probably never talked with anyone about his basic self-disturbances. Empirical research on self-disturbance indicates that the ASE specifically captures schizophrenia spectrum vulnerability, rather than a general psychosis proneness.

Clinical staging model of psychosis: a critical review

Clinical staging differs from conventional diagnostic practice in that it defines the progression of disease in time and where a person lies along this continuum of the course of illness [23] and can provide a clinical-decisional framework for person-tailored early intervention [67]. Therefore, clinical staging not only defines the extent of progression of a disorder at a particular point in time, but also where a person lies along the continuum of the course of an illness [101]. The rationale of such developmental model is that the earlier in the course of illness the treatment is offered, the safer and the more effective it should be in terms of long-term outcomes [102].

The clinical staging model is already widely used in medicine for those disorders that are potentially severe and inclined to progress if untreated. This is the case of the majority of psychiatric disorders, although the clinical staging model is not yet common in the psychiatric practice where disorders are strictly defined by outright symptomatic criteria. The concept of clinical staging related to early psychosis indicates a continuum of increasing risk, in which initially unspecific conditions phenotypically overlapping with the initial stages of other disorders gradually progress to more crisply defined clinical-diagnostic profiles. A clinical staging model of psychotic and severe mood disorders, composed of four different developmental stages, has been developed [23]:

- *Stage 0*: comprises asymptomatic individuals with an increased risk for psychotic disorders;
- *Stage 1*: is divided in two subgroups. Stage 1a consists of individuals with mild or non-specific symptoms and with mild functional decline. Stage 1b coincides with UHR

individuals. These two subgroups are quite similar to early/late initial prodromal states described by German Research Group;

- *Stage 2*: includes individuals with a first psychotic/severe mood disorder;
- *Stage 3*: consists of three subgroups (incomplete remission [3a], remission and relapse [3b], and multiple relapses [3c];
- *Stage 4*: is characterized by the persistence of the psychotic/severe mood disorder.

For each of these developmental stages of the disorder, target populations, referral sources and potential therapies are proposed (for details, see the Table 1).

Table 1 – The clinical staging model framework for psychotic and severe mood disorder (adapted from McGorry et al., 2006) [23].

Stage	Definition	Target population and referral sources	Potential interventions
0	Increased risk of psychotic/severe mood disorder No symptoms	1st degree teenage Relatives of a proband	Improved mental health literacy Family education Drug education Brief cognitive skills training
1a	Mild/non-specific symptoms Mild functional change/decline	Screening of teenage population Primary care physicians School counsellors	Formal mental health literacy Family psychoeducation Formal CBT Active substance misuse reduction
1b	UHR	Primary care physicians Educational agencies Welfare agencies Emergency services	Family psychoeducation, formal CBT Active substance misuse reduction ω3 fatty acids Atypical antipsychotics Antidepressants, mood stabilizers
2	First episode of psychotic or severe mood disorder	Primary care physicians Welfare agencies Emergency services Specialist care agencies Drug/alcohol services	Family psychoeducation Formal CBT Active substance abuse reduction ω3 fatty acids Atypical antipsychotics Antidepressants, mood stabilizers
3a	Incomplete remission	Primary and specialist care services	As for stage 2 but with additional emphasis on medical and psychosocial strategies to achieve full remission
3b	Recurrence or relapse of psychotic or mood disorder with residual symptoms or decline in neurocognition	Primary and specialist care services	As for stage 3a but with additional emphasis on relapse prevention and strategies to detect early warning signs
3c	Multiple relapses Impact of illness is objectively present	Specialist care services	As for stage 3b but with additional emphasis on long-term stabilisation
4	Severe persistent unremitting illness	Specialised care services	As for stage 3c but with more emphasis on tertiary treatment and social participation

The usefulness of this model as a guide to early interventions is rather transparent since contemporary classifications (e.g. DSM, ICD) do not offer a clear framework for describing and managing the widespread subthreshold symptomatology that characterizes the early phases of psychosis [103]. Indeed, to date, DSM and ICD criteria allow the diagnosis of stable disorders (e.g.

schizophrenia), but not developmental conditions. However, although in the new DSM-5 “Attenuated Psychotic Syndrome” has been added in the appendix as a condition of further study, some refinements are necessary.

Due to the non-specific nature of prodromal symptoms, there are reasonable concerns about labelling early psychotic phases. First of all, there is the conceptual and practical danger that risk could be seen as disorder [101]. This is why the DSM-5 former proposal “psychosis risk syndrome” has been replaced by “attenuated psychosis syndrome”. Moreover, since psychotic experiences can appear even in benign conditions and in the general population, the possibility to expose false positives to unnecessary medication is real [104]. Indeed, the majority of these patients will not develop a psychotic disorder, calling the safety and utility of treatment in question [101]. In a recent meta-analysis, transition rates of 15% at 1 year, 19.4% at 2 years, 25.3% at 3 years, and 37% at 4 years were found [30]. Another important counterargument is that (at risk) psychotic-spectrum patients, once labelled, might begin to see themselves as defective, unworthy, shameful as well as discriminated and stigmatized by others. It is likely that knowing that one is at risk to develop a disabling psychotic disorder will have an impact on how the person views himself and plans for the future [105].

On the other hand, the clinical staging model and the inclusion of ARMS in traditional diagnostic systems could have potential benefits. The conceptualization of stigmatizing phenomena as existing across a continuum within the general population suggests the possibility that liability to psychosis is simply a human vulnerability depending on the interaction of both genetic and non-genetic risk factors, not differently from other medical fields where gradations of parameters or symptoms confer quantified risk for outright disease. Moreover, the coding of ARMS in traditional diagnostic systems would include a large number of patients that, at present, are not enrolled in psychiatric services, even if they have high levels of suffering. Indeed, according to both ARMS and APS criteria, symptoms must be sufficiently distressing and disabling enough to lead to help-seeking [101]. Therefore, early clinical management could not only prevent a possible transition to psychosis, but it can also ameliorate the impaired quality of life of these patients. Furthermore, clinical staging substitutes taxonomy of risk to a categorical concept of psychiatric diseases hopefully leading to a rational stratification of treatment according to the different developmental stages of a disease [106]. In this sense, psychosocial counselling and support should be more tailored to the early phases, in which no specific symptoms are detectable, while psychoeducation, family intervention, cognitive behavioral therapy and eventually psychopharmacology would

progressively become more pertinent with the emergence of more characteristic prodromal and psychotic states [41].

In *conclusion*, a contemporary early detection approach, while shaping pragmatic-descriptive criteria to conduct rational intervention-based research in help-seekers at high risk of imminent onset of psychosis, has overlooked fundamental clinical phenomena associated with the prodromal phases of psychotic disorders. Although some of the phenomenological insights have been incorporated in the at risk BS criteria (i.e. COPER/COGDIS), further contributions of phenomenologically-oriented psychopathology are worth emphasizing. First, on the clinical-phenotypic level, recent empirical research has shown the relevance of structural disorders of subjectivity (i.e. self-disturbance) as an early phenotypic marker of vulnerability to schizophrenia spectrum conditions (including both psychotic and not psychotic expressions) [107]. Thus, integrating the exploration of self-disorders in contemporary ARMS models could further identify (within the pool of subjects at increased risk of transition to psychosis) those who harbor a higher vulnerability to schizophrenia. Second, on a more comprehensive level, a phenomenologically-guided approach can provide a more experience-close explication of the early clinical phenomena that accompany the development of psychosis. This is of value for both early risk stratification and for psychosocial and educational support.

Perspective investigations of early psychosis: rationale and recommendations

In psychiatry, as in medicine, strenuous efforts are made to predict and, subsequently, prevent diseases before their first manifestation and the development of significant disability [108]. In psychosis research, this approach has already been pursued over the past two decades within the framework of indicated prevention in help-seeking samples [109]. A successful preventive intervention relies on the accuracy of risk detection (i.e. on the detection of CHR) [30].

Prevalence and burden of psychotic disorders

The defining characteristic of psychosis is the presence of positive symptoms (i.e. delusions, hallucinations and positive formal thought disorders), yet again confirmed as the key features of psychotic disorders in DSM-5 [110]. The lifetime prevalence of psychoses is estimated between 0.2 and 3.5%, their annual incidence between 0.01 and 0.035%, with growing numbers reported in Europe where, within 12 months, approximately 3.7 million adults (0.8%) had been affected in 2005 and as much as 5 million (1.2%) in 2011 [111]. Approximately 10-15% of all psychoses are Early-Onset Psychoses (EOP) manifesting before the age of 18, and about 1-3% are Very-Early-Onset Psychoses (VEOP) with an onset before the age of 13 [112].

Following (positive) psychotic episodes, negative symptoms commonly persist, and are associated with cognitive impairments and psychosocial disabilities [79]. This is a main reason why such a relatively infrequent disorder is responsible for the sixth largest share of disability-adjusted life years (DALYs) in adults in Europe (i.e., 637.693 DALYs) [111], and the third largest of all main brain disorders worldwide (16.8 million DALYs) [113]. Despite the infrequency of VEOP and EOP, schizophrenia is one of the ten main causes of DALYs in 10- to 14-year-old boys and 15- to 19-year-old girls [114]. Thus, at € 93.9 billion of total direct health care, direct non-medical and indirect costs of brain disorders in Europe in 2010 attributed to psychoses, only the costs for mood disorders and dementia were higher [115]. In addition, the burden caused by stigma and discrimination is also among the highest in psychosis [116].

Etiological and pathogenetic aspects in psychoses

Psychoses are increasingly considered as a brain development disorder with polygenic heredity [117]. As with other complex diseases, research is now focusing on characterizing the polygenic factors and clarifying their variable phenotypic expression. This pathogenesis seems to be greatly

influenced by both rare gene variants with large effects, and interactions between different genes of small effect as well as genes and environment [118]. Contributory environmental risk factors include exposure to viral agents in the second trimester of pregnancy, birth complications, childhood trauma, migration, the quality of the rearing environment, socio-economic disadvantage, urban birth, living in urban areas and using illicit drugs (particularly cannabis). However, with odds ratios of around 2, each of these factors increase lifetime-risk for psychosis only slightly [119] and causality can be difficult to determine.

Rationale for a prevention of psychoses

The epidemiological, clinical and etiopathogenic aspects of psychoses outlined above, and the lack of a therapeutic breakthrough in the treatment of the disorder itself make psychotic disorders a worthwhile target for preventive measures prior to their first manifestation. In principle, prevention can be offered: universally to the general, unselected population; selectively to healthy individuals with a known risk factor of the disease; or by indication to persons already suffering from first complaints and impairments and who are actively seeking advice and help [31].

The universal and the selective approach cannot be implemented effectively-at least to date-due to: the low incidence of psychoses in the general population, lack of sufficient etiological knowledge and of risk factors of sufficiently large effect. The indicated approach is currently regarded as the most appropriate prevention strategy for psychoses [120], because the majority of FEP psychosis patients report having suffered from mental problems including risk symptoms and increasing psychosocial impairment for an average 5-year period prior to the onset of psychosis [121] (Figure 1). This strategy is supported by consistently reported negative effects of long Duration of Untreated Illness (DUI) and DUP on outcome [47] that may even be aggravated in EOP, because more pronounced neurodevelopmental and cognitive deficits, the insidious onset of less pronounced positive symptoms and/or the atypical clinical picture of the beginning EOP - potentially misinterpreted as “adolescent crisis” - might act as further delaying factors [122].

The clinical high risk (CHR) state of psychoses

Currently, there are two main complementary approaches to the characterization of the CHR state of psychoses: the ultra-high risk (UHR) and the basic symptoms criteria (Figure 1) [121]. The alternative UHR criteria, which comprise the attenuated psychotic symptom (APS) criterion, the brief limited intermittent psychotic symptom (BLIPS) criterion, and the genetic risk and functional

decline (GRFD) criterion (Table 2), were originally developed with the explicit aim of detecting an imminent risk for psychoses, i.e. persons at risk for developing a first-episode within the next 12 months [124].

Figure 1 – Model of the early course of psychosis (adapted from Fusar-Poli et al., 2012) [121].

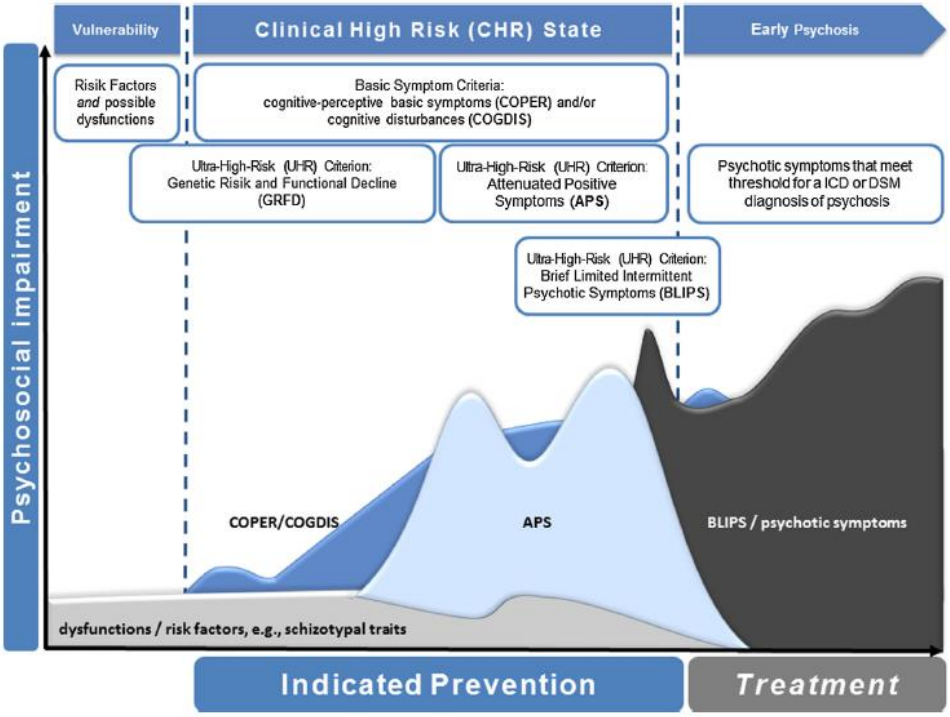


Table 2 - General definition of ultra-high risk (UHR) criteria.

Symptomatic approach
A. Presence of at least any 1 Brief Limited Intermittent Psychotic Symptom (***BLIPS***):
Hallucinations
Delusions
Formal thought disorders
B. Presence of at least any 1 attenuated psychotic symptom (***APS***):
Ideas of reference
Odd beliefs or magical thinking, including ideas of grandiosity
Paranoid ideation
Unusual perceptual experiences
Odd thinking and speech

Constrictive 'state-trait' approach

C. Presence of a genetic risk factor (family history of psychosis; schizotypal personality disorder in the individual) in combination with a recent significant decline in psychosocial functioning (GRFD)

Presence of at least any one of A, B or C to meet UHR criteria

While their operationalization usually hardly differs with respect to these broad definitions, the associated requirements in particular of APS and BLIPS criteria can differ considerably between assessments (Table 3) [124].

Table 3 – Comparison of additional requirements of symptomatic UHR criteria in the CAARMS and the Structured Interview for Psychosis Risk Syndromes (SIPS).

Scale	Onset	Frequency	Substance-use, co-morbidities	Functioning
Attenuated psychotic symptoms (APS)				
SIPS	Development or increase by 1 point in severity within the past year	Average frequency of at least once per week in the past month	Not the effect of substance use and not better explained by a mental disorder	Irrespective of current or past functioning
CAARMS early versions	Present for at least 1 week within the past year and not more than 5 years	Frequency of several times per week	Irrespective of relation to substance use or other mental disorders	Irrespective of current or past functioning
CAARMS 2006 version	Symptoms present in the past year	At least once a month to twice a week–more than one hour per occasion OR At least 3 to 6 times a week–less than one hour per occasion	Irrespective of relation to substance use or other mental disorders	30% drop in SOFAS score from premorbid level, sustained for a month and occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer
Brief limited intermittent, i.e. transient psychotic symptoms (BLIPS)				
SIPS	Development within the past 3 months	Several minutes a day at least 1/month and no more than 1 hour a day for 4 days a week (on average) for 1 month	Symptoms are not seriously dangerous or disorganizing, not the effect of substance use and not better explained by a mental disorder	Irrespective of current or past functioning
CAARMS early versions	Occurrence within the past year	Duration of episode less than a week	Irrespective of relation to substance use or other mental disorders	Irrespective of current or past functioning
CAARMS 2006 version	Symptoms occurred during last year	At least 3 to 6 times a week–more than an hour per occasion OR At least daily–less than an hour per occasion	Irrespective of relation to substance use or other mental disorders	30% drop in SOFAS score from premorbid level, sustained for a month and occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer

Legend – SOFAS = Social and Occupational Functioning Assessment Scale.

In contrast to the UHR criteria, the criteria based on basic symptoms (i.e. the cognitive-perceptive basic symptoms [COPER] criterion and the cognitive disturbances [COGDIS] criterion) (Table 4) [125] were developed to detect the risk for psychosis as early as possible in the development of the illness, ideally before functional impairments appeared (for details, see also Figure 1).

Since EOP were reported to present a slightly different onset and clinical picture compared to adult-onset psychoses [30], early detection in children and adolescents might be confronted with additional challenges. This is supported by first reports on conversion rates in adolescent risk samples between age 12 and 18 [126], indicating that lag time to conversion might be longer and, consequently, conversion rates in the first years following initial risk assessment might be lower. Furthermore, recent studies reported high prevalence rates of (attenuated) psychotic symptoms [30], in particular of hallucinations, in children and young adolescents, which seem to decrease with age [127] and to remit spontaneously in about three quarters [128]. Thus, it was recently argued that the validity of current risk criteria needs to be examined in and possibly adapted to children and adolescents.

Table 4 – Basic symptom criteria

Cognitive-Perceptive Basic Symptoms (COPER)
Presence of ≥ 1 of the following 10 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months and first occurrence ≥ 12 months ago:
Thought interference*
Thought perseveration
Thought pressure*
Thought blockages*
Disturbance of receptive speech*
Decreased ability to discriminate between ideas/perception, fantasy/true memories
Unstable ideas of reference*
Derealization
Visual perception disturbances (excl. hypersensitivity to light and blurred vision)
Acoustic perception disturbances (excl. hypersensitivity to sounds)
Cognitive Disturbances (COGDIS)
Presence of ≥ 2 of the following 9 basic symptoms with a SPI-A score of ≥ 3 within the last 3 months:
Inability to divide attention
Thought interference*
Thought pressure*
Thought blockages*
Disturbance of receptive speech*
Disturbance of expressive speech
Unstable ideas of reference*
Disturbances of abstract thinking
Captivation of attention by details of the visual field

Legend – SPI-A = Schizophrenia Proneness Instrument, Adult version.

Conversion rates to psychosis

In a recent meta-analysis on transition prevalence to psychosis [30], the pooled conversion rate in UHR samples increased from 9.6% at 6 months to 15.0% at 1 year, 19.4% at 2 years, 29.1% at 3 years, and 37.0% at > 4-year follow-up. In COGDIS samples, the respective numbers ranged from 25.3% at 1 year to 28.4% at 2 years, 50.0% at 3 years, 54.9% at 4 years, and 61.3% at > 4 years. A 6-month conversion rate of 13.9% was only reported by one study.

Irrespective of a potential co-occurrence of criteria, UHR, COPER and COGDIS samples did not significantly differ in 6-month, 1- and 2-year conversion rates, but only in longer term conversion rates, due to higher rates in both COPER and COGDIS compared to UHR samples [30]. With regard to the analyses of UHR studies reporting conversion rates separately for the three UHR criteria (APS, BLIPS and GRFD), pooled conversion rates differed significantly at 1-, 2- and 3-year follow-ups, mainly due to higher conversion rates in BLIPS (ranging from 13.3% at 6 months to 46.6% at 2 years and 51.8% at 3 years) and lower in GRFD samples (ranging from 0.0% at 1 year to 1.9% at 2 years) [30]. Finally, the pooled conversion rate in APS samples ranged from 7.7% at 6 months to 14.9% at > 4-year follow-ups of child/adolescent samples [129]. In this systematic meta-analysis, the European Psychiatric Association (EPA) also analyzed pooled effects of both "UHR plus COGDIS" and "UHR and/or COGDIS" on 2-year conversion rates. Results indicated a significant pooled sample effect that did not significantly differ from each other or from UHR or COGDIS when these were considered irrespective.

EPA recommendation on early detection in psychosis

Based on the results of meta-analyses, evidence-based recommendations for early detection of psychosis were formulated by EPA that improved upon those of previous expert consensus guidelines (specifically, at a grade of recommendation of "C" for recommendations 1-5 and at grade "D" for the expert consensus-based recommendation 6) [30].

<u>Recommendation 1</u>

The EPA considers that the following 3 CHR criteria should be alternatively used in the early detection of psychosis when past or present psychosis and causation by a somatic illness had been ruled out:

- at least any one attenuated psychotic symptom (i.e. (1) unusual thought contents or delusional ideas not held with full conviction, including ideas of reference not immediately rectified by

cognition, (2) perceptual aberrations or hallucination with remaining insight, or (3) disorganized communication or speech that is still comprehensible and responds to structuring in the interview) that meets the additional requirements of either SIPS or CAARMS (for details, see the Table 3);

- at least any two self-experienced and self-reported cognitive basic symptoms rated irrespective of their appearance in the interview (i.e. (1) interference of completely insignificant thought contents, (2) blockage of thoughts not explained by lack of concentration or attention, (3) thought pressure by thoughts unrelated to a common topic, (4,5) disturbances of receptive or expressive speech in everyday use of native language, (6) inability to divide attention between tasks relating to different senses and generally not requiring full attention each such as making a sandwich and talking to someone, (7) disturbance in the immediate recognition and understanding of any kind of abstract, figurative or symbolic phrases or contents, (8) subjective experience of self-reference that are almost immediately rectified by cognition, and (9) captivation of attention by insignificant details of the visual field that impairs paying attention to more relevant stimuli) that have not been present in what the patient considers his/her premorbid stage, have occurred at least on a weekly basis for some time in the past 3 months and are not an effect of drug use;
- at least any one transient psychotic symptom (i.e., delusion, hallucination, formal thought disorder) that meets the additional requirements of either SIPS or early CAARMS (Table 2).

This recommendation did not include the basic symptom criterion COPER because of its large overlap with COGDIS and, compared to COGDIS, its lesser degree of evidence due to the very small number of studies of that only the study on that the basic symptom criteria were developed exceeded 2-year follow-up [125].

Recommendation 2

The EPA considers that a genetically increased risk of psychosis by a positive family history of psychosis in at least one first-degree biological relative should not be used as a clinical indicator of a CHR on its own, even if accompanied by functional deficits and mental problems. Rather, it should be regarded as a general risk factor indicating an already increased pre-CHR assessment risk for psychosis that should be taken into account in patients meeting the above CHR criteria. Patients not presenting the above CHR criteria but a genetic risk and other mental problems should however be encouraged to present again for a CHR assessment should they note the onset of mental problems resembling CHR symptoms.

Recommendation 3

In line with the general EPA guidance on prevention of mental disorders [108] whose aims include reduction of the burden of mental disorders by improvement in quality of life and productivity of individuals, the EPA considers that a significant decline in occupational and/or social functioning (and, relatedly, in productivity) should not be an obligate requirement in the above CHR criteria for the lack of evidence for an improvement of prediction by this addition [30]. However, it should be considered as an indication of an imminence of risk of conversion and CHR patients with a significant functional decline should be considered at high need for treatment.

Recommendation 4

The EPA considers that the above CHR criteria should only be applied in persons already distressed by mental problems and seeking help for them or persons seeking clarification of their current risk for a vulnerability for psychosis, e.g. by genetic risk. Any clinical screening of other persons seems not warranted by current scientific evidence.

Recommendation 5

The EPA considers that the above CHR criteria should only be used and communicated with out-most care in children and young adolescents in whom they should nevertheless be assessed and monitored. In late adolescence, however, the CHR criteria seem to be as applicable as in adults. Indeed, pairwise comparisons indicated lower conversion rates in child/adolescent samples (aged < 18 years) compared to young adult populations (aged 18-35 years) at 2 and > 4 years. In contrast, conversion rates in youth samples (i.e. ≥ 50% minors [median or mean age ≤ 18 years or mean age ≤ 18 with an upper standard deviation still spanning patients ≤ 18 years) never differed significantly from those in adults [30]. The only significant difference to the total sample conversion rates occurred for child/adolescent individuals at > 4 years with an additional trend result at 6 months and 2 years [30].

Recommendation 6

The EPA considers that a trained specialist (psychiatrist, clinical psychologist or equivalent mental health professional) with sufficient experience in CHR should carry out the assessment; if referral to a specialist is not possible, the responsible clinician should consult a trained specialist on the case, e.g. by phone; and specialized early detection services should be prepared to give such advice, e.g.,

within the framework of telephone consultation hours. Case conferences with experts in early detection of psychoses are even advised for mental health specialists.

In *conclusion*, the young field of preventive research in psychosis has already resulted in sufficient evidence to formulate recommendations for an early detection of psychosis in the clinical practice. Yet, EPA meta-analysis revealed significant heterogeneity of conversion rates that needs to be addressed in future studies in order to develop more sophisticated prediction models that can be easily translated into clinical practice and address the special characteristics and treatment needs of different patient groups [30]. Moreover, the success of preventive approaches also depends on a sufficiently high rate of target persons who are reached by it. Thus, to reach also CHR persons who do not actively seek help for their mental problems, more research in the general population is needed to develop ethically justified means such as well-validated and reliable screening instruments on the basis of those already proposed [130].

Perspective investigations of early psychosis: screening and in-depth assessment instruments

A long-lasting interest in subthreshold signs of schizophrenia has in the 1990s led to attempts at systematic detection of this condition [9]. Traditional psychopathological assessment instruments were not sufficiently sensitive to subthreshold conditions of schizophrenia and other psychoses, and therefore a number of new assessment instruments have been constructed.

Currently, the field is dominated by two main approaches: one inspired from a traditional Positive and Negative Syndrome Scale (PANSS) approach [75], focusing on Attenuated Positive Symptoms (APS) [123]. The other is based on a detailed phenomenological way of describing disturbances prior to onset of psychosis, the Basic Symptoms (BS) approach [33]. The BS presumably characterize the early prodromal phase whereas the APS presumably characterize the late prodromal phase (for details, see also Figure 1). In addition to these measures, screening instruments have been developed for recruitment purposes [130].

Five main instruments constructed for assessing a possible prodromal state were detected: the CAARMS [38], the SIPS [75], the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [84], the Schizophrenia Prediction Instrument (Adult [SPI-A] and Child-Youth [SPI-CV] version) [86, 87], and the ERIraos (a 2-step instrument) [76]. Five screening instruments were also detected: PRODscreen [131], Prodromal Questionnaire (PQ) [132], Youth Psychosis At Risk Questionnaire (Y-PARQ) [131], SIPS screen [134], and the early detection Primary Care Checklist (PCCL) [135]. Additionally, another instrument, Examination of Anomalies in Self-experience (EASE) [100] will be described, even if not specifically developed for prodromal symptoms, as it targets phenomena of potential importance when detecting individuals in a prodromal phase [136]. Before the description of the individual instruments, a short comment on previous instruments on subthreshold psychotic symptoms is given for the purpose of clarification.

Scales of schizotypy and psychosis proneness

Schizotypal conditions are by many researchers regarded as subclinical manifestations of schizophrenia, possibly related to a vulnerability of the disorder [137]. Symptoms of schizotypy are attenuated forms of the fundamental symptoms of schizophrenia, in particular expressive symptoms like reduced expression of affect, interpersonal isolation and eccentricity. Brief intermittent psychotic episodes and thought disorders can be part of the clinical picture, but reality testing is essentially intact. Examples of schizotypy scales are Schizotypal Personality Questionnaire (SPQ)

[138], scales of physical and social anhedonia [139], aberrant perception [140], and magical ideation [141]. However, the predictive value of scales of schizotypy and psychosis proneness in a 10-year follow-up of college students was low (i.e. 0.1% for schizophrenia) [142].

In particular, symptoms in the prodromal state of schizophrenia can be similar to those of schizotypy [143]. Ideally, the course of symptoms reveals the difference. Conceptually-defined prodromal symptoms have appeared recently and as a deviation from the person's habitual mode of experience/behavior. In contrast, the trait-like symptoms of schizotypy are stable. In the instruments described below, this distinction is reflected in the criteria of duration/novelty of symptoms, or in a recent drop in general functioning [136].

Assessment of the pre-onset phase

Scales constructed for the assessment of a putative prodromal state are mainly based on one of the two following approaches, and will be described accordingly: (1) the APS approach (i.e. CAARMS and SIPS) or (2) the BS approach (i.e. BSABS and SPI-A). EASE is partially based on the presence of BS [100]. ERIraos is based on multiple levels of risk assessment [76]. The instruments are constructed for the monitoring of symptoms on regular assessments, and intensity, duration, frequency and degree of conviction is registered in order to provide a detailed picture of the course of symptoms [136].

Screening instruments constructed so far are mainly based on the APS approach (except from the checklist of ERIraos), and include items with binary options of response. Only the SIPS screen allows for a graduation of symptoms.

Attenuated positive symptoms approach

The two instruments based on the APS approach (i.e. CAARMS and SIPS) are similar but not identical. The set of criteria of an at-risk or putative prodromal state were originally developed by Yung and colleagues [27] in Melbourne, Australia, based on a combination of state and trait factors. The operationalization of these criteria differs slightly (for detailed comparison of the intake criteria see also the Table 3).

<u>CAARMS</u>

It is a semi-structured interview developed by Yung and co-workers at the PACE clinic in Melbourne, Australia [38]. A person is in an at-risk mental state when meeting one or more of the

above Ultra High Risk (UHR) criteria. Operationalization of the UHR criteria was originally performed with already existing instruments: the Brief Psychiatric Rating Scale (BPRS) [144] and the Comprehensive Assessment of Symptoms and History (CASH) [145]. The operationalization of the criteria has since been constructed within the CAARMS manual.

Symptoms in CAARMS are divided into 7 subscales. Only scores on the subscale of positive symptoms are included when evaluating the UHR criteria. On several symptoms, both subjective experience and objective observation is rated separately. The subscales cover: (1) positive symptoms (disorders of thought content, perceptual abnormalities, disorganized speech); (2) cognitive change; (3) emotional disturbance; (4) negative symptoms; (5) behavioral change; (6) motor physical change; (7) general psychopathology. Some BS are included in the interview. Dimensions of intensity (0-6), frequency/duration (0-6) and fluctuation of symptoms (0-2) are scored separately.

In a pilot evaluation of CAARMS, the concurrent validity of a CAARMS-defined UHR state and the previous BPRS/CASH-defined UHR state was good [38]. A 6-month follow-up study of 150 non-psychotic, help-seeking individuals demonstrated that meeting the CAARMS-defined UHR criteria significantly predicted psychosis as opposed to not meeting the criteria (sensitivity 0.83, specificity 0.74) [38]. The instrument demonstrated good discriminant validity (as 48 controls scored significantly lower on the CAARMS than 49 individuals in a UHR mental state). Inter-rater reliability of the CAARMS subscales demonstrated excellent values, with intra class correlations (ICC) in the range of 0.62–0.93 (only one subscale was below 0.7). A screening questionnaire (Y-PARQ) [133] has been constructed on the basis of CAARMS.

SIPS

It is a semi-structured interview, developed by McGlashan and colleagues in New Haven, CT, USA [75]. A person is in a putative prodromal state when meeting one or more of the above Criteria of Prodromal Syndromes (COPS). SIPS is composed of: COPS, Presence of Psychosis Scale, Scale of Prodromal Syndromes (SOPS), Global Assessment of Functioning (GAF) [146], a checklist for schizotypal personality disorder and a questionnaire of family history of mental illness [147].

Symptoms are divided into 4 subscales. Only the ratings on positive symptoms (SOPS, P1-P5) are used for an evaluation of the subject meeting the COPS. The subscales cover: (1) positive symptoms (P1: unusual thought content/delusional ideas, P2: suspiciousness/persecutory ideas, P3: grandiosity, P4: perceptual abnormalities/hallucinations, P5: conceptual disorganization); (2)

negative symptoms; (3) disorganization; (4) general symptoms. Intensity of symptoms is rated (0–6), ascertained from information about onset, duration, frequency, intensity, degree of affect and conviction [75].

In a preliminary validity study, agreement on prodromal/non-prodromal status was 93%, demonstrating excellent inter-rater reliability on categorical measure [148]. Reliability analysis of severity on SOPS items (2–3 raters) revealed an ICC value of 0.95 for total score, and above 0.75 for each subscale. A validity study prolonging follow-up has reported preliminary data on transition rates at 12 and 24 months: 50% and 62% respectively (sensitivity 100%, specificity 73% at 24 months) [147]. SIPS is the basis of a screening instrument, SIPS screen [131].

Basic symptoms approach

BSABS

It was published in Germany in 1987 based on the work of Huber and colleagues [84]. It is a detailed outline of the so called BS of schizophrenia. BS are subtle, subjectively experienced disturbances seen in the domains of perception, cognition, language, motor function, will, initiative and level of energy and stress tolerance. These disturbances are presumed to be the phenotype of underlying neurophysiological deficits, and as such, BS are closely linked to the hypothetical core vulnerability of schizophrenia [79].

The scale consists of 6 subscales of BS: (A + B) scales of dynamic deficits; (C) cognitive disturbances; (D) cenesthetic experiences; (E) central vegetative disturbances; and (F) autoprotective behavior. Each BS is rated as present or absent. Examples of statements revealing the presence of the individual BS are given in the manual together with useful inquiries.

Specific disturbances of cognition, speech and perception have shown a significant predictive value of developing schizophrenia [30]. In details, in a study of 110 out-patients with at least one BS, 70% developed schizophrenia in an average follow-up of 9.6 years (specificity 0.59, false-positive predictions 20%) [125]. In the control group of 50 out-patients without BS, the absence of BS excluded schizophrenia with a probability of 96% (sensitivity 0.98, false-negative predictions 1.3%). Ten symptoms predicted schizophrenia with a probability of 71–91% (i.e. COGDIS and COPER) [30]. Cluster analysis of BS has resulted in the SPI-A [86].

SPI-A

It was developed by Schultze-Lutter and Klosterkotter in Cologne, Germany [86], applying cluster and facet analyses to data from 79 subjects in a prodromal phase from the Cologne Early Recognition (CER) study and from 346 remitted patients with schizophrenia [87]. BS are assumed to be detectable prior to the APS, and SPI-A has been developed as a supplement to SIPS/CAARMS and PANSS. Indeed, symptoms rated as severe on SPI-A should correspond to symptoms of moderate severity on SIPS, and symptoms rated as severe on SIPS should correspond to moderate ratings on PANSS [136].

SPI-A consists of 6 subscales covering (1) overstrain; (2) emotional deficits; (3) cognitive impediments; (4) cognitive disturbances; (5) body perception disturbances; (6) perception and motor disturbances and estrangement. The symptom severity (0–6) is scored according to occurrence/frequency and severity, and in some instances also to the quality of being new or different, subjective burden and amount of coping required.

Preliminary results indicate good inter-rater reliability of SPI-A with a concordance rate of 89% and good construct validity [136]. Preliminary findings on predictive validity of SPI-A have indicated that 25 of 147 (17%) who have reported experiencing at least one BS have developed schizophrenia within the average of 12 months [150]. Moreover, significant differences were found between the depressive and the prodromal group in terms of symptom structure, whereas the symptom structure of the prodromal and the schizophrenia group was almost identical [136]. A child- and youth version (SPI-CY) [87] has also been published, with items targeting children between 8 and 18 years, including information from parents.

ERIraos

It was developed by Hafner and Maurer in Mannheim, Germany, within the German Research Network on Schizophrenia [151]. ERIraos is a two-step inventory. First part is a checklist of 17 items, constructed as a screening instrument - questionnaire or interview - for application in primary care institutions. The checklist consists of 13 unspecific signs, three signs of the supposed late prodromal phase and one psychotic item, as well as questions concerning distress, gradient of change and presence of trait risk factors [152]. A pre-established cut-off score determines the eventual referral to an early recognition center, where the second part of the instrument is conducted. This is a symptom list of 110 items for incipient schizophrenia, based on data from the Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and other

Psychosis (IRAOS) [151], BSABS, SIPS, CAARMS and other instruments [136]. These items cover symptoms like disturbance of sleep and appetite, changes in personality, dysfunctional behavior, anxiety and obsessive–compulsive symptoms, thought disorder, disorders of self and delusions, impaired bodily sensations (cenesthesia), abnormal perceptions and motor disorders. In addition, instruments for the registration of obstetric complications and deficit in childhood are part of the inventory.

EASE

It is a semi-structured symptom checklist developed by Parnas and co-workers in Hvidovre, Denmark, Oslo, Norway and Aachen, Germany [100]. In opposition to the other instruments above-mentioned, this scale is not specifically developed for the assessment of a putative prodromal state. It does however explore phenomena which on an empirical basis are regarded as important phenomenological aspects in the pre-onset phase [153], but also in manifest schizophrenia and schizotypy [100]. EASE focuses on experiential anomalies of self-awareness and disorders in the sense of one's subjecthood. Many items overlap with BSABS, but only items associated with self-experience are included. Other items are based on the authors' own experience and phenomenological orientation [136].

The interview consists of 57 items that are divided into 5 subscales: (1) cognition and stream of consciousness; (2) disorders of self-awareness and presence; (3) bodily experience; (4) transitivism/demarcation; and (5) existential re-orientation (solipsistic experience). Symptoms are rated in terms of frequency/severity (0–3) and as to specific patterns. Inter-rater reliability showed good Cohen's kappa coefficients ranging between 0.6 and 1.0 [136].

Screening instruments

PRODscreen

It is a screening questionnaire, developed by Heinimaa and colleagues in Turku, Finland [131]. It is based on items from SIPS, IRAOS and BSABS. The purpose of PRODscreen was to detect persons with elevated risk of psychosis, who will subsequently be assessed with SIPS. PRODscreen is suitable for telephone interview and self-rating. The instrument contains background data, seven items of general functioning (current situation and changes during past year), 10 items of general

symptoms and 12 items of more specific psychosis-like character. As in SIPS, the main focus is APS.

In studies of validity and reliability, PRODscreen has correctly identified a SIPS-defined prodromal state in 77% of cases from a mixed sample, distinguishing prodromal from non-prodromal subjects with a sensitivity of 80% and a specificity of 75% [131].

Prodromal Questionnaire

The screening instrument PQ was developed at the UCLA in Los Angeles by Loewy and co-workers [132]. It contains 92 statements for self-completion (true/false), deriving from subscales of positive, negative, disorganizing and general symptoms. PQ items are based on SIPS, SPQ, and a few original items based on the authors' own experience. For each item is included the assessment of distress (0-3).

A good concurrent validity of PQ-positive subscale against SIPS on prodromal/psychosis outcome vs. neither was demonstrated [132]. With a cut-off on 8 or more items of positive symptoms, sensitivity is 90% and specificity 49% [136]. The instrument, however, is not sensitive to the threshold between prodromal and psychotic state. PQ has been also validated in a non-clinical population consisting of a large sample of undergraduate students.

Y-PARQ

This screening instrument was developed in Utah by Ord and co-workers [133]. It consists of 92 items for self-rating (yes/no), describing positive, affective and negative symptoms of prodromal schizophrenia. This instrument is based on CAARMS, and has been tested on 648 high school students belonging to an isolated population in Micronesia with elevated rates of familial schizophrenia. High scores of the 24 most discriminating positive symptom questions were used for identifying potential prodromal adolescents. Preliminary data showed a positive predictive value of a CAARMS-defined at-risk mental state of 82.4% [136].

SIPS screen

This instrument was developed by Miller and colleagues [134] at the PRIME clinic in New Haven, CT, USA. It consists of 12 items covering positive symptoms, each one rated between 0 ("definitely disagree") and 6 ("definitely agree"). The screening instrument showed a sensitivity of 0.90 and indicated perfect specificity [134].

PCCL

It has been developed by French and co-workers [135] as a quick and easy to use tool administered by the primary care practitioners to help identifying young people who may be in the early stages of psychosis and to make quick, appropriate referrals to specialist services. This checklist, which should take no longer than 5 minutes to be completed, includes items relating to general, psychological, and social functioning (e.g. “arguing with friends and family”, “spending more time alone”, “sleep difficulties” and “depressive mood”), as well as items relating to psychotic-like experiences such as hallucinations, delusions (e.g. paranoia and ideas of reference) and disorganized speech and thinking.

Each checklist item has an allocated numerical value, ranging from 1 to 5, depending on its perceived relevance to overall psychosis risk. By summing the scores of each endorsed checklist item, a total score (ranging from 0 to 55) can be calculated for each individual. According to the PCCL scoring rules, positive screen outcome for further assessment of psychosis risk can be reached in two ways: (a) a global score of 20 or above, or (b) endorsement of one or more of five specific key-items (13-16 and 20), conceived as indicative of psychosis risk even if observed in isolation (i.e. independently of the final PCCL score ≥ 20). Those five key-items are designed to capture attenuated positive psychotic-like experiences (such as hallucinations, delusions and ideas of reference: e.g. “hearing things that other cannot” and “feeling that events or other people’s actions have a special meaning for you”) or state/trait vulnerability features (i.e. “first-degree family history of psychosis plus increased stress or deterioration in functioning”).

In *conclusion*, the most frequently used criteria in studies detecting individuals in an at-risk mental state are based on the APS, operationalized either by SIPS or CAARMS. So far, these criteria seem valid in detecting samples at increased risk of psychosis, even though a significant proportion of the individuals do not cross the threshold of full-blown psychosis. The presence of BS has shown the most significant predictive values of later schizophrenia, but these predictions are based on a much longer follow-up interval (average 9.6 years).

As demonstrated by data on PQ [132], screening in the general population is problematic. Previous studies also reveal a high prevalence of possible prodromal or positive symptoms in non-clinical populations [154], indicating that the experience “per se” of these symptoms is not necessarily associated with mental health problems. Simple “yes/no” screening instruments leave no room for an elaboration of the experienced symptom, in terms of, e.g. intensity, degree of distress and

frequency. For recruitment purposes, sensitivity of screening instruments is important. But as specificity is very low when applied to the general population [136], at the present state of research screening instruments should be used exclusively in clinical populations, as recommended in EPA guidance on early detection of psychosis [30].

The theoretical grounding of the above-mentioned instruments has developed instruments that focus on quantified descriptions of symptoms and signs, based on the tradition of an objective and descriptive approach to psychopathology. Probably, all researchers in the field wish to understand the phenomenology of the persons in the at-risk group [99]. Indeed, one of the possible changes in the subjective experience in the development of psychosis is a fundamental change in the usual taken-for-granted experience of the sense of self and sense of embeddedness in the world. Examples of these changes are a pervasive lack of identity, feelings of being non-existent, distortions of an immediate first-person perspective in the experience of the self and the world, and hyper-reflectivity [100]. According to the phenomenological tradition, it is the structure or form of experience which is transformed during psychotic development, i.e. a prereflective transformation. These phenomena seem to play a core role in the phenomenology of the prodromal phase of schizophrenia, and are manifestations of the phenomena which in German-speaking literature are called “Ich-storungen” [136].

Thus, interviews focusing on anomalies of self-experience (such as the EASE) [100], which are common characteristics of the otherwise heterogeneous clinical picture of schizophrenia spectrum disorders, are a desirable addition to the previously mentioned instruments. However, time will show whether future studies using the EASE instrument lead it into a similar “quantification trap” as indicated above, and thus reifying the items [136].

AIM

Considering this background, *aim* of the present research was to validate some of the most widely used screening and in-depth assessment instruments for early detection of psychosis. Specifically, after a detailed description of the research setting (i.e. the "Reggio Emilia At-Risk Mental States" [ReARMS] program) (study 1), we assessed psychometric properties of the Italian versions of the following tools:

1) the Primary Care CheckList (i.e. the "*Checklist per la Valutazione dell'Esordio Psicotico*" [CVEP]) [155] (study 2);
2) the brief versions of the "Prodromal Questionnaire" (i.e. *PQ-B* and *PQ-16*) [156, 157] (study 3 and study 4);
3) the *CAARMS* [38] (study 5); and
4) the "Aberrant Salience Inventory" (*ASI*) (study 6) [158].

Once validated in an Italian clinical population of adolescent and young adult help-seekers, these instruments can be usefully administered within specialized programs and strategies for the early detection of psychosis in the Italian public network of mental health departments.

STUDY 1
THE "REGGIO EMILIA AT-RISK MENTAL STATES" PROGRAM

The "Reggio Emilia At-Risk Mental States" program: a diffused, "liquid" model of early intervention in psychosis implemented in an Italian Department of Mental Health

In the last 25 years, since the seminal works of McGorry and McGlashan [46, 129], the paradigm of early intervention in psychosis (EIP) has obtained increased attention in the scientific community, sprouting focused protocol of care that have been implemented in EIP programs and sometimes in autonomous EIP services within the mental health care network of different countries [159]. This interest is raised by its rational foundation: early detection and intervention in psychosis (and in psychosis-risk syndromes) has been expected to reduce inpatient care, treatment drop-out, morbidity and its related disability, as well as to Psychotic disorders (particularly schizophrenia) are serious illnesses which typically emerge during improve long-term outcome of illness [160]. Indeed, diagnosis and treatment of psychosis are often delivered some time later the onset of the disorder, leaving the patient untreated for a long time [161]. In this regard, it has been widely demonstrated that DUP was related to short- and medium-term outcomes, with shorter DUP being associated to better outcome [162].

Furthermore, as psychoses are one of the main contributors to the global burden of disease in the world, leaving a psychotic disorder untreated may have serious consequences in terms of health, functioning, and quality of life of the affected patients and their families, as well as in terms of costs for the society related to unemployment, lost opportunities and treatment [163]. Evidence that EIP programs can sensibly decrease the negative impact of DUP and both direct and indirect costs of care, contributed to spread interest in the EIP model as well [11].

EIP in Italy

Over the past 40 years, a deep-reaching change of the mental health care system has occurred in Italy. This reorganization resulted in a comprehensive and integrated system of community-based mental health departments that are interconnected with general hospital (where the operating psychiatric wards for acute treatment are located) and the network of the other community services (such as general practitioners, schools, social agencies), covering all the needs of child, adolescent and adult populations in terms of mental health [164]. All psychiatric services are free of charge for the patients and their families, as costs of assessment and treatment are covered by general taxation.

Therefore, the threshold for access to these services is very low. Indeed, patient can book a visit even without a formal indication by his/her general practitioners. According to Cocchi and colleagues [165], this community mental health care system is particularly favorable for the implementation of the early intervention paradigm within the Italian public psychiatric services.

The establishment of the pilot program "Programma 2000", the first service in Italy specifically targeting the early detection and intervention on individuals with FEP, ongoing in Milan since 1999 [166], and the publishing of the Italian national guidelines on "early intervention in schizophrenia" [167] have both motivated the implementation of specific services aimed to the early detection, enrolment and intervention for young people with FEP and in need of treatment for prodromal signs of psychosis (such as the UHR mental states) [11]. Since the innovative boost of "Programma 2000", a nationwide diffusion of EIP programs is spreading throughout the Italian public network of mental health, albeit slowly and with most services adopted a generalist approach not centered on the suggested Italian national guidelines or on evidence-based protocols [168].

In September 2012, after being involved in the GET-UP trial (that was a study protocol aimed to evaluate the 9-month effectiveness and the feasibility in real-world routine clinical settings of an EIP-based multicomponent psychosocial intervention compared with Treatment As Usual [TAU] in a large cohort of FEP patients recruited from a 10 million inhabitant catchment area) [169], the General Direction of the Emilia-Romagna Health Care Service financed a regional project (the "Progetto Regionale Esordi Psicotici" [PREP]) with the aim of implementing innovative protocols of intervention based on the EIP model within all the Emilia Romagna Departments of Mental Health [170]. Specifically, main objectives of this project were: (a) to train the professional staff of each regional department of mental health on the theoretical and operational cores of the EIP model, and (b) to established a specialized EIP program within all departments, aimed to the assessment, diagnosis and treatment of FEP patients according to well-defined, state-of-art guidelines on the topic [171].

The ReARMS protocol

In this regional context (i.e. under the aegis of PREP), the Reggio Emilia Department of Mental Health developed a specific EIP protocol (the "Reggio Emilia At-Risk Mental States" [ReARMS] program) that had to be applied not through a centralized ("stand-alone") departmental service, but through a diffused ("liquid") infrastructure branched within the network of all the Adult Mental Health Services (AMHS) and all the Child and Adolescent Mental Health Services (CAMHS) of the Reggio Emilia province, a semi-urban catchment area of approximately 550.000 inhabitants, in the northern Italy [170]. ReARMS program was established in order to offer a dedicated, evidence-

based and expertise-driven protocol of care to adolescents and young adults experiencing a FEP or in the prodromal phase of psychosis [172, 173].

The term “liquid” has been used to better describe a model through which specialized EIP knowledge and competence were disseminated in all the Reggio Emilia CAMHS and AMHS in order to reach and train the number of mental health professionals as largest as possible. This diffused infrastructure made it feasible to create multiple, specialized multi-professional teams (i.e. psychiatrists, psychologists, case managers for early rehabilitation) capable of widely delivering EIP intervention throughout the entire territory of the catchment area [170].

Specifically, reasons that supported the decision to implement ReARMS protocol were: (a) to improve the quality of the processes and outcomes of intervention, establishing a specialized EIP program aimed to the early assessment, diagnosis and treatment of young people with FEP or at UHR of psychos, according to well-defined, state-of-art guidelines on the topic; (b) to reduce the variability of treatments, standardizing them in all the CAMHS and AMHS of the Reggio Emilia Department of Mental Health; (c) to allow an accurate evaluation of the adherence of interventions provided in the ReAMS protocol to the EBM-oriented recommendations and (d) to make the planned care pathway transparent to the outside [174].

Main objectives of the ReARMS protocol were: (a) to optimize the early detection of FEP and UHR individuals using specific Comprehensive Assessment of At-Risk Mental States (CAARMS)-defined diagnostic criteria [38]; (b) to reduce DUP and DUI, as well as the time between the onset of a relevant psychiatric symptom and an integrated case management by local CAMHS or AMHS in order to promote a clinical, social, and personal recovery as wide and as early as possible; (c) to train professional staff members of each CAMHS and AMHS on the theoretical and operational cores of the EIP model, thus increasing their skills on early detection and intervention in FEP and UHR subjects, and improving the quality of the provided treatment through a specific, shared care pathway consistent with the international guidelines; (d) to reduce personal and social stigma associated with psychosis, promoting social and interpersonal inclusion and (e) to provide a dedicated, evidence-based and expertise-driven protocol of care to young people with FEP or UHR mental states, implementing a homogeneous, targeted, and cohesive work methodology based on specific and appropriate interventions [174]. For these purposes, the Reggio Emilia Department of Mental Health preferred to apply the ReARMS protocol not through a centralized (stand-alone) departmental service (such as “Programma 2000”) [166], but through a diffused infrastructure mainly focused on the continuous education and training of mental health care professionals working within each CAMHS and AMHS (i.e. psychiatrists, neuropsychiatrists, psychologists, nurses, professional educators, social assistants and psychiatric rehabilitation therapists) [170], with

the aim of raising their awareness on the importance of early detection and referral of FEP and UHR individuals, and disseminating knowledge of the multi-dimensional protocol of care provided by the ReARMS program [171, 175]. In this sense, a "liquid" EIP model was preferred for ensuring the best local diffusion of the ReARMS interventions and their highest delivery to the users. Over time, more attention should be paid to schools and the public in general through awareness campaigns.

Aims of the current study are (a) to describe the general organization of the ReARMS program, the first example of diffused EIP model in Italy that specifically involved CAMHS and recruited adolescents and young people specifically meeting defined criteria for UHR mental states (together with FEP patients) and (b) to analyze specific process indicators of the ReARMS protocol (e.g. number of subjects who were referred to the service, who were enrolled and entered treatment, who turned down the proposed treatment, and who dropped out shortly [within 1 year] after accepting the therapeutic proposal) during its first 5 years of clinical activity.

METHODS

Participants

Data were collected during the baseline routine assessment of the help-seeking adolescents and young adults entering the ReARMS protocol between September 2012 and December 2017. All participants (n = 311) and their parents (if they were minors) agreed to participate to the research and gave their informed consent. Relevant ethical approvals were sought for the study. The current research has been also carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments including humans.

ReARMS inclusion criteria were: (a) specialist help-seeking; (b) age between 13 and 35 years; (c) presence of UHR criteria defined by the CAARMS [38] or (d) a DUP < 2 years in case CAARMS-defined FEP criteria are detected at baseline assessment. In this regard, within the early intervention paradigm, a DUP less than 24 months is considered the limit to start a specific EIP protocol of care [176]. Indeed, recent reviews and meta-analyses showed that shorter DUP was associated to a better long-term outcome of illness [177].

According to CAARMS operational criteria [38], UHR status is defined as follows: (a) Attenuated Psychotic Symptoms (APS), including subjects with sub-threshold positive psychotic symptoms during the past year; (b) Brief, Limited, and Intermittent Psychotic Symptoms (BLIPS), including people who experienced episodes of full-blown positive psychotic symptoms that have lasted no longer than a week and spontaneously ceased (i.e. without antipsychotic medications); and (c) Genetic Risk and Functioning Deterioration (GRFD) syndrome, including individuals with a schizotypal personality disorder or with a first-degree relative diagnosed with frank psychotic

disorder, combined with evidence of deterioration in functioning in the last year. Moreover, according to the psychosis criteria defined by the CAARMS [38], the threshold of first full-blown psychotic episode (FEP) is defined by operationalized clear-cut levels of fully positive symptoms occurring for >1 week, either daily or > 3 times a week with each symptom continuing for >1 hour on each occasion.

ReARMS exclusion criteria were: (a) history of affective and non-affective psychotic disorders (i.e. at any time before ReARMS enrolment), according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR) [178]; (b) history of previous exposure to antipsychotics; (c) current substance dependence (but not current substance abuse, as defined in the DSM-IV-TR) [178]; (d) known intellectual disability (< 70) and (e) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. In the ReARMS protocol, we considered previous exposure to antipsychotic (i.e. at any time before ReARMS enrolment) as an equivalent of past psychotic episode. Indeed, according to the psychosis criteria defined by the CAARMS [38], the threshold of full-blown psychotic episode is essentially that at which antipsychotic medication would probably be commenced in common clinical practice.

Assessment and diagnosis

All subjects entering the ReARMS protocol underwent a comprehensive, multidimensional evaluation [171, 174]. In this study, the following standardized instruments were considered:

1) a socio-demographic/clinical schedule, in which information was collected on age, gender, ethnic group, years of education, marital status, source of referral, family psychiatric history, history of substance abuse and attempted suicide, previous hospitalization (i.e. before ReARMS enrolment), previous specialist contact (both as single consultation and taking charge at CAMHS or AMHS), DUP (defined as the period of treatment delay [in weeks] between onset of psychotic symptoms and pharmacotherapy initiation) [179], and duration of untreated illness (DUI, defined as the interval [in weeks] between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment) [180]. DUI and DUP were based on interviews with the patient and of at least one key informant (usually a close relatives, preferable a parent). A history of suicide attempt and of illicit substance abuse was also considered as an indicator of illness severity. Indeed, as these events/conditions are likely to raise concern in the family, they may also induce contact-seeking with psychiatric services [159].
2) CAARMS: a semi-structured clinical interview designed to cover different features of attenuated psychopathology, as well as functioning (via the integrated Social and

Occupational Functioning Assessment Scale module) [38]. It takes approximately 1 to 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). These items can also be clustered in 7 subscales: "Positive Symptoms", "Cognitive Change, Attention and Concentration", "Emotional Disturbance", "Negative Symptoms", "Behavioral Change", "Motor/Physical Changes", and "General Psychopathology". 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 [38]. CAARMS interviews were conducted by clinical psychologists, psychiatrists, and neuropsychiatrists trained by the main author of the approved Italian version (CAARMS-ITA) [181], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability of the assessment. The intra-class correlation coefficients of each CAARMS-ITA subscales showed good to excellent inter-rater reliability [182, 183].

The axis-I diagnosis was made according to DSM-IV-TR criteria [178] by two trained ReARMS team members, using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [184]. After CAARMS interviews, participants were divided into three groups according to UHR/psychosis criteria [38]: (a) UHR+ group (ie, APS, BLIPS and GRFD), (b) FEP group and (c) UHR- group (ie, those individuals who were under the threshold of the CAARMS inclusion criteria).

The ReARMS protocol: Processes and procedures

ReARMS protocol is composed of the following five processes: (a) identification, (b) assessment, (c) intervention in FEP patients: acute phase or relapse, (d) intervention in UHR individuals (i.e. BLIPS, APS and GRFD) and (e) intervention in FEP patients: maintenance treatment. All processes are divided into distinct procedures, each one structured in specific settings, mental health professionals involved, duration, timing and scheduling [174] (for details, see also Appendix S1).

The Identification process includes a pre-clinical triage service conducted by trained non-medical personnel, using the screening schedule for psychosis [185]. In case of positive outcome of the screening, the patient is then assigned to a ReARMS multi-professional team, generally within 3 weeks. The first filtering (screening) step is mainly meant to maximize appropriate referrals to the ReARMS program (i.e. eligibility) and avoid over-inclusion of subjects clearly outside the severity threshold for presumed psychosis risk spectrum [186]. In line with a diffused, "liquid" EIP model, each professional of this ReARMS team (i.e. psychiatrist, neuropsychiatrist, psychologist, case-

manager for early rehabilitation) belongs to one of the CAMHS or AMHS in which the Reggio Emilia Department of Mental Health is articulated.

The Assessment process involves a first clinical interview for completing the socio-demographic/clinical schedule, and the administration and scoring of the ReARMS assessment battery for a baseline in-depth diagnostic and psychopathological evaluation [170]. Based on the assessment outcome, a psychodiagnostic report and a case formulation are drawn up. ReARMS early identification of young people with FEP/UHR mental states was mainly based on the CAARMS interview [38], which was carried out by trained clinicians. After CAARMS interview, individuals who are under the threshold of the CAARMS inclusion criteria (i.e. UHR-cases) exit from the ReARMS protocol, but receive appropriate advice for future intervention, which is composed of TAU for their principal DSM-IV-TR axis I diagnosis (e.g. pharmacotherapy, supportive psychotherapy [as appropriate]). However, these individuals remain worthy of clinical attention and are recalled for the annual follow-up administration of the ReARMS assessment battery in order to evaluate for the possible onset of attenuated or full-blown psychotic symptoms [187].

According to their symptoms, FEP and UHR subjects are provided with a comprehensive 5-year intervention package including pharmacological treatment and a multi-element psychosocial intervention (combining individual Cognitive-Behavioral Therapy [CBT], psychoeducational sessions for family members and a recovery-oriented case management for early rehabilitation), according to current guidelines [13, 176, 188]. Interventions provided to all individuals/relatives were supervised by a team of departmental experts. The prescription of antipsychotics is avoided unless UHR subjects (a) have an imminent risk of suicide or severe violence, (b) are overwhelmed by abruptly worsening full-blown psychotic symptoms, (c) are rapidly deteriorating in daily functioning or (d) do not respond to any other treatment [13]. Low-dose atypical antipsychotics are used. Selective serotonin reuptake inhibitor or benzodiazepines are used to treat depressive symptoms, anxiety and insomnia.

Individual CBT is based on the model developed by Fowler, Garety, and Kuipers [189], which has already been evaluated in randomized controlled trials [190]. An optimal number of 20 CBT sessions per patient (each lasting 60 minutes) are delivered during a time frame of 12 months, with weekly sessions held during the first 3 months. In the second year, at least 10 CBT sessions per patient are offered. In the maintenance phase (i.e. from third to fifth year), booster sessions on specific symptomatic areas are eventually provided. Clinical psychologist using individual CBT received specific training programs [170].

Family intervention is based on the model proposed by Kuipers, Leff, and Lam [191]. In the first year, psychoeducation for family members consists of an optimal number of 10 cognitive/behavioral-oriented sessions over 12 months with each individual family, with at least six sessions held during the first 4 months. Starting from the second year and based on functioning and specific symptomatic areas, booster sessions are eventually delivered. Similarly, each mental health professional (i.e. clinical psychologist, psychiatric nurse or educator and psychiatric rehabilitation therapist) using psychoeducation received specific training programs [170].

For case management, every patient/family has a dedicated case manager that coordinates all planned interventions, in particular those aimed to a recovery-oriented early rehabilitation [170, 174]. In the first year, at least 24 sessions per patient (each lasting 60 minutes) are provided. Later (i.e. from second to fifth year), at least 50 sessions per patient (each lasting 60 minutes) are delivered, according to social and occupational functioning. A specific training program on case management is also given to each mental health professional (i.e. psychiatric nurse or educator, social assistant and psychiatric rehabilitation therapist) [170].

At the end of each training program, an assessment of the competence achieved was performed, and detailed intervention manuals based on international standards were given to each mental health professionals as a standard to be followed for the treatment. Interventions provided to all individuals/relatives are steadily supervised by a team of departmental experts, who held meetings every month and are regularly available for consultation. However, ReARMS interventions were expected to begin as soon as the subject was stabilized (i.e. when he was in a clinical condition allowing him to collaborate in at least brief clinical evaluation) and after he has been assessed with the baseline ReARMS assessment battery [170].

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 [192]. All tests were two-tailed. Threshold of significance was set at $p = 0.05$. Descriptive data included mean values and SD for continuous variables, and absolute and relative frequencies for categorical variables. Cross-sectional analyses on the socio-demographic and clinical characteristics among the three groups (i.e. FEP, UHR+ and UHR-) were assessed with analysis of variance, using Fisher's Least Significant Difference to correct for multiple comparisons involving normally distributed variables. The Kruskal-Wallis test was used for variables that were not normally distributed and post-hoc analyses were performed by using the Mann-Whitney U test. A $\chi 2$ test (with Yates' correction when appropriate) or Fisher's exact test (when any expected frequency was <1 or 20% of expected frequency was ≤ 5) were employed for categorical data.

In particular, we examined the following process indicators of the first 5 years of ReARMS clinical activity: (a) the number of subjects who were referred to the protocol, (b) the number of subjects who completed the assessment battery, (c) the number of subjects who were enrolled and entered ReARMS intervention, (d) the number of subjects who turned down the proposed treatment, (e) the number of subjects who dropped out shortly (within 1 year) after accepting the therapeutic proposal and (f) the percentages of diagnostic categorization (ie, FEP, UHR+ or UHR-). Furthermore, we compared the 1-year ReARMS rate of dropped-out individuals with that observed in a sample composed of all (n = 250) the FEP patients (i.e. with DSM-IV-TR schizophrenia, affective [bipolar or major depressive] psychosis, brief psychotic disorder, schizophreniform disorder, psychotic disorder not otherwise specified and substance-induced psychotic disorder), aged 13 to 35 years, consecutively referred to all the CAMHS and AMHS of the Reggio Emilia Department of Mental Health in the 5 years preceding the implementation of the ReARMS protocol (i.e. from August 2007 to August 2012). This pre-ReARMS drop-out rate was calculated on data collected from audits on clinical records.

RESULTS

A total of 311 subjects (175 males [56.3%]; mean age at entry = 21.26 ± 5.83 years) have been consecutively referred to the ReARMS protocol since its establishment (available data were from September 2012 to December 2017) (Figure 2).

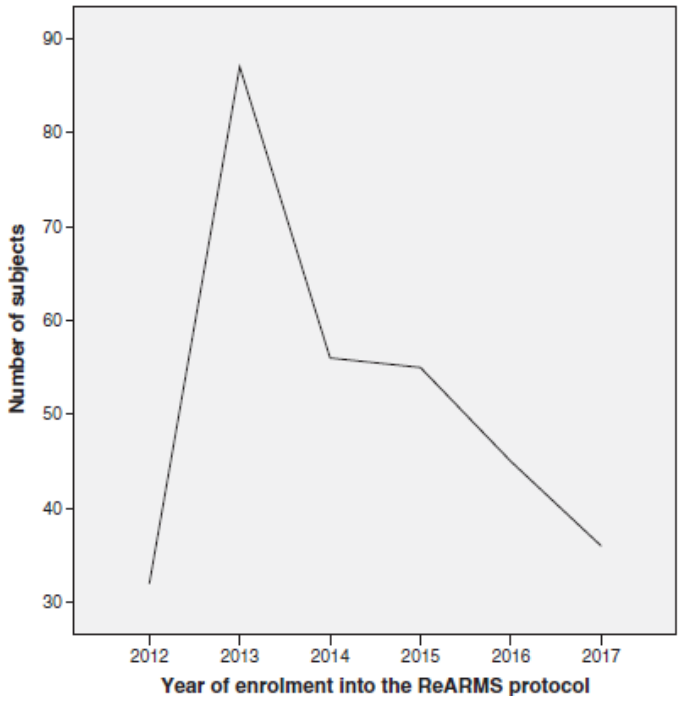


Figure 2 - Enrollment into the ReARMS protocol (n = 311); ReARMS = Reggio Emilia At-Risk Mental States.

Eleven participants did not complete the baseline evaluation. Among those who completed the baseline assessment (n = 300), 95 (31.7%) individuals did not meet UHR/FEP defined criteria [38] and were grouped as UHR-. Therefore, 205 (68.3%) participants were offered a dedicated protocol of care: 154 (75.1%) of these individuals accepted and were enrolled in the program, 19 (9.3%) refused, and 32 (15.6%) dropped out during the first year of treatment (i.e. after accepting the therapeutic proposal) (Figure 3).

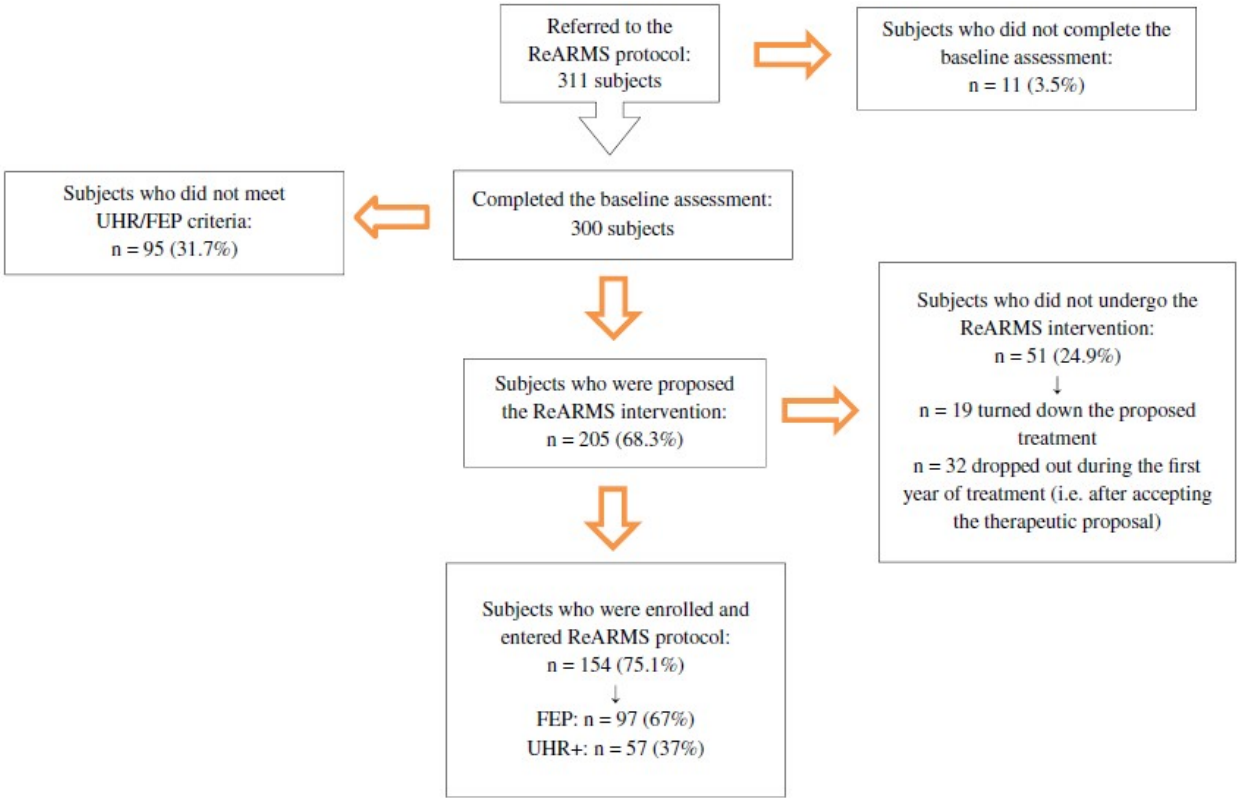


Figure 3 - Flowchart of referrals to the ReARMS protocol (September 2012 to December 2017) (n = 311); ReARMS = Reggio Emilia At-Risk Mental States; UHR = Ultra-High Risk; FEP = First Episode Psychosis; UHR- = participants who did not meet UHR/FEP-defined criteria; UHR+ = participants who met UHR-defined criteria.

This 1-year rate of dropped-out individuals was significantly lower than those (n = 88 [35.2%]) observed in a sample of 250 FEP patients, aged 13 to 35 years, consecutively referred to all the CAMHS and AMHS of the Reggio Emilia Department of Mental Health in the 5 years preceding the implementation of the ReARMS protocol (Figure 4). The UHR- cases and those who refused the ReARMS intervention received appropriate advice for future treatment.

Among the UHR+ group (n = 79; 26.3% of participants who completed the baseline assessment), 72 met APS criteria (91.1% of the UHR+ subjects), three met BLIPS criteria and four met GRFD

criteria. In this subsample, major depression (without psychotic features) was the most frequent diagnosis (n = 40; 50.6%) at initial examination, followed by anxiety disorders (specifically panic disorder, generalized anxiety disorder, obsessive-compulsive disorder and phobic disorders) (n = 22; 27.8%), schizotypal personality disorder (n = 14; 17.7%) and brief psychotic disorder (n = 3; 3.9%).

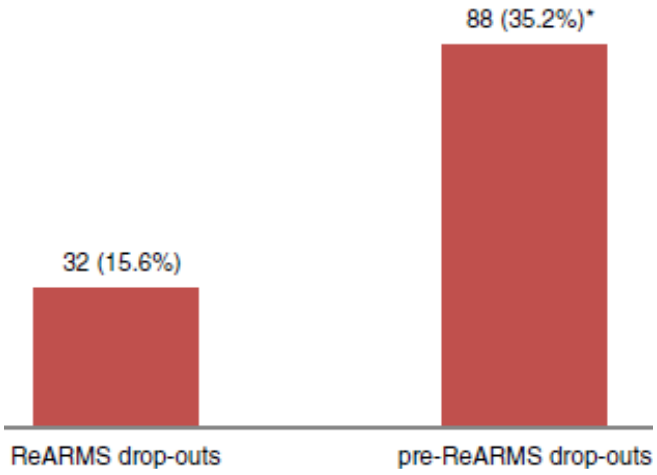


Figure 4 - Comparison of 1-year rate of dropped-out individuals between the ReARMS protocol (n = 205) and the 5 years preceding the implementation of the ReARMS protocol (pre-ReARMS; n = 250) in the Reggio Emilia Department of Mental Health. ReARMS = Reggio Emilia At-Risk Mental States; frequencies, percentages and X^2 test value are reported; *X^2 = 12.30; p = 0.001.

The FEP group (n = 126; 42% of the total sample) consisted of patients with DSM-IV-TR schizophrenia (n = 56; 44.4% of FEP patients), psychotic disorder not otherwise specified (n = 31; 24.6%), affective (bipolar or major depressive) psychosis (n = 30; 23.8%) and substance-induced psychotic disorder (specifically with onset during abuse/intoxication) (n = 9; 7.2%).
The remaining 95 participants (31.7% of the total sample) were below the CAARMS threshold for being considered at risk for psychosis, and composed the UHR− group. They were diagnosed with DSM-IV-TR depressive disorders (n = 39; 41.1% of UHR− individuals), anxiety disorders (n = 29; 30.5%), and non-schizotypal personality disorder (n = 27; 28.4%) (i.e. borderline, avoidance, or narcissistic personality disorder).

Socio-demographic and clinical characteristics

The socio-demographic and clinical variables of the total sample and the three subgroups are reported in the Table 5.

Table 5 – Demographic and clinical characteristics of the total sample and the three subgroups.

Variable	Total sample (n=300)	UHR- (n=95)	UHR+ (n=79)	FEP (n=126)	Statistics (F/X^2)	Post hoc test
Gender (males)	165 (55.5%)	45 (47.7%)	36 (45.6%)	84 (66.7%)	12.00[b]	FEP >UHR+=UHR-
Ethnic group (white Caucasian)	259 (86.3%)	80 (84.2%)	69 (87.3%)	110 (87.3%)	0.53	-
Marital status						
Unmarried	277 (92.3%)	83 (87.4%)	78 (98.7%)	116 (92.1%)	8.75	-
Married	20 (6.7%)	11 (11.3%)	1 (1.3%)	8 (6.3%)		
Separated/divorced	3 (1.0%)	1 (1.1%)	0 (0.0%)	2 (1.6%)		
Age at entry	21.15 ± 5.85	20.14 ± 6.28	18.59 ± 4.39	23.14 ± 5.66	16.81[a]	FEP >UHR+=UHR-
Education (in years)	11.51 ± 2.42	11.48 ± 2.39	11.22 ± 2.33	11.71 ± 2.50	1.00	-
Family psychiatric history	166 (56.3%)	43 (46.2%)	43 (55.1%)	80 (64.5%)	7.27[c]	FEP>UHR-
First-degree relative with psychosis	41 (13.9%)	8 (8.6%)	10 (12.8%)	23 (18.5%)	4.50	-
DUI (in weeks)	81.74 ± 59.33	72.98 ± 57.87	72.12 ± 48.49	95.56 ± 65.33	4.57	-
DUP (in weeks)	-	-	-	46.98 ± 48.49	-	
History of substance abuse	94 (31.3%)	24 (25.3%)	14 (17.7%)	56 (44.4%)	18.50[a]	FEP>UHR+=UHR-
History of attempted suicide	27 (9.0%)	8 (8.4%)	10 (12.7%)	9 (7.1%)	1.86	-
Previous hospitalization	85 (28.3%)	13 (13.7%)	11 (13.9%)	61 (48.8%)	43.14[a]	FEP >UHR+=UHR-
Previous specialist contact	145 (48.3%)	51 (53.7%)	39 (49.4%)	55 (43.7%)	2.23	-

Legend – DUI = Duration of Untreated Illness; DUP = Duration of Untreated Psychosis; CAARMS = Comprehensive Assessment of At-Risk Mental States; FEP = patients with First-Episode Psychosis; UHR = Ultra-High Risk; UHR+ = individuals who met CAARMS-defined UHR criteria; UHR- = individuals who did not meet CAARMS-defined UHR/FEP criteria. Frequencies and percentages, mean ± standard deviation, one-way Anova test (F), Kruskal-Wallis test (χ^2), and Chi-squared test (X^2) values are reported; [a]$p<0.001$; [b]$p<0.01$; [c]$p<0.05$.

In comparison with UHR+ and UHR-, FEP individuals showed significantly higher mean age at entry and a preponderance of males. No between-group differences in terms of ethnic group, marital status and years of education were found.

FEP patients had also significantly higher percentages of history of substance abuse and previous hospitalization than the other two subgroups. Moreover, exclusively in comparison with UHR-, FEP subjects showed a significantly higher frequency of family psychiatric history. No between-group differences in terms of DUI and percentages of first-degree relative with psychosis, history of attempted suicide, and previous specialist contact were observed.

Source of referral

Referrals to the ReARMS program exponentially increased during the first year of its implementation in the Reggio Emilia Department of Mental Health (n = 86 subjects enrolled per year in 2013). Then, it decreased in the following years of clinical activity and settled down to an enrolment rate value equal to 36 subjects per year in 2017 (Figure 2).

The vast majority of participants were referred by general practitioners (33.3%), emergency room/general hospital (24%), or they were self-referred (15%) (Table 6). In particular, compared

with UHR+ and UHR-, FEP patients contacted significantly more often emergency room and general hospital as specific settings where formulating the first request for specialist help in their pathways to treatment. Differently, in comparison with UHR+ and UHR-, FEP subjects were significantly less often self-referred or referred by school/social services. However, no between-group differences in terms of referral by general practitioners, family members and private/public mental health care professionals were found.

Table 6 - Pattern of referral in the total sample and the three subgroups.

Pattern of referral	Total sample (n=300)	UHR- (n=95)	UHR+ (n=79)	FEP (n=126)	Statistics (X^2)	Post hoc test
General practitioners	100 (33.3%)	38 (40.0%)	28 (35.4%)	34 (27.0%)	4.34	-
Emergency room/general hospital	72 (24.0%)	12 (12.6%)	14 (17.7%)	46 (36.5%)	19.25[a]	FEP >UHR+=UHR-
Self-referral	45 (15.0%)	19 (20.0%)	15 (19.0%)	11(8.7%)	6.73[b]	UHR-=UHR+>FEP
Family involvement	37 (12.3%)	12 (12.6%)	8 (10.1%)	17 (13.5%)	0.52	-
Public/private mental health care professional	24 (8.0%)	5 (5.3%)	5 (6.3%)	14 (11.1%)	2.92	-
Drug dependence department	7 (2.3%)	2 (2.1%)	1 (1.3%)	4 (3.2%)		
Private psychiatrist/psychologist	11 (3.7%)	1 (1.1%)	3 (3.8%)	7 (5.6%)		
Eating disorder care service	6 (2.0%)	2 (2.1%)	1 (1.3%)	3 (2.4%)		
School/Social services	22 (7.3%)	9 (9.5%)	9 (11.4%)	4 (3.2%)	5.96[b]	UHR-=UHR+>FEP

Legend – FEP = First-Episode Psychosis; UHR = Ultra-High Risk; UHR+ = individuals who met CAARMS-defined UHR criteria; CAARMS = Comprehensive Assessment of At-Risk Mental States; UHR- = individuals who were below CAARMS-defined UHR/FEP criteria. Frequencies, percentages, and Chi-squared test (χ^2) values are reported; [a]$p<0.001$, [b]$p<0.01$.

DISCUSSION

The ReARMS protocol is the first example of diffused EIP model in Italy that specifically involved CAMHS and recruited (together with FEP) adolescents and young adults meeting specific CAARMS-defined criteria for an UHR mental state [170, 171].

The ReARMS protocol: process indicators

Main aim of this study was to examine specific process indicators of the ReARMS protocol. Approximately 300 young individuals, aged 13 to 35 years, have been consecutively referred to the ReARMS program in the 5 years following its establishment. In comparison with the referral rate observed in "Programma 2000" [165], our finding is definitely higher, suggesting that a diffused, "liquid" infrastructure specifically involving all the local CAMHS and AMHS is probably more able to effectively meet and respond to the care needs of help-seeking users, placing in close proximity with them. Indeed, in 11 years of clinical activity (from January 1999 to December 2010), about 400 young subjects, aged 17 to 30 years, were assessed in the "Programma 2000", the first Italian EIP centralized service ongoing in Milan within the Department of Mental Health of the

“Niguarda Ca’ Granda” Hospital, a catchment area catering to approximately 200 000 inhabitants [159]. Still on the Italian scene, but in line with our finding, about 340 help-seeking young individuals, aged 12 to 35 years, were included in the “Liberiamo Il Futuro” (LIF) project between January 2012 and June 2015. LIF was a project carried out by the contribution of Sapienza University of Rome and all the AMHS and CAMHS of one of the eight Local Health Districts of Rome (i.e. the Rome area H, a catchment area of approximately 500 000 inhabitants), with the aim of deeper assessing psychological problems of adolescents and young adults and identifying individuals at high-risk for developing psychosis [193].

However, it must be emphasized a progressive decrease of referrals over time, after a definitely higher peak occurred during the first year of clinical activity of the ReARMS protocol. This finding suggests that more attention should uninterruptedly be paid to all the potential sources of referrals to EIP services (e.g. general practitioners, emergency room, general hospitals, family members, school and social agencies) through awareness campaigns and professional training courses. Differently, in the “Programma 2000” referrals increased overtime, with 20 subjects enrolled per years in the latter years of the program [159]. In comparison with this result, ReARMS enrolment rates remained overall higher, even in 2017, when it reached a value of 36 individuals enrolled per year.

In the Italian context, an innovative feature of the ReARMS protocol is the direct involvement of the CAMHS in order to define individualized pathways of care as soon as possible and to create an early continuity of intervention with AMHS. Indeed, adolescents receiving care from CAMHS are at high risk of falling through the child-adult service gap as they cross the transition boundary between services, or experience poor care, leading to high risk of disengagement from services and discontinuity of care [194]. In this regards, data suggest that only a small proportion (approximately 20%) of adolescents treated by CAMHS move to AMHS in Italy [195], and Italian programs addressing the problem of the lack in continuity of care for various reasons struggle to be established [193]. As focusing on transitional care has the potential for transforming outcomes in youth mental health, it is therefore necessary to urgently develop and implement reformed service models that are specifically geared to meeting the unique needs and preferences of adolescents and young adults rather than strictly aligned to chronology and rigid diagnostic boundaries, and provide high-quality evidence-based interventions that promote well-being, self-sufficiency, and autonomy [196].

Still on the Italian scene, another specific feature of the ReARMS protocol is the targeted recruitment of adolescents and young people specifically meeting defined criteria for UHR mental states (together with FEP patients). For this purpose, the original English version of the CAARMS was translated into Italian by a team of experienced mental health professionals after obtaining

permission from the original authors (CAARMS-ITA) [181, 182]. In this regards, it is necessary to specify that "Programma 2000" also recruited UHR individuals, but without using a specific in-depth structured interview. Indeed, to be enrolled as UHR, subjects had to have a score ≥ 12 on the "Early Recognition Inventory retrospective assessment of symptoms checklist" (ERIraos-CL), a 17-item screening checklist intended to select people needing a more in-depth assessment. This threshold score on the ERIraos-CL better defined patients at risk of psychosis transition in the German schizophrenia network study [76, 197].

Among subjects who completed the ReARMS assessment battery at baseline, about one third (31.7%) did not meet UHR/FEP-defined criteria. However, more than two thirds were offered a dedicated protocol of care: of them, approximately 75% accepted and were enrolled in the program, 10% refused and 15% dropped out during the first year of treatment (i.e. after accepting the therapeutic proposal). These findings are substantially in line with those reported by Cocchi and co-workers [159] in 11 years of activity of "Programma 2000" (i.e. 25.4% = subjects who were rejected because they did not comply with UHR/FEP criteria, 61.1% = subjects who were proposed the specific EIP treatment: of them, 7.1% turned down the proposed intervention, 6.3% dropped out shortly after accepting the therapeutic proposal, and 86.5% were enrolled and entered treatment). Therefore, the ReARMS protocol appears to be generally well accepted by help-seeking adolescents and young adults, with a low rate of 1-year dropped-out individuals. In particular, this rate is significantly lower than those observed in an age-paired sample of FEP patients consecutively referred to CAMHS and AMHS of the Reggio Emilia Department of Mental Health in the 5 years preceding the implementation of the ReARMS protocol (i.e. from September 2007 to August 2012), to which a generalist TAU was proposed.

The baseline prevalence of UHR diagnosis among individuals entering the ReARMS protocol was 26.3%, similar to what observed in Italian comparable studies (i.e. 24.7% [159]; 18.9% [193]). In line with findings reported in the literature [198], our UHR subjects almost exclusively met APS criteria (more than 90%), and major depression was the most frequent diagnosis (> 50%) at initial examination, followed by anxiety disorders (about 30%). Therefore, persons who merit clinical care within the UHR paradigm have multiple psychopathology issues apart from APSs. Issues such as anxiety and depression, but also negative symptoms, increasing stress sensitivity and deteriorating social and role function, are increasingly being recognized as critical aspects for clinical attention [199]. Unavoidably, it is necessary to consider multiple targets for a wider spectrum of interventions, both for secondary prevention of psychosis and also to address the full range of UHR psychopathology and functional consequences.

Similarly, the baseline prevalence of FEP diagnosis (42%) among patients entering the ReARMS protocol was consistent with what reported (46.2%) in the first 11 years of activity of "Programma 2000" [159], with schizophrenia as markedly prevalent DSMIV-TR diagnosis (approximately 45%).

Socio-demographic and clinical characteristics

In line with findings reported in other Italian comparable studies [159, 169], compared with UHR- and UHR+, FEP patients assessed in the ReARMS protocol showed significantly higher mean age at entry and a preponderance of males. These results confirm the well-known earlier onset of psychosis in males, especially in early adulthood [200]. Differently, UHR mental states occurred more frequently in adolescence, hence the importance of overcoming the child-adult service gap and implementing reformed service models that are not strictly aligned to chronology and rigid diagnostic boundaries [196].

FEP patients entering the ReARMS protocol had also significantly higher percentages of history of substance abuse and previous hospitalization than UHR+ and UHR- subgroups. In line with what reported by Cocchi and colleagues [159], these findings confirm an overall greater clinical severity in FEP subjects. Indeed, it is very likely that a FEP onset prompted patients and their families to access the health care system via a specialized psychiatric contact (such as a hospitalization), as well as to practice substance abuse as specific self-treatment [201].

Source of referral

The majority (about 33%) of individuals enrolled in the ReARMS protocol were mainly referred by general practitioners. Differently, in 10 years of activity of "Programma 2000", patients were more likely to contact this EIP program through the referral of a mental health care professional (68.9%) [159]. This finding reflects the close relationship built up over time between CAMHS and AMHS of the Reggio Emilia Department of Mental Health and general practitioners, following the reform law 180, enforced in 1978, which produced a substantial change in the architecture of the Italian mental health system [11]. Indeed, this reorganization resulted in a comprehensive and integrated system of community-based mental health departments that are interconnected with the network of general hospitals, general practitioners, and other community services (e.g. school and social agencies) [164]. This historical collaboration is further strengthened by having structured a diffused EIP model rather than a centralized departmental service.

However, compared to the other two subgroups, FEP patients entering the ReARMS protocol contacted significantly more often emergency rooms and general hospitals (36.5%) as specific settings where formulating their first request for specialist help. In all likelihood, this result confirm

the greater clinical severity of FEP subjects and is in line with what reported by Cocchi and co-workers [159], who observed that FEP patients were more often referred to the "Programma 2000" by a public or private mental health professional.

Differently, in comparison with FEP, UHR+ individuals are more often self-referred or referred by school/social services to the ReARMS protocol. These results are not consistent with what reported in other Italian comparable study. In particular, 33% of UHR subjects were referred by family members to LIF project [193] and 62% joined "Programma 2000" through the referral of a public or private mental health professional [159].

Limitations

A major methodological limitation is that we had no control data, either for a site that does not have an established EIP or historical data prior to the establishment of the EIP. So, we cannot exclude that the changes we observed over time in the pattern of referrals to the ReARMS protocol were the result of changes in public attitudes or in awareness of mental health issue unrelated to the establishment of the EIP.

Secondly, in comparing our findings with those of other Italian study [159, 193], it is necessary to take into consideration any possible regional difference in terms of catchment area size and local organization of mental health services. Indeed, since health care in Italy is provided and financed by eminently regional organisms, there could be considerable structural and functional gaps among different departments of mental health.

CONCLUSIONS

A specific protocol for the early detection and intervention on young people at UHR of psychosis (together with FEP patients) in Italian CAMHS and AMHS is feasible and clinically relevant, also in adolescence [203]. In particular, it is necessary to immediately define individualized, EIP-based pathways of care for these individuals, and to create a specific continuity of care between CAMHS and AMHS [196]. Indeed, young people receiving care from CAMHS are at high risk of falling through the child-adult service gap as they cross the transition boundary between services. In this context, EIP programs could be an important driving factor for the organizational reform of CAMHS and AMHS [199].

Furthermore, the experience of ReARMS protocol suggests that a "liquid" EIP infrastructure rather than a centralized departmental service could be further strengthened the interconnection between the comprehensive and integrated system of community-based mental health departments and the network of general hospitals, general practitioners and the other community agencies.

Overcoming the gap between child and adult mental health services: the "Reggio Emilia At-Risk Mental States" protocol.

In the last two decades, the paradigm of "Early Intervention in Psychosis" (EIP) [129] has reached increased attention in the scientific community, leading to the development of dedicated protocol of care that have been implemented in EIP programs and/or in autonomous EIP services within the mental health care network of different countries [11]. This high consideration is linked to the evidence that EIP has been demonstrated to reduce inpatient care, treatment drop-out, morbidity and disability, as well as to improve long-term outcomes of illness [160].

The "Reggio Emilia At-Risk Mental States" program

In September 2012, after being involved in the GET-UP trial (a study protocol aimed to evaluate the feasibility in real-world routine clinical settings of a multicomponent psychosocial intervention compared to treatment as usual in a large cohort of patients with FEP recruited from a 10 million-inhabitant catchment area) [203], and under the aegis of the "Regional Project on Early intervention in Psychosis" (RP-EIP) [188], the Reggio Emilia Department of Mental Health developed a specific EIP program (the "Reggio Emilia At-Risk Mental States" [ReARMS] protocol) to be applied not through a centralized departmental service (such as "Programma 2000" in Milan) [166], but through a diffused infrastructure branched within the network of all the Reggio Emilia Adult and Child/Adolescent Mental Health Services (AMHS and CAMHS) [174], a semi-urban catchment area of about 550.000 inhabitants in the northern Italy. ReARMS program was established in order to offer a dedicated, evidence-based and expertise-driven protocol of care to adolescents and young adults experiencing a FEP or in the prodromal phase of a psychosis [170]. Interestingly, this is the first example in Italy of EIP model that specifically involved CAMHS and recruited adolescents specifically meeting defined diagnostic criteria for an UHR mental state (together with FEP patients), in order to define an evidence-based, individualized pathway of care as soon as possible and to create a continuity of intervention between CAMHS and AMHS through a shared and co-constructed personalized planning.

In this regards, the comprehensive, pan-European survey by the MILESTONE Consortium on the architecture and functioning of CAMHS has clearly indicated that there are more differences than communalities across European Union countries [205], within the glaring problem that the organization of services and the distribution of resources are often not based on users' perspectives and needs (as they should be) [196]. Such macroscopic heterogeneity and distance from users' needs is even more problematic as it fails to match the natural pattern of emerging mental disorders

in young people [205]. Indeed, young individuals, aged 12-25 years, have the highest incidence and prevalence of mental illness across the lifespan, while also having the worst access and engagement with mental health services compared to all the other age groups [206]. Thus, the division of mental health care along the pediatric/adult model, inspired by the traditional organization of somatic medicine, is not appropriate, as this division cuts across the age when risk for mental disorders peaks, with obvious consequences in term of discontinuity of care, under-treatment, and unmet needs [196].

Aims of the current retrospective study were (a) to describe the macroscopic organization of the ReARMS protocol and (b) to analyze patterns of referral and ReARMS process indicators (e.g. number of subjects who were referred to the service, who met defined-FEP/UHR diagnostic criteria, who turned down the proposed treatment, who dropped out shortly [i.e. within 1 year] after accepting the therapeutic proposal, and who were enrolled and entered treatment) in *adolescent* help-seekers during the first five years of clinical activity.

METHODS

Participants

Data were collected during the baseline routine assessment of the help-seeking adolescents entering the ReARMS protocol between September 2012 and December 2017. All participants (n = 125) and their parents agreed to participate to the research and gave their written informed consent after the procedure had been fully explained. Relevant local ethical and Institutional Review Board approvals were sought for the study. The current research has been also carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments including humans.

For the purpose of this study, inclusion criteria were: (a) specialist help-seeking; (b) age between 13 and 18 years; (c) presence of UHR criteria defined by the CAARMS [38]; or (d) a DUP < 2 years in case CAARMS-defined FEP criteria are detected at baseline assessment. In this regard, within the EIP paradigm, a DUP less than 24 months is considered the limit to start a specific EIP protocol of care [14]. Indeed, recent reviews and meta-analyses showed that a shorter DUP was associated to better long-term outcomes of FEP [162, 177].

According to CAARMS operational criteria [38], UHR status is defined as follows: (a) Attenuated Psychotic Symptoms (APS), including individuals characterized by sub-threshold positive psychotic symptoms during the past year; (b) Brief, Limited, and Intermittent Psychotic Symptoms (BLIPS), comprising adolescents who experienced episodes of full-blown positive psychotic symptoms that have lasted no longer than a week and spontaneously ceased (i.e. without

antipsychotic medications); and (c) Genetic Risk and Functioning Deterioration (GRFD) syndrome, including subjects with a schizotypal personality disorder or with a first-degree relative diagnosed with frank psychotic disorder, combined with evidence of deterioration in functioning in the last year. Moreover, according to the psychosis criteria defined by the CAARMS [38], the threshold of full-blown psychotic episode (FEP) is defined by operationalized clear-cut levels of fully positive symptoms occurring for > 1 week, either daily or > 3 times a week with each symptom continuing for > 1 hour on each occasion.

ReARMS exclusion criteria were: (a) history of affective and non-affective psychotic disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR) [178]; (b) history of previous exposure to antipsychotics; (c) current substance dependence; (d) known intellectual disability (IQ < 70); and (e) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. In the current study, we considered previous exposure to antipsychotic (i.e. before ReARMS enrollment) as an equivalent of past psychotic episode. Indeed, according to the psychosis criteria defined by the CAARMS [38], the threshold of full-blown psychotic episode is essentially that at which antipsychotic medication would probably be commenced in common clinical practice.

Assessment and diagnosis

All subjects entering the ReARMS protocol underwent a comprehensive, multidimensional evaluation [170]. In this study, the following standardized instruments were considered:

(a) An ad-hoc socio-demographic/clinical schedule, in which information was collected on age, gender, ethnic group, years of education, marital status, pattern of referral, family psychiatric history, history of substance abuse and attempted suicide, previous hospitalization (i.e. before ReARMS enrollment), previous specialist contact (both as single consultation and taking charge at CAMHS), DUP (defined as the period of treatment delay [in weeks] between onset of psychotic symptoms and pharmacotherapy initiation) [179], and Duration of Untreated Illness (DUI, defined as the interval [in weeks] between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment) [180]. DUI and DUP were based on interviews with the patient and of at least one key informant (in this young population, usually a parent). A history of suicide attempt and of illicit substance abuse was also considered as an indicator of illness severity. Indeed, as these events/conditions are likely to raise concern in the family, they may also induce contact-seeking with psychiatric services [159].

(b) CAARMS: a semi-structured clinical interview designed to cover different features of attenuated psychopathology, as well as functioning (via the integrated SOFAS [Social and

Occupational Functioning Assessment Scale] module) [38]. 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). These items can be clustered in 7 subscales: "Positive Symptoms", "Cognitive Change, Attention and Concentration", "Emotional Disturbance", "Negative Symptoms", "Behavioral Change", "Motor/Physical Changes", and "General Psychopathology". 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 [38]. CAARMS interviews were conducted by clinical psychologists, psychiatrists, and neuropsychiatrists trained by the main author of the approved Italian translation (CAARMS-ITA) [181], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability of the assessment. The Intra-Class Correlation (ICC) coefficients of each CAARMS-ITA subscales showed good to excellent interrater reliability [183].

The axis-I diagnosis was made according to DSM-IV-TR criteria [178] by two trained ReARMS team members, using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I) [184]. After CAARMS interviews, participants were divided into three groups according to UHR/psychosis criteria [38]: (a) UHR+ group (i.e. APS, BLIPS and GRFD), (b) FEP group, and (c) UHR- group (i.e. those individuals who were under the threshold of the CAARMS inclusion criteria).

Procedures

All the help-seeking adolescents referred to the ReARMS protocol were assigned to a multi-professional team, generally within 2-3 weeks [174] (for details, see also supplementary materials [Appendix S1]). However, ReARMS interventions were expected to begin as soon as the subject was stabilized (i.e. when she/he was in a clinical condition allowing her/him to collaborate in at least a brief clinical evaluation) and after she/he has been assessed at baseline with the ReARMS assessment battery [170, 171]. In the ReARMS program, early identification of adolescents with FEP/UHR mental states was a 2-step procedure [174]. The first screening step included a triage service using the "Screening Schedule" for Psychosis (SS) [185], performed by general service staff members. The second step consisted of the CAARMS interview to investigate the clinical status (i.e. psychosis risk, psychosis, or neither) [38], carried out by trained clinicians. The first filtering step was mainly meant to maximize appropriate referrals to the ReARMS protocol (i.e. eligibility) and to avoid over-inclusion of subjects clearly outside the severity threshold for presumed psychosis risk spectrum [172].

At baseline, the ReARMS assessment process involved a first clinical interview for compilation of the ad-hoc socio-demographic/clinical schedule and the administration and scoring of the ReARMS assessment battery for an in-depth diagnostic and psychopathological evaluation [174] (for details, see also supplementary materials [Appendix S1]). After CAARMS interview, individuals who were under the threshold of the CAARMS inclusion criteria (i.e. UHR- group) exited from the ReARMS protocol, but received appropriate advice for future treatment. These subjects also remained worthy of clinical attention for the re-administration of ReARMS assessment battery in an annual program of follow-up re-evaluation [171].

According to their symptoms, FEP and UHR adolescents were then provided with a comprehensive five-year intervention package including pharmacological treatment and a multi-element psychosocial intervention (combining individual CBT, psychoeducational sessions for family members, and a recovery-oriented case management), according to current guidelines [13, 176, 188] (for details, see also Supplementary Materials [Appendix S1]). The prescription of antipsychotics is avoided unless UHR individuals (a) had an imminent risk of suicide or severe violence, (b) were overwhelmed by abruptly worsening full-blown psychotic symptoms, (c) were rapidly deteriorating in daily functioning, or (d) did not respond to any other treatment [13]. Low-dose atypical antipsychotics are used. Selective serotonin reuptake inhibitor or benzodiazepines are used to treat depressive symptoms, anxiety, and insomnia.

Individual CBT is based on the model developed by Fowler and colleagues [189]. An optimal number of 20 CBT sessions per patient (each lasting 60 minutes) were delivered during a time frame of 12 months, with weekly sessions held during the first 3 months. In the second year, at least 10 CBT sessions per patient were offered. In the maintenance phase (i.e. from third to fifth year), booster sessions on specific symptomatic areas were eventually provided. Clinical psychologist using individual CBT received specific training programs [174].

Family intervention is based on the model proposed by Kuipers and co-workers [191]. In the first year, it consisted of an optimal number of 10 sessions over 12 months with each individual family, with at least 6 sessions held during the first 4 months. Starting from the second year and based on functioning and specific symptomatic areas, booster sessions were eventually delivered. Similarly, each mental health professional (i.e. clinical psychologist, psychiatric nurse or educator, and psychiatric rehabilitation therapist) using psychoeducation for family members received specific training programs [174].

For case management, every patient/family had a dedicated case manager that coordinated all planned intervention, in particular those aimed to a recovery-oriented early rehabilitation [171]. In the first year, at least 24 sessions per patient (each lasting 60 minutes) were provided. Later (i.e.

from second to fifth year), at least 50 sessions per patient (each lasting 60 minutes) were delivered, according to social and occupational functioning. A specific training program on case management was also given to each mental health professional (i.e. psychiatric nurse or educator, social assistant and psychiatric rehabilitation therapist) [174].

At the end of each training program, an assessment of the competence achieved was performed, and detailed intervention manuals based on international standards were given to each mental health professionals as a standard to be followed for the treatment. Interventions provided to all individuals/relatives were steadily supervised by a team of departmental experts, who held meetings every month and were regularly available for consultation.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 [192]. All tests were two-tailed. Threshold of significance was set at $p = 0.05$. Descriptive data included mean values and standard deviation for continuous variables, and absolute and relative frequencies for categorical parameters. Cross-sectional analyses on the sociodemographic, clinical, and psychopathological characteristics among the three groups (i.e. FEP, UHR+, and UHR-) were assessed with ANOVA, using Fisher's Least Significant Difference (LSD) to correct for multiple comparisons involving normally distributed variables. The Kruskal-Wallis test was used for parameters that were not normally distributed, and post-hoc analyses were performed by using the Mann-Whitney U test. A Chi-square test (with Yates' correction when appropriate) or Fisher's exact test (when any expected frequency was < 1 or 20% of expected frequency was ≤ 5) were employed for categorical data.

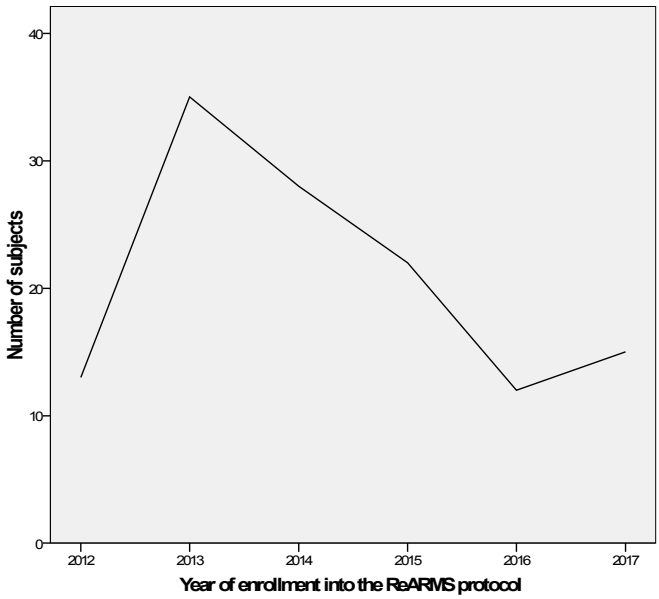
RESULTS

The ReARMS protocol: process indicators

A total of 125 adolescents (65 females [52%]; 105 white Caucasian [84%]; mean age = 15.78 ± 1.68 years) have been consecutively referred to the ReARM protocol since its establishment in Reggio Emilia CAMHS (available data were from September 2012 to December 2017) (Figure 5).

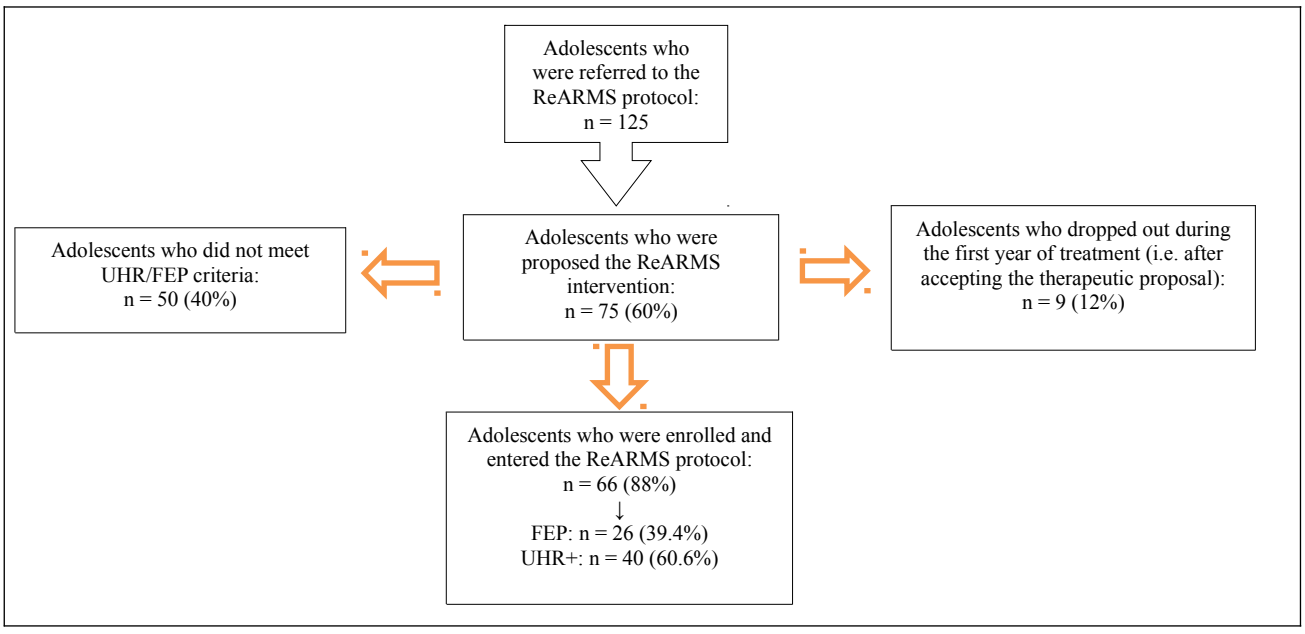
Among these, 50 (40%) subjects did not meet UHR/FEP defined criteria [38] and were grouped as UHR-. Therefore, 75 (60%) individuals were offered a dedicated protocol of care: of them, 66 (88%) accepted and were enrolled in the program, while 9 (12%) dropped out during the first year of treatment (i.e. after accepting the therapeutic proposal) (Figure 6). However, UHR- cases received appropriate advice for future treatment.

Figure 5 - Enrollment into the ReARMS protocol in Reggio Emilia CAMHS (n = 125) (available data from September 2012 to December 2017).



Legend - ReARMS = Reggio Emilia At-Risk Mental States; CAMHS = Child and Adolescent Mental Health Services.

Figure 6 – Flowchart of referrals to the ReARMS protocol in Reggio Emilia CAMHS (available data from September 2012 to December 2017) (n = 125).



Legend – ReARMS = Reggio Emilia At-Risk Mental States; CAMHS = Child and Adolescent Mental Health Services; UHR = Ultra-High Risk; FEP = First Episode Psychosis; UHR+ = participants who met UHR-defined criteria.

Among the UHR+ group (n = 44; 35.2% of the total sample), 40 adolescents met APS criteria (90.9% of the UHR subgroup), 2 met BLIPS criteria, and 2 met GRFD criteria. In our UHR+ sample, major depression was the most frequent diagnosis (n = 22; 50%) at initial examination, followed by anxiety disorders (n = 13; 29.5%), schizotypal personality disorder (n = 7; 15.9%), and brief psychotic disorder (n = 2; 4.6%).

The FEP group (n = 31; 24.8% of the total sample) consisted of patients with DSM-IV-TR schizophrenia (n = 14; 45.2%), psychotic disorder not otherwise specified (n = 9; 29%), affective (bipolar or major depressive) psychosis (n = 7; 22.6%), and substance-induced psychotic disorder (n = 1; 3.2%).

The remaining 50 adolescents (40% of the total sample) were below the CAARMS threshold for being considered at risk for psychosis and composed the UHR- group. They were diagnosed with DSM-IV-TR depressive disorders (n = 21; 42%), non-schizotypal personality disorder (n = 18; 36%) (i.e. borderline, avoidance, or narcissistic personality disorder), and anxiety disorders (n = 11; 22%).

Sociodemographic and clinical data

The socio-demographic and clinical variables in the total sample and in the three subgroups are reported in Table 7.

Table 7 – Demographic and clinical characteristics of the total sample and the three subgroups.

Variable	Total sample (n=125)	UHR- (n=50)	UHR+ (n=44)	FEP (n=31)	Statistics (F/X^2)	Post hoc test
Gender (females)	65 (52%)	25 (50%)	26 (59.1%)	14 (45.2%)	1.55	-
Ethnic group (Caucasian)	105 (84%)	42 (84%)	38 (86.4%)	25 (80.6%)	0.44	-
Age at entry	15.78 ± 1.68	15.78 ± 1.76	15.45 ± 1.60	14.23 ± 1.59	1.95	-
Education (in years)	10.46 ± 1.64	10.64 ± 1.77	10.23 ± 1.54	10.52 ± 1.59	0.75	-
Family psychiatric history	47 (37.9%)	21 (42.9%)	11 (25%)	15 (48.4%)	6.07[b]	FEP>UHR+
First-degree relative with psychosis	15 (12.1%)	5 (10.2%)	3 (6.8%)	7 (22.7%)	4.52	-
DUI (in weeks)	85.10 ± 52.79	80.65 ± 53.34	68.93 ± 40.64	115.29 ± 56.35	9.54[a]	FEP >UHR+=UHR-
DUP (in weeks)	-	-	-	47.35 ± 42.80	-	-
History of substance abuse	23 (18.4%)	9 (18%)	4 (9.1%)	10 (32.3%)	6.51[b]	FEP>UHR+
History of attempted suicide	9 (7.2%)	2 (4%)	6 (13.6%)	1 (3.2%)	4.23	-
Previous hospitalization	22 (17.6%)	8 (16%)	5 (11.4%)	9 (29%)	4.06	-
Previous specialist contact	70 (56%)	28 (56%)	23 (52.3%)	19 (61.3%)	0.60	-

Legend – DUI = Duration of Untreated Illness; DUP = Duration of Untreated Psychosis; CAARMS = Comprehensive Assessment of At-Risk Mental States; FEP = patients with First-Episode Psychosis; UHR = Ultra-High Risk; UHR+ = individuals who met CAARMS-defined UHR criteria; UHR- = individuals who did not meet CAARMS-defined UHR/FEP criteria. Frequencies and percentages, mean ± standard deviation, one-way Anova test (F), Kruskal-Wallis test (χ^2), and Chi-squared test (χ^2) values are reported; [a]$p < 0.01$; [b]$p < 0.05$.

No between-group difference in terms of gender, ethnic group, marital status (all participants were unmarried), age, and years of education was found. In comparison with UHR+, FEP adolescents showed significantly longer DUI (115.29 ± 56.35 vs 68.93 ± 40.64, Z = -3.03, p = 0.002) and higher percentages of family psychiatric history (15 [48.4%] vs 11 [25.0%], $\chi 2 = 4.39$, degree of freedom [df] = 1, p = 0.036) and history of substance abuse (10 [32.3%] vs 4 [9.1%], $\chi 2 = 6.43$, df = 1, p = 0.011). No between-group difference in terms of percentages of first-degree relatives with psychosis, history of attempted suicide, previous hospitalization, and previous specialist contact was observed.

Interestingly, more than half (n = 70 [56%]) of adolescents assessed in the ReARMS protocol had a history of previous specialist contact, mainly represented as a full taking charge at CAMHS (n = 65/70 [92.8%]) rather than a single consultation (5/70 [7.2%]). Considering only FEP patients, this percentage reached a value of 61.3% (n = 19/31). Both in FEP and UHR+ subgroup, learning disorders were the most frequent diagnosis (respectively, n = 10 [22.7%] and n = 8 [42.1%]), followed by anxiety disorders (respectively, n = 7 [16%] and n = 6 [31.6%]) and conduct disorders (respectively, n = 5 [10.3%] and n = 4 [12.8%]).

Patterns of referral

Referrals to the ReARMS protocol exponentially increased during the first year of implementation of the program in the Reggio Emilia CAMHS (n = 35 adolescents enrolled per year in 2013). Subsequently, it progressively decreased to an enrollment rate of 12 individuals per year in 2016, than to go back to a value of 15 subjects per year in 2017 (Figure 5).

The vast majority of adolescents entered the ReARMS protocol were mainly referred by general practitioners (n = 40; 32%), family members (n = 20; 16%), or school/social services (n = 19; 15.2%) (Table 8). No between-group difference in terms of pattern of referral was found.

Table 8 - Pattern of referral in the total sample and the three subgroups.

Pattern of referral	Total sample (n=125)	UHR- (n=50)	UHR+ (n=44)	FEP (n=31)	Statistics (X^2)	Post hoc test
General practitioners	40 (32%)	16 (32%)	15 (34.1%)	9 (29%)	0.21	-
Emergency room/general hospital	19 (15.2%)	6 (12%)	8 (18.2%)	5 (16.1%)	0.72	-
Self-referral	18 (14.4%)	8 (16%)	5 (11.4%)	5 (16.1%)	0.51	-
Family involvement	20 (16%)	9 (18%)	6 (13.6%)	5 (16.1%)	0.33	-
Public/private mental health care professional	9 (7.2%)	3 (6%)	2 (4.5%)	4 (12.9%)	2.08	-
School/Social services	19 (15.2%)	8 (16%)	8 (18.2%)	3 (9.7%)	1.06	-

Legend – FEP = First-Episode Psychosis; UHR = Ultra-High Risk; UHR+ = individuals who met CAARMS-defined UHR criteria; CAARMS = Comprehensive Assessment of At-Risk Mental

States; UHR- = individuals who were below CAARMS-defined UHR/FEP criteria. Frequencies, percentages, and Chi-squared test (χ^2) values are reported.

DISCUSSION

Main aim of the current study was to describe the macroscopic organization of the ReARMS protocol, the first example in Italy of a diffused, "liquid" EIP model that peculiarly involved CAMHS and recruited adolescents meeting CAARMS-defined diagnostic criteria for a UHR mental state (together with FEP patients) [170]. Specifically, reasons that supported the decision to implement the ReARMS protocol were: (a) to improve the quality of interventions (both in processes and outcomes), establishing a specialized EIP program aimed to the early detection, diagnosis and treatment of UHR and FEP adolescents according to well-defined, state-of-art guidelines on the topic; (b) to reduce the variability of treatments; (c) to allow an accurate evaluation of the adherence of interventions to the evidence-based recommendations; and (d) to make the planned care pathway transparent to the outside [174].

Main objectives of the ReARMS protocol were: (a) to optimize the early detection of FEP and CAARMS-defined UHR mental states; (b) to reduce DUP and DUI, as well as the time between the onset of relevant psychiatric symptoms and an integrated case management by the local CAMHS in order to promote a clinical, social, and personal recovery as wide and as early as possible; (c) to train professional staff members of each CAMHS on the theoretical and operational cores of the EIP model, with the aim of increasing their skills on early detection and intervention in FEP and UHR individuals, and improving the quality of treatments through a specific, shared care pathway consistent with international guidelines; (d) to reduce personal and social stigma associated with psychosis, promoting social and interpersonal inclusion; and (e) to provide a dedicated, evidence-based and expertise-driven protocol of care to adolescents with FEP or UHR mental states, implementing a homogeneous, targeted, and cohesive work methodology based on specific and appropriate interventions [174].

For these purposes, the Reggio Emilia Department of Mental Health preferred to apply the ReARMS protocol not through a centralized departmental service (such as "Programma 2000") [166], but through a diffused ("liquid") infrastructure branched within the network of all the Reggio Emilia CAMHS [141]. Indeed, from its establishment, using special regional funds provided by RP-EIP, ReARMS protocol mainly focused on the education and training of mental health care professionals working within each CAMHS (i.e. neuropsychiatrists, psychologists, educators, social assistants, and psychiatric rehabilitation therapists). The aim was to raise awareness on the importance of early detection and referral of patients with FEP or UHR mental state, and to

disseminate knowledge of the multi-dimensional protocol of care applied in the ReARMS program [171]. In this context, a "liquid" infrastructure was preferred to ensure the best possible local dissemination of the ReARMS interventions and their highest delivery to the users. Over time, more attention should be paid to schools and the public in general through awareness campaigns.

The ReARMS protocol was composed of the following five processes: (a) Identification, (b) Assessment, (c) Intervention in FEP patients: acute phase or relapse, (d) Intervention in UHR individuals (i.e. BLIPS, APS, and GRFD), and (e) Intervention in FEP patients: maintenance treatment. All processes are divided into distinct procedures, each one structured in specific settings, mental health professionals involved, duration, timing, and scheduling [174] (for details, see also Supplementary Materials [Appendix S1]).

The ReARMS protocol: process indicators

One hundred-twenty five adolescents, aged 13-18 years, have been consecutively referred to the ReARMS protocol in the first five years of clinical activity. This finding is slightly lower than what reported in the very few other comparable studies [159, 165, 193]. In particular, approximately 250 help-seekers, aged 12-18 years, were included in the "Liberiamo Il Futuro" (LIF) project between January 2012 and June 2015. LIF was a project carried out by the contribution of Sapienza University of Rome and all the CAMHS of one of the eight Local Health Districts of Rome (i.e. the Rome area H, a catchment area of approximately 500.000 inhabitants) with the exclusively purpose of deeper assessing psychological problems of adolescents and identifying individuals at high-risk for developing psychosis [193]. Therefore, as an EIP centralized departmental service, an EIP diffused infrastructure specifically involving all the local CAMHS appears to be equally able to meet and respond to the specific care needs of young help-seeking users, but placing in close proximity with them and disseminating an EIP knowledge in several professionals working in all departmental areas.

However, it is important to underline the evidence of a progressive decrease of referrals over time, after a clearly high peak occurred during the first year of ReARMS establishment. Thus, more attention should uninterruptedly be paid to all the potential sources of referrals to EIP services (i.e. general practitioners, emergency room and general hospitals, family members, schools and social services) through awareness campaigns and professional training courses. Differently, in the "Programma 2000" referrals increased overtime, with 20 subjects enrolled per years in the last years of clinical activity [159]. However, this result (reported in a sample of young people aged 17-30 years) is substantially in line with those observed in the ReARMS protocol, even in 2017 when the enrollment rate reached a value of only 15 adolescents enrolled per year.

On the Italian scene, a specific innovative feature of the ReARMS program is the direct involvement of all the CAMHS of the Reggio Emilia Department of Mental Health in order to immediately define evidence-based, individualized pathways of care and to create a continuity of intervention between CAMHS and AMHS as soon as possible. Indeed, adolescents receiving care from CAMHS are at high risk of falling through the child-adult service gap as they cross the transition boundary between services, or experience poor care, leading to high risk of disengagement from services and discontinuity of care [194]. In this regards, data suggest that only a small proportion (approximately 20%) of adolescents treated by CAMHS move to AMHS in Italy [195], and Italian programs addressing the problem of the lack in continuity of care for various reasons struggle to be established [193]. As focusing on transitional care has the potential for transforming outcomes in youth mental health [160], it is therefore necessary to urgently develop and implement reformed service models that are specifically geared to meeting the unique needs and preferences of adolescents rather than strictly aligned to chronology and rigid diagnostic boundaries, and provide high quality evidence-based interventions that promote well-being, self-sufficiency, and autonomy [196].

In the Italian context, another peculiar feature of the ReARMS protocol is the targeted recruitment of adolescents specifically meeting defined diagnostic criteria for UHR mental states (together with FEP patients). For this purpose, the original English version of the CAARMS was translated into Italian (CAARMS-ITA) by a team of experienced mental health professionals after obtaining permission from the original authors [182]. In this regards, it is necessary to specify that "Programma 2000" also recruited UHR individuals, but without using a specific in-depth structured interview. Indeed, to be enrolled as UHR, subjects had to have a score ≥ 12 on the "Early Recognition Inventory retrospective assessment of symptoms checklist" (ERIraos-CL), a 17-item screening checklist intended to select people needing a more in-depth assessment [197]. This threshold score on the ERIraos-CL better defined patients at risk of psychosis transition in the German schizophrenia network study [159].

Among subjects assessed in the ReARMS protocol at baseline, 40% did not meet UHR/FEP-defined criteria. Therefore, approximately two thirds (60%) were offered a dedicated protocol of care: of them, the vast majority (88%) accepted and were enrolled in the program, and only 12% dropped out during the first year of treatment (i.e. after accepting the therapeutic proposal). These findings are substantially in line with those reported in 11 years of activity of the "Programma 2000" (i.e. 61.1% = subjects who were proposed the specific EIP treatment; of them, 7.1% turned down the proposed intervention, 6.3% dropped out shortly after accepting the therapeutic proposal, and 86.5% were enrolled and entered treatment) [159]. Overall, the ReARMS protocol appears to be

generally well accepted by adolescent help-seeking users, with a low 1-year rate of dropped-out individuals.

The baseline prevalence of UHR diagnosis among adolescents entering the ReARMS protocol was approximately 35%. This result is slightly higher than what observed in Italian comparable studies: i.e. 24.7% [159] and 18.9% [193]. Moreover, in line with findings reported in the literature [121, 198], our UHR subjects almost exclusively met APS criteria (more than 90%) and major depression was the most frequent diagnosis (50%) at initial examination, followed by anxiety disorders (about 30%). Therefore, subjects who merit clinical care within the UHR paradigm show to be affected by multiple psychopathology issues apart from attenuated psychotic symptoms. Issues such as anxiety and depression, but also negative symptoms, increasing stress sensitivity, and deteriorating social and role function, are increasingly being recognized as critical aspects for clinical attention [199]. Unavoidably, it is necessary to consider multiple targets for a wider spectrum of interventions, both for secondary prevention of psychosis and also to address the full range of UHR psychopathology and functional consequences.

Differently, the baseline prevalence of FEP diagnosis (approximately 25%) among patients entering the ReARMS protocol was lower than what reported (46.2%) in a sample of young people, aged 17-30 years, during the first eleven years of activity of "Programma 2000" [159], with schizophrenia as markedly prevalent DSM-IV-TR diagnosis (about 45%). This finding confirms that UHR mental states occur more frequently in adolescence than full-blown FEP, hence the importance of overcoming the child-adult service gap and implementing reformed service models that are not strictly aligned to chronology and rigid diagnostic boundaries, but that are based on users' need and perspectives [195, 196].

Sociodemographic data, psychopathology and functioning

In comparison with UHR+, FEP adolescents entering the ReARMS protocol had significantly longer DUI and higher percentages of family psychiatric history and history of substance abuse. In line with what reported by Cocchi and co-workers [159], these findings confirm the greater importance of family burden in FEP patients and their higher clinical severity. Indeed, it is very likely that a FEP onset prompted patients to practice substance abuse as a self-treatment [201], postponing access to health care system and lengthening DUI.

Finally, a large majority of FEP/UHR+ adolescents assessed in the ReARMS protocol showed a previous specialist contact, mainly represented as a full taking charge at CAMHS for learning disorders. These findings suggest the importance of considering learning deficits also as possible early features which mark the prodromal phase of psychosis, especially in adolescence, and the

need to involve school professionals in early signaling and referral to CAMHS of individuals with presumed psychotic experiences.

Patterns of referral

The majority (about 1/3) of adolescents enrolled in the ReARMS protocol were mainly referred by general practitioners. Differently, in eleven years of activity of "Programma 2000", patients were more likely to contact this EIP program through the referral of a public/private mental health care professional (68.9%) [159]. This finding reflects the close relationship built up over time between CAMHS of the Reggio Emilia Department of Mental Health and general practitioners, following the reform law 180, enforced in 1978, which produced a substantial change in the architecture of the Italian mental health care system [165]. Indeed, this reorganization resulted in a comprehensive and integrated system of community-based mental health departments that are interconnected with the network of general hospitals (where the operating psychiatric wards for acute treatment are located), general practitioners and other community services (e.g., school and social agencies) [164]. This historical collaboration is further strengthened by having structured an EIP liquid infrastructure rather than a centralized departmental service, that is a program probably more capable of creeping widely into the depth of local CAMHS and leading general practitioners to a greater awareness of the crucial importance of early detection and intervention in psychosis for reducing severity and persistence of illness, specifically in a target population of adolescents. However, in line with findings reported in other Italian comparable studies [159, 193], school and family members are other important sources of referral to EIP services. Therefore, more attention should continuously be paid over time to school and social agencies in general through awareness campaigns on early detection and treatment of psychosis [207].

Limitations

A major methodological limitation of the present study is the relatively small sample size, which prevented the execution of multivariate analyses and, in all likelihood, limited the chance of finding associations for some occurrence. For example, the lack of between-group differences in some sociodemographic and clinical variables among the three subgroups most likely could be because each diagnostic subsample was too small to reliably detect these variabilities.

Secondly, we had no control data or historical data prior to the establishment of the EIP protocol. So, we cannot exclude that the changes we observed over time in the pattern of referrals to the ReARMS program were the result of changes in public attitudes or in awareness of mental health issue unrelated to the establishment of the EIP service.

CONCLUSION

Early detection and intervention on adolescents at UHR of psychosis (together with FEP) in Italian CAMHS are feasible, clinically relevant, and recommended [175, 202]. In particular, it is absolutely necessary to immediately define evidence-based, personalized pathways of care for young people with psychosis spectrum disorders attending CAMHS, as well as to create a continuity of interventions between CAMHS and AMHS [196]. Indeed, adolescents receiving care from CAMHS are at high risk of falling through the child-adult service gap as they cross the transition boundary between services. In this context, EIP programs could be an important driving factor for the organizational reform of CAMHS and AMHS [199].

As young individuals aged 12-25 years have the highest incidence and prevalence of mental illness across the lifespan, while also having the worst access to and engagement with mental health services compared to all the other age groups, we cannot postpone a radical review of the structure and resourcing of health care for young people in transition from childhood to adulthood any longer [196]. To be sustainable, this review should be guided by emerging research evidence from the new youth mental health framework. Indeed, the creation of youth-friendly primary care platforms, together with a structural redevelopment and enhancement of contemporary CAMHS, represents a huge opportunity to bridge the serious gap between child-adolescent and adult psychiatry [207]. Bridging this gap might be achievable through a framework shift that incorporates the full continuum of service response within a promotion and prevention framework for youth mental health. Indeed, besides the quality and accessibility of youth mental health, a crucial driving principle should be the stepwise gradient of increasing intensity and specificity of treatment, inspired by a developmentally informed clinical staging model [207].

Finally, the clinical experience of ReARMS protocol in the real world suggests that an EIP liquid infrastructure rather than a centralized departmental service could be further strengthened the interconnection between the comprehensive and integrated system of community-based mental health departments and the network of general hospitals, general practitioners, and the other community agencies (such as school and social services).

STUDY 2

THE "CHECKLIST PER LA VALUTAZIONE DELL'ESORDIO PSICOTICO"

Validation of the "early detection Primary Care Checklist" in an Italian community help-seeking sample: the "Checklist per la Valutazione dell'Esordio Psicotico" (CVEP)

In the past 20 years, the early detection of young people considered at risk of developing psychosis has long been a research focus. Nowadays, it is not only possible to reliably identify these young people [104], but also to provide interventions that can prevent or delay the onset of a first episode of psychosis [2]. However, translating the early detection research framework into successful clinical care pathways relies, in part, on the recognition of these young people at the earliest point in their help-seeking trajectory [68].

General practitioners are obviously central in this respect as they are often the first point of contact for these young people and are generally involved before emergency services [208]. Therefore, despite primary care has clearly an essential role in identifying potential clinically high risk individuals, relatively few screening instruments have been designed to be implemented in this setting. Indeed, gold standard assessment tools for identifying young people at risk of developing psychosis (such as the CAARMS) [38] require high levels of specialist training and lengthy administration time, making them impracticable for use by busy primary care practitioners.

Although some shorter screening instruments have been developed [130], only the "early detection Primary Care Checklist" (PCCL) [155] has been specifically designed for use by primary care practitioners. As alternative screening tools, the self-report "Prodromal Questionnaire" (PQ) [156] has been shown to have good sensitivity (90%) and specificity (49%) in a sample of young people referred to an early detection clinic, but it is estimated to take around 20 minutes to complete with 92 items, making its feasibility for use in primary care settings questionable. The "Screen for Prodromal symptoms of psychosis" (PROD-screen) [131] and the "Basel Screening Instrument for Psychosis" [209] (Riecher-Rossler et al., 2008) have similar completion times, the latter being designed for administration by specialist mental health rather than primary care practitioners. Other, much shorter, self-report screens have been shown to have excellent sensitivity and specificity in either small samples (e.g. the "Structured Interview for Prodromal Syndromes (SIPS) Screen") [134] or in samples comprising of psychiatric outpatients (eg, the "Prime-Screen Revised"), arguably a rather different population than those targeted in the very early detection of young people at risk of developing psychosis.

The “Checklist per la Valutazione dell’Esordio Psicotico” (CVEP) [211] is the Italian adaptation of the PCCL for experimental use (for details, see also Appendix S2). The PCCL has been developed as a quick and easy to use tool administered by the primary care practitioners to help identifying young people who may be in the early stages of psychosis and to make quick, appropriate referrals to specialist services. One problematic issue associated with screening for this population is that low level psychotic symptoms are allegedly reported in the general population as well [212]. What seems to distinguish these common experiences with experiences that imply somebody may be at risk of developing psychosis is the frequency of the experiences and the level of subjective distress associated with them [213]. With this issue in mind, the PCCL has been specifically designed for help-seeking populations (such as those contacting primary care because they are distressed by their experiences) and not as a population wide screen.

The current study aims to assess the concordant validity of the CVEP by comparing its outcomes to the outcomes of a standardized assessment for “at risk mental states” (i.e. the CAARMS) in a sample of Italian young help-seekers referred to the Reggio Emilia Department of Mental Health.

METHODS

Participants

The concordant validity of the CVEP was tested in a sample of 168 individuals, aged between 13 and 35 (mean = 22.35 ± 6.17 years), who were referred to the “Reggio Emilia At Risk Mental States” (ReARMS) program, an early detection infrastructure developed under the aegis of the Regional Project on Early Detection of Psychosis in the Reggio Emilia Department of Mental Health [170]. The referrals were mainly performed by general practitioners (50%), family members (22%), hospital emergency rooms (13%), school and social services (10%). All of the referred individuals were screened at a triage service for the presence of positive psychotic symptoms, negative symptoms (e.g. apathy, anhedonia, social withdrawal), or severe decline in social and/or occupational functioning.

The inclusion criteria were age 13-35, a DUP < 2 years, and CAARMS criteria for psychosis or Ultra-High Risk (UHR) status (i.e. APS, BLIPS and/or GRFD). Exclusion criteria were those individuals suffering from mental retardation or organic mental disorders. The ReARMS team is specialized in identifying young people who may be at UHR of developing psychosis as measured by the CAARMS.

All help-seekers entering the ReARMS protocol agreed to participate in the study and gave their written informed consent to the psychopathological assessment, composed - among others [171] - by the CAARMS (approved Italian translation) [181] and the CVEP. Relevant ethical and local

research and development approvals were sought for the study. The present study has also been performed in accordance with the ethical standards of the Declaration of Helsinki, as revised in Brazil 2013.

Over the course of the study, out of 168 people assessed by the ReARMS team, 120 met CAARMS criteria for UHR status or overt first-episode psychosis (FEP) (UHR = 42 [35%]; FEP = 78 [65%]) (Table 9).

Table 9 – Sociodemographic data, CAARMS criteria and screen outcomes.

Variable	Total sample (n=168)	CAARMS- (n=48)	CAARMS+ (n=120)	χ^2/t/Z
Gender (males)	99 (58.9%)	25 (52.1%)	74 (61.7%)	0.93
Ethnic group (white Caucasian)	149 (88.7%)	41 (85.4%)	108 (90.0%)	0.33
Mother language (Italian)	153 (91.1%)	46 (95.8%)	107 (89.2%)	1.14
Age	22.35 ± 6.17	22.13 ± 6.92	22.44 ± 5.88	-0.29
Years of Education	11.72 ± 2.50	11.35 ± 2.57	11.87 ± 2.47	-1.20
DUI (in weeks)	96.20 ± 6.15	109.72 ± 5.81	82.68 ± 6.50	0.76
CVEP "binary response" total score	8.73 ± 2.33	7.34 ± 2.14	10.12 ± 2.52	-4.96[a]
Screen positive outcome	138 (82.1%)	20 (41.7%)	118 (98.3%)	71.24[a]
Screen negative outcome	30 (17.9%)	28 (58.3%)	2 (1.7%)	-
only CVEP tot.≥ 20				
Screen positive outcome	117 (69.6%)	6 (12.5%)	111 (92.5%)	100.04[a]
Screen negative outcome	51 (30.4%)	42 (87.5%)	9 (7.5%)	-

Legend – CAARMS = Comprehensive Assessment of At-Risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico; DUI = Duration of Untreated Illness; frequencies and percentages, mean ± standard deviation, chi-squared (χ^2) test, Student's t test, and Mann-Whitney test (Z) values are reported; [a]$p<0.001$.

For the specific purposes of this study, indeed, UHR and FEP participants were both considered as CAARMS positive cases (CAARMS [+]), since it is not the aim of the PCCL/CVEP to distinguish between those at risk (UHR) of and those experiencing psychosis (FEP). However taking into consideration the applicability of the CVEP in those services that just have a FEP or a UHR clinic, we decided to test the concordant validity of the instrument presenting 3 forms of the analysis: CAARMS [+], FEP only, and UHR only. The remaining 48 participants were below the threshold for being considered at risk of developing psychosis (CAARMS [-]).

CAARMS

The CAARMS is a semi-structured interview schedule designed to identify people who were at UHR of developing psychosis. It takes approximately 1-1.5 hours to complete and requires specialist training for its administration. It has been shown to have good-to-excellent concurrent, discriminate and predictive validity and excellent inter-rater reliability [38]. The CAARMS defines the following 3 sub-criteria and 1 or more need to be fulfilled to be considered at UHR of developing psychosis: (1) GRFD syndrome: family history of psychosis in a first-degree relative combined with 30% drop in functioning or chronic low functioning, as measured by the "Global Assessment of Functioning" [146]; (2) APS: sub-threshold psychotic symptoms within the past 12 month; and (3) BLIPS: criteria for psychosis met for less than 7 days at a time, and ceasing spontaneously, that is, without the use of anti-psychotic medication.

The ReARMS team routinely uses the CAARMS in the initial assessment to determine whether a person 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 adaptation [181], who was trained at Orygen YRC in Melbourne. Regular CAARMS supervision sessions and scoring workshops ensure the inter-rater reliability of these assessments. By using the CAARMS as a gold standard, the concordant validity of the CVEP can be established.

CVEP

The CVEP (for details, see also Appendix S2) is the Italian adaptation of the PCCL [211], that was originally translated as part of an overarching educational program for general practitioners in Reggio Emilia Mental Health Department and later incorporated in the ReARMS protocol [171]. The PCCL is a 20-item checklist designed to facilitate the identification of young people who may be at an UHR of developing psychosis by primary care clinicians. The checklist, which should take no longer than 5 minutes to be completed, includes items relating to general, psychological and social functioning (e.g. "arguing with friends and family", "spending more time alone", "sleep difficulties", and "depressive mood") as well as items relating to psychotic symptoms such as hallucinations, delusions and disorganized speech and thinking. Each checklist item has an allocated numerical value, ranging from 1 to 5, depending on its perceived relevance to overall psychosis risk. By summing the scores of each endorsed checklist item, a total score (ranging from 0 to 55) can be calculated for each individual. According to the original CVEP/PCCL scoring rules, positive screen outcome for further assessment of psychosis risk can be reached in 2 ways: (1) a global score of 20 or above, or (2) endorsement of 1 or more of 5 specific key-items (13 to 16 and 20) conceived

as indicative of psychosis risk even if observed in isolation (i.e. independently of the final CVEP/PCCL score above 20). Those 5 key-items are designed to capture attenuated positive psychotic symptoms (such as hallucinations, delusions and ideas of reference [e.g. "feeling hearing or seeing things that other cannot" and "feeling that everyday things have a special meaning just for you"]) or state/trait vulnerability features (i.e. "first-degree family history of psychosis plus increased stress or deterioration in functioning").

Upon making a referral to ReARMS protocol, referrers were asked to complete the CVEP before completing other scales. In a small minority of cases, where it is not possible to ensure checklist at the point of referral, referrers were contacted and asked to retrospectively complete the checklist on the basis of the first referral report in the clinical file.

Statistical analysis

For the specific purposes of this study, as we were interested in testing the screening features of the CVEP against the CAARMS risk threshold, the sample was initially dichotomized as follows: CAARMS [+], that is, those who were above CAARMS UHR threshold (that is UHR and FEP), and CAARMS [-], that is, those who are below such threshold. The two subgroups were compared on demographic, clinical and psychopathological parameters. Categorical data were compared by chi-squared ($\chi 2$) test with Yates' correction, while quantitative variables were compared using the Mann-Whitney's unpaired U test or the Student's unpaired t-test (where appropriated). In examining the sensitivity and specificity values of the screening tool, we used not only the original CVEP cut-off [155], but also 2 additional cut-offs composed respectively by a CVEP total score of 20 or above and the endorsement of 1 or more of the 5 specific key-items (13 to 16 and 20) (Appendix S2). However, considering the applicability of the CVEP in those services that just have only a FEP or a UHR clinic, we also tested the sensitivity/specificity trade-off of the instrument respectively in FEP and UHR subgroup. Moreover, correlations between CVEP total score and CAARMS subscale scores were carried out through the use of Spearman's rank correlation coefficient. Finally, simple cross-tabulations of the individual CVEP item scores against CAARMS outcome to identify the more discriminant CVEP items in terms of sensitivity and specificity were carried out. Prior to these analyses, in order to better balance the psychometric load of each items, all 20 CVEP items were coded in terms of a binary response of whether they were endorsed or not.

RESULTS

Table 9 shows the demographic characteristics and screening outcomes of the sample as a whole and for the two subgroups, that is, those meeting or above the UHR threshold (CAARMS [+], n =

120) and those below the UHR threshold (CAARMS [-], n = 48). No significant differences were found between groups in terms of gender, ethnic group, first language, age, years of education and DUI, meant as the interval between the onset of a psychiatric clinically relevant symptom and the administration of the first pharmacological treatment.

In comparison with CAARMS [-] participants, CAARMS [+] individuals showed significantly higher CVEP "binary response" total score (Table 9). Moreover, within CAARMS [+] subgroup, UHR individuals (n = 42) showed lower CVEP "binary response" total score in comparison with FEP subjects (n = 78) (mean = 10.12 ± 2.52 vs 12.25 ± 2.36; Z = −4.10; p < .001).

Table 10 presents the results of Spearman's correlations between CVEP "binary response" total score and CAARMS subscales. The CVEP "binary response" total score was significantly correlated with all CAARMS subscales.

Table 10 - Spearman's correlations between CVEP "binary response" total score and CAARMS dimension subscores.

CVEP "binary response" total score	ρ
CAARMS dimension scores	
Positive symptoms	0.605[a]
Cognitive change	0.523[a]
Emotional disturbance	0.503[a]
Negative symptoms	0.404[a]
Behavioral change	0.522[a]
Motor/Physical changes	0.205[b]
General psychopathology	0.347[a]

Legend – CVEP = Checklist per la Valutazione dell'Esordio Psicotico; CAARMS = Comprehensive Assessment of At-Risk Mental States; Spearman's rank correlation coefficient (ρ) values are reported; [a]p<0.01; [b]p<0.05.

Of the 120 CAARMS [+] participants, 118 also had a concordant positive screen outcome (Table 9). This means that in this sample, the screening tool has a high sensitivity value of 0.983 (118/120) with a positive predictive value of 0.855 (118/[118 + 20]). Table 9 also shows that of the 48 CAARMS [-] participants, 28 had a concordant CVEP screen negative result, meaning that CVEP has a 0.583 (28/48) specificity with a negative predictive value of 0.933 (28/[28 + 2]).

Given the high sensitivity level and lower specificity of the CVEP, further analysis of the collected data was taken to improve the ool has a high specificity values of 0.875 (42/48) with a negative predictive value of 0.823 (42/[42 + 9]). When only the endorsement of 1 or more of the 5 specific key-items as CVEP cutoff was used, the screening tools showed similar values of sensitivity (0.975

[117/120]) and specificity (0.583 [28/48]) to those previously obtained using the original CVEP cut-off.

UHR group

No significant differences were found between UHR participants and CAARMS [-] control group in terms of gender (male: 20 [47.6%] vs 25 [52.1%]; $\chi^2 = 0.179$; p = .673), ethnic group (Caucasian: 38 [90.5%] vs 41 [85.4%]; $\chi^2 = 0.325$; p = .174), first language (Italian: 39 [92.9%] vs 46 [95.8%]; $\chi^2 = 0.315$; p = .169), age (mean = 20.28 ± 5.15 years vs 22.13 ± 6.92 years; t = -1.89; p = .098), years of education (mean = 11.76 ± 2.43 years vs 11.35 ± 2.57 years; t = -0.770; p = .443), and DUI (in weeks: mean = 81.59 ± 5.60 vs 109.72 ± 5.81; t = -1.75; p = .085). When the original CVEP cutoff was used, 40 of the 42 UHR individuals had a concordant positive screen score. This means that in this subgroup, the screening tool reaches a sensitivity value of 0.952 (40/42) with the same specificity level previously obtained in the CAARMS [-] control group (0.583 [28/48]). When only a CVEP global score of 20 or above as CVEP cut-off was used, the instrument showed a significant improvement of the specificity value (0.875 [42/48]), as previously established in the CAARMS [-] control group, but a clear worsening of the sensitivity level (0.786 [33/42]).

FEP group

No significant differences were found between FEP participants and control group (42 UHR and 48 CAARMS [-] individuals) in terms of gender (male: 54 [69.2%] vs 45 [50.0%]; $\chi^2 = 3.67$; p = .066, ethnic group (Caucasian: 70 [89.7%] vs 79 [87.8%]; $\chi^2 = 2.80$; p = .423), first language (Italian: 68 [87.2%] vs 85 [94.4%]; $\chi^2 = 6.78$; P = 0.342), age (mean = 22.04 ± 5.65 years vs 20.88 ± 6.26 years; t = -1.40; p = .165), years of education (mean = 11.92 ± 2.51 years vs 11.54 ± 2.50 years; t = -0.977; p = .330), and DUI (in weeks: mean = 86.79 ± 6.60 vs 98.64 ± 5.70; t = -1.57; p = .098). When the original CVEP cut-off was used, all 78 FEP participants had a concordant positive screen score, meaning that in this subgroup CVEP has an optimal sensitivity value of 0.100 (78/78). However, of the 90 control cases, only 30 also had a concordant negative screen result, meaning that in this sample the screening tool reaches a low sensitivity value of 0.333 (30/90). When only a CVEP total score of 20 or above as CVEP cut-off was used, the screening tool maintained the same optimal sensitivity level (0.100 [78/78]) with a clear improvement of specificity (0.567 [51/90]).

Simple cross-tabulations

Simple cross-tabulations of the individual CVEP item scores against CAARMS outcome indicated the more discriminant item in terms of sensitivity and specificity (Table 11).

Table 11 – Simple cross tabulations for individual checklist (CVEP) item and corresponding CAARMS outcomes.

Checklist item/outcome	Sensitivity	Specificity
1. Spending more time alone	**0.875**	0.479
2. Arguing with friends and family	-	-
3. The family is concerned	**0.950**	0.313
4. Excess use of alcohol	-	-
5. Use of street drugs	-	-
6. Sleep difficulties	-	-
7. Poor appetite	-	-
8. Depressive mood	-	-
9. Poor concentration	**0.875**	0.292
10. Restlessness	-	-
11. Tension and nervousness	-	-
12. Less pleasure from things	-	-
13. Feeling people are watching you	**0.833**	**0.708**
14. Feeling or hearing things that others cannot	-	-
15. Ideas of reference	**0.717**	**0.896**
16. Bizarre ideas	0.575	**0.875**
17. Odd manner of thinking or speech	0.467	**0.917**
18. Inappropriate emotional responses	0.342	**0.938**
19. Odd behaviour or appearance	0.408	**0.875**
20. First-degree family history of psychosis + increased stress or deterioration of functioning	0.217	**0.958**

Legend – CVEP = Checklist per la Valutazione dell'Esordio Psicotico; CAARMS = Comprehensive Assessment of At-Risk Mental States. Sensitivity and specificity values are reported.

In comparison with CAARMS [-] participants, CAARMS [+] individuals showed significantly higher percentages of endorsement of the following 10 CVEP item: "Spending more time alone", "The family is concerned", "Poor concentration", "Feeling people are watching you or giving you a hard time for no reason", "Ideas of reference", "Bizarre ideas", "Odd manner of thinking or speech", "Inappropriate emotional responses", "Odd behavior or appearance", and "First-degree

family history of psychosis plus increased stress or deterioration in functioning". The sensitivity and the specificity of each resulted significant CVEP item are shown in Table 11. However, although there was a relationship between any CVEP item score and outcome, the association was not in the direction originally hypothesized. For example, "Excess use of alcohol" is associated with lower risk of being CAARMS positive outcome (i.e. CAARMS[+]/CVEP[+] = 17 [14.2%] vs CAARMS[+]/CVEP[-] = 103 [85.8%]).

DISCUSSION

The concordant validity of the CVEP was assessed comparing its outcomes to the outcomes of a standardized assessment for "at risk mental states" (i.e. the CAARMS) in a sample of Italian young help-seekers referred the ReARMS program.

In comparison with CAARMS [-] participants, CAARMS [+] individuals showed significantly higher CVEP total score. Moreover, within the last subgroup, patient who had experienced a FEP showed significantly higher CVEP total score in comparison with people at UHR. On a dimensional level, CVEP total score was positively associated with CAARMS sub-scores, suggesting that increasing CVEP scores relate to the severity of both psychotic and general psychopathology.

In the original version, PCCL authors hypothesized that a total checklist score of 20 points or more, and/or the endorsement of any of the 5 key-items would indicate a screen positive result and therefore the need for a specialist assessment. Adopting this approach in our sample, the CVEP was found to have an excellent sensitivity of 0.983, indicating that it correctly identified more than 98% of people who met UHR or FEP criteria (118/120) according to the CAARMS and missed only less than 2% of these UHR/FEP participants (2/120) (Table 9), with an excellent positive predictive value of 0.855. In other words, it had a probability that a person with a CVEP positive screen outcome really either met or exceeded UHR criteria greater than 85%. Moreover, the checklist showed a lower specificity value of 0.583, meaning that it incorrectly identified approximately 42% of individuals who did not meet UHR/FEP criteria (20/48) as being in need of a specialist assessment, with an excellent negative predictive value of 0.933. In other words, it had a probability that an individual with a CVEP negative screen outcome really did not meet UHR/FEP criteria greater than 93%. Such lower specificity has implications both in terms of rational resources allocation (e.g. avoiding unnecessary and lengthy assessment) and of clients comfort (i.e. avoiding distress and delays in adequate pathways to care for non-relevant assessments). However, these values are in line with those of other screening tools for this population, including the PQ that revealed a sensibility of 0.9 and a specificity of 0.49 in a sample of 113 young people referred to a specialist early detection clinic [156]. Unlike the 92-item self-report PQ, the CVEP can be quickly

administered by general practitioners, making it ideal for use in primary care settings. These results are also substantially in line with those showed in the PCCL original validation study [135], although CVEP sensitivity and specificity values are overall slightly higher.

Taking account the applicability of the CVEP in those services that just have a FEP or a UHR clinic, we tested the sensitivity/specificity trade-off of the instrument respectively in FEP and UHR subgroup. Adopting the original CVEP cut-off, the screening tool showed an excellent sensitivity value of 0.952 in the UHR sample and an optimal sensitivity level of 0.100 (but with a significant worsening of the specificity [0.333]) in the FEP subgroup. In examining the concordant validity of the CVEP, the balance between sensitivity and specificity should not to be the same for FEP and UHR group. Indeed, it is not ideal to miss any cases of FEP, and therefore, a high sensitivity is clearly preferred. Because UHR individuals may not develop a psychotic disorder, a high sensitivity may not to be as essential for this subgroup.

Given the lower specificity/high sensitivity trade-off of the CVEP and the considerable specificity/sensitivity feature of some of the items (Table 11), a psychometric strategy to optimize the screening potential of the CVEP is to consider 2 subcomponents: (1) items with excellent sensitivity (between 0.833 and 0.950), such as "Spending more time alone", "The family is concerned", "Poor concentration" and "Feeling people are watching you or giving you a hard time for no reason" and (2) items with excellent specificity (between 0.875 and 0.938), such as "Ideas of reference", "Bizarre ideas", "Odd manner of thinking or speech", "Inappropriate emotional responses", "Odd behavior or appearance" and "First-degree family history of psychosis plus increased stress or deterioration in functioning". The 4 "sensitivity" items might be more useful in identifying individuals with a positive CAARMS outcome (who either met or exceeded UHR criteria), whereas the 6 "specificity" items might be more important in identifying people with a negative CAARMS outcome (who did not meet UHR/FEP criteria).

Contrary to the initial hypothesis that the endorsement of a checklist item would be associated with a positive CAARMS outcome, some of the CVEP items (e.g. "Depression" and "Tension or nervousness") were more frequent in participants who did not meet UHR criteria, increasing the likelihood of identifying as positive individuals with a negative CAARMS outcome. In other words, these items were associated with a lower risk of being CAARMS positive outcome, meaning that they were in fact more likely to be predictive of a CAARMS negative outcome. Moreover, other CVEP items, including "Excess use of alcohol", "Use of street drugs (including cannabis)", "Poor appetite" and "Feeling, hearing or seeing things that others cannot", were more frequently absent in individuals who either met or exceeded UHR criteria, meaning that they could in fact increase the likelihood of identifying as negative participants with a positive CAARMS outcome.

Limitations

In this study, the concordant validity of the checklist was established by using the CAARMS as "gold standard". The CAARMS identifies people who are at UHR of developing psychosis but the majority of these individuals will likely not go on to experience psychosis at all [42]. The current study has not included a follow-up methodology and as such it is not possible to establish the predictive validity of the tool, that is, how well the checklist identifies people who do go on to experience psychosis. Therefore, it is not possible to say if the checklist identifies a subgroup of people who, although meet UHR criteria according to the CAARMS, are more or less likely to experience psychosis than previously researched samples.

Psychotic symptoms have been shown to be commonly experienced in the general population [212] and as such a population wide screen would be expected to yield a high false positive rate. High rates have been observed when other screening tools have been applied to similar samples [132]. The sample used in the current study was made up of young people referred to specialist early detection team and probably contained a much higher incidence of UHR cases than would be expected in the general population.

The checklist was completed by those people making referrals to the early detection centers and not by participants themselves, as is reflective of the checklist intended use. However, these referrers had specialist knowledge of psychosis. Therefore, a validation of the CVEP in a way that is representative of a primary care setting or other non-specialist organizations must be done. It will contribute to verify the current potential feasibility of utilization in a number of non-specialist settings. In particular, the checklist seems to be easy and quick to administer as screening tool for use in primary care setting and by the wide range of organizations that may have contact with young people who are at risk of psychosis.

CONCLUSIONS

The CVEP appears to be a useful screen for young people who may be at risk of experiencing psychosis, with an excellent sensitivity value of 0.983 but only a good specificity value of 0.583. Simple cross-tabulations of the individual item scores against CAARMS outcome indicated that a subset of items might be promising to further improve the CVEP specificity value. The derivation of optimal methods of combining item scores in order to discriminate between CAARMS positives and negatives could be carried out applying a statistical exploratory analysis through the use of logistic regression models.

However, it is important to highlight that the CVEP is not a diagnostic instrument. A screen positive result indicates only the need for a further specialist assessment and should not be equated to a diagnostic evaluation or a marker for the initiation of any treatment [135]. Similarly, a screen negative may instead reflect the lack of trust between client and clinician and the level of engagement should be taken into consideration. In this instance, the tool may be used to monitor symptoms as opposed to facilitate discharge. Also, the checklist is not intended to be used as population-wide screen. It has been designed to build on the skills, strengths and experience that non-specialist practitioners already have, with the specific aim to help them deciding whether a referral is warranted and to bridge primary care with secondary care and specialist services. Future research should focus on the continued evaluation of this checklist performance in primary care settings, particularly thinking about service configuration and ease of access to early intervention teams. It would also be of interest to assess the predictive validity by analyzing transition to psychosis in relation to checklist outcome.

Identifying Italian adolescents in the early stage of psychosis:
findings from the "Reggio Emilia At-Risk Mental States" program.

In the last 25 years, there has been an increasing interest in the early detection of psychotic disorders, especially in the definition of reliable and valid criteria for identifying young people at clinical high risk (CHR) of developing psychosis [214]. Recognition of these young individuals at the earliest point in their help-seeking trajectory and understanding the type and the severity of their psychopathology are core-prerequisites for implementing successful clinical care pathways [172, 215].

Early Intervention in Psychosis (EIP) as action strategy is structured into different working phases, mainly focused on (a) reducing the time lag between the clinical onset of illness and the administration of the first appropriate (psychosocial/pharmacological) treatment, (b) restoring good levels of daily functioning as soon as possible, and (c) curbing detrimental factors involving in quality of life deterioration [202]. However, recognition of attenuated psychotic symptoms that may become more persistent and progressively transitioning to full-blown psychosis, is highly dependent from setting and coordinating at least some of the following key-elements: (a) local, non-specialized public health care services, (b) school and social agencies, (c) specific expertise on mental health, (d) accurate and flexible diagnostic tools, and (e) a simplification of formal and informal care pathways for CHR individuals, especially in adolescence [175]. As General Practitioners are often the first point of contact for help-seeking people, primary care necessarily plays an essential role in identifying potential CHR individuals [172]. Therefore, crucial in this effort is to develop quick and easy to use screening tools. However, very few screeners have been designed to be implemented in this setting. To date, the "early detection Primary Care Check-List (PCCL) [155] is the only screening questionnaire specifically developed for use in primary care. In the original PCCL validation study, this instrument showed 89% sensitivity and 60% specificity in identifying young people in the early stages of psychosis in a sample of 176 help-seekers referred to early detection teams across the United Kingdom [135].

The "Checklist per la Valutazione dell'Esordio Psicotico" (CVEP) [211]is the Italian adaptation of the PCCL for experimental use (for details, see also supplementary materials [Appendix S2]). While most of the screening tools for early detection of psychosis generally require high levels of specialist training and expertise, the CVEP has been specifically designed to help primary care practitioners in identifying young people who may be in the early stages of psychosis and to make quick and appropriate referrals to mental health care services in Italy [215]. In the CVEP validation preliminary study, this questionnaire showed an excellent 98% sensitivity and a good 58%

specificity in identifying young people with First Episode Psychosis (FEP) or an Ultra-High Risk (UHR) mental state in a sample of 168 help-seekers referred to an Italian Mental Health Department [175]. However, one emerging problematic issue associated with screening for this population is that low level psychotic experiences are allegedly reported in the general population as well, especially in adolescence [202, 213]. With this issue in mind, the CVEP has been specifically adapted in Italian language for help-seeking populations (such as those contacting primary care because they are distressed by their psychopathological experiences) and not as a population wide screen [175].

The present study aims to assess the concordant validity of the CVEP by comparing its outcomes with those of a gold-standard assessment tool for identifying young people at risk of psychosis (i.e. the CAARMS) [38], focusing on a sample of Italian help-seeking adolescents referred to the Reggio Emilia Department of Mental Health.

SUBJECTS AND METHODS

Participants

The concordant validity of the CVEP was examined in a sample of 129 adolescents, aged 13-18 years (mean age = 15.81 ± 1.67 years, 68 [52.7%] females, 110 [85.3%] white Caucasian), who entered the "Reggio Emilia At-Risk Mental States" (ReARMS) program between September 2012 to December 2017. ReARMS protocol is an EIP infrastructure developed under the aegis of the "Regional Project on early intervention in psychosis" in all of adult and child-adolescent mental health services of the Reggio Emilia Department of Mental Health, a catchment area of approximately 550.000 inhabitants (105.000 of them are minors) in the Northern Italy [170].

ReARMS project specifically aims (a) to detect individuals with FEP and at high risk of psychosis according to CAARMS-defined FEP/UHR criteria [38] among young adult and adolescent help-seekers (aged 13-35 years), and (b) to offer evidence-based intervention that are supposed to be effective in FEP/UHR subjects (i.e. individual Cognitive-Behavioral Therapy [CBT], psychoeducational sessions for family members, intensive case management, and pharmacotherapy [as appropriate]) [171].

Referrals to the ReARMS protocol were mainly performed by General Practitioners, family members, school and social services, emergency room, or they were self-referred. All of them were screened at a triage service for the presence of positive psychotic symptoms, negative symptoms, and severe decline in social and occupational functioning, using the Screening Schedule for psychosis (SS) [185] (Jablensky et al. 1992) (for details, see also supplementary materials [Appendix S1]). Such triage was mainly meant to maximize appropriate referrals to the ReARMS

project and avoid over-inclusion of subjects clearly outside the severity threshold for presumed psychosis risk spectrum [171].

For the specific purpose of this study, inclusion criteria were (a) specialist help-seeking; (b) age between 13 and 18 years; (c) presence of CAARMS-defined UHR criteria (i.e. "Attenuated Psychotic Symptoms" [APS], "Brief Limited Intermittent Psychotic Symptoms" [BLIPS], and "Genetic Risk and Functioning Deterioration" syndrome [GRFD]) [38] or (d) Duration of Untreated Psychosis (DUP) < 2 years if FEP criteria defined by the CAARMS are detected at baseline. Help-seeking adolescents who were under the FEP/UHR diagnostic threshold were considered as CAARMS negative cases. ReARMS team members are specialized in identifying young people who may be at UHR of developing psychosis as measured by the CAARMS [182].

Exclusion criteria were: (a) previous full-blown psychotic episodes, either schizophrenic and affective, as defined in the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR) [178] with DUP > 2 years; (b) past exposure to antipsychotics; (c) current substance dependence; (d) known mental retardation (Intelligence Quotient < 70), and (e) head injury, neurological illness, or any other medical condition presenting with psychiatric symptoms.

All adolescent help-seekers entering the ReARMS protocol and their parents agreed to participate in the research and gave their written informed consent to the psychopathological assessment, composed – among others - by the CAARMS (approved Italian version [CAARMS-ITA]) [181] and the CVEP. Patient anonymity has been rigorously preserved. Relevant local ethical approvals were sought for the study, which has been also conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experimental including humans.

Instruments

CAARMS

The CAARMS is a semi-structured clinical interview designed to cover different aspects of attenuated psychopathology, as well as functioning (via the integrated SOFAS [Social and Occupational Assessment Scale] module) [38]. It takes approximately 1-1.5 hours to be administered and is composed by 27 items (each one rated in terms of intensity [0-6] and frequency/duration [0-6]), which can be clustered in 7 dimensions: (a) "Positive Symptoms", (b) "Cognitive Change, Attention and Concentration", (c) "Emotional Disturbance"; (d) "Negative Symptoms", (e) "Behavioral Change", (f) "Motor/Physical Changes", and (g) "General Psychopathology". CAARMS interviews were conducted by clinical psychologists and neuropsychiatrists trained by the main author of the CAARMS-ITA [184], who was trained at Orygen, the National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS

supervision sessions and scoring workshops ensured the inter-rater reliability of the assessment. Good-to-excellent interrater reliability was found using the intra-class correlation coefficient of each CAARMS-ITA dimension [183].

The "Positive Symptoms" dimension (i.e. hallucinations, delusions, and thought disorder) is used for determining both the UHR criteria (i.e. APS, BLIPS, and GRFD) and the threshold for full-blown psychosis [38]. In details, the CAARMS defines the following three sub-criteria and one or more need to be fulfilled to be considered at UHR of developing psychosis: (a) GRFD syndrome: a trait/state risk condition in which the individual has a family history of psychosis (in first-degree relatives) or a schizotypal personality disorder along with low functioning maintained for $\leqslant$ 1 month (as measured by the SOFAS); (b) APS: sub-threshold positive symptoms within the past 12 months, and (c) BLIPS: criteria for psychosis met for < 1 week and ceasing spontaneously within 1 week (i.e. without antipsychotic medication [38].

CVEP

The CVEP (for details, see also supplementary materials [Appendix S2]) [211] was originally translated as part of an overarching educational program for general practitioners in the Reggio Emilia Department of Mental Health, and later incorporated in the ReARMS protocol [171]. It is the Italian adaptation of the PCCL [155], a 20-item checklist specifically designed to facilitate the early identification of young people who may be at UHR of developing psychosis by primary care professionals. This instrument should take no longer than 5 minutes to be completed and includes items relating to general, psychological, and social functioning (e.g. "arguing with friends and family", "spending more time alone", "sleep difficulties" and "depressive mood"), as well as statements relating to psychotic symptoms (such as hallucinations, delusions, and disorganized speech).

Each item has an allocated numerical value, ranging from 1 to 5, depending on its perceived relevance to overall psychosis risk. By summing the scores of each endorsed item, a total score (ranging from 0 to 55) can be calculated. According to the original CVEP/PCCL scoring rules, positive screen outcome for further assessment of psychosis risk can be reached in two ways: (a) a global score of $\geq$ 20, or (b) endorsement of one or more of five specific key-items (13-16 and 20) conceived as indicative of psychosis risk even if observed in isolation (i.e. regardless of a CVEP total score $\geq$ 20). These five key-items are specifically developed to capture attenuated positive symptoms (such as hallucinations, delusions, and ideas of reference [e.g. "feeling hearing or seeing things that other cannot", "feeling that everyday things have a special meaning just for you"]) or

state/trait vulnerability features (i.e. "first-degree family history of psychosis plus increased stress or deterioration in functioning").

Upon making a referral to the ReARMS protocol, referrers were asked to complete the CVEP before completing other assessment scales. In a small minority of cases, where it is not possible to ensure checklist at the point of referral, referrers were contacted and asked to retrospectively complete the checklist on the basis of the first referral report in the clinical file.

Procedures and statistical analysis

For the purpose of the study (i.e. field-testing the screening features of the CVEP against the CAARMS risk threshold), UHR and FEP adolescents were both considered as CAARMS positive cases (CAARMS+). Indeed, it is not the aim of the CVEP/PCCL to discriminate between young individuals at risk of and those experiencing full-blown psychosis. However, taking into consideration the applicability of the CVEP in those services that just have a FEP or a UHR clinic, we decided to test the concordant validity of the instrument presenting three forms of the analysis: CAARMS+, FEP only, and UHR only. The participants who were below the threshold for being considered at risk of developing psychosis were grouped as CAARMS negative cases (CAARMS-).

The two subgroups were firstly compared on demographic, clinical, and psychopathological parameters. All statistics were two-tailed, with $\alpha = 0.05$. Due to non-normality in all explorations (Kolmogorov-Smirnov statistic with Lilliefors significance correction: $p < 0.05$), non-parametric tests were used. In between-group comparison, quantitative variables were analysed using the Mann-Whitney U test. Categorical data were compared by Chi-squared (χ^2) test with Yates' correction (or Fisher's exact test [as appropriate]: i.e. if any expected frequency was < 1 or 20% of expected frequency was ≤ 5). By using the CAARMS as a gold standard, the concordant validity of the CVEP was then established. In examining the sensitivity and specificity values of the screening tool, we used not only the original proposed CVEP cut-off [211], but also an additional cut-off exclusively composed by a CVEP total score of ≥ 20. Moreover, agreement between CVEP total score and CAARMS outcomes was used to assess concurrent validity by generating Receiver Operating Characteristic (ROC) curve in order to calculate the optimal cut-off balancing the best sensitivity and specificity. However, considering the applicability of the CVEP in those services that have just only a FEP or a UHR clinic, we also tested the sensitivity/specificity trade-off of the screening instrument in the FEP and the UHR subgroup, respectively.

Prior to the following statistical analyses, in order to better balance the psychometric load of each CVEP item, all of the 20 statements of the instrument were coded in terms of a binary response of whether they were endorsed or not. First of all, associations between CVEP total score and

CAARMS dimension subscores were carried out using Spearman's rank correlation coefficients. Then simple cross-tabulations of the individual CVEP item scores against CAARMS outcome to identify the more discriminant CVEP items in terms of sensitivity and specificity were also carried out using Cohen's K coefficients. Finally, we firstly performed a logistic regression analysis with all of the CVEP items as independent variables and the CAARMS positive outcome as dependent variable. Secondly, CVEP explanatory parameters were also selected using a for block selection procedure. In details, considering their perceived relevance to overall psychosis risk (ranging from 1 to 5) (see also supplementary materials [Appendix S2]), each item group was entered as independent block for determining the more predictive item within each group.

RESULTS

Over the course of the study, 80 out of 129 adolescents assessed by the ReARMS team met CAARMS criteria for FEP or UHR status (FEP = 34 [26.4% of the total sample]; UHR = 46 [35.7%]) (table 12). The remaining 49 (38%) participants were under the threshold for being considered at risk of developing psychosis and were grouped as CAARMS negative cases (CAARMS-).

Table 12 – Sociodemographic data, CAARMS criteria and screen outcomes.

	Total sample (n=129)	CAARMS- (n=49)	CAARMS+ (n=80)	χ^2/Z
Gender (females)	68 (52.7%)	25 (51.0%)	43 (53.8%)	0.91
Ethnic group (white Caucasian)	110 (85.3%)	42 (85.7%)	68 (85.0%)	0.01
Mother tongue (Italian)	119 (92.2%)	47 (95.9%)	72 (90.0%)	0.32
Age	15.81 ± 1.67	15.73 ± 1.75	15.86 ± 1.62	-0.27
Years of Education	10.48 ± 1.66	10.65 ± 1.79	10.38 ± 1.59	-0.72
DUI in weeks	83.34 ± 52.94	81.26 ± 52.75	84.75 ± 53.49	-0.16
CVEP total score	22.63 ± 9.60	14.31± 6.47	27.73 ± 7.40	-8.13[a]
CVEP "binary response" total score	9.48 ± 3.13	7.04 ± 2.67	10.98 ± 2.36	-6.93[a]
Screen positive outcome	106 (82.2%)	27 (55.1%)	79 (98.8%)	36.59[a]
Screen negative outcome	23 (17.8%)	22 (44.9%)	1 (1.3%)	-
only CVEP tot.≥ 20				
Screen positive outcome	77 (59.7%)	6 (12.2%)	71 (88.8%)	73.92[a]
Screen negative outcome	52 (40.3%)	43 (87.8%)	9 (11.2%)	-

Legend – CAARMS = Comprehensive Assessment of At-Risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico; frequencies and percentages, mean ± standard deviation, chi-squared (χ^2) test and Mann-Whitney test (Z) values are reported; [a]$p<0.001$.

Table 12 also shows demographic characteristics and screening outcomes of the sample as a whole and for the two subgroups (i.e. CAARMS+ and CAARMS-). No significant inter-group difference in terms of gender, ethnic group, mother tongue, age at baseline, years of education, and "Duration of Untreated Illness" (DUI) (defined as the interval time [in weeks] between the onset of a prominent psychiatric symptom and the administration of the first psychological/pharmacological treatment) [180].

In comparison with CAARMS-, CAARMS+ adolescents showed higher CVEP total scores (table 12). Moreover, within the CAARMS+ subsample, UHR participants had lower CVEP total scores compared to FEP patients (as an example, we reported CVEP "binary response" total score: mean ± standard deviation = 10.30 ± 2.31 vs 11.88 ± 2.16; Z = -2.81; p = 0.005).

Spearman's correlations between CVEP "binary response" total score and CAARMS dimension subscores in the total sample are reported in the Table 13. The CVEP "binary response" total score was significantly correlated with all CAARMS subscale scores.

Table 13 - Spearman's correlations between CVEP "binary response" total score and CAARMS dimension subscores.

CVEP "binary response" total score	ρ
CAARMS dimension scores	
Positive symptoms	.667[a]
Cognitive change	.426[a]
Emotional disturbance	.490[a]
Negative symptoms	.535[a]
Behavioral change	.503[a]
Motor/Physical changes	.472[a]
General psychopathology	.556[a]

Legend – CVEP = Checklist per la Valutazione dell'Esordio Psicotico; CAARMS = Comprehensive Assessment of At-Risk Mental States; Spearman's rank correlation coefficient (ρ) values are reported; [a]p<0.001.

Out of the 80 CAARMS+ adolescents, 79 also had a concordant positive CVEP screen outcome (table 12). This means that the screening tool has an excellent sensitivity value of 0.988 with a positive predictive value of 0.745 (79/[79+27]). Moreover, the table 1 shows that 22 out of the 49 CAARMS- participants had a concordant CVEP screen negative result, meaning that the screening questionnaire has a 0.449 specificity with a negative predictive value of 0.956 (22/[22+1]). Given the high sensitivity level and the lower specificity of the CVEP emerging in the current study, further analysis of the collected data was taken to improve the sensitivity/specificity trade-off.

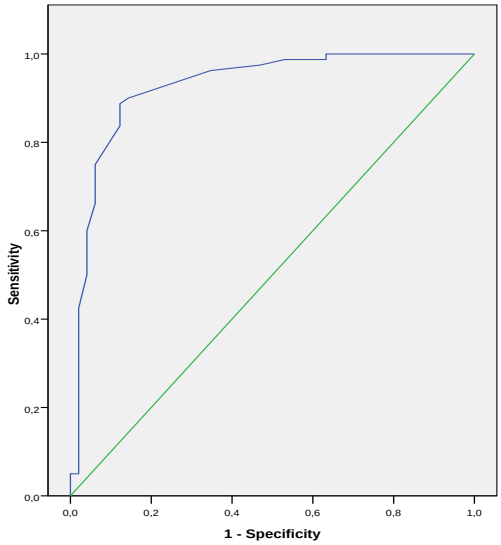
In details, when only a total score of ≥ 20 as CVEP cut-off was used, 71 of 80 CAARMS+ adolescents showed a concordant positive CVEP screen outcome (Table 12). This means that the screening tool maintains an excellent sensitivity value of 0.888, with a positive predictive value of 0.922 (71/[71+6]). Moreover, 43 out of the 49 CAARMS- participants had a concordant screen negative result, meaning that the screening instrument also achieves a better and excellent specificity values of 0.875 (42/48), with a negative predictive value of 0.823 (42/[42+9]). Finally, using a cut-off threshold of ≥ 16 on CVEP total score, we found a better sensibility value of 0.963, while maintaining a good 0.653 specificity (Table 14 and Figure 7]).

Table 14 - CAARMS diagnostic classification accuracy by CVEP cut-off scores within the total sample (n = 129).

CVEP cut-off score	Sensitivity	Specificity
≥ 16	0.963	0.653
≥ 17	0.938	0.735
≥ 19	0.900	0.857
≥ 20	0.888	0.875
≥ 21	0.838	0.878
≥ 22	0.750	0.939

Legend – CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico.

Figure 7 - Receiver Operating Characteristic (ROC) curve generated to assess concurrent validity between CVEP total score and CAARMS outcomes within the total sample (n = 129).



Legend - CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico.

UHR group

No significant difference between UHR and CAARMS- adolescents in terms of gender (female: 28 [60.9%] vs 25 [51.0%], χ^2 = 0.933, p = 0.334), ethnic group (white Caucasian: 40 [87.0%] vs 42 [85.7%], χ^2 = 0.031, p = 0.860), mother tongue (Italian: 44 [95.7%] vs 47 [95.9%], χ^2 = 0004, p = 0.949), age at baseline (mean ± standard deviation = 15.52 ± 1.60 years vs 15.73 ± 1.75 years, Z = -0.831, p = 0.406), years of education (mean ± standard deviation = 10.28 ± 1.53 years vs 10.65 ± 1.79 years, Z = -0.904, p = 0.366), and DUI (in weeks: mean ± standard deviation = 63.97 ± 41.77 vs 81.26 ± 52.75, Z = -1.580, p = 0.114) were found.

When the original CVEP cut-off score of ≥ 20 was used, 45 of the 46 UHR individuals had also a concordant positive CVEP screen result, suggesting an excellent sensitivity of 0.978 with a poor 0.449 specificity value (22/49). Using only a cut-off threshold of ≥ 20 on CVEP total score, we found a significant improvement of specificity (0.878 [43/49]) while maintaining a good-to-excellent sensitivity level (0.826 [38/46]). Generating a ROC curve in order to calculate the best diagnostic accuracy measures, an optimal CVEP cut-off score of ≥ 16 balanced an excellent 0.935 sensitivity with an acceptably good specificity value of 0.653 (Table 15).

Table 15 – CAARMS diagnostic classification accuracy by CVEP cut-off scores within the subsample composed by UHR and CARMS- adolescents (n = 95).

CVEP cut-off score	Sensitivity	Specificity
≥ 15	0.957	0.531
≥ 16	0.935	0.653
≥ 17	0.891	0.735
≥ 19	0.848	0.857
≥ 20	0.826	0.878
≥ 21	0.739	0.878

Legend – CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico; UHR = Ultra-High Risk; CAARMS- = adolescents who were below CAARMS-defined criteria for First Episode Psychosis or UHR mental state.

FEP group

No significant difference between FEP and CAARMS- adolescents in terms of gender (male: 19 [55.9%] vs 24 [49.0%], χ^2 = 0.383, p = 0.536), ethnic group (white Caucasian: 22 [82.4%] vs 42 [85.7%], χ^2 = 0.175, p = 0.679), mother tongue (Italian: 28 [82.4%] vs 47 [95.9%], χ^2 = 0.12, p = 0.915), age at baseline (mean ± standard deviation = 16.32 ± 1.55 years vs 15.73 ± 1.75 years, Z = -

1.55, p = 0.121), years of education (mean ± standard deviation = 10.50 ± 1.67 years vs 10.65 ± 1.79 years, Z = -0.251, p = 0.802), and DUI (in weeks: mean ± standard deviation = 112.46 ± 55.57 vs 81.26 ± 52.75, Z = -1.95, p = 0.068) was found.

When the original CVEP cut-off was used, all FEP participants had a concordant positive CVEP screen result, suggesting an optimal sensitivity value of 0.100 (34/34). However, only 22 out of 49 CAARMS- individuals had also a concordant negative CVEP screen score, meaning that the screening tool showed a low sensitivity value of 0.449. Using only a total score of ≥ 20 as CVEP cut-off threshold, the screening instrument maintained an excellent 0.971 sensitivity (33/34), with a clear improvement of specificity (0.878 [43/49]). Engendering a ROC curve in order to evaluate the best diagnostic accuracy measures, a CVEP cut-off score of ≥ 17 balanced an optimal 0.100 sensitivity with an acceptably good-to-excellent specificity value of 0.735 (Table 16).

Table 16 – CAARMS diagnostic classification accuracy by CVEP cut-off scores within the subsample composed by FEP and CAARMS- adolescents (n = 83).

CVEP cut-off score	Sensitivity	Specificity
≥ 15	0.100	0.531
≥ 16	0.100	0.653
≥ 17	0.100	0.735
≥ 19	0.971	0.857
≥ 20	0.971	0.878
≥ 21	0.912	0.932

Legend – CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico; FEP = First Episode Psychosis; CAARMS- = adolescents who were below CAARMS-defined criteria for FEP or UHR mental state.

Simple cross-tabulations

Table 17 shows simple cross-tabulations of the individual CVEP item scores against CAARMS outcome, pointing out the more discriminant item in terms of sensitivity and specificity. In this regards, we found a statistically significant outcome agreement for the following twelve CVEP item: "Spending more time alone", "Depressive mood", "Poor concentration", "Restlessness", "Less pleasure from things", "Feeling people are watching you", "Feeling or hearing things that others cannot", "Ideas of reference", "Bizarre ideas", "Odd manner of thinking or speech", "Inappropriate emotional responses", and "Odd behaviour or appearance". However, although there was a relationship between any CVEP item score and CAARMS outcome, the association was not

always in the direction originally hypothesized. Indeed, "Excess use of alcohol" and "Poor appetite" are associated with lower risk of being CAARMS positive outcome.

Table 17 – Simple cross tabulations for individual checklist (CVEP) item and corresponding CAARMS outcomes.

Checklist item/outcome	K	Sensitivity	Specificity
1. Spending more time alone	0.215[b]	**0.888**	0.306
2. Arguing with friends and family	0.050	-	-
3. The family is concerned	0.117	-	-
4. Excess use of alcohol	-0.041	-	-
5. Use of street drugs	0.028	-	-
6. Sleep difficulties	0.157	-	-
7. Poor appetite	-0.030	-	-
8. Depressive mood	0.240[b]	**0.800**	0.429
9. Poor concentration	0.199[c]	**0.838**	0.347
10. Restlessness	0.245[b]	**0.750**	0.490
11. Tension and nervousness	0.107	-	-
12. Less pleasure from things	0.300[a]	**0.800**	0.490
13. Feeling people are watching you	0.435[a]	**0.750**	0.694
14. Feeling or hearing things that others cannot	0.205[b]	0.438	**0.796**
15. Ideas of reference	0.407[a]	0.525	**0.939**
16. Bizarre ideas	0.337[a]	0.488	**0.898**
17. Odd manner of thinking or speech	0.215[b]	0.375	**0.878**
18. Inappropriate emotional responses	0.210[b]	0.388	**0.857**
19. Odd behaviour or appearance	0.268[a]	0.450	**0.857**
20. First-degree family history of psychosis + increased stress or deterioration of functioning	0.065	-	-

Legend - CVEP = Checklist per la Valutazione dell'Esordio Psicotico; CAARMS = Comprehensive Assessment of At-Risk Mental States; Cohen's K coefficient, sensitivity, and specificity values are reported; [a]$p<0.001$; [b]$p<0.01$; [c]$p<0.05$.

Logistic Regression

In the total sample, considering all the CVEP items as independent variables, only three explanatory parameters (i.e. "Feeling or hearing things that others cannot", "Ideas of reference", and "Bizarre ideas") entered into a logistic regression model with a statistically significant power, showing positive regression coefficients (Table 18). The percentage of correct dichotomized ascription using this model for predicting CAARMS positive outcome in the total group was 88.4%.

Using a for block selection procedure that took into consideration each item perceived relevance to overall psychosis risk (ranging from 1 to 5), we selected the following ten more predictive CVEP item for a CAARMS positive result: "Spending more time alone", "Poor appetite", "Depressive

mood", "Less pleasure from things", "Feeling people are watching you", "Feeling or hearing things that others cannot", "Ideas of reference", "Bizarre ideas", "Inappropriate emotional responses" and "Odd behaviour or appearance" (Table 19). Only one ("Poor appetite") of them had a negative regression coefficient. However, together they showed a percentage of correct dichotomized ascription for predicting CAARMS positive outcome in the total sample equal to 86%.

Table 18 – Logistic regression of CAARMS outcomes by CVEP item "binary response" scores within the total sample (n = 129): baseline model (all predictors entered at step 1).

Parameters	B	SE	Wald	df	p	OR	95% CI for OR	
							Lower	Upper
1. Spending more time alone	0.640	0.991	0.416	1	0.519	1.896	0.272	13.236
2. Arguing with friends and family	0.650	0.749	0.753	1	0.385	1.916	0.441	8.319
3. The family is concerned	0.739	1.116	0.438	1	0.508	2.094	0.235	18.664
4. Excess use of alcohol	-0.467	1.415	0.109	1	0.741	0.627	0.039	10.043
5. Use of street drugs	0.797	1.272	0.393	1	0.531	2.219	0.184	26.822
6. Sleep difficulties	0.807	0.770	1.099	1	0.294	2.242	0.496	10.143
7. Poor appetite	-0.757	0.788	0.923	1	0.337	0.469	0.100	2.197
8. Depressive mood	0.914	0.767	1,420	1	0.233	2.495	0.555	11.223
9. Poor concentration	0.216	0.780	0.077	1	0.782	1.241	0.269	5.731
10. Restlessness	-0.074	0.737	0.010	1	0.920	0.929	0.219	3.940
11. Tension and nervousness	0.311	0.897	0.120	1	0.729	1.365	0.235	7.918
12. Less pleasure from things	1.397	0.857	2.654	1	0.103	4.043	0.753	21.702
13. Feeling people are watching you	1.009	0.642	2.469	1	0.116	2.744	0.779	9.665
14. Feeling or hearing things that others cannot	1.620	0.696	5.411	1	**0.020**	5.051	1.290	19.773
15. Ideas of reference	2.255	0.872	6.684	1	**0.010**	9.534	1.725	52.682
16. Bizarre ideas	1.663	0.849	3.839	1	**0.049**	5.273	0.999	27.823
17. Odd manner of thinking or speech	1.341	0.855	2.461	1	0.117	3.822	0.716	20.408
18. Inappropriate emotional responses	1.044	0.849	1.511	1	0.219	2.840	0.538	14.997
19. Odd behaviour or appearance	1.090	0.750	2.116	1	0.146	2.975	0.685	12.930
20. First-degree family history of psychosis + increased stress or deterioration of functioning	1.662	1.128	2.169	1	0.141	5.270	0.577	48.119
Costante	-6.287	1.699	13.691	1	0.000	0.002	-	-
Overall model fit test → χ^2 = 91.702, p = 0.0001; overall correct predictive percentage = 88.4%								
Associated strength → Cox-Snell R^2 = 0.509, Negelkerke R^2 = 0.692								

Legend – CAARMS = Comprehensive Assessment of At-Risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico (Feo & Raballo, 2007); B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degree of freedom, p = statistical significance, OR = odd ratio; 95% CI = 95% confidence intervals; Chi-squared (χ^2) test, overall correct predictive percentage, Cox-Snell R^2, and Negelkerke R^2 values are reported.

Table 19 – Logistic regression of CAARMS outcomes by CVEP item "binary response" scores within the total sample (n = 129): final model (all predictors entered for subsequent blocks corresponding to each item group).

Parameters	B	SE	Wald	df	p	OR	95% CI for OR	
							Lower	Upper
1st Block								
1. Spending more time alone	1.280	0.501	6.532	1	**0.011**	3.596	1.348	9.596
2. Arguing with friends and family	0.177	0.403	0.193	1	0.660	1.194	0.541	2.633
3. The family is concerned	0.890	0.643	1.919	1	0.166	2.436	0.691	8.584
4. Excess use of alcohol	-1.318	0.877	2.257	1	0.133	0.268	0.048	1.494
5. Use of street drugs	0.937	0.752	1.553	1	0.213	2.552	0.585	11.137
Costant	-1.443	0.717	4.056	1	0.044	0.236	-	-
Overall model fit test → χ^2 = 13.025, p = 0.023; overall correct predictive percentage = 67.4% Associated strength → Cox-Snell R^2 = 0.096, Negelkerke R^2 = 0.131								
2nd Block								
6. Sleep difficulties	0.998	0.480	4.317	1	0.068	0.309	0.113	0.845
7. Poor appetite	-1.174	0.513	5.235	1	**0.022**	2.713	1.058	6.956
8. Depressive mood	1.170	0.502	5.445	1	**0.020**	3.223	1.206	8.614
9. Poor concentration	0.488	0.516	0.894	1	0.344	1.629	0.593	4.476
10. Restlessness	0.806	0.496	2.641	1	0.104	2.240	0.847	5.923
11. Tension and nervousness	-0.111	0.554	0.040	1	0.841	0.895	0.302	2.651
12. Less pleasure from things	1.043	0.488	4.571	1	**0.033**	2.836	1.091	7.376
Constant	-1.970	0.641	9.436	1	0.002	0.139	-	-
Overall model fit test → χ^2 = 29.396, p = 0.0001; overall correct predictive percentage = 74.4% Associated strength → Cox-Snell R^2 = 0.204, Negelkerke R^2 = 0.277								
3rd Block								
13. Feeling people are watching you	1.931	0.417	21.440	1	**0.000**	6.895	3.045	15.612
14. Feeling or hearing things that others cannot	1.136	0.463	6.021	1	**0.014**	3.113	1.257	7.710
Constant	-0.893	0.330	7.325	1	0.007	0.409	-	-
Overall model fit test → χ^2 = 31.555, p = 0.0001; overall correct predictive percentage = 74.4% Associated strength → Cox-Snell R^2 = 0.217, Negelkerke R^2 = 0.295								
4th Block								
15. Ideas of reference	2.339	0.686	11.641	1	**0.001**	10.376	2.706	39.779
16. Bizarre ideas	1.545	0.591	6.824	1	**0.009**	4.688	1.471	14.942
17. Odd manner of thinking or speech	0.898	0.605	2.201	1	0.138	2.454	0.750	8.031
18. Inappropriate emotional responses	1.157	0.564	4.213	1	**0.040**	3.181	1.054	9.605
19. Odd behaviour or appearance	1.120	0.566	3.908	1	**0.048**	3.063	1.010	9.295
20. First-degree family history of psychosis + increased stress or deterioration of functioning	1.126	0.758	2.203	1	0.138	3.083	0.697	13.628
Constant	-1.412	0.373	14.307	1	0.000	0.244	-	-
Overall model fit test → χ^2 = 60.601, p = 0.0001; overall correct predictive percentage = 82.9% Associated strength → Cox-Snell R^2 = 0.375, Negelkerke R^2 = 0.510								

Legend – CAARMS = Comprehensive Assessment of At-Risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico (Feo & Raballo, 2007); B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degree of freedom, p = statistical significance, OR = odd ratio; 95% CI = 95% confidence intervals; Chi-squared (χ^2) test, overall correct predictive percentage, Cox-Snell R^2, and Negelkerke R^2 values are reported.

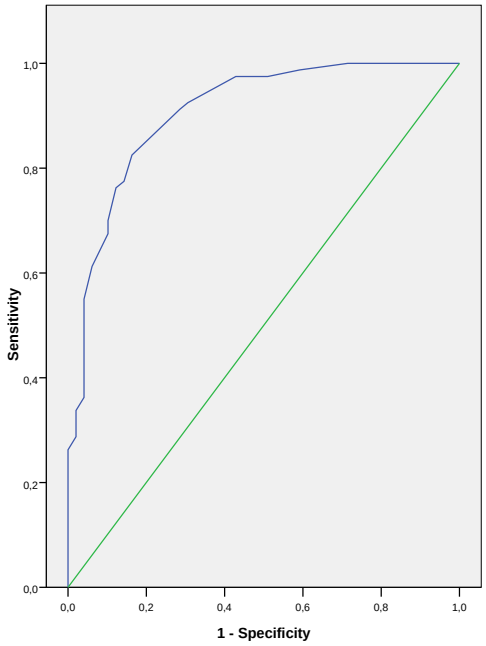
Finally, considering a new version of the CVEP exclusively composed by these ten selected item (CVEP-10), we generated a ROC curve in order to calculate the best diagnostic accuracy measures of this novel short tool. Specifically, we found an optimal cut-off threshold of ≥ 8 on CVEP-10 total score balancing an excellent 0.975 sensitivity with an acceptably good specificity level of 0.571 (Table 20 and Figure 8]).

Table 20 – CAARMS diagnostic classification accuracy by cut-off scores of the ten more predictive CVEP item group within the total sample (n = 129).

CVEP cut-off score	Sensitivity	Specificity
≥ 8	0.975	0.571
≥ 9	0.925	0.694
≥ 10	0.913	0.714
≥ 11	0.825	0.837
≥ 12	0.775	0.857

Legend – CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico.

Figure 8 – Receiver Operating Characteristic (ROC) curve generated to assess concurrent validity between total score of the ten more predictive CVEP item group and CAARMS outcomes within the total sample (n = 129).



Legend - CAARMS = Comprehensive Assessment of At-risk Mental States; CVEP = Checklist per la Valutazione dell'Esordio Psicotico (Feo & Raballo, 2007).

DISCUSSION

Aim of this study was to assess the concordant validity of the CVEP comparing its outcomes with those of a standardized clinical interview for "at risk mental states" (i.e. the CAARMS) in a sample of Italian help-seeking adolescents referred to the ReARMS project.

In comparison with CAARMS-, CAARMS+ adolescents had significantly higher CVEP total scores. Moreover, within the latter subgroup, FEP patients showed greater CVEP total scores in comparison with UHR peers. Therefore, on a dimensional level, these findings confirm that also in an Italian adolescent age population, CVEP total scores are positively associated with CAARMS sub-scores; that is, increasing CVEP scores relate to the severity of both psychotic and general psychopathology [172].

Adopting the PCCL original cut-off [155] that the authors hypothesized for indicating the need for a specialist assessment, the CVEP showed an excellent sensitivity (approximately 99%), but an insufficiently low specificity value of about 45%. Consistently to what reported in our CVEP preliminary validation study on an adolescent and young adult mixed help-seeking population [172], such poor specificity has crucial implications both in terms of clients comfort (i.e. avoiding distress and delays in adequate care pathways for non-relevant assessments) and rational resources allocation (e.g. avoiding unnecessary and lengthy evaluation process).

However, these results are substantially in line with those reported in the PCCL validation study (i.e. 89% sensitivity and 60% specificity in identifying young people in the early stages of psychosis within a sample of 176 help-seekers referred to early detection teams across the United Kingdom) [135] and with diagnostic accuracy measures of other screening tools for this population, including the "Prodromal Questionnaire" (PQ) that revealed a 90% sensibility and a 49% specificity in a sample of 113 young adults referred to a specialist early detection clinic [132]. Unlike the self-report 92-item PQ, the PCCL/CVEP is specifically designed to be quickly administered by general practitioners, making it ideal for use in primary care settings.

To improve the CVEP specificity level, using only a total score of ≥ 20 as CVEP cut-off achieved an excellent 87% specificity, while maintaining an excellent sensitivity value of approximately 89%. However, according to Loewy and co-workers [132], for screening purposes a greater weighting should be given to sensitivity over specificity as part of a 2-step screening process, also in order to avoid that a certain number of young people who would appropriate for early intervention are not being identified. Indeed, in most cases, having a few more false positives is less of an issue than missing appropriate individuals from a clinical perspective. Moreover, a high sensitivity level implies that full assessment burden can be considerably reducing with little impact on missing UHR/FEP individuals [215]. Therefore, a cut-off threshold with an excellent sensitivity value might be appropriate even if total diagnostic accuracy statistics are slightly lower. In the present study, a promising cut-off of ≥ 16 on CVEP total score had an excellent 96% sensibility and a good 65% specificity when used in an Italian adolescent help-seeking population. In this regards, these screening results are definitely better than those reported using a brief 16-item version of the

Prodromal Questionnaire (PQ-16) in a sample of 72 help-seeking adolescents referred to Italian child and adolescent mental health services (i.e. 77% sensitivity, 54% specificity) [187].

Taking account the applicability of the CVEP in those services that just have only a FEP or a UHR service, we tested the sensitivity/specificity trade-off of the instrument in the FEP and the UHR subgroup, respectively. Adopting the CVEP original cut-off, the screening tool had an excellent sensitivity value of approximately 98% in the UHR sample and an optimal sensitivity level of 100% in the FEP group (but with a significant worsening of the specificity level down to 45%). In examining the concordant validity of the CVEP, the balance between sensitivity and specificity should not to be the same for FEP and UHR subgroup. Indeed, it is not ideal to miss any cases of FEP, and therefore a high sensitivity level is clearly preferred. Since UHR individuals may not necessarily develop a psychotic disorder, a high sensitivity value may not to be as essential for this subsample. In this regards, in order to improve specificity level of the screening tool in these two subgroups, we found that a cut-off threshold of $\geq$ 16 on CVEP total score achieved a good specificity value of 65% (with a 94% sensitivity) in the UHR adolescents, while a CVEP total score of $\geq$ 17 maintained a 100% sensitivity in FEP patients, together with an increasing specificity up to 74%. In summary, concordant validity of the CVEP improves for lower cut-off scores in UHR people than in FEP patients (at least, within an Italian adolescent help-seeking population).

However, these promising CVEP cut-off values could be inadequate in UHR/FEP young adults, who (particularly those aged > 21 years) showed progressively lower scores on self-reported prodromal symptoms [186]. Even if there is evidence suggesting that in adolescents higher scores on self-report scales are less associated with UHR/FEP status [212], this higher prodromal scoring may also be one of the potential determinants of the early help-seeking behaviour in clinical adolescent populations. Overall, this indicates that screening tools for early detection of psychosis probably requires age-adapted cut-off scores.

Given the lower specificity/high sensitivity trade-off of the CVEP and the considerable specificity/sensitivity feature of some of the items (Table 17), a psychometric strategy to optimize the screening power of the CVEP is to consider two different subcomponents: (a) items with good-to-excellent sensitivity (between 0.750 and 0.888), i.e. “Spending more time alone”, “Depressive mood”, “Poor concentration”, “Restlessness”, “Less pleasure from things” and “Feeling people are watching you”, and (b) items with excellent specificity (between 0.796 and 0.939), i.e. “Feeling or hearing things that other cannot”, “Ideas of reference”, “Bizarre ideas”, “Odd manner of thinking or speech”, “Inappropriate emotional responses”, and “Odd behaviour or appearance”. The six “sensitivity” items might be more useful in identifying individuals with a positive CAARMS outcome (i.e. who either met or exceeded UHR criteria), whereas the six “specificity” items might

be more helpful in detecting people with a negative CAARMS result (i.e. who did not meet UHR/FEP criteria).

Contrary to the initial hypothesis that the endorsement of a checklist item would be associated with a positive CAARMS outcome [155], two CVEP statements (i.e. “Excess use of alcohol” and “Poor appetite”) had a negative between-outcome agreement and were more frequent in participants who did not meet UHR/FEP criteria, increasing the likelihood of identifying individuals with a negative CAARMS result as positive screening cases. Thus, these items appear to be associated with a low risk of CAARMS positive outcome and more likely to be predictive of a CAARMS negative result.

As a psychometric alternative, we performed a logistic regression analysis with CVEP items as explanatory parameters and the CAARMS positive outcome as dependent variable. Using a for block selection procedure that considered each item perceived relevance to overall psychosis risk, we identified ten more predictive CVEP item (i.e. “Spending more time alone”, “Poor appetite”, “Depressive mood”, “Less pleasure from things”, “Feeling people are watching you”, “Feeling or hearing things that others cannot”, “Ideas of reference”, “Bizarre ideas”, “Inappropriate emotional responses” and “Odd behaviour or appearance”) (Table 19), of which only one (“Poor appetite”) with a negative regression coefficient. A new short version of the CVEP composed by these ten selected item (CVEP-10) could further reduce the tool administration time in primary care settings, while maintaining an adequate concordant validity. In this regards, in the present study, using a threshold of ≥ 8 on CVEP-10 total score, an excellent 97% sensitivity balanced an acceptably good specificity level of more than 57%. However, further studies on larger samples

Limitations

Several limitations should be acknowledged. Firstly, in the current study, the concordant validity of the CVEP was established by using the CAARMS as “gold standard”. The CAARMS specifically identifies young people who are at UHR of developing psychosis, but the majority of these individuals likely will not go on to experience a full-blown psychosis at all [175]. The present research has not included a follow-up methodology and as such it is not possible to establish the predictive validity of the tool. Thus, further longitudinal studies are needed.

Secondly, psychotic experiences have been shown to be common in the general population, especially in adolescents [202], and as such a population wide screen would be expected to yield a high false positive rate. Indeed, high rates have been reported when other screening tools have been applied to similar samples [130]. Likewise, the sample in the present study was made up of adolescents referred to specialist early detection team and probably contained a much higher incidence of UHR cases than would be expected in the general population.

Finally, the CVEP was completed by those people making referrals to the early detection centres and not by participants themselves, as is reflective of the checklist intended use. However, these referrers had specialist knowledge of psychosis. Therefore, a validation of the CVEP in a way that is representative of a primary care setting (or other non-specialist organizations) is needed. It will contribute to verify the current potential feasibility of utilization in a number of non-specialist settings.

CONCLUSIONS

The CVEP appears to be a useful screen for adolescents who may be at risk of experiencing psychosis. In particular, the checklist seems to be easy and quick to administer as screening tool for use in primary care setting and by the wide range of organizations that may have contact with UHR young individuals.

However, it must be emphasized that the CVEP is not a diagnostic instrument. A screen positive result indicates only the need for a further specialist assessment and should not be equated to a diagnostic evaluation or a marker for the initiation of any treatment [172]. Similarly, a screen negative may instead reflect the lack of trust between client and clinician, and the level of engagement should be taken into consideration.

Moreover, the CVEP is not intended to be used as population wide screen [215]. It has been designed to build on the experience, skills, and strengths that non-specialist practitioners already have, with the specific purpose to help them deciding whether a referral is warranted and to bridge primary care with specialist mental health services. Future studies should focus on the continued evaluation of this checklist performance in primary care settings, particularly thinking about service configuration and ease of access to early intervention teams.

STUDY 3 - THE ITALIAN VERSION OF THE 16-ITEM PRODROMAL QUESTIONNAIRE (iPQ-16)

The Italian version of the 16-item Prodromal Questionnaire (iPQ-16): field-test and psychometric features

In the last two decades, the research focus moved from early recognition and phase-specific intervention in First-Episode Psychosis (FEP) to the pre-onset/prodromal phase [13, 68]. In this context, McGorry and colleagues [28] proposed a specific subset of criteria - so called "Ultra-High Risk" (UHR) - to identify three subgroups of individuals with an imminent (but not inevitable) risk of psychotic disorder. Those are: (a) "Attenuated Psychotic Symptoms" (APS), (b) "Brief Limited Intermittent Psychotic Symptoms" (BLIPS) and (c) "Genetic Risk and Functioning Deterioration" syndrome" (GRFD) [38].

In the "Diagnostic and Statistical Manual of mental disorders, Fifth Edition" (DSM-5) [110], the "Attenuated Psychosis Syndrome" has been included as a new nosographic category that requires further study. Its diagnostic criteria depend heavily on the UHR criteria using clinical interviews (such as the "Comprehensive Assessment of At-Risk Mental States" [CAARMS]) [216]. This approach requires a suitable diagnostic screening instrument with which people with suspected UHR features can be detected for further in-depth diagnostic interviews. Several self-report screening instruments have been developed to effectively identify an attenuated psychosis syndrome, including the Prodromal Questionnaire (PQ-92 items) [132]. However, the PQ-92 has a too long administration time to be useful as routine screening tool [156]. Hence, Ising and co-workers developed a 16-item version of the PQ (i.e. the PQ-16) [157], which showed good psychometric properties for screening large help-seeking sample in general mental health care services for nonpsychotic disorders [217]. In adults, a cut-off score of ≥ 6 predicts CAARMS UHR/psychosis diagnosis with high sensitivity (87%) and specificity (87%) [157]. These results were similar to those of the PQ-92.

To the best of our knowledge, no study to validate the PQ-16 in UHR/psychosis enriched samples has been reported in the literature to date [218]. However, outside the Netherlands, two other studies conducted in general mental health help-seeking populations should be mentioned: a research by Chen and co-workers [219] evaluating the Chinese version of the PQ-16 for identifying psychosis risk in 101 psychiatry outpatient help-seekers (published in Mandarin on a Chinese mental health journal) and a study by O'Donoghue and colleagues [220] examining the screening

performance of the questionnaire in 147 young people attending a youth mental health service in Melbourne, Australia. The current study was therefore designed to test the validity and the reliability of the Italian version of the PQ-16 (iPQ-16) in an UHR/psychosis enriched sample of young adult help-seekers.

MATERIALS AND METHODS

Setting

As detailed in Appendix S1, the "Reggio Emilia At-Risk Mental States" (ReARMS) project is an early detection infrastructure developed under the aegis of the "Regional Project on Early Detection and Intervention in Psychosis" in the Reggio Emilia Department of Mental Health [170]. This large semirural catchment area consists of approximately 550.000 inhabitants, of whom nearly 460.000 are > 18-year-old. The ReARMS project aims: (a) to identify people with FEP and individuals at high clinical risk according to UHR criteria [38] among help-seeking adolescents and young adults (13-35 years) through a 2-step procedure, and (b) to provide evidence-based interventions that are supposed to be effective in UHR/FEP subjects (i.e. intensive case management, family psychoeducation, individual cognitive-behavioral therapy, pharmacological treatment [as appropriate]).

The first screening step included a triage service using the "Screening Schedule" for Psychosis (SS) [185]. The second step included the "Comprehensive Assessment of At-Risk Mental States" (CAARMS) [38] to investigate the clinical status (i.e. psychosis risk, psychosis, or neither). Screening was performed by service staff, whereas 2-step assessment was carried out by trained, project clinicians. Indeed, the ReARMS team is specialized in detecting young people at UHR of psychosis as measured by the CAARMS.

The SS for psychosis [185] is a checklist containing demographic, history, psychopathological and behavioral items, all dichotomous (yes/no), which constituted inclusion and exclusion criteria for ReARMS protocol eligibility [170, 171]. Those were: (a) age between 13 and 35 years; (b1) presence, in the preceding 12 months, of at least one of the following psychotic symptoms: hallucinations or pseudo-hallucinations in any modality; delusions and/or ideas of reference; qualitative thought or speech disorder; qualitative psychomotor disorder; or gross behavioral abnormalities representing a break in the person's previous pattern; or (b2) at least one of the following abnormalities indicative of a substantial modification of personality or behavior and suggestive of psychotic disorder: loss of interest, initiative, and drive leading to deterioration of daily performance; onset of social withdrawal; episodic severe excitement, purposeless destructiveness or aggression; episodic or persistent states of overwhelming fear or anxiety; or gross

and persistent self-neglect; (c) first-in-lifetime contact with any "helping agency" within the last three months, occasioned by the above mentioned symptoms and behaviors; (d) presence of a "Duration of Untreated Psychosis" (DUP) < 2 years; (e) absence of clinical evidence of organic cerebral disorder, including central nervous system damage due to alcohol or drug abuse, and manifest in either delirium or dementia, with or without peripheral neuropathy; and (f) presence of an Intelligence Quotient (IQ) ≥ 50. Since 1-step screening was performed by general service staff members before individual entering the ReARMS protocol, it was unknown the exact proportion of people who were screened out with SS.

For the purpose of the study (i.e. field-testing the psychometric properties of the PQ-16), we focused on young adults to create a sample comparable to the one assessed by Ising and co-workers [157] in the validation study of the original Dutch version of the PQ-16. Complying with the declaration of Helsinki, relevant ethical approvals were locally sought for the research.

Participants

In the current research, all participants were young adult help-seekers (aged 18-35 years) consecutively referred to the 7 adult outpatient mental health services of the Reggio Emilia Department of Mental Health between September 2012 and July 2016. Referrals were mainly performed by General Practitioners (50%), family members (22%), emergency room (13%), school and social services (10%).

For the purpose of the study, inclusion criteria were: (a) specialist help-seeking; (b) age between 18 and 35 years; and (c) presence of UHR criteria defined by the CAARMS (i.e. APS, BLIPS, and/or GRFD) or (d) DUP < 2 years in case FEP is detected in the initial assessment. Individuals who were below the CAARMS UHR/FEP threshold were considered as CAARMS negative cases in order to test the PQ-16 specificity.

The exclusion criteria were coupled on the psychometric approach adopted by Ising and colleagues [157] in the validation study of the original Dutch version of the PQ-16: (a) history of frank psychotic episodes, either affective or schizophrenic, as described in the "Diagnostic and Statistical Manual of mental disorders, Fourth Edition, Text Revised" (DSMIV-TR) [178], (b) history of previous exposure to antipsychotics, (c) current use of antipsychotic doses > 15 mg haloperidol equivalents, (d) current substance dependence, (e) severe learning disability or known mental retardation (IQ < 70), (f) neurological disease or any other medical disorder associated with psychiatric symptoms, (g) poor fluency in the Italian language, (h) residence outside the catchment area, and (i) a "Global Assessment of Functioning" (GAF) score of 65 points or above. All these exclusion criteria have been applied after the SS administration in order to create a sample

comparable to the one assessed by Ising and co-workers [157] in the validation study of the original Dutch version of the PQ-16.

Over the course of the study, 154 individuals (67 females and 87 males; mean age = 23.73 ± 5.36 years) consecutively participated at the intake interview within the ReARMS protocol. All help-seekers entering the project agreed to participate in the research and gave their informed consent to the psychopathological evaluation, composed - among others - by the CAARMS (approved Italian version [CAARMS-ITA]) [181] and the PQ-16 (authorized Italian adaptation) (for details, see also supplementary materials [Appendix S3]) [221]. Therefore, iPQ-16 was administered after the SS for psychosis. Moreover, CAARMS assessors were blinded to the iPQ-16 scores. The average length of time between iPQ-16 being administered and the CAARMS was approximately 7 days (mean ± SD = 6.50 ± 2.70 days).

Measures

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) [38]. It takes approximately 1-1.5 hours to be administered and consists of 27 items, each one calculated in terms of frequency/duration (0-6) and intensity (0-6). Those items can be clustered in 7 subscales: (a) “Positive Symptoms”, (b) “Cognitive Change, Attention and Concentration”, (c) “Emotional Disturbance”, (d) “Negative Symptoms”, (e) “Behavioral Change”, (f) “Motor/Physical Changes”, and (g) “General Psychopathology”.

The CAARMS “Positive Symptoms” subscale, which covers delusions, hallucinations and thought disorder, is used to determine both the threshold for psychosis and the UHR criteria. UHR status is defined as follows: (a) GRFD group: schizotypal personality disorder in the individual or history of psychosis in a first-degree family member associated with 30% decrement in functioning for at least 1 month or chronic low functioning, as measured by the *GAF* scale (approved Italian version) [222] (the drop in functioning is estimated by subtracting the present GAF-score from the utmost GAF score in the past year); (b) APS group: subthreshold positive psychotic symptoms within the past 12 months; and (c) BLIPS group: criteria for psychotic disorder met for < 7 day and remitting spontaneously (i.e. without antipsychotic medication). According to the psychosis criteria defined by the CAARMS [38], the threshold of full-blown psychotic episode depends on operationalized clear-cut levels of frank positive symptoms occurring for at least 1 week.

For the specific purposes of this study, since PQ-16 is not sufficiently sensitive for discriminating between the threshold of UHR state and full-blown psychosis because it only assesses the

prevalence and not the intensity of prodromal symptoms [157], UHR and FEP individuals were both grouped as CAARMS positive cases (CAARMS [+]). The participants who were below the UHR threshold were classified as CAARMS negative cases (CAARMS [-]).

CAARMS interviews are conducted by specialized personnel including clinical psychologists and psychiatrists, who underwent collective supervision by the main author of the approved Italian translation [181], who was trained at Orygen, the National Youth Research Center in Melbourne, Australia. The inter-rater reliability of these assessments was ensured by regular CAARMS scoring workshops and supervision sessions. The intra-class correlation coefficients of each CAARMS-ITA subscale showed good to excellent reliability [182, 183], in line with the original validation study by Yung and co-workers [38]. Indeed, the interrater reliability for the overall score was 0.91 and above 0.74 for all the subscales.

The *PQ-16* [157] is a self-report instrument specifically designed to detect people at risk of psychosis. It is composed of nine items on perceptual aberrations/hallucinations, five items on unusual thought content/delusions, and two negative symptoms. This instrument only takes approximately 3 min to be completed and assesses the presence of positive and negative symptom items on a true/false Likert-scale, according to the individual subjective experience in the last month. Distress is added on a 4-point scale for each endorsed item (from “0” = “no distress” to “3” = “severe distress”). The PQ-16 can be scored by the total number of symptoms endorsed (range 0-16) or the sum of distress scores (range 0 – 48). When using the symptom total score, a cut-off threshold of ≥ 6 appeared appropriate in general mental health settings [157, 219]. Using the distress score, a threshold of ≥ 8 was supported in general mental health help-seeking populations [219].

In a recent systematic review on psychosis risk screening in different populations using PQ in its different iterations, Savill and colleagues [218] suggested that no appropriate PQ-16 thresholds were identified in UHR/psychosis samples and so careful piloting of any threshold adopted in this setting would be recommended. For the purpose of this study (the first conducted in an UHR/FEP enriched population), we firstly focused on a symptom total score cut-off of ≥ 6 to compare our results with primary findings reported by Ising and co-workers in the validation study of the original Dutch version of the PQ-16 [157]. However, since distress/impairment related to psychotic-like experiences appeared to be a key predictor of concurrent and later psychosis [223] and using the distress scale, rather than the symptom total score, seemed to improve the accuracy of the PQ-16 (in particular, its specificity) [218], our statistical analysis also considered the total distress score and its potential cut-off thresholds.

Statistical analysis

Data were analyzed using the "Statistical Package for Social Science" (SPSS) 15.0 for Windows [192]. The overall validation procedure of the iPQ-16 was modeled on the methodological procedure used by Ising and colleagues in the validation study of the original Dutch version of the PQ-16 [157]. Since we were interested in testing the screening features of the iPQ-16 against the CAARMS risk threshold, the sample was dichotomized as follows: CAARMS [+], i.e. those who were above CAARMS UHR threshold (that is UHR and FEP), and CAARMS [-], i.e. those who are below such threshold. The two subgroups were compared on psychopathological, clinical, and socio-demographic parameters. Categorical data were analyzed using Chi-squared (χ^2) test with Yates' correction. Quantitative variables were examined using the Mann-Whitney's U test or the Student's t-test - as appropriate.

As measure of reliability, the internal consistency of the iPQ-16 was assessed using the Cronbach's α statistics within the total sample. A sufficient internal consistency was represented by a score above 0.65 [157]. Moreover, we examined how each iPQ-16 item correlated with the overall questionnaire score. Correlations less than $r = 0.30$ indicated that the item might need to be removed from the questionnaire to make it more reliable [224]. Finally, we were interested in Cronbach's alpha score if each item was deleted. If this score went up after the item was deleted, removal of this item should be considered to increase questionnaire reliability [224].

We also investigated the concurrent validity of the iPQ-16 by comparing its results to CAARMS outcomes. In the total sample, we examined diagnostic accuracy measures, i.e. specificity, sensitivity, negative and positive predictive values (NPV and PPV), and negative and positive likelihood ratios (LR- and LR+), that balance sensitivity against specificity. In interpreting likelihood ratios (LRs), we followed Jaeschke and colleagues [225]: LRs of 0.5-2 altered pre-test probability to a small (and rarely important) degree, LRs of 2-5 and 0.2-0.5 generated small (but sometimes important) changes in probability, and LRs of 5-10 and 0.1-0.2 generated moderate shifts in pre-test to post-test probability. As an additional measure of concurrent validity, the correspondence of positive results on the iPQ-16 (i.e. a symptom total score ≥ 6) and on the CAARMS (i.e. a score ≥ 3 on at least one positive symptom item) was also examined by Cohen's kappa statistics. Finally, following the methodological approach employed by Ising and colleagues [157], we conducted a biserial correlation to evaluate the association between iPQ-16 total scores and CAARMS diagnosis.

To test whether different iPQ-16 cut-offs might increase concurrent validity, Receiver Operating Characteristic (ROC) curve was firstly plotted in the total sample for the iPQ-16 symptom total score against outcome in the CAARMS (i.e. CAARMS [+] vs CAARMS [-] diagnosis). According

to Hosmer and co-workers [226], we interpreted the area under the ROC curve (AUC) as follows: AUC ≤ 0.5 no discrimination, 0.51-0.69 unacceptably low, 0.70-0.79 acceptable, 0.80-0.89 excellent, and ≥ 0.90 outstanding. To evaluate the concurrent validity of potentially suggested better cut-offs, we again conducted Cohen's kappa statistics and diagnostic accuracy measures. Additionally, we tested Cohen's kappas for significant improvement against the concurrent validity of the traditional ≥ 6 cut-off using 1-sided 1-dimensional χ^2 tests [227].

Two criteria were also used to confirm optimal cut-off point from ROC curve, giving equivalent weight to specificity and sensitivity: (a) points on ROC curve closest to the point (0, 1) and (b) the Youden index (J) [228]. In details, to identify the optimal cut-off discriminating CAARMS [+] from CAARMS [-] individuals, we calculated the distance (d) between the point (0,1) and each cut-off point on ROC curve, and detected the point where this distance was minimal: d = √ [(1-sensibility)^2 + (1-specificity)^2]. The Youden index (J) was the point on the ROC curve which was farthest from random chance diagonal line and therefore maximized the difference between true positive rate (sensitivity) and false positive rate (1-specificity): J = max (sensitivity + specificity - 1).

In addition, since distress related to psychotic-like experiences was a key predictor of concurrent and later psychosis [223] and the distress scale appeared to significantly improve the PQ-16 specificity [218], we repeated concurrent validity analyses for the iPQ-16 total distress score within the total sample.

Finally, the predictive validity of the iPQ-16 was tested by consecutively identifying people with an iPQ-16 cut-off score of ≥ 6 on symptom total score who were below the CAARMS psychosis threshold [38] at the baseline assessment. Twenty four individuals were followed-up for at least 1 year within the ReARMS protocol. We calculated whether the ≥ 6 cut-off score had any value in predicting the development of a FEP according to CAARMS-defined criteria.

RESULTS

Sample characteristics

Table 21 shows screening outcomes and demographic characteristics of the total sample and the two subgroups, i.e. CAARMS [+] (n= 112) and CAARMS [-] (n = 42). No significant differences were found in terms of gender, ethnic group, mother tongue, age, years of education, and "Duration of Untreated Illness" (DUI), meant as the interval between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment [180].

In comparison with CAARMS [−], CAARMS [+] individuals showed significantly higher iPQ-16 symptom total score and total distress score (Table 21). However, within CAARMS [+] subgroup,

no difference was found between people at UHR (n= 30) and FEP (n= 82) (symptom total score: mean ± standard deviation = 6.37 ± 3.42 vs 6.54 ± 3.87; Z = -0.026; p = 0.979; total distress score: 16.71 ± 8.30 vs 17.03 ± 12.11; Z = -0.578; p = 0.563).

Table 21 – CAARMS criteria, demographic and clinical data.

	Total sample (n = 154)	CAARMS (−) (n = 42)	CAARMS (+) (n = 112)	χ^2/t/Z
Gender (males)	87 (56.5%)	20 (47.6%)	67 (59.8)	1.850
Ethnic group (Caucasian)	138 (89.6%)	37 (88.1%)	101 (90.2%)	0.070
Mother tongue (Italian)	137 (89.0%)	39 (92.9%)	98 (87.5%)	0.616
Age	23.73 (5.36)	24.29 (5.81)	23.52 (5.20)	0.791
Years of education	12.02 (2.45)	11.88 (2.59)	12.07 (2.40)	−0.429
DUI (in weeks)	102.44 (10.70)	127.29 (11.33)	93.08 (11.34)	0.093
iPQ-16 symptom total score (range 0–16)	5.60 (3.72)	3.21 (2.41)	6.49 (3.74)	−5.228*
iPQ-16 total distress score (range 0–48)	14.27 (11.04)	7.40 (6.84)	16.95 (11.20)	−5.568*

Legend. Frequencies and percentages, mean (standard deviation), chi-squared (χ^2) test (with Yates correction), Student's *t*-test, and Mann-Whitney U test (Z) values are reported.
* $p < 0.001$.

Reliability

Across the entire sample, the iPQ-16 symptom total score showed a Cronbach's alpha of 0.809. All item-total correlations were higher than 0.30, with the exception of item 1 (“I feel uninterested in the things I used to enjoy”) and 14 (“I often feel that others have it in for me”) (r = 0.130 and r = 0.261 respectively) (Table 22). Thus, most items appeared to be worthy of retention, resulting in a decrease in the alpha if deleted. Exceptions to this were item 1 and 14, which would increase the Cronbach's alpha up to the value of 0.818. Thus, removal of these items should be considered.

Concurrent validity

At the proposed PQ-16 symptom total score threshold of ≥ 6 [157], 72 participants (46.8%) scored positive; of these, 68 (94.4%) also scored ≥ 3 on any positive CAARMS item (i.e. meeting or above the UHR threshold - CAARMS [+]). Altogether, 44 participants (39.3%) with any CAARMS positive score ⩾ 3 were missed by this PQ-16 cutoff, and 4 (9.5%) were falsely identified. Cohen’s kappa was 0.394, consistent with a fair agreement [229].

With regard to the diagnostic accuracy at the proposed PQ-16 cut-off of ≥ 6 on symptom total score, sensitivity was 0.607, specificity 0.905, PPV 0.944, NPV 0.463, LR+ 6.38, and LR− 0.43 (Table 23). Thus, at this threshold, the iPQ-16 symptom total score was slightly better in ruling in than in ruling out possible UHR/psychosis status, generating moderate shifts in pre-test to post-test

probability [225]. However, the iPQ-16 symptom total score showed a significant correlation with the CAARMS diagnosis (r= 0.394; p = 0.0001).

Table 22 – Internal consistency of iPQ-16.

iPQ-16 item	Item-total correlation	Cronbach's alpha if item deleted
1. **I feel uninterested in the things I used to enjoy.**	**0.130**	**0.818**
2. I often seem to live through events exactly as they happened before (déjà vu).	0.517	0.791
3. I sometimes smell or taste things that other people can't smell or taste.	0.465	0.798
4. I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears.	0.371	0.801
5. I have been confused at times whether something I experienced was real or imaginary.	0.511	0.792
6. When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes.	0.434	0.798
7. I get extremely anxious when meeting people for the first time.	0.301	0.808
8. I have seen things that other people apparently can't see.	0.543	0.791
9. My thoughts are sometimes so strong that I can almost hear them.	0.522	0.791
10. I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me.	0.322	0.805
11. Sometimes I have felt that I'm not in control of my own ideas or thoughts.	0.508	0.792
12. Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of.	0.499	0.793
13. I have heard things other people can't hear, like voices of people whispering or talking.	0.582	0.788
14. **I often feel that others have it in for me.**	**0.261**	**0.810**
15. I have had the sense that some person or force is around me, even though I could not see anyone.	0.398	0.800
16. I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.	0.351	0.803

Legend. Correlation r coefficients and Cronbach's alpha values are reported. The iPQ-16 items with an item-total correlation lower than 0.30 are reported in bold.

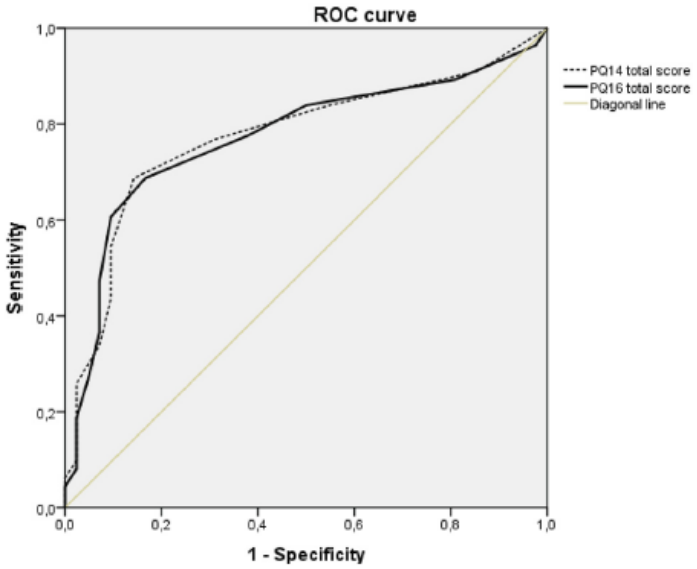
Table 23 – CAARMS diagnostic accuracy by iPQ-16 cut-off scores.

iPQ-16 cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	Cohen's kappa	J	d
Symptom total score (range 0–16)									
≥2	89.22 (82.03–94.34)	19.05 (8.60–34.12)	74.63 (71.48–77.54)	40.00 (22.67–60.25)	1.10 (0.94–1.29)	0.56 (0.25–1.28)	0.100	0.083	0.762
≥3	83.93 (75.79–90.19)	50.00 (34.19–65.81)	81.74 (76.60–85.96)	53.65 (40.95–66.25)	1.68 (1.23–2.30)	0.32 (0.19–0.54)	0.347	0.339	0.525
≥4	77.68 (68.84–85.00)	61.90 (45.64–76.43)	84.47 (78.50–89.01)	50.98 (40.62–61.26)	2.04 (1.37–3.04)	0.36 (0.24–0.55)	0.371	0.396	0.441
≥5	68.75 (59.30–77.17)	83.33 (68.84–93.03)	91.67 (84.69–95.63)	50.00 (42.40–57.60)	4.13 (2.07–8.21)	0.38 (0.28–0.51)	**0.431**	**0.521**	**0.354**
≥6	60.71 (51.04–69.81)	90.48 (77.38–97.34)	94.44 (86.87–97.76)	46.34 (40.20–52.59)	6.38 (2.48–16.39)	0.43 (0.34–0.56)	0.394	0.512	0.404
≥7	47.32 (37.81–56.98)	92.86 (80.52–98.50)	94.64 (85.37–98.16)	39.80 (35.24–44.54)	6.63 (2.19–20.06)	0.57 (0.47–0.69)	0.284	0.402	0.531
Total distress score (range 0–48)									
≥6	82.91 (74.84–89.23)	47.92 (33.29–62.81)	79.51 (74.50–83.75)	53.49 (41.18–65.38)	1.59 (1.20–2.11)	0.36 (0.22–0.59)	0.318	0.308	0.442
≥7	82.05 (73.88–88.53)	60.42 (45.27–74.23)	83.48 (77.91–87.86)	58.00 (46.82–68.41)	2.07 (1.45–2.97)	0.30 (0.19–0.47)	0.420	0.425	0.336
≥8	79.49 (71.03–86.39)	60.42 (45.27–74.23)	83.04 (77.32–87.54)	54.72 (44.16–64.87)	2.01 (1.40–2.88)	0.34 (0.22–0.52)	0.387	0.399	0.362
≥9	74.36 (65.46–81.98)	68.75 (53.75–81.34)	85.29 (79.00–89.94)	53.35 (45.26–69.36)	2.38 (1.54–3.67)	0.37 (0.26–0.54)	0.395	0.431	0.354
≥10	74.36 (65.46–81.98)	79.17 (65.01–89.53)	89.69 (83.23–93.85)	55.88 (47.39–64.05)	3.57 (2.04–6.26)	0.32 (0.23–0.46)	0.477	0.535	0.299
≥11	73.50 (64.55–81.23)	83.33 (69.78–92.52)	91.49 (84.98–95.33)	56.34 (48.19–64.16)	4.41 (2.32–8.38)	0.32 (0.23–0.44)	**0.498**	**0.568**	**0.293**
≥12	70.94 (61.83–78.96)	85.42 (72.24–93.93)	92.22 (85.55–95.96)	54.67 (47.03–62.09)	4.86 (2.43–9.74)	0.34 (0.25–0.46)	0.483	0.564	0.318
≥13	65.81 (56.47–74.33)	85.42 (72.24–93.93)	91.67 (84.57–95.67)	50.62 (43.72–57.49)	4.51 (2.25–9.06)	0.40 (0.30–0.53)	0.426	0.512	0.363

Legend. 95% CI = confidence intervals, PPV = positive predictive value, NPV = negative predictive value, LR^+ = positive likelihood ratio, LR^- = negative likelihood ratio, Cohen's kappa, J = Youden index, and d = distance between the point (0,1) at each cut-off point on the ROC curve are reported. The most promising iPQ-16 cut-off thresholds balancing the best sensitivity and specificity (and their related diagnostic accuracy measures) are reported in bold.

ROC curve was plotted for the iPQ-16 symptom total score to predict CAARMS diagnosis (UHR/psychosis) (Figure 9). The AUC was acceptable and significant (0.773, SE = 0.040, 95% CI = 0.694 – 0.852, p = 0.0001) [226]. Cohen's kappa and accuracy measures of different thresholds for iPQ-16 symptom total score revealed that, overall, the ≥ 5 cut-off performed best in terms of kappa value, distance (d) of points on ROC curve closest to the point (0,1), and Youden index (J) (Table 23), balancing the best sensitivity and specificity. Compared to the original cut-off of ≥ 6, the ≥ 5 threshold increased sensitivity value up to 0.688, while maintaining a good to excellent specificity of 0.833. Regarding likelihood ratios (i.e. LR+ = 4.13 and LR- = 0.38), iPQ-16 cutoff of ≥ 5 only changed post-test probabilities to a small degree. Yet, difference between Cohen's kappa of the ≥ 6 and ≥ 5 cut-off was significant (χ^2 = 39.34; p = 0.0001).

Figure 9 - Receiver Operating Characteristics (ROC) curves of iPQ-16 and iPQ-14 symptom total score predicting UHR/psychosis diagnosis vs no CARMSS diagnosis.



Legend - iPQ-14 = the Italian version of the 16-item Prodromal Questionnaire with item 1 and 14 deletion.

Considering removal of iPQ-16 item1 and 14, ROC curve was plotted for the remaining iPQ-14 symptom total score to predict CAARMS diagnosis (UHR/psychosis) (Figure 9). The AUC was slightly more significant and acceptable compared to iPQ-16 symptom total score (0.786, SE = 0.040, 95% CI = 0.708 – 0.864, p = 0.0001) [225]. Cohen's kappa and accuracy measures of different thresholds for iPQ-14 symptom total score showed that, overall, the ⩾3 cut-off performed

best in terms of kappa and d values, increasing sensitivity up to 0.7768 with a specificity of 0.714 (Table 24).

Table 24 - CAARMS diagnostic classification accuracy by iPQ-14 cut-off scores.

iPQ-14 cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	Cohen's kappa	J	d
≥2	84.82 (76.81–90.90)	45.24 (29.85–61.33)	80.51 (75.63–84.61)	52.78 (39.21–65.95)	1.55 (1.16–2.06)	0.34 (0.19–0.58)	0.315	0.301	0.452
≥3	77.68 (68.84–85.00)	71.43 (55.42–84.28)	87.88 (81.65–92.20)	54.55 (44.71–64.04)	2.72 (1.67–4.43)	0.31 (0.21–0.46)	**0.448**	0.491	**0.305**
≥4	66.96 (57.44–75.56)	88.10 (74.37–96.02)	95.73 (86.70–97.18)	50.00 (42.89–57.11)	5.62 (2.45–12.94)	0.38 (0.28–0.50)	0.445	0.551	0.344
≥5	50.89 (41.27–60.46)	90.48 (77.38–97.34)	93.44 (84.64–97.36)	61.69 (53.52–69.40)	5.34 (2.07–13.81)	0.54 (0.44–0.67)	0.300	0.414	0.500

Legend. iPQ-14 = the Italian version of the 16-item Prodromal Questionnaire with item 1 and 14 deletion; 95% CI = confidence intervals, PPV = positive predictive value, NPV = negative predictive value, LR^+ = positive likelihood ratio, LR^- = negative likelihood ratio, Cohen's kappa, J = Youden index, and d = distance between the point (0,1) at each cut-off point on the ROC curve are reported. The most promising iPQ-14 cut-off threshold balancing the best sensitivity and specificity (and its diagnostic accuracy measures) is reported in bold.

With regards to the diagnostic accuracy at the proposed PQ-16 total distress score cut-off of ≥ 8 [219], sensitivity was 0.7949, specificity 0.6042, PPV 0.8304, NPV 0.5472, LR+ 2.01, and LR- 0.34 (Table 23). Moreover, ROC curve plotted for the iPQ-16 total distress score showed an AUC comparable to iPQ-16 symptom total score (0.776; SE= 0.038; 95 CI = 0.701 ‐ 0.851; p = 0.0001). Cohen's kappa and accuracy measures of different thresholds for the iPQ-16 total distress score revealed that, overall, the ⩾11 cut-off performed best in terms of Youden index, kappa and d values (Table 23), balancing the best sensitivity and specificity. Indeed, compared to the ≥ 8 cut-off, the ≥ 11 threshold increased specificity value up to 0.8333, while maintaining a specificity of 0.7350. Regarding likelihood ratios (i.e. LR+ = 4.41 and LR- = 0.32), iPQ-16 cut-off of ≥ 11 on total distress score only changed post-test probability to a small degree.

Predictive validity

Seven of 24 participants scoring ≥ 6 on the iPQ-16 symptom total score who did not meet the CAARMS psychosis criteria at the baseline assessment, did not finish the 1-year follow-up period. Five of these individuals had a follow-up period of b1 year. The other two participants went out of the ReARMS protocol catchment area and they could not be contacted for the follow-up assessment. After 12 months of follow-up, 1 (5.9%) of the 17 remaining individuals developed a FEP. However, among iPQ-16 negative screens another psychosis conversion was found. Considering an iPQ-16 cut-off of ⩾5 on symptom total score at the baseline, both transitions to psychosis have been detected (i.e. 2 [8.7%] of the 23 participants who finished the 1-year follow-up period).

DISCUSSION

To the best of our knowledge, despite the abundant literature on the source tool (i.e. PQ-92), no study to validate the PQ-16 in an UHR/FEP enriched clinical sample has been performed [218]. In the current study, we examined iPQ-16 psychometric properties (i.e. its reliability and validity in detecting UHR or psychosis status) in consecutive help-seeking presenters to the 7 adult outpatient mental health services of the Reggio Emilia Department of Mental Health.

In comparison with CAARMS [-], CAARMS [+] individuals showed significantly higher iPQ-16 total scores. On a dimensional level - as expected on the basis of the PQ-16 item composition - these findings suggest that increasing PQ-16 scores are associated with the severity of both psychotic and general psychopathology, as well as the intensity of distress related to prodromal symptoms.

Reliability

We found excellent reliability of the iPQ-16 with regard to internal consistency of the symptom total score and item-total correlations. Similarly, in a Dutch adult help-seeking sample attending to a secondary mental health care service, the PQ-16 showed good internal consistency ($\alpha = 0.774$) [157]. Reliability in our clinical sample was even better than the high reliability reported for the Chinese PQ-16 version ($\alpha = 0.750$) in 101 help-seekers from a psychiatry outpatient center [219] and the Dutch PQ-16 version ($\alpha = 0.790$) in 176 help-seeking adolescents (aged 12-17 years) attending one of the three Child and Adolescent Mental Health Services in Rotterdam in the Netherlands [217]. Thus, in our sample, iPQ-16 had demonstrated a satisfactory internal consistency for a screener that has to come before a clinical interview [157]. Reliability of the PQ-16 appears to be good in different samples and cultures.

However, in our sample all item-total correlations were higher than 0.30, with the exception of item1 and 14. Therefore, although most items appeared to be worthy of retention because of resulting in a decrease in the alpha if deleted, removal of item 1 and 14 should be considered for slightly increasing in alpha value. Among the most discriminating items that contributed to scoring above the cut-off score, three perceptual abnormalities/hallucinations (item 8, item 9, and item 13) were also identified (Table 22). These findings point to the centrality of perceptual aberrations for the development of psychotic phenomena [230].

Concurrent validity

With regard to the diagnostic accuracy at the proposed PQ-16 cut-off of ≥ 6 on symptom total score [157], in our sample sensitivity (61%) was lower than previously reported for the PQ in its various

versions [231]. However, this result was similar to that (62%) observed by Kotzalidis and co-workers [227] in the validation study of the Italian version of the 92-item PQ.

In the current study, at the proposed PQ-16 cut-off value of ≥ 6, PPV (94%) was higher than previously reported, with values ranging between 29% and 59% [157, 219, 220, 227, 231, 232]. In particular, PPV was only equal to 38% in the validation study of the Italian version of the 92-item PQ [227]. Our result reflects a very high probability that a subject has an UHR state or a full-blown psychosis as specified by the CAARMS criteria, if the iPQ-16 shows a positive test result. The difference between these findings may be the result of differences in selection procedures. In fact, first screening procedure in the ReARMS protocol included a triage service using the SS for psychosis [185], which probably already excluded a certain amount of true negative cases.

In our sample, specificity (91%) is consistent with that previously reported. Indeed, specificity values were also good to excellent in the Dutch study validating the original PQ-16 at a cut-off of 6 or more prodromal symptoms [157] and in the validation study of the Italian version of the 92-item PQ [227] (87% and 82%, respectively). However, at the same cut-off threshold, PQ-16 specificity decreased to 66% when administered to 101 help-seekers from a psychiatry outpatient service in China [219].

Otherwise, our NPV (46%) was definitely lower than previously reported ones, with values ranging between 88% and 100% [157, 220, 232]. Kotzalidis and co-workers [227] found a NPV of 91% in the validation study of the Italian version of the 92-item PQ. The difference between these findings may be the result of the same differences in selection procedures previously mentioned.

Overall, our findings suggest that the iPQ-16 at the proposed cut-off is slightly better in ruling in than in ruling out possible UHR status or psychosis in Italian young adult help-seekers, with a LR+ (6.38) that exceeded the threshold of LRs that generate moderate shifts in pretest to post-test probability [225]. However, LRs suggested that enthusiasm about the PQ-16 as a screener for UHR/psychosis status might better be put in a more moderate perspective, at least as regards concurrent validity [227].

The majority of psychometric studies of the various PQ versions were dedicated to its criterion validity, mainly to concurrent validity, much less frequently to predictive validity [231]. Accuracy measures only give a rough measure of criterion validity, which is more adequately expressed as Cohen's chance-corrected kappa [227]. In our study, Cohen’s kappa (0.394) was consistent with a fair agreement of positive results on the iPQ-16 (i.e. a symptom total score ≥ 6) and on the CAARMS (i.e. a score ≥ 3 on at least one positive item). This result indicated a discrete concurrent validity, which was slightly improved lowering the iPQ-16 threshold score at ≥ 5, with a Cohen’s kappa up to 0.431 and consistent with a moderate agreement [229]. Furthermore, using the total

distress score, a cut-off threshold of ≥ 11 increased kappa value up to 0.498. However, as previously reported [156, 157], the iPQ-16 symptom total score showed a significant correlation with the CAARMS diagnosis, confirming a good convergent validity of the iPQ-16 version.

ROC curve results, which were plotted for the iPQ-16 total score to predict CAARMS diagnosis, showed a significant and acceptable AUC, and confirmed that the ≥ 5 iPQ-16 cut-off performed best also in terms of Youden index (J) and distance (d) of points on ROC curve closest to the point (0, 1), balancing the best sensitivity and specificity. Compared to the original PQ-16 cut-off of ≥ 6, the ≥ 5 threshold increased sensitivity value (69%), while maintaining a good to excellent specificity (83%).

However, according to Loewy and colleagues [132], since for screening purposes greater weighting should be given to sensitivity over specificity as part of a two-step screening process, our sensitivity scores are quite low and mean that a certain number of people who would appropriate for early intervention services are not being identified. Therefore, a lower cut-off value might be appropriate, even if total accuracy statistics are slightly lower.

In the present study, a cut-off of ≥ 3 on iPQ-16 symptom total score showed a sensitivity of 84% with a specificity value of 50%. As an alternative, using the iPQ-16 total distress score, the proposed cut-off of ≥ 8 [219] revealed an 80% sensitivity with a 60% specificity. If we considered a threshold of ≥ 6 on total distress scale, sensitivity score went up to 83% in presence of 48% specificity. Finally, if we used iPQ-14 symptom total score, a cut-off of ≥ 2 had 85% sensitivity with 45% specificity. A higher sensitivity implies that full assessment burden ban be considerably reducing with little impact on missing UHR/FEP individuals [220].

In summary, according to Ising and co-workers [157], a good screener requires acceptable psychometric properties and practical benefits. Overall, the Italian version of the PQ-16 predicted UHR/psychosis with excellent specificity and good sensitivity, comparable to 92-item homologue [227]. Moreover, the iPQ-16 appears to be a suitable screening instrument. Indeed, it takes only few minutes to be completed. It also seems to reliably separate no CAARMS diagnosis from UHR/psychosis, potentially reducing the number of individuals to submit to following in-depth clinical interviews, which could lead to anxiety and unnecessary concern [233].

Therefore, iPQ-16 is a quick and systematic screening process that seems to allow early detection and treatment of UHR patients to prevent or delay transition to psychosis. Indeed, a quick referral to a FEP service should be made to shorten the DUP in order to improve prognosis and reduce costs in the long term [234].

Predictive validity

After 12 months of follow-up, approximately 9% of our participants scoring an iPQ-16 symptom total score of ≥ 6 who were below the CAARMS psychosis threshold at the baseline assessment developed a FEP.

Limitations

Firstly, a possible weakness of this research is that the iPQ-16 was completed in a population "enriched" for the target diagnoses, i.e. young adults help-seekers with clinical features of possible psychosis and a decline in social functioning. Therefore, the screening instrument is not yet useable in the general population, in which psychotic symptoms occur commonly, but are transient in most cases, are not necessarily accompanied by distress or treatment seeking, and are not inevitably followed by a transition to psychosis [157, 235]. Indeed, many false positives would be identified. However, for general population screening, there is some evidence to suggest that PQ-16 might be appropriate, so long as total distress score rather than symptom total score are used, and that cut-off threshold is set higher [218]. In particular, in non-help-seeking settings a distress score of ≥ 9 was supported [232].

Another weakness is that the iPQ-16 is not sensitive enough to discriminate between UHR states and psychotic disorder [157]. Intensity of items and distress may be more useful than presence of items in discriminating between UHR and psychosis. However, because the iPQ-16 is proposed as a screening tool followed in the second phase of assessment by the CAARMS interview that can perform this discrimination well, it seems to be less relevant.

Another limitation is the small number of CAARMS [-] participants (n = 42). Moreover, the ability of the instrument to include cases appears to be slightly higher than its ability to exclude them, so it may miss some cases worthy of further investigation [227]. About this, Ising and colleagues [157] included 4-point scale questions on distress following each PQ-16 item to examine if this enhanced the PPV of the instrument. However, in the present study the PPV was excellent.

Finally, since the SS for psychosis [185] was used before the iPQ-16 administration in the ReARMS protocol, this is likely to impact the generalizability of our findings. Indeed, the PQ would ideally be used as the first step in a 2-stage screening process [132]. Therefore, by excluding a certain amount of true negative cases in the pre-PQ step, this would reduce the specificity of the screener and may explain why lower cut-off values could not be used which would have boosted the sensitivity up from its current levels of approximately 60-75%.

CONCLUSION

The Italian version of the PQ-16 showed satisfying psychometric properties. Yet optimal cut-off to improve concurrent validity and, consequently, economic and clinical usefulness has still to be determined through multicentric testing. Moreover, the iPQ-16 seems to be a suitable screening tool for routine use in mental health care services. Indeed, it is short and therefore easy to implement in routine assessment. Finally, the iPQ-16 can be helpful in identifying potential psychotic symptoms for further exploration in an early phase, especially in young adults and adolescents with low functioning.

Screening for psychosis risk among help-seeking adolescents: application of the Italian version of the 16-item prodromal questionnaire (iPQ-16) in child and adolescent neuropsychiatry services.

Psychoses are severely disabling disorders and their life-changing impact is even more prominent in adolescence [236]. Several studies suggested that early intervention might improve outcome and reduce psychosis treatment-related costs [157, 187]. In this context, McGorry and colleagues [28] proposed the notion of "Ultra-High Risk" (UHR) mental states to identify individuals with prospectively high (but not inevitable) imminent risk of developing psychosis. The UHR criteria focus mainly on attenuated positive symptoms and are commonly assessed by the "Comprehensive Assessment of At-Risk Mental States" (CAARMS) [38] or the "Structured Interview of Prodromal/Psychosis-Risk Syndromes" (SIPS) [75]. In a recent meta-analysis, the pooled transition rate of UHR status to full-blown psychosis has been reported to be 15% at 1 year, 19.4% at 2 years and 29.1% at 3 years [30].

Despite being essential for the accurate identification of UHR states [237], semi-structured assessment interviews (such as CAARMS and SIPS) generally require additional intensive training of mental health specialists and several hours of clinicians' time [238]. Therefore, self-report screening instruments play an important role in preselecting potential UHR individuals for subsequent in-depth clinical assessment [231]. One of these screeners is the 92-item Prodromal Questionnaire (PQ-92), which is based on the SIPS [132]. Using a cut-off score of 18 or more positive symptoms, PQ-92 was reported to predict SIPS-UHR status with 82% sensitivity and 49% specificity among adolescents referred to a general mental health clinic (n = 80; 15-18 years) [239]. However, the PQ-92 is too time-consuming for routine screening because of the long administration time. Hence, Ising and co-workers [157] developed a shorter, 16-item version (PQ-16), which showed good psychometric properties for screening a large help-seeking population in adult mental health services. Indeed, a cut-off of ≥ 6 on symptom total score predicted CAARMS UHR/psychosis diagnosis with high sensitivity (87%) and specificity (87%) [157]. Moreover, de Jong and colleagues [217] tested the PQ-16 in a population of adolescents referred to 3 child and adolescent mental health services in the Netherlands, showing an acceptable internal consistency (Cronbach's alpha = 0.79) and a percentage of 34.7% reaching the PQ-16 cut-off of ≥ 6 on symptom total score (n = 176; 12-17 years).

To the best of our knowledge, with the exception of the Netherlands, no study using the PQ-16 in an adolescent clinical sample has been reported up to now. Thus, in the present research we aimed to

test the reliability and the validity of the Italian version of the PQ-16 (iPQ-16) to screen for UHR/psychosis in a population of help-seeking adolescents.

METHODS

Setting

The "Reggio Emilia At-Risk Mental States" (ReARMS) program is an early detection infrastructure developed under the aegis of the "Regional Project on Early Detection of Psychosis" in the Reggio Emilia Mental Health Department [170, 171]. This large semirural catchment area consists of approximately 550.000 inhabitants, of whom nearly 105.000 are <18-year-old [240]. The ReARMS project aims: (1) to identify people with First-Episode Psychosis (FEP) and individuals at high clinical risk according to the UHR criteria [38] among help-seeking adolescents and young adults (13-35 years) through a 2-step procedure, and (2) to provide evidence-based interventions that are supposed to be effective in UHR/FEP subjects (i.e. intensive case management, family psychoeducation, individual cognitive-behavioral therapy, pharmacological treatment [as appropriate]) [170]. The first filtering step included a pre-clinical triage service, conducted by trained nonmedical personnel, using the "Screening Schedule" for Psychosis (SS) [185]. Such triage was mainly meant to maximize appropriate referrals to the ReARMS project and avoid overinclusion of subjects clearly outside the severity threshold for presumed psychosis risk spectrum [171]. The second step included a comprehensive multidimensional battery [170] including the PQ-16, followed by the administration of the "Comprehensive Assessment of At-Risk Mental States" (CAARMS) [38] to define the clinical status (i.e. psychosis risk, psychosis or neither) and the consequent access to the ReARMS clinical-therapeutic pathways [170]. In sum, an initial pre-ReARMS screening was performed by non-medical service staff weighting the appropriateness of the referrals (i.e. eligibility), whereas the ReARMS 2-step assessment was carried out by trained, project clinicians.

The pre-ReARMS evaluation was based on the SS for psychosis [185], a brief checklist containing demographic, history, psychopathological and behavioral items, all dichotomous (yes/no), which operationalized inclusion and exclusion criteria for ReARMS protocol eligibility [170] (for details, see also supplementary materials [Appendix S1]). Those were: (1) age between 13 and 35 years; (2a) presence, in the preceding 12 months, of at least 1 of the following psychotic symptoms: hallucinations or pseudo-hallucinations in any modality; delusions and/or ideas of reference; qualitative thought or speech disorder; qualitative psychomotor disorder; or gross behavioral abnormalities representing a break in the person's previous pattern; or (2b) at least 1 of the following abnormalities indicative of a substantial modification of personality or behavior and

suggestive of psychotic disorder: loss of interest, initiative, and drive leading to deterioration of daily performance; onset of social withdrawal; episodic severe excitement, purposeless destructiveness or aggression; episodic or persistent states of overwhelming fear or anxiety; or gross and persistent self-neglect; (3) first-in-lifetime contact with any "helping agency" within the last 3 months, occasioned by the above mentioned symptoms and behaviors; (4) presence of a "Duration of Untreated Psychosis" (DUP) < 2 years; (5) absence of clinical evidence of organic cerebral disorder, including central nervous system damage due to alcohol or drug abuse, and manifest in either delirium or dementia, with or without peripheral neuropathy; and (f) presence of an Intelligence Quotient (IQ) ≥ 50.

For the purpose of the study (i.e. field-testing the psychometric properties of the PQ-16 in an adolescent clinical sample), we focused on young help-seekers aged 13-17 years. Complying with the Declaration of Helsinki, relevant ethical approvals were locally sought for the study.

Participants

In the current research, all participants were help-seeking adolescents, aged 13 to 17 years, consecutively referred between September 2012 and December 2016 to the 6 child and adolescent neuropsychiatry services of the Reggio Emilia Mental Health Department. Referrals were mainly carried-out by General Practitioners, family members, emergency room, school and social services.

For the purpose of the study, inclusion criteria were: (1) specialist help-seeking; (2) age between 13 and 17 years; and (3) presence of UHR criteria defined by the CAARMS (i.e. "Attenuated Psychotic Symptoms" [APS], "Brief Limited Intermittent Psychotic Symptoms" [BLIPS], and/or "Genetic Risk and Functioning Deterioration" [GRFD]), or (4) a DUP < 2 years in case FEP was detected at the initial assessment. The exclusion criteria were matched on the procedure adopted by Ising et al. (2012) to validate the original Dutch version of the PQ-16: (1) history of past 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) [178], (2) history of previous exposure to antipsychotics, (3) current substance dependence, (4) severe learning disability or known mental retardation (Intelligence Quotient < 70), (5) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms, (6) insufficient fluency in the Italian language and (7) residency outside the catchment area.

All adolescent help-seekers entering the ReARMS project and their parents agreed to participate in the research and gave their informed consent to psychopathological assessment, composed - among others [171] - by the CAARMS (approved Italian translation) (CAARMS-ITA) [181] and the PQ-16 (authorized Italian adaptation) (iPQ-16) [221] (for details, see also supplementary materials

[Appendix S3]). The present study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Measures

The *CAARMS* is a semi-structured clinical interview designed to cover different aspects of attenuated psychopathology as well as functioning (via the integrated SOFAS ["Social and Occupational Functioning Assessment Scale"] module) [38]. It takes approximately 1 to 1.5 hours to administer and consists of 27 items, each one rated in terms of intensity (0-6) and frequency/duration (0-6). These items can be clustered in 7 subscales: "Positive Symptoms", "Cognitive Change, Attention and Concentration", "Emotional Disturbance", "Negative Symptoms", "Behavioral Change", "Motor/Physical Changes" and "General Psychopathology". The CAARMS "Positive Symptoms" subscale, which covers delusions, hallucinations and thought disorder, is used to determine both UHR criteria and threshold for psychosis. UHR status is defined as follows: (1) "GRFD": schizotypal personality disorder in the subject or family history of psychosis in a first-degree relative combined with 30% drop in functioning for at least 1 month or chronic poor functioning, as measured by the SOFAS scale (decline in functioning is calculated by subtracting current SOFAS score from the highest SOFAS score in the past year: scores ranges from 1 to 100, with ≤ 50 the poor functioning cut-off); (2) "APS": subthreshold positive psychotic symptoms within the past 12 month and (3) "BLIPS": criteria for psychosis met for ≤ 7 day at a time and ceasing spontaneously (i.e. without antipsychotic medication). According CAARMS-defined psychosis criteria [38], full-blown psychotic episode threshold is defined by operationalized clear-cut levels of positive psychotic symptoms occurring for ≥ 1 week, either on a daily basis or > 3 times/week with each symptom continuing for >1 hour on each occasion. CAARMS interviews were conducted by clinical psychologists and psychiatrists who received training by the senior author of the approved Italian translation [181], who was previously trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability.

The *PQ-16* is a self-report questionnaire used to screen individuals for the risk of psychosis. It consists of 9 items on perceptual abnormalities/hallucinations, 5 items on unusual thought content/delusional ideas/paranoia, and 2 negative symptoms. This instrument only takes approximately 3 minutes to complete and assesses the presence of positive and negative symptom items on a 2-point scale (true/false), according to the participant's subjective experience in the last month. Distress is added on a 4-point scale for each endorsed item ("no distress-much distress"). When an item is marked as false, the item is rated 0; if an item is marked as true, the answer is rated

according to the severity of distress experienced from 0 (“none”) to 3 (“severe”). The PQ-16 can be scored by the total number of symptoms endorsed (range 0-16) or the sum of distress scores (range 0-48). When using the symptom total score, a cut-off threshold of ≥ 6 appeared appropriate in general mental health setting [157]. Using the distress total score, a threshold of ≥ 8 was supported in general mental health help-seeking population [219].

Statistical analysis

The overall validation procedure of the iPQ-16 was modelled on the methodological approach employed by Ising and co-workers [157] to validate the original Dutch versions of the PQ-16. For the specific purpose of this study (we were interested in testing the screening features of the iPQ-16 against the CAARMS risk criteria), since PQ-16 is less sensitive for distinguishing between the threshold of psychosis risk and clinical psychosis because it only measures the prevalence and not the intensity of symptoms [157], UHR and FEP participants were both considered as CAARMS positive cases (CAARMS [+]). The participants who were below the threshold for being considered at risk of developing psychosis were classified as CAARMS negative cases (CAARMS [-]). These 2 sub-groups were compared on demographic, clinical and psychopathological parameters. Due to non-normality (Kolmogorov-Smirnov, with Lilliefors significant correction, $p < 0.05$ in all exploration), the rank-scaled and categorical variables were analyzed using non-parametric statistics (i.e. χ^2 test with Yates' correction and Mann-Whitney's unpaired U test).

As measure of reliability, internal consistency of the iPQ-16 was examined using Cronbach’s alpha statistics within the total sample. A score above 0.65 was considered sufficient internal consistency [157]. Furthermore, we examined how each iPQ-16 item correlated with the questionnaire total score. Correlations less than $r = 0.30$ indicated that the item might need to be removed from the questionnaire to make it more reliable [224]. Finally, we focused on Cronbach’s alpha score with each deleted item. If this score increased after the item was deleted, removal of this item could be considered to increase questionnaire reliability [224].

In the present study, we also investigated the concurrent validity of the iPQ-16 by comparing its results to the outcomes of a standardized assessment for “at-risk mental states” (i.e. the CAARMS). In the total sample, we first calculated diagnostic accuracy measures, that is, sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-), that balance sensitivity against specificity. According to Jaeschke and colleagues [225], likelihood ratios (LRs) of 1 to 2 and 0.5 to 1 alter pre-test probability to a small (and rarely important) degree; LRs of 2 to 5 and 0.2 to 0.5 generate small (but sometimes important) changes in probability and LRs of 5 to 10 and 0.1 to 0.2 generate moderate shifts in pre-test to post-test

probability. Concurrent validity, that is, the correspondence of positive results on the iPQ-16 (i.e. a symptom total score ≥ 6 [that is the original cut-off threshold proposed by Ising and co-workers] [157]) and on the CAARMS (i.e. a score of ≥ 3 on at least 1 positive symptom item) was also examined by Cohen's kappa. Moreover, following the methodological approach employed by Ising and colleagues [157], a biserial correlation was used to evaluate the association of the iPQ-16 symptom total score with CAARMS diagnosis. Finally, iPQ-16 total score correlations with CAARMS "Positive Symptoms" and "Negative Symptoms" subscale scores were carried out.

To test whether different iPQ-16 cut-offs might enhance concurrent validity in the total sample, Receiver Operating Characteristic (ROC) curve was firstly plotted for the iPQ-16 symptom total score against outcome in the CAARMS (i.e. no CAARMS diagnosis vs CAARMS UHR/psychosis). In interpreting the area under the ROC curve (AUC), we followed what reported by Hosmer and colleagues [226], that is, AUC ≤ 0.5 no discrimination, 0.51 to 0.69 unacceptably low, 0.70 to 0.79 acceptable, 0.80 to 0.89 excellent and ≥ 0.90 outstanding. To assess the concurrent validity of potentially suggested better cut-offs, we again conducted Cohen's kappa and diagnostic accuracy measures. Furthermore, 2 criteria were used to confirm optimal cut-off point from ROC curve, giving equal weight to sensitivity and specificity: (1) points on ROC curve closest to the point (0, 1) and (2) the Youden index (J) [228]. In detail, to identify the optimal cut-off for distinguishing cases from non-cases, we calculated the distance (d) between the point (0, 1) and each observed cut-off point on ROC curve, and located the point where this distance was minimum: $d = \sqrt{[(1\text{-sensibility})^2 + (1\text{-specificity})^2]}$. The Youden index (J) was the point on the ROC curve which was farthest from line of equality (or random chance diagonal line). The main aim of Youden index is to maximize the difference between true positive rate (sensitivity) and false positive rate (1-specificity): J = max (sensitivity + specificity − 1). In addition, since the distress scale appeared to improve the PQ-16 sensitivity [218, 240], we repeated concurrent validity analyses for the iPQ-16 total distress score within the entire sample.

Finally, the predictive validity of the iPQ-16 was tested by consecutively identifying people with a cut-off of ⩾6 on iPQ-16 symptom total score (i.e. the PQ-16 original cut-off threshold proposed by Ising and colleagues [157]) who did not meet CAARMS psychosis criteria at baseline. We calculated whether the ⩾6 cut-off score of the iPQ-16 had any predictive value regarding the development of a psychotic disorder according to CAARMS-defined criteria [38].

Analyses were conducted using the "Statistical Package for Social Science" (SPSS) 15.0 for Windows [192].

RESULTS

Sample characteristics

Over the course of the study, 72 individuals (37 males, 51.4%) consecutively underwent an intake interview within the ReARMS protocol in the 6 child and adolescent neuropsychiatry services of the Reggio Emilia Mental Health Department. Age ranged from 13 to 17 years (median = 15.50 years, interquartile range = 3.0 years). Fifteen patients were first-time diagnosed with a psychotic disorder (FEP) within our 2-step clinical interviews (9 schizophrenia, 3 bipolar I disorder with psychotic features and 3 psychotic disorder not otherwise specified). Twenty-nine met UHR criteria and 28 were neither at UHR nor psychotic. Most UHR participants (n = 26, 89.7%) were considered at-risk for APS, 2 (6.9%) for BLIPS, and 1 (3.4%) for GRFD. UHR/psychosis status was not associated with gender (χ^2 = 0.087; p = 0.768) or age (Z = -0.316, p = .752). The age distribution of the sample was skewed towards the right (skewness = -0.398; Kolmogorov-Smirnov, p < 0.001).

Table 25 shows demographic characteristics and screening outcomes of the entire sample and of the CAARMS [+] (n = 44) and CAARMS [-] (n = 28) sub-samples. No significant differences were found between groups in terms of gender, ethnic group, mother tongue, age, years of education and "Duration of Untreated Illness" (DUI), that is, time (in weeks) from onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment [180].

Table 25 – CAARMS criteria, demographic and clinical data.

	Total sample (*n* = 72)	CAARMS (−) (*n* = 28)	CAARMS (+) (*n* = 44)	χ^2/Z
Gender (males)	37 (51.4%)	15 (53.6%)	22 (50.0)	0.087
Ethnic group (Caucasian)	63 (87.5%)	25 (89.3%)	38 (86.4%)	0.134
Mother tongue (Italian)	67 (93.1%)	26 (96.3%)	41 (93.2%)	0.001
Age	15.50 (3)	16 (2.75)	15 (3)	−0.316
Years of education	10 (2)	10 (2.75)	10 (2)	−0.598
DUI (in weeks)	80 (11)	84 (11)	75 (11)	−0.796
iPQ-16				
Symptom total score (range 0-16)	7 (6)	5 (7.50)	8 (5.25)	−2.815*
Total distress score (range 0–48)	17 (19)	8.50 (16.50)	21 (16.50)	−3.957*

Abbreviations: CAARMS, comprehensive assessment of at-risk mental states; CAARMS [+], adolescents meeting or above CAARMS criteria; CAARMS [−], adolescents below CAARMS criteria; DUI, duration of untreated illness; iPQ-16, 16-item prodromal questionnaire—Italian version. Frequencies and percentages, median (interquartile range), χ^2 test (with Yates correction) and Mann-Whitney *U* test (*Z*) values are reported. *P < .01.

In comparison with CAARMS [-], CAARMS [+] adolescents showed significantly higher iPQ-16 total scores (Table 1). However, within the CAARMS [+] sub-group, no difference in iPQ-16 total scores between UHR and FEP individuals were found (symptom total score: median = 8, interquartile range = 4.75 vs median = 9.50, interquartile range = 7.50; Z = -1.178; p = 0.239; total

distress score: median = 21, interquartile range = 16 vs median = 21.50, interquartile range = 27.25; Z = -0.988; p = 0.333).

Reliability

Across the entire sample (n = 72), Cronbach's alpha for the symptom total score on the iPQ-16 was 0.827. All item-total correlations were greater than 0.30, with the exception of item 7 ("I get extremely anxious when meeting people for the first time"; r = 0.234) (Table 26).

Table 26 – Internal consistency of iPQ-16.

iPQ-16 item	Item-total correlation	Cronbach's alpha if item deleted
1. I feel uninterested in the things I used to enjoy.	0.363	0.821
2. I often seem to live through events exactly as they happened before (deja-vu).	0.465	0.816
3. I sometimes smell or taste things that other people can't smell or taste.	0.309	0.826
4. I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears.	0.458	0.816
5. I have been confused at times whether something I experienced was real or imaginary.	0.575	0.808
6. When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes.	0.478	0.816
7. **I get extremely anxious when meeting people for the first time.**	**0.234**	**0.830**
8. I have seen things that other people apparently can't see.	0.517	0.812
9. My thoughts are sometimes so strong that I can almost hear them.	0.484	0.814
10. I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me.	0.383	0.820
11. Sometimes I have felt that I'm not in control of my own ideas or thoughts.	0.398	0.820
12. Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of.	0.463	0.816
13. I have heard things other people can't hear, like voices of people whispering or talking.	0.564	0.810
14. I often feel that others have it in for me.	0.383	0.821
15. I have had the sense that some person or force is around me, even though I could not see anyone.	0.536	0.811
16. I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.	0.389	0.820

Abbreviations: iPQ-16, 16-item Prodromal Questionnaire—Italian version. Correlation *r* coefficients and Cronbach's alpha values are reported.

Thus, most items appeared to be worthy of retention, resulting in a decrease in the alpha if deleted. Exception to this was item 7, with an increase in the Cronbach's alpha up to .830 if deleted. Thus, removal of this item might be considered [224].

Concurrent validity

At the proposed PQ-16 threshold of ≥ 6 on symptom total score [157], 46 adolescents (64.8%) scored positive; of these, 33 (71.7%) also scored ≥ 3 on any positive CAARMS item (i.e. they were CAARMS [+]). Altogether, 10 participants (21.1%) with any CAARMS positive score ≥ 3 were missed by this PQ-16 cut-off, and 13 (18.3%) were falsely identified. Cohen's kappa was 0.309, consistent with a fair agreement [229].

Table 27 – CAARMS diagnostic classification accuracy by iPQ-16 cut-off scores.

PQ-16 cut-off	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	Cohen's kappa	*J*	d
Symptom total score									
≥ 4	88.37 (74.92-96.11)	39.29 (21.50-59.42)	69.09 (61.95-75.43)	68.75 (46.12-84.97)	1.46 (1.1.06-2.00)	0.30 (0.12-0.76)	0.299	0.277	0.618
≥ 5	79.07 (63.96-89.96)	46.43 (27.51-66.13)	69.39 (60.84-76.78)	59.09 (41.67-74.50)	1.48 (1.01-2.15)	0.45 (0.22-0.91)	0.265	0.255	0.575
≥ 6	76.74 (61.37-88.24)	53.57 (33.87-72.49)	71.74 (62.27-79.61)	60.00 (44.08-74.05)	1.65 (1.07-2.54)	0.43 (0.23-0.83)	**0.309**	**0.303**	**0.519**
≥ 7	67.44 (51.46-80.92)	57.14 (37.18-75.54)	70.73 (60.04-79.54)	53.33 (40.06-66.15)	1.57 (0.98-2.53)	0.57 (0.33-0.97)	0.243	0.246	0.538
Total distress score									
≥ 8	82.86 (71.97-90.82)	47.50 (31.51-63.82)	73.42 (66.87-79.07)	61.29 (46.26-74.44)	1.58 (1.15-2.16)	0.36 (0.20-0.66)	0.319	**0.304**	**0.447**
≥ 9	82.61 (71.59-90.68)	50.00 (33.80-66.20)	74.03 (67.24-79.83)	62.50 (47.46-75.24)	1.65 (1.19-2.29)	0.35 (0.19-0.63)	0.340	0.326	0.427
≥ 10	81.16 (69.94-89.57)	55.00 (38.49-70.74)	75.68 (68.44-81.70)	62.86 (49.05-74.85)	1.80 (1.26-2.59)	0.34 (0.19-0.60)	**0.371**	0.362	**0.391**
≥ 11	76.81 (65.09-86.13)	60.00 (43.33-75.14)	76.81 (68.93-83.18)	60.00 (47.68-71.18)	1.92 (1.29-2.87)	0.39 (0.23-0.64)	0.368	0.368	0.392
≥ 12	72.46 (60.38-82.54)	62.50 (45.80-77.27)	76.92 (68.53-83.61)	56.82 (45.58-67.40)	1.93 (1.26-2.96)	0.44 (0.28-0.69)	0.342	0.350	0.416

Abbreviations: CAARMS, comprehensive assessment of at-risk mental states; CI, confidence intervals; Cohen's kappa, *J* = Youden index; d, distance between the point (0,1) at each cut-off point on the ROC curve; iPQ-16, 16-item Prodromal Questionnaire—Italian version; LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value. PQ-15 is not a PQ-version, but the iPQ-16 with item 7 deleted. The best Cohen's kappa, J, and d values balancing sensitivity and specificity are in bold.

With regard to the diagnostic accuracy at the proposed PQ-16 cut-off of ≥ 6 on symptom total score, sensitivity was 0.767, specificity 0.536, PPV 0.717, NPV 0.600, LR+ 1.65 and LR− 0.43 (Table 27). Thus, at this threshold, the iPQ-16 score was slightly better in ruling out than in ruling in possible UHR/psychosis status. In fact, according to Jaeschke and co-workers [225], although LR+ was in the range that altered pre-test probability to a small and rarely important degree, LR- generated small (but sometimes important) changes in pre-test to post-test probability. Furthermore, symptom total score on the iPQ-16 was significantly correlated with CAARMS diagnosis (UHR/psychosis or neither: r = 0.346, p = 0.003), as well as with CAARMS "Positive Symptoms" and "Negative Symptoms" sub-scale scores (r = 0.579, p < 0.001; and r = 0.253, p = 0.032). Finally, we found no significant correlation between iPQ-16 total score and age (r = −0.107, p = 0.372), and no age differences between individuals with or without an iPQ-16 cut-off score of ≥ 6 (median = 15 years and interquartile range = 3.00 years vs median = 16 years and interquartile range = 3.75 years; Z = -0.314, p = 0.754).

ROC curve was plotted for iPQ-16 symptom total score to predict no CAARMS diagnosis vs CAARMS UHR/psychosis. The AUC was significant and acceptable for the symptom total score (0.704, SE = 0.064, 95% CI = 0.578-0.830, p = 0.004) [226]. Cohen's kappa and accuracy measures of different thresholds for iPQ-16 symptom total score revealed that, overall, the suggested ≥ 6 cut-off performed best in terms of kappa value, LR+, distance (d) of points on ROC curve closest to the point (0, 1), and Youden index (J) (Table 27), balancing the best sensitivity and specificity.

With regards to the diagnostic accuracy at the proposed PQ-16 total distress score cut-off of ≥ 8 [219], sensitivity was 0.829, specificity 0.475, PPV 0.734, NPV 0.613, LR+ 1.58 and LR- 0.36 (Table 27). Moreover, ROC curve plotted for the iPQ-16 total distress score showed an AUC comparable to iPQ-16 symptom total score (i.e. 0.713; SE = 0.053, 95% CI = 0.608-0.817, p = 0.001). Cohen's kappa and accuracy measures of different thresholds for the iPQ-16 total distress score revealed that, overall, the ≥ 10 cut-off performed best in terms of kappa and d values (Table 27), balancing the best sensitivity and specificity. Furthermore, compared to the ≥ 6 cutoff on the iPQ-16 symptom total score, the ≥ 10-threshold on total distress score increased sensitivity and specificity values up to 0.812 and 0.550, respectively. Regarding LRs, iPQ-16 cut-off threshold of ≥ 10 on total distress score was slightly better in ruling out than in ruling in possible UHR/psychosis status, maintaining a LR- value in the range that generated small, but sometimes important, changes in pretest to post-test probability [225].

Predictive validity

Seven of 35 adolescents who had scored ≥ 6 on the original iPQ-16 symptom total score [157] and did not meet CAARMS psychosis criteria at baseline, did not complete the 12-month follow-up period. Five of these individuals had a follow-up period of less than 1 year. The other 2 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, 2 (7.1%) of the 28 remaining individuals who scored ≥ 6 on the iPQ-16 symptom total score and did not meet CAARMS psychosis criteria at baseline, developed a FEP. Among iPQ-16 negative screens, no psychosis conversion was found.

DISCUSSION

In the current study, we examined psychometric properties of the Italian version of the PQ-16 (i.e. reliability and validity in detecting UHR or psychosis status) in consecutive help-seeking adolescents referring to the 6 child and adolescent mental health services of the Reggio Emilia Mental Health Department. Although the small sample size was relatively small (n = 72), the results shave potential implications with respect to the screening for psychotic risk in adolescence and

developmental years (even if our research is better characterized as a pilot study rather than a full validation study).

In comparison with CAARMS [-], CAARMS [+] individuals showed significantly higher iPQ-16 total scores. On a dimensional level, this finding suggests that increasing PQ-16 scores relate to the severity of psychotic psychopathology.

Reliability

We found excellent reliability of the iPQ-16 with regard to internal consistency of the symptom total score ($\alpha = 0.827$). Similarly, in a Dutch help-seeking adult population accessing a secondary mental health care service, the PQ-16 showed good internal consistency, with a Cronbach's alpha for the symptom total score = 0.774 [157]. Reliability in our adolescent clinical sample was even better than the high reliability reported for the Chinese PQ-16 version in 579 college students (Cronbach's alpha = 0.72) [232] and the Dutch PQ-16 version in 176 help-seeking adolescents (aged 12-17 years) attending the 3 child and adolescent mental health services in Rotterdam in the Netherlands (Cronbach's alpha = 0.79) [217]. In the present study, iPQ-16 showed a Cronbach's alpha which we regard as satisfactory internal consistency for a screening measure that has to be followed by a clinical interview [157]. Therefore, similarly to the Italian version of the 92-item PQ ($\alpha = 0.720$ for the total score) [227], reliability of the iPQ-16 appears to be good in different samples and cultures.

In our sample, the correlation coefficient r was > 0.30 for all items, except item 7 ("I get extremely anxious when meeting people for the first time"). The removal of this item could be considered, as its deletion would slightly increase Cronbach's alpha to 0.830. However, it should be considered that Cronbach's statistics is not an item discrimination analysis, but it only measures how well the items of an instrument hang together.

Concurrent validity

In the Dutch study validating the PQ-16 in an adult population seeking help for nonpsychotic disorders in routine mental health care services, Ising and colleagues [157] observed good concurrent validity with the interview-based CAARMS diagnoses. A PQ-16 cut-off of ≥ 6 on symptom total score had a high true positive rate (87%) and high specificity (87%) in differentiating UHR/psychosis individuals from those with no CAARMS diagnosis, with a PPV of 44%. In the study of Chen and co-workers [232] conducted on a mixed adolescent/young adult Chinese college student population (16-22 years), a PQ-16 cut-off of ≥ 6 showed an optimal sensitivity value of

100% in detecting UHR individuals with the interview-based SIPS diagnoses, but a lower specificity (63%, with a PPV = 41% and a NPV = 100%).

Regarding diagnostic accuracy at the proposed PQ-16 cut-off of ≥ 6 on symptom total score, sensitivity in our sample (77%) was lower than previously reported. However, our result was better than that (63%) observed by Kotzalidis and colleagues [227] in the validation study of the Italian version of the PQ-92 in an adolescent/adult mixed population of help-seekers (12-36 years) referred to 12 pediatric and adult outpatient mental health departments of the semirural Rome 6 area.

Furthermore, at the proposed PQ-16 cut-off ≥ 6, our PPV (72%) was much higher than previously reported for various PQ versions (i.e. PPV ranging between 29% and 44%) [157, 227, 231, 232]. The difference between these findings may be the result of differences in selection procedures and PQ versions adopted. In fact, first screening procedure in the ReARMS protocol included a triage service using the SS [185], which could already have ruled out many true negative cases.

In our sample, specificity (54%) is consistent with that previously reported by Chen and co-workers [232] (63% in Chinese college students), but lower than what was observed in the Dutch study validating the original PQ-16 (87% in adult help-seekers) [157] and in the Italian validation study of the PQ-92 (82% in an adolescent/adult mixed population of help-seekers) [227]. Similarly, our NPV (60%) was lower than previously reported, with values ranging between 90% and 100% [157, 232]. The difference between these findings might be due to differences in sample age and/or in the selection procedures previously mentioned. The impact of age should be assessed in future studies, as higher score on the PQ-92 positive sub-scale (in particular on perceptual abnormalities) were associated with younger age in an adolescent help-seeking sample [238]. Thus, iPQ-16 might possibly require age-adapted cut-off scores. However, in a sample of 176 Dutch help-seeking adolescents, de Jong and colleagues [217] found no significant correlation between PQ-16 symptom total score and age, and no age-related differences in the number of individuals scoring above the proposed ≥ 6 cut-off score. Although preliminary, in our research we found no evidence of the need for an age-adapted cut-off, at least for the 13 to 18 year range.

Overall, our findings seem to suggest that the iPQ-16 at the proposed cut-off of ≥ 6 on symptom total score [157] is slightly better in ruling out than in ruling in possible UHR status or psychosis in Italian adolescent help-seekers. Indeed, a LR- of 0.43 was in the range that generated small, but sometimes important, changes in pre-test to post-test probability [225]. However, the low LR values suggest that enthusiasm about the iPQ-16 as a first-line screener for UHR/psychosis status might better be put in a more moderate perspective, at least as regards concurrent validity [227]. Accuracy measures only give a rough measure of criterion and concurrent validity, which are more adequately expressed as Cohen's chance-corrected kappa [227]. In our research, Cohen's kappa was 0.309,

consistent with a fair agreement of positive results on the iPQ-16 (i.e. a symptom total score of ≥ 6) and on the CAARMS (i.e. a score of ≥ 3 on at least 1 positive item) [229]. However, as previously reported [132, 157], iPQ-16 symptom total score was significantly correlated with CAARMS diagnosis (UHR/psychosis or neither) as well as with CAARMS positive and negative sub-scores, confirming a good convergent validity of the Italian PQ-16 version.

ROC curve results, which were plotted for iPQ-16 symptom total score to predict no CAARMS diagnosis vs CAARMS UHR/psychosis, showed a significant and acceptable AUC (0.704), and confirmed that the ≥ 6 PQ-16 cut-off performed best in terms of Cohen's kappa, distance (d) of points on ROC curve closest to the point (0, 1), and Youden index (J), balancing the best sensitivity and specificity.

However, according to Loewy and colleagues [132], since for screening purposes greater weighting should be given to sensitivity over specificity as part of a 2-step screening process, a sensitivity score of 77% means that a certain number of people who would appropriate for early intervention services are not being identified. Therefore, a lower cut-off value might be appropriate, even if total accuracy statistics are slightly less powerful. In the present study, a cut-off of ≥ 4 on iPQ-16 symptom total score showed a sensitivity of 88% with a specificity value of approximately 40%.

As an alternative, using the iPQ-16 total distress score, the proposed cut-off of ≥ 8 [219] revealed 82% sensitivity with 47% specificity. If we considered a threshold of ≥ 10 on total distress score (which performed best in terms of Cohen’s kappa and d values), sensitivity value reached 81% in presence of 55% specificity.

In summary, the Italian version of the PQ-16 seems to predict UHR/psychosis in an adolescent help-seeking sample with good sensitivity and sufficient specificity, substantially comparable to the much longer Italian version of the 92-item PQ. Furthermore, the iPQ-16 appears to be a suitable and practical screening measure as it takes only few minutes to complete. In fact, it is sufficiently able to reliably separate UHR/psychosis from no CAARMS diagnosis, reducing the number of in-depth interviews to an acceptable amount. An important point to consider in screening an adolescent help-seeking population at risk for an emergent psychotic disorder is the role of stigma and resources [157, 240]. In fact, false detection of individuals could lead to unnecessary concern and anxiety [233]. In addition, a systematic and quick screening process with the PQ-16 in the adolescent help-seeking population attending mental health care services might allow an earlier identification and treatment of patients that might prevent or delay transition to psychosis [187]. Furthermore, quick referrals to first episode psychosis services might shorten DUP, improving outcome and saving costs in the long term [234].

Predictive validity

After 12 months of follow-up, about 7% of our adolescents who had scored ≥ 6 on the iPQ-16 symptom total score and did not meet CAARMS psychosis criteria at baseline, developed a FEP. When examining these findings, some methodological peculiarities of the present study must be considered. In particular, ReARMS project included a first screening step using the SS [185], which might have already excluded some adolescents with an UHR status in addition to many true negative cases. Thus, our results may differ from what could be found in a follow-up study using PQ-16 as first screening procedure.

Furthermore, ReARMS project is a clinically protocol providing evidence-based interventions that are supposed to be effective in UHR/FEP individuals (i.e. intensive case-management, family psycho-education, individual cognitive-behavioral therapy within the framework of assertive community treatment, antipsychotic medication [as appropriate]) [170]. Finally, 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 placebo group or other treatment), but evenly delivered to all UHR/FEP adolescents.

Limitations

A limitation of this study is that the iPQ-16 is performed in a sample that is "enriched" for the target diagnoses with adolescents seeking help for symptoms of possible psychosis and impairment in social functioning. Therefore, the results cannot be generalized to non-help-seeking populations of the same age.

Another limitation - which is partly related to the actual scope of the PQ-16 as a screener - is that PQ-16 is not sensitive enough to distinguish between UHR syndromes and psychosis [157], which requires a further assessment step. Indeed, intensity of symptoms and suffering (distress) may be more important than presence of symptoms per se in distinguishing between psychosis risk and psychosis.

Another possible weakness is the small sample size. This could affect the conclusion on the quality of the instrument, especially given the small number of interviewees who were screened as negatives (n = 28). Moreover, given the limited age range (13 to 17 years), we could not exclude that the lack of any detectable age effect on iPQ-16 was due to power issues (i.e. sample underpowered), however given the important cognitive-affective, developmental and maturational changes going on in such age span, it is unlikely that important age-related differences would not emerge. Furthermore, the ability of the instrument to include cases appears to be sufficient, but it may still miss some cases worthy of further investigation. Thus, Ising and co-workers [157]

included 4 Likert scale questions on distress following each individual PQ-16 item, in order to investigate if this increased the PPV of the instrument. Finally, since the iPQ-16 was a second stage screening in our research, it seems hard to draw definitive conclusions about whether this instrument should be used as a first screening procedure in adolescent help-seeking populations.

CONCLUSION

The Italian version of the iPQ-16 showed satisfactory psychometric properties for routine use in child and adolescent mental health services. It is also short and therefore easy to implement in routine assessment. Moreover, the iPQ-16 can be useful to bring up potential psychotic symptoms for further exploration in an early stage. This might ultimately reduce the DUP of help-seekers with undetected psychosis, and improve the timely identification of individuals with an attenuated psychotic syndrome in routine mental health care services [241]. Clearly, this is even more important in developmental years, particularly when dealing with adolescent help-seekers with initial deterioration of the quality of life and increasing low functioning [30, 235].

STUDY 4 – THE ITALIAN ADAPTATION OF THE PRODROMAL QUESTIONNAIRE – BRIEF VERSION (IPQ-B)

The Italian version of the Brief 21-item Prodromal Questionnaire: Field-test, psychometric properties and age-sensitive cut-offs

Specialist treatment for Ultra-High Risk (UHR) mental states can effectively reduce psychosis conversion rate [214]. However, identifying individuals with UHR remains a significant challenge [218]. Although structured interviews, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) [38] or the Structured Interview for Prodromal States (SIPS) [75], can reliably diagnose UHR states [237], they generally require extensive training to be administered and can take hours to be completed [238]. Therefore, an array of self-report screening tools has been developed to preselect potential UHR individuals for subsequent in-depth clinical assessment [231]. Although these self-report instruments cannot reliably differentiate between people with UHR or First Episode Psychosis (FEP), accumulating empirical evidence suggests that they are sufficiently sensitive and specific to detect the majority of those individuals that merit a more comprehensive evaluation for putative UHR or FEP [242].

The 92-item Prodromal Questionnaire (iPQ-92) [132], which is based on the SIPS, is the most commonly used screener in the literature [242]. Rietdijk and co-workers [243] found that using the PQ-92 in secondary mental health care services resulted in a threefold increase in detection of UHR, relative to standard referral methods. However, the PQ-92 remains rather time consuming for routine screening. Thus, Loewy and colleagues [156] developed a Brief 21-item version (PQ-B), focusing on the positive symptom items of the PQ-92, since they are the essential ones for interview-based diagnoses of symptomatic prodromal syndromes (i.e., Attenuated Psychotic Symptom [APS] and Brief Limited Intermittent Psychotic Symptoms [BLIPS]). A cut-off of ≥ 6 on the PQ-B total distress score predicted SIPS-UHR/psychosis diagnosis with high sensitivity (88%) and good specificity (68%) [156]. In a recent systematic review on psychosis risk screening in different populations using the PQ in its different iterations, Savill and co-workers [218] suggested that in UHR/psychosis enriched samples with a lower prevalence (< 40%) of UHR/psychosis individuals, a total distress score of ≥ 18 would be recommended. Moreover, PQ-B scores showed good psychometric properties in nonclinical adolescent populations as well [244, 245].

To the best of our knowledge, no study using the PQ-B in an Italian clinical sample has been reported in the literature to date. Indeed, the only previous exploratory study, which revealed good

internal consistency and 1-month test-retest stability, was conducted on a sample of Italian non-help-seeking undergraduate students [246]. Thus, in the current protocol, we wanted to test the reliability and the validity of the Italian version of the PQ-B (iPQ-B) for screening purposes in a population of adolescent and young adult community help-seekers.

METHODS

Setting

The "Reggio Emilia At-Risk Mental States" (ReARMS) project is an early detection infrastructure implemented under the aegis of the "Regional Project on Early Detection of Psychosis" in the Reggio Emilia Department of Mental Health, in Northern Italy [170]. This semirural catchment area is composed of approximately 550,000 inhabitants, of whom nearly 105.000 are < 18-year-old [171]. The ReARMS project aims (a) to detect individuals with FEP or a clinical high risk according to UHR criteria [38] among help-seeking adolescents and young adults (13-35 years) through a 2-step procedure and (b) to provide evidence-based interventions that are supposed to be effective in UHR/FEP subjects (i.e., intensive case management, family psycho-education, individual cognitive-behavioral therapy, pharmacological treatment [as appropriate]) [170, 171].

The first filtering step included a pre-clinical triage service, conducted by trained non-medical personnel, using the Screening Schedule for Psychosis [185]. Such triage was mainly meant to maximize appropriate referrals to the ReARMS project and avoid over-inclusion of subjects clearly outside the severity threshold for presumed psychosis risk spectrum. The second step included a comprehensive multidimensional battery [171] including the PQ-B and the CAARMS [38] to define the clinical status (i.e., psychosis risk, psychosis, or neither) and the consequent access to the ReARMS clinical-therapeutic pathways. In sum, an initial pre-ReARMS screening was performed by non-medical service staff weighting the appropriateness of the referrals (i.e., eligibility), whereas the ReARMS 2-step assessment was carried out by trained, project clinicians.

Ethical approval from the local research Ethics Committee was obtained for the study. The current research has also been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Participants

Psychometric properties of the iPQ-B were tested in a sample of help-seeking adolescents and young adults, aged 13-35 years, consecutively attending to all of child/adolescent and adult mental health care services of the Reggio Emilia Department of Mental Health between September 2012

and September 2017. Referrals were mainly performed by General Practitioners, family members, emergency room, general hospital and school and social services.

For the specific purpose of the study (i.e., testing psychometric properties of the iPQ-B), ReARMS inclusion criteria were (a) specialist help-seeking; (b) age between 13 and 35 years; (c) presence of UHR criteria defined by the CAARMS (i.e., APS, BLIPS, and/or Genetic Risk and Functioning Deterioration [GRFD]) or (d) a Duration of Untreated Psychosis (DUP) < 2 years in case FEP is detected with the CAARMS interview. Individuals who were below the CAARMS UHR/FEP threshold were considered CAARMS negative cases in order to test PQ-B specificity.

The exclusion criteria were matched on the procedure adopted by Loewy et al. [11] to validate the original version of the PQ-B (a) history of well-established psychosis with a DUP > 2 years, (b) current substance dependence, (c) known mental retardation (Intelligence Quotient < 70) and (d) neurological disorders (such as temporal lobe epilepsy), head injury or any other medical condition associated with psychiatric symptoms. In addition to these exclusion criteria, (e) history of previous exposure to antipsychotics, (f) insufficient fluency in the Italian language and (g) living outside the catchment area were selected.

All help-seekers entering the ReARMS project or their parents agreed to participate to the research and gave their written informed consent to the psychopathological assessment, composed - among others - by the CAARMS (approved Italian translation) (CAARMS-ITA) [181], the “Positive and Negative Syndrome Scale” (PANSS; approved Italian version) [247] and the PQ-B (authorized Italian version) (iPQ-B) [248]. Considering potential sources of bias included in the QUADAS tool for the “Quality assessment of Diagnostic Accuracy Study” [249, 250], CAARMS assessors were blinded to the iPQ-B scores. Moreover, the iPQ-B and the CAARMS were completed on the same day.

Measures

The *CAARMS* is a semi-structured clinical interview designed to cover different aspects of attenuated psychopathology as well as functioning (via the integrated SOFAS [“Social and Occupational Functioning Assessment Scale”] module) [38]. It takes approximately 1-1.5 h 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 7 subscales: (a) “Positive Symptoms” (i.e. disorders of thought content, perceptual abnormalities, disorganized speech); (b) “Cognitive Change, Attention and Concentration” (i.e. subjective experience and observed cognitive change); (c) “Emotional Disturbance” (i.e. subjective emotional disturbance, observed blunted affect, observed inappropriate affect); (d) “Negative Symptoms” (i.e. alogia, avolition/apathy, anhedonia);

(e) “Behavioral Change” (i.e. 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) GRFD: schizotypal personality disorder in the patient or family history of psychosis in a first-degree relative combined with 30% drop in functioning for ≥1 month or chronic low functioning, as measured by the SOFAS scale (decline in functioning is calculated by subtracting the current SOFAS score from the highest SOFAS score in the past year); (b) APS: subthreshold positive symptoms within the past 12 month; and (c) BLIPS: criteria for psychosis met for < 7 day at a time and ceasing spontaneously (i.e., without antipsychotic medication). According to psychosis criteria defined by the CAARMS [38], the threshold of full-blown psychotic episode is defined by operationalized clear-cut levels of fully positive symptoms occurring for ≥ 1 week, either on a daily basis or > 3 times a week with each symptom continuing for > 1 h on each occasion. CAARMS interviews are conducted by specialized clinical psychologists and psychiatrists, trained by the main author of the approved Italian translation [181], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability of these assessments.

The *PANSS* (authorized Italian version) [247] is a 30-item scale specifically designed to assess the severity of psychotic symptoms, subdivided into 3 major psychopathological dimensions: (a) “Positive Symptoms” (i.e. delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution and hostility); (b) “Negative Symptoms” (i.e. blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking); and (c) “General Psychopathology” (i.e. somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance). Each item can be rated from 1 (“absent”) to 7 (“extreme”).

The *PQ-B* [156] is a self-report questionnaire used to screen individuals for the risk of psychosis. It only takes approximately 4 min to be completed and comprises of 21 items recording positive

symptoms experienced over the past month. For each endorsed symptom, responders rate whether they found it distressing or impairing, ranging from 1 (“strongly disagree”) to 5 (“strongly agree”), with a 4 or 5 indicating distress [156]. The PQ-B has been adopted as a screening tool using the total number of items endorsed (“symptom total score”), the number of items that are identified as distressing (“distressing item total score”) (both range 0-21) and the total distress score (range 0-105), with the latter method recommended by Loewy and colleagues [156]. In their recent systematic review on psychosis risk screening using the PQ, Savill and co-workers [218] examined 8 diagnostic accuracy studies using the PQ-B. Of these, one evaluated the number of distressing symptoms endorsed in a UHR/psychosis-enriched sample and found a threshold of ≥ 4 distressing items as optimal cut-off [223]. Six studies examined the total distress score for screening: in samples with a very high prevalence (~80%) of UHR/psychosis individuals, a total distress score of ≥ 6 was supported [156], whereas in similar settings with a much lower prevalence (< 40%), a total distress score ≥ 18 was recommended [223, 251]. Finally, 4 studies adopted the total number of symptoms endorsed as cut-off: in a sample with a very high proportion of UHR/psychotic participants, a cut-off score of ≥ 3 symptoms endorsed was supported [156], whereas in a lower prevalence sample from a similar setting, a higher threshold of ≥ 9 was identified (albeit below 75% sensitivity) [223]. The Italian version of the PQ-B [248] (for details, see also supplementary materials [Appendix S4]) is based on gold standard methods recommended by the International Test Commission guidelines for translating and adapting tests [252].

Statistical Analysis

The overall validation procedure of the iPQ-B was mainly modelled on the methodological procedure adopted by Loewy and colleagues [156] to validate the original version of the PQ-B. Given that the PQ - in its different iterations - was not designed to make a distinction between UHR and full-blown psychosis but rather to determine whether individuals were experiencing at least APSs to a level where a more thorough evaluation was necessary [156], the sample was dichotomized as follows: CAARMS (+), that is, those participants who met CAARMS UHR/psychosis criteria and CAARMS (-), that is, those individuals who were below CAARMS UHR threshold.

Data were analyzed using the “Statistical Package for Social Science” 15.0 for Windows [192]. Additional statistical analysis was performed using the R package (version 3.5) [253]. After distributions of all quantitative variables were examined for violations of normality assumption, descriptive analyses included median and interquartile range (IQR) for not normally distributed parameters, and absolute and relative frequencies for categorical data. In between-group

comparisons on demographic, clinical and psychopathological characteristics, the Mann-Whitney U test was used for scale-ranked data and quantitative variables that were not normally distributed. Chi-square test with Yates' correction was also employed for categorical data.

As reliability measure, internal consistency of the iPQ-B was examined using Cronbach's statistics within the total sample. A score above 0.65 was considered sufficient internal consistency [224]. However, due to the limitation of Cronbach's alpha [254], Omega (ω) coefficient was also estimated [244].

Agreement between iPQ-B total scores and CAARMS outcomes was used to assess concurrent validity by generating Receiver Operating Characteristic (ROC) curves and calculating areas under the curve. In the total sample, we calculated diagnostic accuracy measures, that is, specificity, sensitivity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios (LR- and LR+) that balance sensitivity against specificity. In interpreting LRs, we followed Jaeschke and colleagues [225]: LRs of 0.5-2 altered pretest probability to a small (and rarely important) degree, LRs of 2-5 and 0.2-0.5 generated small (but sometimes important) changes in probability and LRs of 5-10 and 0.1-0.2 generated moderate shifts in pretest to posttest probability. Moreover, 2 other criteria were used to confirm optimal cut-off point from ROC curve, giving equivalent weight to specificity and sensitivity: (a) points on ROC curve closest to the point (0, 1) and (b) the Youden index (J) [228]. In detail, we calculated the distance (d) between the point (0, 1) and each cut-off point on ROC curve, and detected the point where this distance was minimal: $d = \sqrt{[(1\text{-sensibility})2 + (1\text{-specificity})2]}$. The Youden index (J) was the point on the ROC curve, which was farthest from random chance diagonal line and therefore maximized the difference between true positive rate (sensitivity) and false positive rate (1-specificity): J = max (sensitivity + specificity-1).

As additional measure of concurrent validity, the correspondence of positive results on the iPQ-B (at the different cut-offs) and on the CAARMS (i.e., a score ≥ 3 on at least 1 positive symptom item) was also examined using Cohen's kappa statistics. Finally, following the methodological approach employed by Loewy and co-workers [156] to validate the original version of the PQ-B, correlation analyses between iPQ-B total scores and PANSS/CAARMS subscale scores were performed using Spearman's correlation coefficient.

We also analyzed the effect of gender and age on iPQ-B scores, examining comparisons between males and females, and adolescents and young adults. Moreover, the association between age and iPQ-B scores was explored calculating Spearman's correlation coefficient. Finally, age-related differences on iPQ-B concurrent validity and diagnostic accuracy measures were performed generating ROC curves.

Lastly, the predictive validity of the iPQ-B was tested by consecutively identifying people with iPQ-B scores above the most suitable cut-offs identified in our sample, who did not meet CAARMS psychosis criteria at baseline. We calculated whether these different cut-off thresholds of iPQ-B scores had any predictive value regarding the development of a psychotic disorder according to CAARMS-defined criteria [38].

RESULTS

Sample characteristics and iPQ-B scores

Over the course of the study, 243 individuals (136 males, 56.0%) consecutively attended an intake interview within the ReARMS protocol. Age ranged from 13 to 35 years (median = 20.00 years, interquartile range = 17-25 years) and the level of education from 7 to 18 years (median = 11 years, interquartile range = 10-13). In the total sample, the distribution of age and level of education (in years) was skewed toward the right (respectively, skewness = 0.598 and 0.385; Kolmogorov-Smirnov test: $p < 0.001$).

Table 28 shows CAARMS screening outcomes, iPQ-B total scores and main demographic characteristics of the total sample and the two subgroups, that is, CAARMS (+) (n = 164) and CAARMS (-) (n = 79).

Table 28 - CAARMS criteria, iPQ-B total scores and sociodemographic characteristics in the total sample and the 2 subgroups.

	Total sample (n = 243)	CAARMS (–) (n = 79)	CAARMS (+) (n = 164)	χ^2/Z
Gender, males	136 (56.0)	40 (50.6)	96 (58.5)	1.351
Ethnic group, Caucasian	212 (87.2)	67 (84.8)	145 (88.4)	0.622
Mother tongue, Italian	220 (90.5)	74 (93.7)	146 (89.0)	1.343
Age	20.00 (17–25)	19 (16–27)	20 (17–25)	–0.120
Years of education	11.00 (13–13)	11.00 (10–13)	11.00 (10–13)	–0.108
iPQ-B symptom total score	7 (3–12)	4 (2–8)	8 (5–13)	–4.937*
iPQ-B distressing item total score	3.5 (1–7)	2 (0–3.25)	5 (2–9)	–5.592*
iPQ-B total distress score	23 (11–421)	13 (5.75–24.25)	30 (16–47)	–5.475*

* $p < 0.01$. Frequencies (and percentages), median (and interquartile range), chi-square (χ^2) test (with Yates' correction), and Mann-Whitney U test (Z) values are reported.

iPQ–B, Italian prodromal questionnaire – brief version; CAARMS, comprehensive assessment of at-risk mental states; CAARMS (+), individuals meeting or above CAARMS criteria; CAARMS (–), individuals below CAARMS criteria.

No significant between-group differences in terms of gender, ethnic group (Caucasian), mother tongue (Italian), age and years of education were found.

One-hundred-three participants met CAARMS FEP criteria. According to DSM-IV-TR criteria [178], 50 of these FEP patients were diagnosed with schizophrenia, 24 with affective psychosis (i.e. bipolar I or major depressive disorder with psychotic features) and 29 with a psychotic disorder not otherwise specified. Moreover, 61 participants met CAARMS UHR criteria. Most of these UHR individuals (n = 56, 91.8%) were considered at-risk for APS, 3 (4.9%) for BLIPS, and 2 (3.3%) for GRFD.

In comparison with CAARMS (-), CAARMS (+) individuals showed significantly higher iPQ-B symptom total scores, distressing item total scores and total distress scores (Table 28). The most significant value was shown by distressing item total score ($Z = -5.592$; $p < 0.001$). However, within the CAARMS (+) subgroup, no difference between UHR and FEP individuals in terms of iPQ-B total scores was found (symptom total score: median = 9, interquartile range = 5.50-13 vs. median = 8, interquartile range = 4-13; $Z = -0.767$, $p = 0.443$; distressing item total score: median = 5, interquartile range = 1-9] vs. median = 5, interquartile range = 2-9; $Z = -0.690$, $p = 0.490$; total distress score: median = 32, interquartile range = 16-47 vs. median = 29, interquartile range = 16-47; $Z = -0.429$, $p = 0.668$).

Reliability

Across the entire sample, iPQ-B total score (i.e. the total distress score) showed a Cronbach's alpha of 0.868 and an Omega coefficient of 0.895.

Concurrent validity and diagnostic accuracy measures

Diagnostic accuracy measures of iPQ-B are shown in Table 29. Using the original PQ-B symptom total score threshold of ≥ 3 [156], we found an excellent sensitivity value (∼91%), but a very poor specificity (28%). Cohen's kappa was 0.221, consistent with a poor agreement [229]. Similarly, the recommended original PQ-B total distress score threshold of ≥ 6 [156] showed 97% sensitivity, 24% specificity, and a Cohen's kappa value of 0.194.

In the present study, a cut-off of ≥ 20 on iPQ-B total distress score increased specificity up to 67%, while maintaining a sensitivity value of approximately 70%. It also showed better values in terms of Cohen's kappa (0.335), J (0.362) and d (0.416) that balanced the best sensitivity and specificity. Moreover, the recommended PQ-B distressing item total score threshold of ≥ 4 [218] slightly lost sensitivity (62%), but enhanced specificity up to 75%, with the best performance in terms of PPV (84%) and J (0.409).

When FEP patients were excluded from the analysis, a threshold of ≥ 21 on the iPQ-B total distress score appeared to be the best cut-off balancing sensitivity and specificity (Cohen's kappa = 0.411, J = 0.417, d = 0.365).

Table 29 - CAARMS diagnostic classification accuracy by iPQ-B cut-off scores within the total sample.

iPQ-B cut-off	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	Cohen's kappa	*J*	*d*
Symptom total score									
≥2	94.51 (89.84–97.46)	16.67 (9.18–26.81)	70.45 (68.20–72.61)	59.09 (39.21–76.38)	1.13 (1.02–1.26)	0.33 (0.15–0.74)	0.138	0.112	0.749
≥3	90.85 (85.36–94.79)	28.21 (18.59–39.53)	75.68 (69.66–75.61)	59.46 (44.64–72.64)	1.27 (1.09–1.47)	0.32 (0.18–0.59)	0.221	0.191	0.607
≥4	84.15 (77.64–89.37)	44.87 (33.59–56.56)	76.24 (72.21–79.85)	57.38 (46.69–67.42)	1.53 (1.24–1.88)	0.35 (0.23–0.54)	0.308	0.290	0.462
≥5	75.61 (68.30–81.97)	51.28 (39.69–72.67)	76.54 (71.89–80.63)	50.00 (41.55–58.55)	1.55 (1.22–1.98)	0.48 (0.34–0.67)	0.267	0.269	0.481
≥6	68.90 (61.22–75.89)	57.69 (45.98–68.81)	77.40 (72.15–81.90)	46.87 (39.61–54.28)	1.63 (1.23–2.15)	0.54 (0.40–0.73)	0.251	0.266	0.490
≥7	60.98 (53.06–68.49)	69.23 (57.76–79.19)	80.65 (74.51–85.59)	45.76 (39.85–51.80)	1.98 (1.39–2.83)	0.56 (0.44–0.72)	0.266	0.302	0.485
≥9	47.59 (39.72–55.49)	81.82 (72.16–89.24)	82.98 (75.26–88.65)	45.57 (41.25–49.26)	2.62 (1.63–4.19)	0.64 (0.54–0.76)	0.219	0.294	0.557
Total distress score									
≥4	96.34 (92.21–98.65)	14.10 (7.26–23.83)	70.22 (68.20–72.16)	64.71 (41.30–82.89)	1.12 (1.02–1.23)	0.26 (0.10–0.68)	0.131	0.104	0.774
≥6	92.07 (86.83–95.71)	24.36 (15.35–35.40)	71.90 (69.13–74.53)	59.38 (43.23–73.22)	1.22 (1.06–1.39)	0.33 (0.17–0.62)	0.194	0.214	0.601
≥13	80.49 (73.59–86.25)	48.72 (37.23–60.31)	76.74 (72.41–80.58)	54.29 (44.68–63.58)	1.57 (1.25–1.97)	0.40 (0.27–0.59)	0.300	0.292	0.458
≥15	76.22 (68.96–82.51)	52.56 (40.93–63.99)	77.16 (72.48–81.25)	51.25 (42.66–59.77)	1.61 (1.25–2.06)	0.45 (0.32–0.64)	0.286	0.288	0.463
≥16	75.61 (68.30–81.97)	53.85 (42.18–65.21)	77.50 (72.75–81.63)	51.22 (42.80–59.57)	1.64 (1.27–2.11)	0.45 (0.32–0.64)	0.291	0.295	0.457
≥17	73.17 (65.70–79.78)	58.97 (47.25–69.99)	78.95 (73.88–83.25)	51.11 (43.82–58.85)	1.78 (1.35–2.36)	0.45 (0.33–0.62)	0.309	0.321	0.437
≥18	71.34 (63.77–78.12)	60.22 (48.74–71.17)	79.05 (73.85–83.45)	50.00 (42.52–57.48)	1.80 (1.34–2.40)	0.48 (0.35–0.64)	0.300	0.316	0.444
≥19	70.73 (63.13–77.57)	64.10 (52.44–74.66)	80.56 (75.19–84.99)	51.02 (43.80–58.20)	1.97 (1.44–2.69)	0.46 (0.34–0.61)	0.326	0.348	0.421
≥20	69.51 (61.85–46.85)	66.67 (55.08–76.94)	81.43 (75.92–85.91)	50.98 (44.03–57.90)	2.09 (1.50–2.90)	0.46 (0.35–0.60)	0.335	0.362	0.416
≥21	67.07 (59.32–74.20)	65.43 (54.04–75.66)	79.71 (74.08–84.38)	49.53 (42.84–56.24)	1.94 (1.41–2.67)	0.50 (0.38–0.66)	0.319	0.350	0.432
≥23	61.59 (53.68–69.06)	71.79 (60.47–81.84)	82.11 (75.95–86.97)	47.06 (41.18–53.02)	2.18 (1.50–3.17)	0.54 (0.42–0.68)	0.293	0.334	0.464
≥25	57.32 (49.37–65.00)	75.64 (64.60–84.65)	83.19 (76.60–88.20)	45.74 (40.41–51.16)	2.35 (1.56–3.56)	0.56 (0.45–0.70)	0.281	0.330	0.486
≥29	51.83 (43.90–59.69)	79.49 (68.84–87.80)	84.16 (77.01–89.39)	43.97 (39.24–48.81)	2.53 (1.59–4.01)	0.61 (0.50–0.74)	0.258	0.313	0.524
≥31	47.56 (39.72–55.49)	80.77 (70.27–88.82)	83.87 (76.25–89.39)	42.28 (37.92–46.76)	2.47 (1.53–4.01)	0.65 (0.54–0.78)	0.229	0.283	0.561
Distressing item total score									
≥1	92.07 (86.83–95.71)	26.92 (17.50–38.16)	72.60 (69.68–75.33)	61.76 (46.07–75.34)	1.26 (1.09–1.45)	0.29 (0.16–0.56)	0.223	0.190	0.613
≥2	76.83 (69.61–83.05)	48.72 (37.23–60.31)	75.90 (71.41–79.89)	50.00 (41.10–58.90)	1.50 (1.19–1.89)	0.48 (0.33–0.68)	0.257	0.255	0.495
≥3	68.90 (61.22–75.89)	61.54 (49.83–72.34)	79.02 (73.64–83.55)	48.48 (41.38–55.65)	1.79 (1.33–2.42)	0.51 (0.38–0.87)	0.284	0.304	0.459
≥4	62.20 (54.30–69.64)	75.64 (64.60–84.65)	84.30 (78.10–88.90)	48.76 (42.98–54.98)	2.55 (1.70–3.84)	0.50 (0.40–0.63)	0.331	0.378	0.437
≥5	54.88 (46.93–62.65)	82.05 (71.72–89.83)	86.54 (79.68–91.33)	46.38 (41.50–51.32)	3.06 (1.86–5.01)	0.55 (0.45–0.67)	0.307	0.368	0.443
≥6	42.07 (34.42–50.02)	85.90 (76.17–72.94)	86.25 (77.90–91.78)	41.36 (37.58–45.25)	2.98 (1.68–5.31)	0.67 (0.58–0.79)	0.218	0.280	0.599

CAARMS, comprehensive assessment of at-risk mental states; iPQ–B, Italian prodromal questionnaire – brief version; PPV, positive predictive value; NPV, negative predictive value; LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; *J*, Youden index; *d*, distance between the point (0, 1) and each cut-off point on the ROC.

Furthermore, iPQ-B total scores were significantly correlated with all PANSS and CAARMS subscale scores (Table 30). Correlations with CAARMS subscales were higher than those with PANSS subscales. All iPQ-B total scores were also significantly correlated with dichotomized CAARMS diagnoses (i.e. CAARMS [+] vs CAARMS [-]).

Table 30 – Spearman's correlations among iPQ-B total scores, age, PANSS and CAARMS subscale scores.

iPQ-B total score	Symptom total score, ρ	Total distress score, ρ	Distressing item total score, ρ
PANSS scores			
Positive symptoms	0.339*	0.372*	0.370*
Negative symptoms	0.523†	0.174†	0.190†
General psychopathology	0.218†	0.262*	0.291*
CAARMS scores			
Positive symptoms	0.410*	0.438*	0.428*
Cognitive change	0.308*	0.364*	0.378*
Emotional disturbance	0.182†	0.205†	0.195†
Negative symptoms	0.178*,†	0.231*	0.271*
Behavioral change	0.178†	0.226*	0.239*
Motor/physical changes	0.094	0.131†	0.158†
General psychopathology	0.211†	0.264*	0.286*
CAARMS diagnoses (i.e. CAARMS [+] vs. CAARMS [–])	0.318*	0.353*	0.360*
Age	–0.229*	–0.215*	0.110

iPQ–B, Italian Prodromal Questionnaire – Brief version; PANSS, Positive and Negative Syndrome Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States. † $p < 0.05$, * $p < 0.001$. Spearman's rank correlation coefficient (ρ) values are reported.

In the present study, no effect of gender on iPQ-B scores was found. In contrast, age showed modest, yet significant, negative correlations with iPQ-B symptom total score and total distress score (Table 30). However, on a closer inspection, we discovered that no-age differences in iPQ-B scores appeared across developmental years (13-18), whereas a modest age-related decline intervened after 21 years. Moreover, younger adolescents (aged ≤ 15 years) showed significantly higher CAARMS "Perceptual Abnormalities" subscale scores (median = 3 [interquartile range = 1.25-4] vs median = 2 [interquartile range = 0-4]. Considering only participants aged ≤ 21 years, age-difference in CAARMS "Perceptual Abnormalities" subscores was replicated.

Finally, when only all the adolescent participants (i.e. aged < 18 years) were included in the analysis, a threshold of ≥ 24 on the iPQ-B total distress score appeared to be a promising cut-off balancing sensitivity and specificity related to CAARMS outcomes (Cohen's kappa = 0.365; PPV = 78%; J = 0.376; d = 0.396), with 72% sensitivity and 64% specificity.

Predictive Validity

Thirteen (i.e. about 18%) of 71 participants who had scored ≥ 20 on iPQ-B total distress score and did not meet CAARMS psychosis criteria at baseline, did not reach the 1-year follow-up assessment time. Eleven of these individuals had a follow-up period of < 1 year (median = 12 weeks [interquartile range = 8-35 weeks]). None of them developed an FEP. The other 2 participants went out of the ReARMS protocol catchment area and they could not be contacted for the follow-up assessment. After 12 months of follow-up, 5 (7%) of the 58 remaining individuals developed an FEP. However, considering a cut-off threshold of ≥ 4 on iPQ-B distressing item total score, the transition rate went up to 11% (i.e., 5/45 individuals completing 1-year follow-up period).

DISCUSSION

To the best of our knowledge, this is the first validation study of the Italian version of the PQ-B in a clinical help-seeking sample of adolescents and young adults. A previous psychometric study by Raballo and co-workers [246] conducted on 243 (109 males and 134 females) undergraduate students (mean age = 24 ± 3 years), revealed good internal consistency (0.820) and 1-month test-retest stability (0.890). The study also found that iPQ-B total distress score was related to measures of psychopathology, with greater association with measures of psychotic-like experiences. The present study is therefore a clinical conceptually extension of such results, as we examined iPQ-B psychometric properties in 243 help-seekers attending to child/adolescent or adult mental health care services.

In comparison with CAARMS (-), CAARMS (+) individuals showed significantly higher iPQ-B symptom total score, distressing item total score and total distress score. On a dimensional level - as expected on the basis of the PQ-B item composition - these results suggest that increasing PQ-B scores are associated with the severity of both psychotic and general psychopathology. No difference in iPQ-B total scores was found between UHR and FEP individuals. This result may be consistent with the fact that PQ-B is not designed to make a distinction between people at risk for psychosis and patients with a full-blown psychotic episode, but rather to determine whether subjects are experiencing at least APSs to a level where a more thorough evaluation is necessary [132, 218].

Reliability

We found excellent reliability of the iPQ-B with regard to internal consistency (Cronbach's alpha = 0.868; Omega coefficient = 0.895) of the recommended iPQ-B total distress score. Similarly, in a comparable adolescent/young adult help-seeking sample (age between 12 and 35 years), Loewy and co-workers [156] found an excellent PQ-B internal consistency with a Cronbach's alpha of 0.853.

Moreover, Xu and colleagues [255] showed an overlapping internal consistency (Cronbach's alpha = 0.897) in Chinese help-seeking individuals (aged 15-45 years) visiting a general mental health setting. Therefore, PQ-B appears to be reliably good in different samples and cultures.

Concurrent validity and diagnostic accuracy measures

Overall, iPQ-B showed good concurrent validity with interview-based CAARMS diagnoses. Indeed, it effectively differentiated between CAARMS (+)/FEP participants versus CAARMS (-) (i.e. non-psychotic spectrum) patients. In our help-seeking sample of adolescents and young adults, a threshold of ≥20 on a total distress score (range 0-105) appears to be a good cutoff, especially in terms of Cohen's kappa (0.335) and d (0.416), balancing 67% sensitivity with 70% specificity. However, the recommended PQ-B distressing item total score threshold of ≥ 4 (range 0-21) [218] can also be considered a promising cut-off. Although it slightly lost sensitivity (62%), its specificity went up to 75%, with the best performances in terms of PPV (84%) and J (0.409). These diagnostic accuracy measures of the iPQ-B are substantially comparable to those of the Italian version of the PQ-92 (sensitivity = 62%, specificity = 82%) [227], but slightly lower than those reported in other PQ-B validation studies, in which sensitivity values varied between 73 and 88% and specificity between 68% and 83% [156, 223, 251, 255].

However, according to Loewy and colleagues [156], since for screening purposes greater weighting should be given to sensitivity over specificity as part of a 2-step screening process, our sensitivity scores are quite low and mean that a certain number of people who would appropriate for early intervention are not being identified. Indeed, in most cases, having a few more false positives is less of an issue than missing appropriate individuals from a clinical perspective. Therefore, a lower cut-off value might be appropriate even if total accuracy statistics are slightly lower. In the current study, a cut-off of ≥ 4 on iPQ-B symptom total score showed a sensitivity of 84% with a specificity value of 45%. As an alternative, using a threshold of ≥ 13 on iPQ-B total distress score, sensitivity score went up to 80.5% in presence of 49% specificity. A higher sensitivity implies that full assessment burden can be considerably reducing with little impact on missing UHR/FEP individuals [242].

Furthermore, according to Savill and co-workers [218], our findings confirm that in UHR/psychosis-enriched samples with a low prevalence (< 40%) of UHR/psychosis individuals, a total distress score cut-off definitely higher than that proposed by Loewy and colleagues [156] must be recommended. In the present study, item distress assessment also appears to be more effective than total number of symptoms endorsed in identifying the most promising cut-off. Moreover, our finding that distress scores, as opposed to symptom total scores, are more accurate in preselecting

UHR/FEP individuals is consistent with much of the current literature [156, 157, 255] and is significant given current guidelines on early detection of psychoses [30].

Finally, the findings that iPQ-B total scores were significantly correlated with dichotomized CAARMS diagnoses (i.e., CAARMS [+] vs. CAARMS [-]) and with all PANSS and CAARMS subscale scores, are a further confirmation of good concurrent validity between iPQ-B and CAARMS outcomes. However, iPQ-B correlations with CAARMS subscores were higher than those with PANSS subscores, confirming - in line with their derivation from SIPS - that iPQ-B items are better phrased to capture attenuated rather than full-blown psychotic symptoms.

In our research, modest, although significant negative correlations between age and iPQ-B total scores were found on the whole sample.

However, consistently with a previous study on the Italian version of the iPQ-16 [204, 256], no age differences in iPQ-B scores were found in participants aged ≤ 21 years. On the contrary, in line with other studies [238, 257, 258], young adults (particularly those aged > 21 years) showed progressively lower scores on self-reported prodromal symptoms.

In our view, these findings do not automatically imply that higher attenuated symptoms are due to the allegedly broad diffusion of psychotic-like experiences among help-seeking adolescents [235, 257], but might be caused by other contextual factors, such as the different referral thresholds for child/adolescent and adult mental health services. Indeed, the referral threshold (for behavioral problems) to child/adolescent mental health services is slightly higher as compared to adult mental health services, and thereby it selects more clinically severe individuals Even if there is evidence suggesting that in adolescents, higher scores on self-report scales (such as the PQ-92) are less associated with UHR/FEP status [30, 257], we wish to emphasize that this higher prodromal scoring may also be one of the potential determinants of the early help-seeking behavior in clinical adolescent populations. In this regard, our younger adolescents showed the significantly higher levels on iPQ-B scores. Overall, this indicates that PQ-B requires age-adapted cut-off scores. Indeed, in our adolescent subsample, a threshold of ≥ 24 on iPQ-B total distress score - which was definitely higher than that (≥ 18) recommended in mixed adolescent/young adult populations [218] - appeared to be a promising cut-off.

Predictive Validity

After 12 months of follow-up, a percentage between 7 and 11% of participants who had scored above the most suitable iPQ-B cut-off thresholds identified in our sample (i.e. ≥ 20 on total distress score or ≥ 4 on distressing item total score) and did not meet CAARMS psychosis criteria at baseline, developed a FEP. When examining this result, some methodological peculiarities of the

current study shall be considered. Indeed, ReARMS is a clinically project providing evidence-based interventions that are supposed to be effective in UHR/FEP individuals (i.e., intensive case-management, family psycho-education, individual cognitive- therapy 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 treatments were not controlled (e.g., against placebo group or other treatments), but evenly delivered to all UHR/FEP participants. Thus, this could affect our current transition rate.

Limitations

First, a possible weakness of this study is that the iPQB was completed in a population "enriched" for the target diagnoses, that is, in a population of adolescent and young adult help-seekers with clinical features of possible psychosis and a decline in social functioning. Therefore, to avoid the risk of increasing false positive, these results should not be extended to broader help-seeking populations attending primary care settings or the general population, in which self-reported psychotic-like symptoms are allegedly not rare, although typically transient, not accompanied by distress (or treatment seeking), and not indicative of imminent transition to clinical psychosis [257]. Indeed, too many false positive would be identified.

Furthermore, any other potential sources of bias inherent to accuracy studies as suggested by the QUADAS tool (such as patient selection criteria, cut-off threshold pre-specification, drop-outs lost to follow-up) must be take into account [250, 251]. In particular, our sample has already been pre-screened using the Screening Schedule for Psychosis [185] and this could have significantly reduced the specificity of the iPQ-B, given a lot of easier to identify CAARMS (-) individuals who would have been removed from the following assessment. Moreover, this could also reduce the generalizability of our findings, given in most cases the iPQ-B would be the first-step screening tool (and not the second).

CONCLUSIONS

The Italian version of the PQ-B showed satisfactory psychometric properties. The iPQ-B had good concurrent validity with interview-based CAARMS diagnoses (potentially reducing the number of individuals to through in-depth clinical interviews) and predicted UHR/psychosis with good sensitivity and specificity that are comparable to its 92-item homologue [227]. For these reasons and its brevity, iPQ-B is a suitable, easily implementable for the systematic identification of help-seeking individuals that would benefit further exploration, particularly among adolescents and

young adults with low functioning. This could clearly facilitate rapid and appropriate referrals to UHR/FEP services that could shorten the DUP and improve the long-term prognosis [234].

STUDY 5

THE ITALIAN VERSION OF THE "COMPREHENSIVE ASSESSMENT OF AT-RISK MENTAL STATES" (CAARMS-ITA)

The approved Italian version of the comprehensive assessment of at-risk mental states (CAARMS-ITA): Field test and psychometric features

In the last two decades, there has been a broadening of research interest in timely recognition and phase-specific treatment of First-Episode Psychosis (FEP) to the pre-onset period or prodromal phase [13]. 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 [20, 35]. 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: (1) "Attenuated Psychotic Symptoms" (APS), which represent subthreshold, attenuated positive symptoms; (2) "Brief Limited Intermittent Psychotic Symptoms (BLIPS), which are transient psychotic symptoms that spontaneously remit within 1 week; and (3) "Vulnerability" (i.e. Genetic Risk and Functioning Deterioration syndrome [GRFD]), 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 sociodemographic risk features (age range: 14-30 years) with state and trait factors (APS, BLIPS, vulnerability) and help-seeking behavior [259]. The focus on help seekers is crucial as it mitigates the potential high number of false positives that might occur when assessing large asymptomatic community samples [68] (Ramella Cravaro & Raballo, 2014).

In the initial years of applying these criteria, approximately 40% of those identified as UHR subsequently developed an FEP within 12 to 30 months [36, 37]. 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% [260]. This decrease has also been empirically verified in a meta-analysis [214]. All the abovementioned 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 [38] to assist the timely identification, risk stratification and longitudinal monitoring of ARMS [261]. 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 [262].

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, which granted the copyright to the CAARMS-ITA in 2008. The CAARMS-ITA (a copy of which is available at https://doi.org/10.1111/eip.12669 [182] - supporting information) was later published under the aegis of the "Emilia-Romagna Regional Project on Early Detection in Psychosis" [170]. To the best of our knowledge, up until now, only pilot psychometric data, derived from a limited sample (i.e. 40 UHR, 10 FEP and 20 healthy controls), with an unofficial, non-authorized and not public Italian version of the CAARMS were published [263]. In this 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 [264] and the Arabic [262] versions of the CAARMS.

METHODS

Participants

All the participants (n = 223) were help seekers recruited through the "Reggio Emilia At-Risk Mental States" (ReARMS) program, 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 [170]. Referrals to ReARMS were mainly made by general practitioners (51%), hospital emergency rooms (22%), family members (15%) and 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 to 3 weeks [171].

The ReARMS team is specialized in identifying young people who are at UHR of developing psychosis as measured by the CAARMS-ITA. ReARMS inclusion criteria are: (1) young individuals seeking the help of a specialist; (2) aged between 13 and 35 years (this extended age range was modelled on the procedure adopted in validation studies of the Japanese and the Arabic version of the CAARMS); and (3) presence of UHR criteria defined by the CAARMS (i.e. APS, BLIPS and/or Vulnerability) or (4) DUP < 2 years in case FEP is detected in the assessment. The exclusion criteria were matched on the study of Miyakoshi and colleagues [264]: (1) 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) [178]; (2) history of previous exposure to antipsychotics; (3) current substance dependence; (4) known mental retardation (IQ < 70); and (5) 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 in the research gave their written informed consent to the psychopathological assessment, composed –among others [170] - by the CAARMS (approved Italian translation) [181] and the PANSS (approved Italian version) [247]. 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 ± standard deviation [SD] = 21.46 ± 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 [178] on the basis of the agreement between 2 trained ReARMS team members. After the interview, the participants were divided into 3 groups on the basis of the UHR criteria: UHR [+] group, FEP group and UHR [−] group (Table 31).

Table 31 – Demographic and clinical characteristics of the three groups.

Variable	UHR [+] (*n* = 55)	FEP (*n* = 104)	UHR [−] (*n* = 64)	Statistical test (X^2)	Post hoc test
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 (y)	11.15 (2.34)	11.75 (2.37)	11.23 (2.45)	1.53	–
DUI (wk)	47.97 (5.01)	48.87 (5.66)	49.15 (7.58)	1.45	–
PANSS					
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 [−]
CAARMS					
Positive symptoms					
Thought content	7.78 (4.54)	15.85 (5.75)	2.28 (2.02)	133.15*	FEP > UHR [+] > UHR [−]
Perceptual abnormalities	4.24 (3.07)	5.30 (5.72)	1.47 (2.29)	29.46*	FEP = UHR [+] > UHR [−]
Disorganized speech	3.16 (2.48)	4.86 (3.86)	1.17 (1.76)	43.49*	FEP > UHR [+] > UHR [−]
Huber's basic symptoms					
Cognitive change	9.80 (6.17)	13.62 (7.23)	4.34 (3.31)	64.43*	FEP > UHR [+] > UHR [−]
Emotional disturbance	4.64 (2.79)	4.99 (3.49)	1.86 (2.24)	37.67*	FEP = UHR [+] > UHR [−]
Avolition/apathy	3.15 (1.56)	3.33 (1.83)	1.42 (1.48)	45.40*	FEP = UHR [+] > UHR [−]
Impaired motor functioning	0.64 (1.21)	1.10 (1.46)	0.28 (0.83)	17.17*	FEP > UHR [−]
Impaired bodily sensation	1.02 (1.56)	1.09 (1.73)	0.95 (1.34)	0.01	–
Impaired autonomic functioning	1.22 (1.52)	1.42 (1.82)	1.28 (1.39)	0.24	–
Impaired tolerance to normal stress	2.91 (1.78)	3.01 (1.87)	2.20 (1.63)	11.04**	FEP > UHR [−]

CAARMS, Comprehensive Assessment of At-Risk Mental States. *P < .001; **P < .01. Frequencies and percentages, mean (SD) and statistic test (X^2) values are reported.

Among the UHR [+] group (n = 55), 36 participants met APS criteria, 14 met the APS and Vulnerability criteria, 2 met Vulnerability criteria, 2 met BLIPS criteria, and 1 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 to 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). These items can be clustered in 7 subscales, including some of Huber's basic symptoms: (1) Positive Symptoms (disorders of thought content, perceptual abnormalities, disorganized speech); (2) cognitive change, attention and concentration (subjective experience and observed cognitive change); (3) emotional disturbance (subjective emotional disturbance, observed blunted affect, observed inappropriate affect); (4) negative symptoms (alogia, avolition/apathy, anhedonia); (5) behavioral change (social isolation, impaired role functioning, disorganizing/odd/stigmatizing behavior, aggressive/dangerous behavior); (6) motor/physical changes (complaints of impaired motor functioning, impaired bodily sensation and impaired autonomic functioning); and (7) 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: (1) 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) [222] (the decline in functioning is calculated by subtracting the current GAF score from the highest GAF score in the past year; scores range from 1 to 100); (2) APS group: sub-threshold positive psychotic symptoms within the past 12 month; and (3) 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 [38], the threshold of a 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 3 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 [181], 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 interrater 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 the 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 3 major dimensions: (1) positive symptoms (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution, hostility); (2) 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 (3) general psychopathology (somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement 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 this study, we use the Italian version of the PANSS, which showed good psychometric properties [247].

Procedures

The overall validation procedure was consistent with the methodological approach employed by Miyakoshi and colleagues [264] and Braham and co-workers [262] to validate the Japanese and the Arabic versions of the CAARMS. In addition to their measures, we also assessed internal consistency.

The *interrater 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 ± SD: 19 ± 3.3 years). Initially, 3 psychologists were trained on the usage of the CAARMS through collective supervision by the main author of the approved Italian translation [181], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Preliminary administration of the instrument to suspected ARMS individuals was conducted before the study. Of the 3 raters, 2 were paired for each interview. Interrater agreement was also assessed for the UHR criteria. To better assess the 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 by evaluating between-group 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 [79, 265].

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. A total of 41 individuals were followed up for at least 1 year in the ReARMS protocol implemented in the Reggio Emilia Department of Mental Health: 24 subjects met the APS criteria, 12 met the APS and Vulnerability criteria, 2 met the Vulnerability criteria, 2 met the BLIPS criteria, and 1 met the BLIPS and Vulnerability criteria. All participants were provided with a comprehensive 2-year intervention package, which included a multi-element psychosocial intervention (combining individual Cognitive-Behavioral Therapy [CBT], psycho-educational sessions for family members and recovery-oriented case management). The prescription of antipsychotics was avoided unless the individual (1) had an imminent risk of suicide or severe violence, (2) was overwhelmed by psychotic symptoms, (3) was rapidly deteriorating or (4) did not respond to any other treatment. Low-dose atypical antipsychotics were used. Selective serotonin reuptake inhibitors 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 to 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 that 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 [192]. Intra-class correlation (ICC) coefficients were calculated to estimate interrater reliability, and the kappa coefficient was calculated to evaluate the interrater agreement on the diagnosis. We also used Cronbach's alpha coefficient to assess the internal consistency. Between-group comparisons were examined by using the Kruskal-Wallis test, and post-hoc analyses were performed 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 sociodemographic variables and the mean ratings of the CAARMS-ITA subscales, PANSS subscales and GAF are reported in Table 31. The three groups showed no differences with regard to 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) [180]. The groups were well matched with regard to sociodemographic variables.

Table 32 – Intra-Class Correlation (ICC) coefficients of the main CAARMS-ITA subscales (n = 30).

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

Reliability

The interrater reliability of the CAARMS-ITA total score was 0.91. Similarly, interrater reliability ranged from very good to excellent for all the 7 subscales and the 3 positive symptom items. The

individual ICC coefficients are reported in Table 32. The kappa coefficient for the agreement on the UHR criteria among the 3 raters was 0.85 ($p < .001$).

With regard to the internal consistency, 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 3 groups (Table 31). 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 3 groups in the PANSS "negative symptoms" and "general psychopathology" subscales scores (Table 31). 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, 5 of the 7 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 3 groups (Table 31). In detail, the scores of these 5 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 33. 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.

Table 33 – Spearman's correlation between CAARMS-ITA and PANSS (n = 223).

CAARMS	PANSS	ρ
Positive symptoms	Positive symptoms	.754*
Thought content	Delusions	.792*
Perceptual abnormalities	Hallucinatory behavior	.640*
Disorganized speech	Conceptual disorganization	.667*
Negative symptoms	Negative symptoms	.644*
Emotional disturbance	Negative symptoms	.653*
General psychopathology	General psychopathology	.649*

*$P < .001$. Spearman ρ correlation coefficient values are reported.

The predictive validity of the CAARMS-ITA was the core end-point measure of the current study. Of the 55 UHR [+] participants, 14 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 4 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. Of the 14 UHR individuals, the 7 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) [13]. Twenty-four (58.5%) of the UHR participants 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 period.

DISCUSSION

The aim of this study was to test the psychometric features of the approved Italian version of the CAARMS (CAARMS-ITA) [181]. 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 a comparison of results across research groups in different countries. Therefore, the concept of ARMS seems to exhibit generalizability across different cultures [262, 264].

Reliability of the Italian version of the CAARMS was assessed with respect to interrater reliability and internal consistency. The ICC coefficients of each CAARMS subscale showed good to

excellent reliability, in line with the original validation study by Yung and co-workers [38]. The interrater 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 interrater reliability of the UHR inclusion criteria defined by CAARMS-ITA was also confirmed to be satisfactory, as observed in the original validation study [38]. With regard to internal consistency, 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 regard 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 demonstrating that the magnitude of their positive symptoms is generally of moderate severity but less marked than in first-episode schizophrenia [266].

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 [267]. In this 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 [268]. 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 the criteria for ARMS usually present with other clinical concerns, particularly anxiety and depression, associated with a marked impairment in psychosocial functioning [263].

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 [265]. In line with our hypothesis, the severity of 5 of the 7 basic symptom subscales adopted in the CAARMS-ITA

was different across the 3 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 signaling the imminent risk of psychosis. However, specific instruments - such as the "Schizophrenia Proneness Instrument", available in adult and child-youth versions [86, 87] - are certainly more suitable for assessing basic symptoms in ARMS individuals, particularly in view of detecting COPER and COGDIS criteria for further risk stratification [30].

With regards to concurrent validity, this 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 the 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 version of the CAARMS [264]. Our results are also in line with the steady decrease in transition rates of UHR individuals observed across continents and institutions, declining to a 12-month rate of approximately 15% [269] (Hartmann et al., 2016). Nelson and co-workers [260], 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: (1) 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); (2) 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); (3) 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.]) [198]; and (4) 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 of psychosis was 21.7% after 1 year [263]. 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 and colleagues [67] 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 CBT 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 and co-workers [270] 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%) [264] and in a North American longitudinal study conducted on 291 subjects across 8 clinical research centers (35.1%) [37]. Our high prescription rate appears to be inconsistent with clinical practice guidelines, according to which psychological intervention (particularly 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 [13]. 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 [13]. 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 4 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 was 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 being 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 [263].

Finally, our follow up was limited to 1 year. Longer-term follow up is recommended to fully detect all the people who will later develop a psychotic episode [30, 67, 260].

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.

Adolescents at ultra-high risk of psychosis in Italian neuropsychiatry services: prevalence, psychopathology and transition rate.

Psychoses are one of the most severe causes of disability in adolescents [271]. In the past two decades, the research focus has moved from timely recognition and phase-specific treatment of First-Episode Psychosis (FEP) to the prodromal phase to detect early signs of the emerging disorder before full-blown symptoms occur [68]. In this context, two different sets of clinical high-risk (CHR) criteria are currently used for early detection of psychosis, regardless of age [30]. A specific subset of criteria, called "Ultra-High Risk" (UHR), was proven to identify three subgroups of individuals with prospectively high (but not inevitable) imminent risk of developing psychosis [272]. Those are: (a) "attenuated psychotic symptoms" (APS), which represent sub-threshold-attenuated positive symptoms; (b) "brief limited intermittent psychotic symptoms (BLIPS), which are transient psychotic symptoms that spontaneously remit within 1 week; and (c) "genetic risk and functioning deterioration syndrome" (GRFD), 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 sustained for at least 1 month. Alternatively, the basic symptoms (BS) criteria were developed to detect the risk for psychosis as early as possible in the development of the disorder, ideally before functional impairment appeared [125]. These criteria require two or more cognitive disturbances (COGDIS) or at least one cognitive or perceptive basic symptom (COPER) [30]. BS refer to subjectively experienced subclinical disturbances in drive, affect, thinking, speech, body as well as sensory perception, motor action, central vegetative functions, and stress tolerance [78].

These two complementary approaches to the characterization of the CHR state of psychoses have been both developed and validated mainly in adults [273]. In a recent meta-analysis, CHR criteria were associated with pooled 1-year conversion rates of 15% for UHR criteria, 25% for COGDIS, and 14% for COPER in predominately adult samples, with lower conversion rates in UHR adolescent samples compared to adult or mixed older adolescent-young adult samples [30]. The detection of children and adolescents at true risk for psychosis may be more challenging using the UHR criteria, given the ongoing age-related developmental processes that can sometimes mimic the clinical presentation of APS or BLIPS [274]. Results from a general population study suggested that APS, especially perception-related APS, were more prevalent in subjects aged < 16 years compared to 16–40-year olds, showing decreasing clinical relevance of APS for psychosocial functioning with decreasing age [275]. However, as BS compared to UHR criteria may have at least equal predictive

power for psychosis [30] and as their combination seems to increase predictive power [276], assessing BS may be particularly helpful in children and adolescents [273].

Anyway, the clinical applicability of the UHR criteria is still under investigation in adolescents [277]. In particular, it is not clear whether these criteria can reliably be applied to this population and how predictive they are of a transition to psychosis [278]. Furthermore, the prevalence of UHR individuals in this age group is not yet completely defined. A systematic review of six epidemiological and five clinical data sets showed that the prevalence of hallucinatory experiences in adolescents ranges from 5 to 9% [279]. However, the prognostic and clinical significance of these symptoms is not comparable with what is observed in help-seeking adolescents meeting UHR criteria. Indeed, in the young general population, sub-threshold psychotic symptoms are usually associated with a very low yearly risk of transitioning to psychosis, approximately around 0.6% [280], only a fraction of the 15% estimated in a recent meta-analysis on young UHR samples at 1-year follow-up period [30].

Early detection and intervention in psychosis are less widespread in Italy than in other European countries. Some pilot programmes have focused specifically on high-risk young adults [166]. Very few specific services for UHR adolescents in Italy have been reported in the literature to date. Among them, a feasibility study on identifying children and adolescents at UHR of developing psychosis conducted by Spada and colleagues [277] in an Italian neuropsychiatry service within the "Mondino" National Neurological Institute (Pavia) and a 12-month psychosis-predictive study performed by Armando and co-workers [271] at the Child and Adolescent Neuropsychiatry unit of the Children Hospital "Bambino Gesù" (Rome) should be mentioned. To the best of our knowledge, no study has explored the predictive validity of UHR criteria in relation to BS criteria in an Italian help-seeking adolescent population.

Aim of the present study is to (1) examine the clinical relevance of a UHR diagnosis in help-seeking adolescents to assess whether a specific UHR service for adolescents could be implemented in the Italian health care system, particularly within the framework of child and adolescent neuropsychiatry units, which usually deal with both general psychiatric and neurological problems in the paediatric population; (2) describe prevalence and severity of positive, negative, general, and basic symptoms in UHR adolescents in relation to FEP and non-UHR (those who did not meet criteria for UHR or FEP diagnosis) adolescents; and (3) investigate the predictive validity of UHR criteria in relation to BS criteria.

METHODS

Participants

All the participants (n = 90) were adolescent help-seekers recruited between 09/2012 and 12/2015 through the "Reggio Emilia At-Risk Mental States" (ReARMS) project, an outpatient early detection infrastructure developed under the aegis of the "Regional Project on Early Detection in Psychosis" within all of child and adolescent neuropsychiatry units of the Reggio Emilia Department of Mental Health [170], which has a semi-urban catchment area of approximately 550,000 inhabitants. They were all individuals aged 13–18 years with signs or symptoms suggesting a FEP or a UHR state for psychosis, referred to ReARMS team for assessment, diagnosis and possibly early intervention. Referrals to ReARMS were mainly performed by general practitioners (GPs), school and social services, family members, and hospital emergency rooms.

The ReARMS team is specialized in identifying young people who may be at ultra-high risk of developing psychosis as measured by the Italian versions of the "comprehensive assessment of at-risk mental states" (CAARMS-ITA) [181]. ReARMS inclusion criteria were: (a) specialist help-seeking; (b) age between 13 and 18 years; and (c) presence of UHR criteria defined by the CAARMS (i.e., APS, BLIPS, and/or GRFD) [22] or (d) DUP ("Duration of Untreated Psychosis") < 2 years in case FEP is detected in the initial assessment (therefore, in the present study FEP patients with a DUP > 2 years were not included). Adolescents not meeting one or more of the above-mentioned UHR criteria were included either in the UHR [-] group (those under the threshold of the CAARMS inclusion criteria) or in the FEP group (those found to meet the CAARMS criteria for psychosis) [22]. Exclusion criteria for all groups were: (a) history of past 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) [178]; (b) history of previous exposure to antipsychotics; (c) current substance-induced mental disorder or substance dependence; (d) known mental retardation (premorbid IQ < 70); and (e) neurological disorders, head injury or any other medical condition that could justify their psychiatric symptoms.

All adolescents entering the ReARMS protocol and/or their parents agreed to participate to the research and gave their written informed consent to the psychopathological assessment, composed - among others [171] - by the CAARMS-ITA (approved Italian translation) [181], the "Positive and Negative Syndrome Scale" (PANSS) (approved Italian version) [247], and the "Schizophrenia Proneness Instrument, Child and Youth version" (SPI-CY) (approved Italian translation) [87]. All individuals assessed in this research were native speakers of Italian. Relevant ethical and local NHS research and development approvals were sought for the study.

Instruments

The *CAARMS* [38] 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 h 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, and disorganized speech); (b) "cognitive change, attention and concentration" (subjective experience and observed cognitive change); (c) "emotional disturbance" (subjective emotional disturbance, observed blunted affect, and observed inappropriate affect); (d) "negative symptoms" (alogia, avolition/apathy, and anhedonia); (e) "behavioral change" (social isolation, impaired role functioning, disorganizing/odd/stigmatizing behavior, and 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, and 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 [38]. UHR status is defined as follows: (a) GRD 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 "Children's Global Assessment Scale" (CGAS), Italian version [281] (the decline in functioning is calculated by subtracting the current CGAS score from the highest CGAS score in the past year; scores ranges from 1 to 100); (b) APS group: sub-threshold 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 (i.e. without antipsychotic medications). According to the psychosis criteria defined by the CAARMS [38], 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 h on each occasion.

The ReARMS team routinely uses the CAARMS in the initial assessment to determine whether an individual meets UHR criteria. These assessments are conducted by specialized personnel including clinical psychologists and neuropsychiatrists, who were trained in the administration of the CAARMS by the main author of the approved Italian translation [181], who was trained at Orygen YRC in Melbourne. Regular CAARMS collective supervision sessions and scoring workshops ensured the inter-rater reliability of these assessments. However, no CAARMS inter-rater reliability measures were carried out.

The PANSS is a 30-item scale specifically designed to assess the severity of psychotic symptomatology, subdivided into three major psychopathological dimensions: (a) "positive symptoms" (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution, and 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, and 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 used the Italian version of the PANSS [24], which has been widely used in the literature to assess psychotic symptoms in adolescent population [247], showing good psychometric properties.

The two BS criteria (COGDIS and COPER) and their 14 constituting BS (i.e. disturbances of abstract thinking, inability to divide attention, disturbance of expressive speech, captivation of attention by details of the visual field, thought interference, thought pressure, disturbance of receptive speech, thought perseveration, thought blockage, decrease ability to discriminate between ideas and perception or fantasy and true memories, unstable ideas of reference, derealization, visual perception disturbances, and acoustic perception disturbances) were assessed using the SPI-CY, Italian version [87]. Overall, the instrument consists of four subscales: adynamia, perception disturbances, neuroticism, and thought and motor disturbances. The SPI-CY showed good acceptability by children and adolescents, and good discriminant validity plus good reliability across trained raters and different settings [282]. The ReARMS team members routinely use the SPI-CY in the initial assessment to determine whether an individual meets BS criteria. They were trained in the administration of the instrument by the main author of the approved Italian translation [87]. Regular SPI-CY collective supervision sessions and scoring workshops ensured the inter-rater reliability of these assessments. However, no SPI-CY inter-rater reliability measures were carried out.

Procedures

All adolescents entering the ReARMS protocol underwent an extensive diagnostic assessment [170]. The axis I diagnosis was made at baseline according to DSM-IV-TR [178] on the basis of the agreement between two trained ReARMS team members. Using the CAARMS and the SPY-CY, the ReARMS team determined whether these individuals met the UHR (GRFD, APS, and/or BLIPS) and/or BS (COPER and COGDIS) criteria. According to CAARMS criteria, between-group

comparisons of demographic, clinical and psychopathological characteristics were carried out. In the current study, we calculated the "duration of untreated illness" (DUI) as the interval (in weeks) between the onset of a clinically relevant psychiatric symptom and the beginning of the first psychological and/or psychopharmacological intervention [180].

All UHR or FEP help-seekers referred to the ReARMS protocol were assigned to a multi-professional micro-equipe, including a child/adolescent neuropsychiatrist, a clinical psychologist, and a case-manager for early rehabilitation, generally within 2–3 weeks. According to their symptoms, those individuals were then provided with a comprehensive 2-year intervention package which included pharmacological treatment and a multi-element psychosocial intervention (combining individual cognitive-behavioral therapy [CBT], psychoeducational sessions for family members, and recovery-oriented case management). They were followed up for1 year after baseline assessment and repeated measures were collected (every 6 months).

According to the current guidelines (such as those of the European Psychiatry Association) [15], in the ReARMS protocol psychosocial interventions were targeted to treat UHR individuals as first-line treatment. These interventions mainly combined individual CBT based on the phase specific model developed by Garety and colleagues [190] (at least 20 sessions in the first year) and family psycho-education (at least 15 sessions over 12 months with each individual family) within the framework of assertive community treatment. The prescription of antipsychotics was avoided unless the UHR 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 second-generation antipsychotics were used (mean risperidone equivalent dose = 2.00 ± 0. 73 mg/day). Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia.

The predictive validity of the UHR criteria was tested by consecutively identifying UHR [+] people according to CAARMS criteria [38]. During the first year of treatment, the participants were usually followed up weekly or after every 2–3 weeks, in accordance with their clinical needs. We calculated the rate of transition to psychosis at 12 months from baseline. Frank psychosis was defined according to the established CAARMS psychosis criteria [38]. Finally, we investigated BS criteria in relation to UHR criteria.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) 15.0 for Windows [192]. Baseline data were examined using descriptive statistics. Descriptive analyses

included mean values and standard deviation (SD) for continuous variables, and absolute and relative frequencies for categorical variables.

The cross-sectional analyses on demographic and clinical characteristics of the sample were assessed with ANOVA, using Fisher's least significant difference (LSD) to correct for multiple comparisons involving normally distributed variables. The Kruskal-Wallis test and the Mann-Whitney U tests for post hoc analyses were used for clinical and psychopathological variables that were not normally distributed. A Chi-square test and Fisher's exact test were employed for categorical variables. Fisher's exact test was used when any expected frequency was less than 1 or 20% of expected frequency was less than or equal to 5.

RESULTS

Over the course of the study, 79 adolescents (41 males and 38 females; mean age ± standard deviation [SD] = 15.20 ± 1.40) consecutively attended an intake interview within the ReARMS protocol in child and adolescent neuropsychiatry services of the Reggio Emilia Department of Mental Health. The remaining 11 patients were excluded for a history of previous exposure to antipsychotics (n = 5), a FEP with a DUP > 2 years (n = 4), and a known mental retardation (n = 2). The majority of these individuals were referred by GPs (38%), school and social services (19%), family members (12.7%), hospital emergency rooms (11.7%), private practitioners (2.5%), or they were self-referred (15.2%).

CAARMS results

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 34). Among the UHR [+] group (n = 25 [31.6%]), seventeen met APS criteria, five met APS and GRD criteria, one met GRD criteria, one met BLIPS criteria, and one met BLIPS and GRFD criteria. According to DSM-IV-TR, they were diagnosed with psychotic disorder not otherwise specified (n = 10), major depressive disorder (n = 8), brief psychotic disorder (n = 4), and schizotypal personality disorder (n = 3).

The FEP group (n = 11 [13.9%]) consisted of patients with a first episode of DSM-IV-TR schizophrenia (n = 5), affective (bipolar or major depressive disorder) psychosis (n = 3), or psychotic disorder not otherwise specified (n = 3).

The remaining 43 participants (54.4%) were below the threshold for being considered at risk of developing psychosis and were grouped in the UHR [-] group. They were diagnosed with depressive disorders (n = 20), anxiety disorders (n = 18), somatoform disorders (n = 3), and adjustment disorders (n = 2).

Demographic, clinical and psychopathological characteristics

The socio-demographic variables and the mean ratings of the CAARMS subscales, PANSS subscales and CGAS are reported in Table 34. The three groups showed no differences on gender, age, years of education, and DUI. The groups were well matched with regards to socio-demographic variables.

Table 34 – Demographic, clinical and psychopathological characteristics of the three groups.

Variable	UHR[−] ($n = 43$)	UHR[+] ($n = 25$)	FEP ($n = 11$)	Statistics (F/X^2)	Post hoc test
Gender (males)	23 (53.5%)	12 (48.0%)	6 (54.6%)	0.23	–
Age	15.35 (1.41)	14.76 (1.33)	15.64 (1.36)	2.07	–
Education (in years)	11.05 (2.48)	10.20 (0.71)	10.36 (1.96)	1.66	–
DUI (in weeks)	30.15 (7.58)	27.97 (5.01)	28.87 (5.60)	1.71	–
CGAS	55.84 (7.84)	46.56 (7.53)	36.95 (9.82)	30.48*	FEP = UHR[+] < UHR[−
PANSS					
Positive symptoms	9.67 (2.99)	14.24 (4.23)	19.72 (6.81)	32.68*	FEP > UHR[+] > UHR[−
Negative symptoms	11.30 (4.91)	18.52 (8.48)	20.64 (8.96)	19.59*	FEP = UHR[+] > UHR[−
General psychopathology	30.81 (5.64)	36.88 (8.72)	40.91 (10.92)	18.86***	FEP = UHR[+] > UHR[−
CAARMS					
Positive symptoms	4.51 (4.14)	15.52 (6.39)	27.64 (15.15)	45.64*	FEP > UHR[+] > UHR[−
Unusual thought content	0.88 (1.14)	2.72 (1.49)	3.73 (2.57)	25.46*	FEP = UHR[+] > UHR[−
Non-bizarre ideas	1.02 (1.24)	2.56 (1.63)	4.82 (2.40)	26.54*	FEP > UHR[+] > UHR[−
Perceptual abnormalities	0.81 (1.18)	2.80 (1.22)	3.82 (2.27)	33.60*	FEP = UHR[+] > UHR[−
Disorganized speech	0.81 (1.26)	2.20 (1.58)	2.73 (2.33)	15.46*	FEP = UHR[+] > UHR[−
Huber's basic symptoms					
Cognitive change	2.40 (1.22)	2.88 (1.48)	4.27 (1.42)	12.50***	FEP = UHR[+] > UHR[−
Emotional disturbance	1.23 (1.29)	2.68 (1.77)	2.79 (2.17)	13.38**	FEP = UHR[+] > UHR[−
Avolition/apathy	1.30 (1.32)	2.76 (1.66)	3.45 (1.51)	21.57*	FEP] > UHR[−]
Impaired motor functioning	0.28 (0.85)	0.64 (1.38)	1.27 (1.68)	6.57*	FEP > UHR[−]
Impaired bodily sensation	0.56 (1.19)	1.19 (1.42)	2.36 (1.81)	10.87**	FEP > UHR[−]
Impaired autonomic functioning	1.60 (1.42)	1.12 (1.54)	1.64 (2.38)	1.35	–
Impaired tolerance to normal stress	2.16 (1.62)	2.32 (1.99)	3.27 (1.90)	3.36	–
Negative symptoms					
Observed blunted affect	0.70 (1.22)	2.00 (1.89)	3.00 (2.24)	15.46*	FEP = UHR[+] > UHR[−
Observed inappropriated affect	0.51 (1.14)	0.88 (1.24)	1.73 (2.24)	4.38	–
Alogia	0.47 (0.98)	1.88 (1.72)	2.36 (2.16)	18.26*	FEP = UHR[+] > UHR[−
Anhedonia	1.51 (1.40)	3.04 (1.64)	3.45 (1.57)	20.94*	FEP = UHR[+] > UHR[−

Frequencies (percentages), mean (standard deviation), and statistic test (F/X^2) values are reported

* $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$

There was significant between-group difference in CGAS scores (Table 34). In detail, CGAS score of the FEP and UHR [+] individuals were significantly lower than those in the UHR [-] participants. Moreover, although global functioning was lower in the FEP group than in the UHR [+] individuals, the difference was not significant (p = 0.230).

The PANSS "positive symptoms" subscale scores were different among the three groups (Table 34). 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.

Furthermore, there were significant differences among the three groups in the PANSS "negative symptoms" and "general psychopathology" subscale scores (Table 34). In detail, the PANSS "negative symptoms" and "general psychopathology" subscale score of the FEP and UHR [+] groups were significantly higher than those in the UHR [-] participants. However, although negative symptoms and general psychopathology were more severe in the FEP group than in the UHR [+] individuals, the differences were not significant ($p = 0.235$ and $p = 0.436$, respectively).

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 bodily sensation) showed significant differences among the three groups (Table 34). In details, 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 and emotional disturbance. Finally, FEP patients experienced subjectively higher cognitive change and emotional disturbance than those in the UHR [+] group, but the differences were not significant ($p = 0.456$ and $p = 0.258$, respectively).

The severity of UHR symptoms as measured by the CAARMS are reported in Table 34. The most intense symptoms experienced by UHR [+] individuals were anhedonia and perceptual abnormalities, followed by avolition/apathy and unusual thought content.

Transition rate

Five of the 25 UHR [+] participants did not complete the 12-month follow-up period. Four of these individuals had a follow-up period of less than 1 year; the other participant moved out of the ReARMS protocol catchment area and could not be contacted for the follow-up assessment. After 12 months of follow-up, 2 of the 20 remaining UHR [+] participants (10%) had transitioned to full-blown psychosis and had been prescribed antipsychotics during the follow-up period. None of these individuals had received specific psychological support (individual CBT and psychoeducational sessions for family members) in addition to recovery-oriented case management. Both individuals needed to be hospitalized during the follow-up.

Out of the remaining 18 UHR [+] participants who did not convert to full-blown psychosis, 11 (55%) were still satisfying inclusion criteria for ARMS at the end of the follow-up: seven subjects met the APS criteria, three met APS and GRFD criteria and one met BLIPS and GRFD criteria. The remaining seven UHR[+] adolescents (35%) went under the threshold of the CAARMS inclusion

criteria, becoming subjects not at clinical high risk of developing psychosis: all of these individuals had received specific psychological support (individual CBT and psychoeducational sessions for family members) in addition to case management. None of the UHR[+] participants who did not convert to full-blown psychosis needed to be hospitalized during the follow-up period. No UHR [-] participants developed a psychotic episode over the follow-up time.

Antipsychotics were prescribed to 5 (25%) UHR [+] participants during the 12-month follow-up period (2 [100%] individuals with psychotic transition vs 3 [16.7%] without psychotic transition). Only three of the 18 UHR [+] individuals who did not progress to psychosis were still being prescribed antipsychotics at 12 months.

BS criteria

Altogether, 37 (46.8%) participants met both COGDIS and COPER criteria, 4 (5.1%) met only COGDIS criteria and 14 (17.7%) only COPER criteria (Table 35). In the UHR [+] group, 20 (80%) met COGDIS and COPER criteria and 5 (20%) met only COPER criteria. All of UHR [+] individuals met COPER criteria.

Table 35 – SPI-CY basic symptoms in the total sample and the three groups.

BS criteria	Total ($n = 79$)	UHR[−] ($n = 43$)	UHR[+] ($n = 25$)	FEP ($n = 11$)	Statistics (X^2)	Post hoc test
COGDIS (items 1-9)	41 (51.9%)	10 (23.3%)	20 (80.0%)	8 (72.7%)	23.49*	FEP = UHR[+] > UHR[−]
COPER (items 5-14)	51 (64.6%)	16 (37.2%)	25 (100%)	10 (90.9%)	31.12*	FEP = UHR[+] > UHR[−]
Thought disturbances	9.68 ± 11.12	4.11 ± 5.37	15.28 ± 12.37	18.72 ± 13.21	21.11*	FEP = UHR[+] > UHR[−]
Perception disturbances	5.72 ± 5.95	3.06 ± 4.03	8.64 ± 6.36	9.45 ± 6.65	19.50*	FEP = UHR[+] > UHR[−]

Thought disturbance items included in BS criteria
1. Inability to divide attention
2. Captivation of attention by details of the visual field
3. Disturbance of expressive speech
4. Disturbances of abstract thinking
5. Thought interference
6. Thought blockage
7. Thought pressure
8. Disturbance of receptive speech
9. Thought perseveration

Perception disturbance items included in BS criteria
10. Unstable ideas of reference
11. Decreased ability to discriminate between ideas/perception, fantasy/true memories
12. Derealization
13. Visual perception disturbances
14. Acoustic perception disturbances

COGDIS cognitive disturbances: at least two symptoms with a SPI-CY score of ≥ 3 within the last 3 months. *COPER* cognitive perceptive, *BS* at least one symptom with a SPI-CY score of ≥ 3 within the last 3 months and first occurrence ≥ 12 months ago. Frequencies (percentages), mean (standard deviation), and statistic test (X^2) values are reported

* $p < 0.001$

Compared to UHR [-] group, both FEP and UHR [+] individuals were more likely to meet COGDIS and COPER criteria, and had more severe thought and perception disturbances. FEP and UHR [+] participants did not differ regarding COGDIS and COPER criteria, and severity of thought and perception disturbances.

Seven of the 33 non-FEP participants who met COGDIS criteria (COGDIS [+]) had a follow-up period of less than 1 year. After 12 months of follow-up, 2 of the 26 remaining COGDIS [+] individuals (7.7%) had transitioned to full-blown psychosis. Eight of the 41 non-FEP participants who met COPER criteria (COPER [+]) did not complete the 12-month follow-up period.
Seven of these individuals had a follow-up period of less than 1 year; the other participant moved out of the ReARMS protocol catchment area and could not be contacted for the follow-up assessment. After 12 months of follow-up, 2 of the 33 remaining COPER [+] individuals (6.1%) had transitioned to full-blown psychosis. This is to say that the two UHR [+] participants who transitioned to full-blown psychosis after 12 months of follow-up, met also both COGDIS and COPER criteria at baseline. They had been prescribed antipsychotics during the follow-up period and had received no specific psychological support (individual cognitive-behavioral therapy and psychoeducational sessions for family members) in addition to case management.

DISCUSSION

Answering the call for more studies addressed to examine if current CHR criteria and approaches have tailored to the special needs of children and adolescents and the distinctive developmental features in the early detection of psychosis [283], the present study explored the clinical relevance of a UHR diagnosis in a help-seeking adolescent population to assess whether a specific UHR service for adolescents could be implemented in the Italian health care system, particularly within the framework of child and adolescent neuropsychiatry units, which usually deal with both psychiatric and neurological problems in the paediatric population. We also described severity of positive, negative, general, and basic symptoms in UHR adolescents in relation to FEP and non-UHR (with other non-psychotic disorders) peers. Finally, we investigated the predictive validity of UHR criteria in relation to BS criteria.
All in all, we showed that the use of the Italian version of the CAARMS [181] to diagnose UHR individuals is not only feasible but also clinically meaningful for a comprehensive assessment [277]. Indeed, it enabled to identify a sample of adolescents with a very high probability of developing psychosis within a short period of time.

CAARMS results

The first aim of the current study was to test the clinical relevance of a UHR diagnosis in an adolescent age group referred to Italian neuropsychiatry services. The prevalence of the UHR diagnosis among the pool of individuals entering the ReARMS protocol (31.6%) is in line than that reported in other studies dealing with mixed older adolescent-young adult population

(approximately 35%) [214]. However, our UHR prevalence is lower than that described by Spada and co-workers [277] in a sample of child and adolescents assessed in neuropsychiatry services in Italy (44%). This difference could be explained by the fact that in their study, the patients were referred mainly by specialists (i.e. with specific mental health competence) from a first-level child and adolescent neuropsychiatry units.

On the contrary, referrals to ReARMS were mainly performed by GPs, school and social services, family members, and hospital emergency rooms. Furthermore, our findings are in line with those reported by Kelleher and colleagues [284] in a systematic review and meta-analysis of 19 population-based studies, in which psychotic symptoms were found to be relatively common in adolescence (the median prevalence was 7.5% among adolescents aged 13-18 years). To understand our higher prevalence (31.6% for UHR [+] and 13.9% for FEP individuals), we need to consider that our sample was made up of a clinical population of adolescent help-seekers (aged 13-18 years) who spontaneously accessed medical services and who showed more severe symptoms than the ones revealed by the review of the above-mentioned population studies.

In a context of extensive and increasing evidence relating to UHR status for psychosis, our results confirm that a specific UHR service or outpatient infrastructure for early detection and intervention in adolescents at risk for psychosis (such as the ReARMS protocol implemented in the Reggio Emilia Department of Mental Health) [170] is feasible and can easily be integrated into the Italian health care system and within the framework of national neuropsychiatry services [277]. In Italy, early interventions in psychosis are less widespread than in other European and non-European countries [166]. Therefore, our preliminary findings, if replicated in even larger samples, should be taken into careful consideration in the future organization of neuropsychiatry services at national and local level. To date, Italian neuropsychiatry services are more often composed of only local outpatient units which receive first-level referrals (mainly from GPs) of patients aged 0-18 years presenting with general neurological and/or psychiatric symptoms.

The Italian version of the CAARMS [181] appears to be easy to administer to adolescents aged 13 years and over, causing no significant distress and discomfort. Possible caveats to the use of the CAARMS for the identification of UHR individuals in the above clinical setting include the need to promote the service across mental health units and GPs, to ensure active cooperation between units, and to allow sufficient time for the semi-structured interview [277]. Despite these caveats, the CAARMS was still judged useful and helpful by all the ReARMS team members for defining the diagnosis (particularly in borderline cases) and giving a more comprehensive and detailed profile of the patient's symptomatology [277].

Clinical and psychopathological characteristics

At the time of accessing the ReARMS protocol, UHR [+] adolescents had a significantly higher level of functioning impairment (as measured with CGAS scores) than did UHR [-] peers. Moreover, although global functioning was lower in the FEP group than in UHR [+] individuals, the difference was not significant. Our findings confirm that the UHR status is a clinical condition characterized by marked psychosocial impairment [285]. Given that young people with ARMS are already functionally impaired at baseline, the risk of stigmatization should be carefully weighed up against the need to provide them with support, irrespective of their longitudinal outcome [274, 277].

In the present study, the most severe symptoms experienced by UHR [+] individuals were anhedonia and perceptual abnormalities, followed by avolition/apathy and unusual thought content. Recent research has highlighted the importance of attenuated psychotic symptoms not only for the increased risk of psychosis, but also in relation to a wide variety of non-psychotic comorbid Axis I disorders [214]. In the study by Spada and colleagues [277], the vast majority (90%) of their UHR [+] adolescents presented with at least one comorbidity on Axis I or II. In detail, mood disorder was the most frequent diagnosis (50%), followed by anxiety disorder (23%). These findings were in line with the results of a population study by Kelleher and co-workers [284], who showed that UHR [+] adolescents reporting psychotic symptoms were at particularly high risk of having multiple co-occurring diagnoses and presented a high prevalence of comorbid depression (40%) and anxiety (15%). Affective and anxiety disorders are the most frequent comorbidities in UHR [+] samples at initial examination [214].

In line with these results, major depression was the most frequent comorbid Axis I diagnosis (28%) in our UHR [+] group, followed by anxiety disorders (12%). Therefore, our findings confirm that attenuated psychotic symptoms may also be important markers of concurrent psychopathology outside the psychotic domain [277]. Generally, the fact that people meeting UHR criteria already suffer from multiple mental and functional disturbances for which they seek help, underscores that these clinical categories identify a group of patients with an unclear trajectory who require evaluation and help, with conversion to psychosis just being one of the several relevant outcomes [286]. However, several authors suggested the hypothesis that mood dysregulation may be a core feature of an impending psychosis and that it may even precede the onset of attenuated positive psychotic symptoms [277]. Furthermore, the UHR features may be superimposed on other spectra, such as affective bipolar and personality disorder, with the result that the global picture is even more blurred in adolescents than in adults [277]. In fact, according to Olvet and co-workers [287], the UHR state for psychosis in adolescents may be indistinguishable from the bipolar prodrome. However, although prodrome onset has been less explored in bipolar disorder (BD), research

suggests the existence of a specific bipolar prodrome [288]. In particular, mood lability and changes in energy level seem to be both common among people with BD and more specific to BD than other symptoms, such as irritability and anxiety [289]. Moreover in a recent meta-analysis of symptom prevalence prior to initial or recurrent mood episodes, van Meter and co-workers [290] found that most people appeared to experience multiple prodromal symptoms that were attenuated forms or constellations of the mood episode that developed, which could have provided an opportunity to identify symptom profiles with a greater predictive validity (e.g., the most common symptoms before an initial manic episode were too much energy, talkative, racing thoughts, elated mood, decreased need for sleep, irritable mood, hyperactive, and overproductive/goal directed).

In the current study, 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 [266].

The severity of the PANSS "negative symptoms" and "general psychopathology" subscales 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 as compared to ARMS individuals [267]. In the present study, the PANSS-negative symptoms and general psychopathology were more severe in the FEP group than in the UHR [+] individuals, but the differences were not significant. Such a result confirms that people with ARMS often present negative symptoms and general psychopathology profiles that share similarities in severity with that of FEP patients and that significantly limit their psychosocial functioning. Indeed, high levels of negative symptoms, significant impairments of academic performance and occupational functioning, and difficulties with interpersonal relationships are often together observed both in FEP that UHR individuals [268]. Furthermore, although our sample is too small to allow the drawing of significant conclusion, this finding is in line with studies by McGorry and colleagues [67] and Piskulic and co-workers [291], who suggested that negative symptoms represent earlier features which mark the prodromal phase in adolescence. Follow-up studies evaluating negative, disorganization and general symptoms in mixed samples of adolescents and young adults already reported an association between negative and disorganization symptoms and conversion to psychosis [292]. This finding suggests that these psychopathological domains might facilitate prediction of psychosis in CHR samples and further differentiate UHR [+] from UHR [−] individuals, in particular in terms of symptom severity [273].

The CAARMS contains several items that assess Huber's basic symptoms, which are thought to be prominent in ARMS individuals and patients with schizophrenia [30]. The severity of five of the seven basic symptom subscales adopted in the CAARMS was different across the three groups. In particular, the scores of the subscales relating to subjective experience of cognitive change and emotional disturbance 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" and "emotional disturbance" subscales in signalling the imminent risk of psychosis. However, specific instruments, such as the "schizophrenia proneness instrument, child and youth version" (SPI-CY) [87] are certainly more suitable for assessing BS in ARMS adolescents, particularly in view of detecting COPER and COGDIS criteria for further risk stratification [30].

Transition rate

We followed up our UHR [+] sample for 1 year and measured the predictive validity of the Italian version of the CAARMS. We found a risk of developing psychosis of 10% over 12 months, which is consistent with the 7% 1-year transition rate recently reported by Welsh and Tiffin [274] in a sample similar in age and size. Furthermore, our result is in line with the cumulative 2-year transition risk of 15% found in UHR [+] adolescents by Ziermans and co-workers [126]. However, our transition risk was lower than those observed in other Italian studies conducted in UHR [+] adolescent populations. Using a survival analysis, Spada and colleagues [277] recently found a cumulative 1-year transition risk of 26.7% in a group of 22 UHR [+] participants aged 12-18 years. Moreover, in a 1-year follow-up study, Armando and co-workers [271] showed that the 20% of 35 UHR [+] individuals (age 9-17 years) had developed schizophrenia. In comparison with these findings, we need to keep in mind that our data were collected in a sample of slightly older adolescents (aged 13 years upwards).

In the present study, the antipsychotic prescription rate in UHR [+] group (25%) was lower than those reported by Spada and co-workers [277] (45.5%). We found that 3 of 5 UHR [+] participants who received antipsychotics did not progress to psychosis during the follow-up period. On the contrary, the remaining two UHR [+] individuals developed psychosis in spite of receiving antipsychotic medications. Therefore, as implicit in their pharmacodynamic effects, antipsychotics could have delayed or avoided the conversion to psychosis in some of those UHR [+] participants. However, only three of the 18 UHR [+] participants who completed the 12-month follow-up period without developing psychosis, were still being prescribed antipsychotics. This might suggest that the continuous prescription of antipsychotics to people with ARMS is not always necessary, especially if multi-element psychosocial intervention was provided.

As commonly observed in other paediatric UHR samples [273], the finding that adolescents without a psychotic disorder received off-label antipsychotic treatment requires critical appraisal. Clinicians should carefully consider the use of antipsychotics that is often in lieu or without prior use of psychosocial treatments, latter of which have even been found to be effective in youth and young adults with ARMS [293]. Care in the use of antipsychotics is clearly in order, given their documented potential for acute and long-term side effects [294] and given the limited data supporting their early use, even if intended toward psychosis prevention [273]. Based on the fact that prospective data clearly suggest that only a minority of people with ARMS transition to a full sychotic disorder over 1-3 years, clinicians may require additional information regarding the inadvisability of first-line antipsychotic use in this population that ought to receive psychosocial interventions first-line instead of, or at least before antipsychotics [30], as well as targeted, evidence-based treatment for non-psychotic disorders if they are distressing or impair functioning [273].

However, in the current study, despite treatment offered during the follow-up period, a substantial proportion of adolescents at UHR for psychosis transit to the full-blown disorder, suggesting the need for more effective intervention in this population [277]. Although this picture suggests that the majority of Italian people with ARMS will not develop a psychotic disorder (at least within the first year after presentation), the purpose of clinical management at this state is not solely to prevent the later onset of a full-blown psychosis but also to ameliorate the presenting symptoms and problems, which are often more of a concern to the individual than their long-term risk of transition [214].

BS criteria

As commonly observed in other adolescent and adult studies, UHR and BS criteria frequently co-occurred [276]. In the present study, 20 (80%) of 25 UHR [+] individuals met COGDIS and COPER criteria and 5 (20%) met only COPER criteria (i.e. all of our UHR [+] adolescents also met COPER criteria at baseline). Compared to UHR [-], both FEP and UHR [+] groups were more likely to meet COGDIS and COPER criteria and reported a greater severity of the thought and perception disturbances included in BS criteria. However, FEP and UHR [+] participants did not differ regarding COGDIS and COPER criteria, and thought and perception disturbances. These findings, linking BS to the psychotic spectrum, are consistent with earlier studies of remitted psychotic adolescents who more frequently reported thought and perception disturbances than adolescents with other psychiatric disorders [295]. However, these studies only assessed presence, but not severity of BS, and did not consider UHR status. Studies of adolescents that compared BS between CHR individuals and non-psychotic psychiatric in- and outpatients also found higher

prevalence and severity of BS in CHR patients [273, 282]. Thus, COGDIS and COPER criteria may be particularly useful in the early detection of UHR adolescents, given the fact that UHR may present with different psychiatric diagnoses, especially major depression, which typically do not predict transition to psychosis [37]. Furthermore, a meta-analysis of studies in individuals at CHR for psychosis recently confirmed that BS criteria strongly increased the odds of identifying early prodromal phases of schizophrenia-spectrum psychoses as opposed to affective psychoses [296].

After 12 months of follow-up, two (7.7%) of 26 COGDIS [+] and two (6.1%) of 33 COPER [+] participants had transitioned to full-blown psychosis. This is to say that the two UHR [+] individuals who had transitioned to full-blown psychosis after 12 months of follow-up, also met both COGDIS and COPER criteria at baseline. These findings suggest that the co-occurrence of UHR and BS criteria may increase the predictive power to detect true prodromal individual who later will develop psychosis. Thus, a combined assessment of early subjective disturbances with observable APS may improve the accuracy of psychosis prediction [273].

They had been prescribed antipsychotics during the follow-up period and had received no specific psychological support (individual cognitive-behavioral therapy and psychoeducational sessions for family members) in addition to case management. Future studies will need to replicate and extend our results in larger adolescent samples.

Following 57 adolescents meeting UHR or COGDIS criteria for 2 years, Ziermans and colleagues [126] found that 15.6% converted to psychosis, with the highest conversion in those meeting both UHR and COGDIS criteria (21.9%). However, compared to 1-year COPER and COGDIS conversion rates in adults (approximately 14 and 25%, respectively, in a recent meta-analysis) [30], our findings are clearly lower, consistent with recently reported low pooled conversion rates in adolescent UHR samples [30, 273]. Furthermore, according to Ziermans and co-workers [126], adolescents are at least three times more likely to have remitted from their CHR state than to develop full-blown psychosis. Lower psychotic conversions in adolescents might also relate to an age-dependent lower clinical significance and higher prevalence of CHR symptoms in children and adolescents compared to adults, which may introduce an age bias in younger individuals around age 15 and 16 [274]. While the presence and the nature of an age cut-off for BS have not been studied, future studies also should examine age effects in clinical and non-clinical populations [273]. Moreover, future research should more closely examine the role of pharmacologic and psychosocial treatment effects on conversion and remission as well as related predictors of risk factors [273]. This need to examine treatment effects also arises in naturalistic studies, as – like in our sample - CHR samples frequently receive medications, including antipsychotics [37].

Limitations

Major methodological limitations of the current study are well acknowledged. First, the small UHR [+] sample size (79 individuals in total, including 25 UHR [+] participants) limited our statistical power to detect true prodromal individual who later developed psychosis. Indeed, the major factor in determining the predicted power of CAARMS and BS criteria 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 CAARMS and BS criteria in the Italian community may be lower than those reported in our research.

Moreover, our UHR [+] participants were also receiving some specific psychological 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 [214]. 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 adolescents. Therefore, in the current follow-up study, the 1-year conversion rate is not exactly equivalent to the predictive value of UHR and BS criteria alone. In addition, because of the observational nature of the study, our results cannot be directly generalized to other prodromal services. Furthermore, our follow-up was limited to 1 year. Long-term follow-up is recommended to fully detect all the people who will later develop a psychotic episode [30].

Finally, in our research, interviews were conducted close to the time of intake (i.e. still within a rather acute state of FEP). While this enabled a reliable distinction between UHR and FEP individuals, this timing might impair reliable assessment of BS that is known to attenuate in the acute psychotic phase [79].

CONCLUSIONS

Despite these limitations, our results show that the identification of adolescents at UHR for psychosis within Italian neuropsychiatry services is feasible and clinically relevant. Both attenuated psychotic symptoms and BS were more prevalent and clinically relevant in FEP and UHR [+]

adolescents than in UHR [-] group. Moreover, BS criteria correlated well with UHR criteria. Given the uncertain outcome of adolescents at CHR of psychosis [30], future research is needed to determine whether the combined assessment of early subjective disturbances with observable APS can improve the accuracy of psychosis prediction [273].

STUDY 6 - THE ITALIAN VERSION OF THE ABERRANT SALIENCE INVENTORY

The approved Italian version of the Aberrant Salience Inventory (ASI): field-test and psychometric properties in a clinical sample of young community help-seekers with early psychosis.

The concept of "*Aberrant Salience*" (AS) was systematized by Kapur (2003) [297] at the beginning of this century. In an influential overview article, he proposed aberrant salience as a conceptual bridge linking the neurobiology (brain), the phenomenological experience (mind) and the pharmacological aspects of psychosis (especially schizophrenia) into a unitary framework [298]. Although the presumed pharmacological and neurobiological (i.e. mainly dopaminergic) components of such hypothesis have not yet been fully confirmed on an empirical level [299], the experiential aspects of AS (i.e. the abnormal attribution of significance to otherwise neutral stimuli resulting in a specific alteration of the figure-background structure of the experiential field) have been recursively acknowledged as potential catalyzers for the development of full-blown psychosis [158].

Since the early description of classical European psychopathology, it is now well known that the prodromal phase of primary delusion is often marked by an impending feeling of meaning that moves from the experiential background, which, previously tacit and familiar, starts to be filled with self-referential and disturbingly salient details, although not yet articulated (e.g. persecutory threats) [93]. With the psychotic transformation of experience, the perceptual background subsequently becomes more intrusive and saturated, with meaningful details that accelerate and trigger the development of abnormal significance attribution [300]. In this sense, AS therefore may be considered as a central and promising construct for the profiling of vulnerability to psychosis [301], particularly in the context of a multiple-gate screening strategy targeting help-seeking adolescents and young adults [186]. Although there is substantial evidence of a continuum in the risk of psychosis from psychosis proneness and subclinical symptoms towards full-blown psychotic episodes [103], mapping AS might enrich the characterization of such continuum [298].

Assessment instruments for AS

AS can be explored through both neurocognitive (i.e. task-based) and experiential (i.e. questionnaire-based) assessment. For example, the Salience Attribution Test (SAT) aims to evaluate the attribution of salience to task-relevant and task-irrelevant stimuli [302]. By its nature, the SAT

is costly and time-consuming, and therefore can be applied to small sample only [298]. As larger populations are necessary to investigate dispositional AS as a risk factor for attenuated psychotic psychopathology, more parsimonious and time-saving tools (such as self-report questionnaire) are needed [240]. To date, the *Aberrant Salience Inventory* (ASI) is the only one self-report instrument available for measuring trait AS.

Developed by Cicero et al. (2010) [158], the ASI was initially conceptualized to assess lifetime occurrence of AS. The reliability and validity of its scores have demonstrated to be good in several USA samples [303]. As self-report tools are sensitive to the cultural context (i.e. they may be affected by differences in language) [304], the cross-cultural adaptation of the ASI in a different country is a necessary preliminary step to assure its generalizability as a measure of the AS construct. In this sense, Preti and Raballo (2011) [305] performed the cultural adaptation of the ASI into Italian (Italy speaks a different language than the USA, and its cultural and socio-economic background is different as well). The ASI translation accuracy was then confirmed and optimized with the help of Cicero and coworkers. This approved Italian version of the ASI showed good reliability and convergent/divergent validity in an Italian nonclinical sample of undergraduate students [306].

Starting from this background, the *aim* of the current study was to investigate the reliability and the validity of the approved Italian version of the ASI in a clinical population of adolescent and young adult help-seekers with First Episode Psychosis (FEP) or at Ultra-High Risk (UHR) of psychotic disorder. Moreover, a Confirmatory Factor Analysis (CFA) was conducted to evaluate the adequacy of the theoretical 5-factor model proposed in the original validation study of the ASI [158]. To the best of our knowledge, up until now, only pilot psychometric data, derived from a limited clinical sample (i.e. 48 psychiatric outpatients [13 with schizophrenia, 12 with major depression, 7 with anxiety disorder and 4 with eating disorder] compared to 64 healthy individuals recruited from the general population), with an unofficial, non-authorized Italian version of the ASI were published [307].

METHODS

Setting

As detailed in Raballo et al. (2014) [171], the "Reggio Emilia At-Risk Mental States" (ReARMS) program is an early detection and intervention infrastructure implemented in the Reggio Emilia Department of Mental Health since September 2012. The ReARMS protocol aims (a) to detect individuals with FEP and at UHR of psychosis according to well-defined diagnostic criteria [38] among adolescent and young adult community help-seekers and (b) to provide evidence-based

interventions that are shown to be effective in FEP/UHR subjects (i.e. individual Cognitive-Behavioral Therapy [CBT], psychoeducational sessions for family members, intensive case management, and pharmacotherapy [as appropriated]) [170, 188].

Participants

Psychometric properties of the approved Italian version of the ASI were tested in a sample of help-seeking (i.e. voluntarily sought treatment) adolescents and young adults, aged 13-35 years, consecutively recruited within child/adolescent and adult mental health services of the Reggio Emilia Department of Mental Health between September 2012 and December 2018. Referrals were mainly performed by General Practitioners, emergency room and general hospital, family members, school, social services, or they were self-referred [172].

For the specific purpose of this study, ReARMS inclusion criteria were: (a) specialist help-seeking; (b) age between 13 and 35 years; (c) presence of UHR criteria as defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS) [38] or (d) a Duration of Untreated Psychosis (DUP, defined as the time interval [in weeks] between the onset of a full-blown psychotic symptom and the administration of the first pharmacological treatment) [179] < 2 years in case FEP is detected at baseline assessment. Specifically, three different subgroups of UHR mental states was identified: (a) Genetic Risk and Functioning Deterioration Syndrome (GRFD), a trait/state risk condition in which the individual has a family history of psychosis (in first-degree relatives) or manifests schizotypal personality disorder along with a low functioning maintained for ≤ 1 month; (b) Brief Limited Intermittent Psychotic Symptoms (BLIPS), i.e. transient positive symptoms that spontaneously disappear within 1 week (i.e. without pharmacological treatment); and (c) Attenuated Psychotic Symptoms (APS), i.e. sub-threshold positive psychotic symptoms [38]. According to the CAARMS diagnostic criteria, FEP threshold is defined by operationalized clear-cut levels of full-blown positive symptoms occurring for the first time for > 1 week, either daily or > 3 time a week with each symptom continuing for > 1 hour on each occasion [38]. Young help-seekers who were below the UHR/FEP threshold were considered as CAARMS negative cases (i.e. CAARMS-).

Exclusion criteria were: (a) history of previous full-blown psychotic episodes, either schizophrenic and affective, as defined in the Diagnostic and Statistical Manual of mental disorders, IV Edition, Text Revised (DSM-IV-TR) [178]; (b) past exposure to antipsychotics; (c) current substance dependence, in accordance with DSM-IV-TR criteria [178], (d) known mental retardation (IQ < 70), (e) neurological disorders (such as temporal lobe epilepsy), head injury or any other medical condition associated with psychiatric symptoms; and (f) insufficient fluency in the Italian language. Specifically, in the ReARMS program we considered previous exposure to antipsychotic

medication (i.e. before ReARMS enrollment) as an equivalent of past psychotic episode. Indeed, according to the CAARMS psychosis criteria [38], the threshold of FEP is essentially that at which antipsychotics would probably be commenced in common clinical practice.

All help-seekers entered the ReARMS protocol and their parents (if minors) agreed to participate to the research and gave their informed consent to the psychopathological assessment prior to their inclusion in the study. Relevant local ethical approvals were sought for the study. The current research has been carried-out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experimental protocols including humans.

Instruments

In the current study, the psychopathological assessment was composed by the CAARMS (approved Italian version [CAARMS-ITA]) [181], the ASI (authorized Italian translation) [305] and the Schizotypal Personality Questionnaire – Brief version (SPQ-B) (approved Italian adaptation) [308].

The *CAARMS* is a semi-structured clinical interview specifically developed to evaluate different aspects of attenuated psychopathology as well as functioning (via the integrated SOFAS ["Social and Occupational Functioning Assessment Scale"] module) [38]. It consists of 27 items (each one rated in terms of intensity [0-6] and frequency/duration [0-6]) that can be clustered in 7 main subscales: (a) "Positive Symptoms"; (b) "Cognitive Change, Attention and Concentration"; (c) "Emotional Disturbance"; (d) "Negative Symptoms"; (e) "Behavioral Change"; (f) "Motor/Physical Changes"; and (g) "General Psychopathology". 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. CAARMS interviews are conducted by specialized clinical psychologists and psychiatrists, trained by the main author of the approved Italian translation (CAARMS-ITA) [181], who was trained at Orygen, The National Centre of Youth Mental Health in Melbourne, Australia. Regular CAARMS supervision sessions and scoring workshops ensured the inter-rater reliability of these assessments. Specifically, the CAARMS-ITA showed good to excellent inter-rater reliability [182, 183].

The *ASI* [158] is a 29-item self-report with a "yes-no" (1-0) format. Items are expected to group into 5 correlated subscales: (a) "Feelings of Increased Significance" (items: 1, 5, 10, 15, 16, 21 and 27), (b) "Sense of Sharpening" (items: 3, 9, 12, 18 and 22), (c) "Impending Understanding" (items: 2, 6, 11, 17 and 29), (d) "Heightened Emotionality" (items: 8, 14, 20, 24, 26 and 28) and (e) "Heightened Cognition" (items: 4, 7, 13, 19, 23 and 25). Scores are assigned by summing the "yes" replies. In the original validation studies by Cicero et al. (2010) [158], the ASI highly discriminated people

with psychosis proneness from controls. Standard procedures were used to translate the ASI into Italian language [304]. Specifically, Preti and Raballo (2011) [305] translated the original English version of the ASI as in Cicero et al. (2010) [158]. This first Italian version was then back-translated into English, and translation accuracy was confirmed by an English-speaking translator and optimized with the help of Cicero and co-workers [298]. The final Italian version of the ASI (for details, see also supplementary materials [Appendix S5]) showed excellent reliability and good convergent, divergent and discriminant validity in an Italian nonclinical sample of undergraduate students [306].

The *SPQ-B* [309] is a brief (22-item) self-report screener for the Schizotypal SPD dimensions (i.e. "Cognitive-Perceptual Deficits", "Interpersonal Deficits and "Disorganization"). This questionnaire is recommended prior to a confirmatory clinical interview [309]. However, its scores significantly correlated with independent clinical ratings of DSM-IV-TR schizotypal personality traits, indicating good to excellent criterion validity [310]. In this research, we used an Italian translation adapted from the original English version [308], which showed good psychometric properties in Italian clinical samples of young people with FEP or at UHR of psychosis [310].

Procedures and statistical analysis

All the participants entered the ReARMS program underwent an extensive diagnostic and psychopathological assessment [170, 171]. The axis-I diagnosis was made according to DSM-IV-TR criteria [178] at least by two trained ReARMS team members using the Structured Clinical Interview for DSM-IV-TR axis I disorders [184]. After CAARMS interviews, adolescent and young adult help-seekers were divided into three groups according to UHR/psychosis criteria: (a) UHR group (i.e. APS, BLIPS and GRFD), (b) FEP group, and (c) CAARMS- group (i.e. those individuals under the threshold of the CAARMS inclusion criteria) [38].

All the UHR/FEP individuals referred to the ReARMS program were assigned to a multi-professional team including a psychiatrist, a clinical psychologist and a case-manager for early rehabilitation, generally within 2-3 weeks. According to their symptoms, UHR/FEP subjects were then provided with a comprehensive 2-year intervention package including (a) a multi-element psychosocial intervention (combining individual CBT, psychoeducational sessions for family members, and a recovery-oriented case management) and/or (b) a pharmacological treatment (as appropriate), according to the current guidelines on the topic [13, 176, 188]. Specifically, the prescription of antipsychotics was avoided unless UHR individuals (a) had an imminent risk of suicide or severe violence, (b) were overwhelmed by abruptly worsening full-blown psychotic symptoms, (c) were rapidly deteriorating in daily functioning, or (d) did not respond to any other

treatment. Low-dose atypical antipsychotics were commonly used. Selective serotonin reuptake inhibitors or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia [170].

The overall validation process of the Italian version of the ASI was modeled on the methodological procedure adopted by Cicero et al. (2010) [158] to validate the original English version of the instrument. Data were analyzed using the Statistical Package for Social Science (SPSS) 15.0 for Windows [192] and R version 3.5.3 [253] with "Psych" and "Lavaan" software packages [311, 312]. Continuous parameters were reported as mean ± standard deviation, whereas categorical variables as absolute frequencies and percentages. All tests were two-tailed, with significance level (α) set at 0.05. Due to non-normality (Kolmogorov-Smirnov test with Lilliefors significance correction: $p < 0.05$) [192] in all explorations, nonparametric statistics were used.

In inter-group comparisons, categorical data were analyzed with Chi-square or Fisher's exact test, as appropriate (i.e. when any expected frequency was < 1 or 20% of expected frequency was ≤ 5). The Kruskal-Wallis and the Mann-Whitney U test (as post-hoc procedure with Holm-Bonferroni correction for multiple comparisons) [313] were used to compare ordinal variables.

In the current study, we measured short-term test-retest *reliability* of the Italian version of the ASI over two weeks calculating Spearman's correlation coefficients of ASI total score and individual ASI item subscores [307] on a subsample of 35 consecutive FEP participants. This rather short-time interval was chosen to limit the possible impact of both symptomatic changes and memory effects [314]. As further reliability measure, internal consistency of the Italian version of the ASI was investigated using Cronbach's alpha within the total sample. A score above 0.70 was considered sufficient internal consistency [244]. Moreover, we examined how each ASI item correlated with the total score. Correlations less than $r = 0.30$ indicated that the item might need to be removed from the questionnaire to make it more reliable [244]. Finally, we were interested in Cronbach's alpha value if each ASI item was deleted. If the α value went up after item deletion, removal of such item should be considered to ameliorate the reliability of the instrument [244].

A CFA was also performed to evaluate the adequacy of the 5-factor structure proposed in the validation study of the original English version of the ASI within the total sample, using the robust weighted least squares (WLSMV) estimator. The WLSMV does not assume normally distributed variables and provides the best option for modeling ordinal data in moderately large samples [315]. The criterion of Brown (2006) [316] was applied to assess CFA results: it recommends the use of 4 common indices to evaluate fit of the overall model and to calculate both the satisfactory global functioning and the model adjustment: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). According to Hu and Bentler (1999) [318], the following general rules of thumb

were used in the current research: TLI/CFI > 0.95 (good fit), 0.90-0.95 (borderline fit) and < 0.90 (poor fit); RMSEA < 0.06 (good fit), 0.06-0.08 (fair fit), 0.08-0.10 (borderline fit) and > 0.10 (poor fit); SRMR < 0.08 (good fit) and > 0.08 (poor fit).

As measure of concurrent *validity*, correlation analyses of ASI total score with CAARMS "Positive Symptoms" dimension, CAARMS "Anhedonia" item and SPQ-B subscale scores were also performed in the total sample, using Spearman's correlation coefficient with Holm-Bonferroni correction to revise p-value for multiple comparisons [313]. Specifically, we examined the convergent validity by testing if the ASI total score was positively correlated with positive symptoms and SPQ-B subscores. Moreover, we explored the divergent validity by testing whether ASI scores were less strongly correlated with anhedonia than SPQ-B measures. In addition, we examined any relevant association of the ASI total score with sociodemographic characteristics (i.e. gender, age, and years of education) and Duration of Untreated Illness (DUI, defined as the time interval [in weeks] between the onset of a prominent psychiatric symptom and the administration of the first pharmacological/psychological treatment) [180] in the total sample, using Mann-Whitney U test or Spearman's correlation coefficients, as appropriate.

In the total sample, agreement between the ASI total score and CAARMS outcomes (i.e. FEP/UHR vs CAARMS-) was also used to assess concurrent validity by generating the Receiver Operating Characteristic (ROC) curve and calculating the area under the ROC curve (AUC). According to Hosmer et al. (2013) [266], we interpreted the AUC as follows: AUC $\leq$ 0.5 (no discrimination), 0.51-0.69 (unacceptably low), 0.70-0.79 (acceptable), 0.80-0.89 (excellent) and $\geq$ 0.90 (outstanding). Moreover, we calculated diagnostic accuracy measures (i.e. specificity, sensitivity, positive and negative predictive values [PPV and NPV] and positive and negative likelihood ratios [LR- and LR+] that balance sensitivity against specificity). In interpreting LRs, we followed Jaeschke et al. (1994) [225]: LRs of 0.5-2 altered pretest probability to a small (and rarely important) degree, LRs of 2-5 and 0.2-0.5 generated small (but sometimes important) changes in probability and LRs of 5-10 and 0.1-0.2 generated moderate shifts in pretest to posttest probability. Moreover, two other criteria were used to confirm optimal cut-off point from ROC curve, giving equivalent weight to specificity and sensitivity: (a) points on ROC curve closest to the point (0, 1) and (b) the Youden index (J) [228]. In detail, we firstly calculated the distance (d) between the point (0, 1) and each cut-off point on the ROC curve, and subsequently detected the point where this distance was minimal: $d = \sqrt{[(1\text{-sensibility})^2 + (1\text{-specificity})^2]}$. The Youden index (J) was the point on the ROC curve that was farthest from random chance diagonal line and therefore maximized the difference between true positive rate (sensitivity) and false positive rate (1-specificity): J = max (sensitivity + specificity – 1).

Finally, the 1-year predictive validity of the ASI was tested by consecutively identifying people with baseline ASI total score above the most suitable cut-offs identified in our total sample, who at the same time did not meet CAARMS psychosis criteria at the initial assessment. In detail, we examined whether these different cut-off thresholds of the ASI total score had any predictive value regarding the development of a psychotic disorder (i.e. a FEP) according to CAARMS-defined diagnostic criteria [38].

RESULTS

Sample characteristics and ASI scores

Over the course of the study, 204 individuals (122 [59.8%] males, 181 [88.7%] white Caucasian, 182 [89.2%] with Italian as mother tongue) consecutively attended an intake interview within the ReARMS program. Age at entry ranged from 13 to 35 years (mean age = 21.23 ± 5.85 years), level of education from 7 to 18 years (mean level of education = 11.65 ± 2.41 years), and the DUI from 4 to 208 weeks (mean DUI = 70.95 ± 62.41 weeks). In the total sample, the distribution of age, years of education (in years) and DUI (in weeks) was skewed towards the left (skewness = 0.660, 0.187, and 0.918, respectively; Kolmogorov-Smirnov test with Lilliefors significance correction: $p < 0.001$, for all explorations). Table 36 shows ASI total scores, sociodemographic and clinical characteristics of the total sample and the three subgroups, i.e. FEP (n = 104; 51.0% of the total sample), UHR (n = 45; 22.1%), and CAARMS- (n = 55; 26.9%).

Table 36 – ASI total scores, sociodemographic and clinical characteristics of the total sample and the three subgroups.

Variable	Total sample (n=204)	CAARMS- (n=55)	UHR (n=45)	FEP (n=104)	χ^2	Post hoc test
Gender (males)	122 (59.8%)	26 (47.3%)	24 (53.3%)	72 (69.2%)	8.22[c]	FEP>CAARMS-[e]
Ethnic group (white Caucasian)	181 (88.7%)	47 (85.5%)	41 (91.1%)	93 (89.4%)	0.89	-
Mother tongue (Italian)	182 (89.2%)	51 (92.7%)	39 (86.7%)	92 (88.5%)	1.07	-
Age	21.23 ± 5.85	22.58 ± 6.32	18.78 ± 4.32	23.04 ± 5.80	12.52[b]	FEP=CAARMS->UHR[d,e]
Education (in years)	11.65 ± 2.41	11.58 ± 2.47	11.47 ± 2.30	11.79 ± 2.46	1.20	-
DUI (in weeks)	70.95 ± 62.41	50.63 ± 54.15	59.61 ± 44.33	87.50 ± 70.73	7.82[c]	FEP>CAARMS-[f]
ASI total score	10.72 ± 7.61	4.87 ± 5.46	12.96 ± 6.24	13.93 ± 7.00	60.59[a]	FEP=UHR>CAARMS-[d]

Legend - Frequencies (percentages), mean ± standard deviation, Kruskal-Wallis and Chi-squared test (χ^2) values are reported. Post-hoc analyses were performed using Mann-Whitney U test. [a]$p<0.001$; [b]$p<0.01$; [c]$p<0.05$; [d]Holm-Bonferroni corrected p-value<0.001; [e]Holm-Bonferroni corrected p-value<0.01; [f]Holm-Bonferroni corrected p-value<0.05. ASI = Aberrant Salience Inventory; DUI = Duration of Untreated Illness; CAARMS = Comprehensive Assessment of At-Risk Mental States; FEP = First Episode Psychosis; UHR = participants who met CAARMS-defined Ultra-High Risk (UHR) criteria; CAARMS- = participants who were below CAARMS-defined UHR/FEP criteria.

Within the UHR group, 39 participants met APS criteria (86.8% of UHR individuals), 3 (6.6%) met BLIPS criteria and 3 (6.6%) met GRFD criteria.

The FEP group consisted of patients with DSM-IV-TR schizophrenia (n = 49; 47.1% of FEP individuals), affective (bipolar or major depressive) psychosis (n = 28; 26.9%), psychotic disorder not otherwise specified (n = 21; 20.2%) and brief psychotic disorder (n = 6; 5.8%).

The remaining participants were below the CAARMS-defined FEP/UHR criteria and composed the CAARMS- subgroup. They were diagnosed with DSM-IV-TR non-schizotypal personality disorder (n = 23; 41.8% of CAARMS- individuals), anxiety disorders (n = 18; 32.7%) and depressive disorders (n = 14; 25.5%).

In comparison with CAARMS-, FEP patients showed a significantly greater percentage of males and a longer DUI. Compared to UHR-, FEP individuals had a significantly older age at the ReARMS enrollment, as well as UHR individuals had a younger age than CAARMS- participants at the baseline assessment. No inter-group difference in terms of ethnic group, mother tongue and years of education was also found (Table 36).

At baseline evaluation, the ASI total score was 10.72 ± 7.61 n the total sample. In comparison with CAARMS-, both UHR and FEP subjects showed significantly higher ASI total scores (Table 36).

Reliability

The ASI was re-administered to 35 consecutive FEP participants after 2 weeks (T1) from the baseline assessment (T0) in order to calculate short-term test-retest reliability. Their sociodemographic characteristics were comparable to those of the total sample, with a mean age of 20.25 ± 1.02 years and a mean level of education of 12.21 ± 1.93 years. Twenty (57.1%) out of the 35 FEP patients were males.

At baseline, their ASI total score was 12.69 ± 7.61, whereas at T1 was 11.53 ± 7.29. Spearman's correlation coefficient (ρ) between ASI total scores at T0 and T1 was 0.815 (p = 0.0001). Likewise, correlation analysis for each ASI item also revealed significant Spearman's correlation coefficients between item subscores at T0 and T1 (ρ ranging from 0.611 to 0.815; p = 0.0001 in all explorations) (Table 37).

Table 37 – Spearman's correlation coefficients between T0 and T1 ASI item scores (n = 204).

T0 ASI item score	T1 ASI item score (ρ)
1) Ti succede mai che certe cose, anche banali e quotidiane, acquistino improvvisamente un significato o un´importanza particolare per te?	0.618
2) Ti capita a volte di sentirti come se fossi sull'orlo di qualcosa di veramente grande o magnifico ma che non riusciresti a definire?	0.672
3) Ti capita a volte di avere l´impressione che i tuoi sensi siano diventati particolarmente acuti o recettivi?	0.661
4) Ti capita mai di sentirti come se stessi rapidamente raggiungendo la massima acutezza o intensità delle tue capacità mentali?	0.632
5) Ti succede di fare caso talvolta a dettagli minori o a particolari cui prima non facevi attenzione e che ora ti sembrano importanti?	0.617
6) A volte, senti il bisogno di fare chiarezza su qualcosa, anche se non sei sicuro di che si tratti?	0.652

7) Ti capita mai di attraversare periodi in cui ti senti particolarmente religioso o interessato ad esperienze di tipo mistico?	0.731
8) Ti capita mai di avere difficoltà a distinguere se sei inquieto, impaurito, preoccupato o in ansia?	0.616
9) Hai mai delle fasi o dei periodi durante i quali la tua coscienza ti pare dilatata o particolarmente intensa?	0.636
10) Senti mai il bisogno di dare un senso a situazioni o eventi apparentemente casuali come coincidenze o incontri occasionali?	0.712
11) Ti capita a volte di sentirti come se stessi sul punto di trovare il pezzo mancante di un puzzle?	0.647
12) A volte hai la sensazione di poter udire o avvertire i suoni in modo più distinto del solito?	0.727
13) Ti capita mai di cogliere un significato insolitamente importante in cose a cui abitualmente non presti particolare attenzione?	0.765
14) Ti capita talvolta che osservazioni o frasi normalmente di scarso rilievo, assumano un significato sfavorevole, quasi di malaugurio?	0.619
15) Ti capitano delle fasi o dei periodi in cui, talvolta, certe canzoni sembrano contenere un significato importante per la tua vita?	0.617
16) A volte attribuisci un´importanza particolare a cose o oggetti che normalmente trascuri?	0.618
17) A volte, hai l´impressione di essere sul punto di scoprire qualcosa di realmente grande o importante, ma di non sapere esattamente di cosa si tratta?	0.615
18) Ti è mai successo di sentire i sapori più intensamente come se il tuo senso del gusto si fosse fatto più acuto?	0.617
19) Ti succede mai di avere l´impressione che i misteri del cosmo si stiano rivelando a te?	0.631
20) Hai delle fasi o dei periodi in cui ti senti eccessivamente eccitato da cose o esperienze che sono normalmente gestibili?	0.704
21) Ti capita spesso di essere affascinato o attratto dalle piccole cose intorno a te?	0.613
22) Ti capita mai che i tuoi sensi sembrino eccezionalmente acuti, chiari o penetranti?	0.616
23) Ti capita mai di sentire come se un intero mondo ti si stesse rivelando?	0.611
24) Avverti mai la sensazione che i confini tra il tuo mondo interno e quello esterno siano svaniti?	0.667
25) Ti capita di avere a volte la sensazione che il mondo stia cambiando e te ne domandi il motivo?	0.614
26) Ti capita mai di avere una sensazione di urgenza inesprimibile, e di non sapere bene cosa fare?	0.618
27) Ti è successo di essere talvolta particolarmente incuriosito da persone, eventi, luoghi, o idee che normalmente non avrebbero alcun interesse per te?	0.815
28) Ti succede mai che i tuoi pensieri e percezioni diventino così rapidi da non riuscire più a seguirli o assimilarli?	0.670
29) Ti capita di notare, talvolta, cose cui prima non avevi fatto caso e che assumono un significato particolare?	0.614

Legend – T0 = Baseline assessment time, T1 = 1-year assessment time, ASI = Aberrant Salience Inventory. Spearman's correlation coefficient (ρ) values are reported.

Within the total sample, the ASI total score showed a Cronbach's alpha of 0.925 (95% Confidence Intervals [CI] = 0.901-0.934). All item-total correlations were higher than 0.30, with the exception of items 8 ("Do you ever have difficulty telling if you are thrilled, frightened, pained or anxious?"; r = 0.179) and 15 ("Do you go through periods in which songs sometimes seem to have an important meaning for your life?"; r = 0.203) (Table 38). Thus, most item appeared to be worthy of retention, resulting in a decrease in the alpha value if deleted. Exceptions to this were the items 8 and 15, for which removal should be considered.

Table 38 - Internal consistency of the ASI (n = 204).

ASI items	Item-total correlation (r)	Cronbach's alpha if item deleted
1) Ti succede mai che certe cose, anche banali e quotidiane, acquistino improvvisamente un significato o un´importanza particolare per te?	0.636	0.921
2) Ti capita a volte di sentirti come se fossi sull'orlo di qualcosa di veramente grande o magnifico ma che non riusciresti a definire?	0.565	0.922
3) Ti capita a volte di avere l´impressione che i tuoi sensi siano diventati particolarmente acuti o recettivi?	0.572	0.922
4) Ti capita mai di sentirti come se stessi rapidamente raggiungendo la massima acutezza o intensità delle tue capacità mentali?	0.448	0.923
5) Ti succede di fare caso talvolta a dettagli minori o a particolari cui prima non facevi attenzione e che ora ti sembrano importanti?	0.592	0.921
6) A volte, senti il bisogno di fare chiarezza su qualcosa, anche se non sei sicuro di che si tratti?	0.601	0.921
7) Ti capita mai di attraversare periodi in cui ti senti particolarmente religioso o interessato ad	0.547	0.922

esperienze di tipo mistico?		
8) Ti capita mai di avere difficoltà a distinguere se sei inquieto, impaurito, preoccupato o in ansia?	0.179	0.927
9) Hai mai delle fasi o dei periodi durante i quali la tua coscienza ti pare dilatata o particolarmente intensa?	0.435	0.924
10) Senti mai il bisogno di dare un senso a situazioni o eventi apparentemente casuali come coincidenze o incontri occasionali?	0.587	0.921
11) Ti capita a volte di sentirti come se stessi sul punto di trovare il pezzo mancante di un puzzle?	0.546	0.922
12) A volte hai la sensazione di poter udire o avvertire i suoni in modo più distinto del solito?	0.518	0.923
13) Ti capita mai di cogliere un significato insolitamente importante in cose a cui abitualmente non presti particolare attenzione?	0.658	0.920
14) Ti capita talvolta che osservazioni o frasi normalmente di scarso rilievo, assumano un significato sfavorevole, quasi di malaugurio?	0.481	0.923
15) Ti capitano delle fasi o dei periodi in cui, talvolta, certe canzoni sembrano contenere un significato importante per la tua vita?	0.203	0.926
16) A volte attribuisci un´importanza particolare a cose o oggetti che normalmente trascuri?	0.623	0.921
17) A volte, hai l´impressione di essere sul punto di scoprire qualcosa di realmente grande o importante, ma di non sapere esattamente di cosa si tratta?	0.570	0.922
18) Ti è mai successo di sentire i sapori più intensamente come se il tuo senso del gusto si fosse fatto più acuto?	0.367	0.925
19) Ti succede mai di avere l´impressione che i misteri del cosmo si stiano rivelando a te?	0.338	0.925
20) Hai delle fasi o dei periodi in cui ti senti eccessivamente eccitato da cose o esperienze che sono normalmente gestibili?	0.624	0.921
21) Ti capita spesso di essere affascinato o attratto dalle piccole cose intorno a te?	0.668	0.920
22) Ti capita mai che i tuoi sensi sembrino eccezionalmente acuti, chiari o penetranti?	0.640	0.921
23) Ti capita mai di sentire come se un intero mondo ti si stesse rivelando?	0.436	0.924
24) Avverti mai la sensazione che i confini tra il tuo mondo interno e quello esterno siano svaniti?	0.451	0.923
25) Ti capita di avere a volte la sensazione che il mondo stia cambiando e te ne domandi il motivo?	0.550	0.922
26) Ti capita mai di avere una sensazione di urgenza inesprimibile, e di non sapere bene cosa fare?	0.572	0.922
27) Ti è successo di essere talvolta particolarmente incuriosito da persone, eventi, luoghi, o idee che normalmente non avrebbero alcun interesse per te?	0.654	0.920
28) Ti succede mai che i tuoi pensieri e percezioni diventino così rapidi da non riuscire più a seguirli o assimilarli?	0.419	0.924
29) Ti capita di notare, talvolta, cose cui prima non avevi fatto caso e che assumono un significato particolare?	0.680	0.920

Legend – ASI = Aberrant Salience Inventory. Correlation r coefficients and Cronbach's alpha values are reported.

CFA

CFI, TLI, RMSEA and SRMR indices were analyzed to assess the adjustment of the original ASI 5-factor model in our total sample (Table 39). Although CFI, TLI and RMSEA were adequate, maintaining acceptable values (i.e. 0.952, 0.946 and 0.059, respectively), SRMR was 0.125, showing a poor fit value [317]. Factor loadings of the ASI items are reported in the Table 3. Specifically, ASI items 8 and 15 had insufficient factor loading values of < 0.45 (i.e. 0.263 and 0.375, respectively).

Concurrent validity

The ASI total score showed significant positive correlations with all CAARMS "Positive Symptoms" and all SPQ-B subscale scores, as well as with CAARMS "Anhedonia" item subscore (Table 40).

In the total sample, the ASI total score had also a significant positive correlation with DUI (Table 39). No significant association of ASI total score with gender, age at entry and years of education was found.

Table 39 - Indices of adjustment and item factor loadings obtained in the Confirmatory Factor Analysis (CFA) of the 5-factor model proposed in the original English version of the ASI [158].

Indice of adjustment	ASI (29 items)	Accepted values			
CFI	0.952	≥ 0.90			
TLI	0.946	≥ 0.90			
RMSEA	0.059	≤ 0.06			
SRMR	0.125	≤ 0.08			
Item	Factor 1 Increased significance	Factor 2 Sense of sharpening	Factor 3 Impending understanding	Factor 4 Heightened emotionality	Factor 5 Heightened cognition
ASI 1	0.854	-	-	-	-
ASI 5	0.841	-	-	-	-
ASI 10	0.790	-	-	-	-
ASI 15	0.375	-	-	-	-
ASI 16	0.849	-	-	-	-
ASI 21	0.877	-	-	-	-
ASI 27	0.834	-	-	-	-
ASI 3	-	0.906	-	-	-
ASI 9	-	0.736	-	-	-
ASI 12	-	0.815	-	-	-
ASI 18	-	0.538	-	-	-
ASI 22	-	0.927	-	-	-
ASI 2	-	-	0.768	-	-
ASI 6	-	-	0.785	-	-
ASI 11	-	-	0.753	-	-
ASI 17	-	-	0.789	-	-
ASI 29	-	-	0.919	-	-
ASI 8	-	-	-	0.263	-
ASI 14	-	-	-	0.673	-
ASI 20	-	-	-	0.814	-
ASI 24	-	-	-	0.703	-
ASI 26	-	-	-	0.740	-
ASI 28	-	-	-	0.581	-
ASI 4	-	-	-	-	0.640
ASI 7	-	-	-	-	0.716
ASI 13	-	-	-	-	0.912
ASI 19	-	-	-	-	0.677
ASI 23	-	-	-	-	0.716
ASI 25	-	-	-	-	0.709

Legend - ASI = Aberrant Salience Inventory; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual. Factor loadings of the ASI items are also reported.

Diagnostic accuracy measures

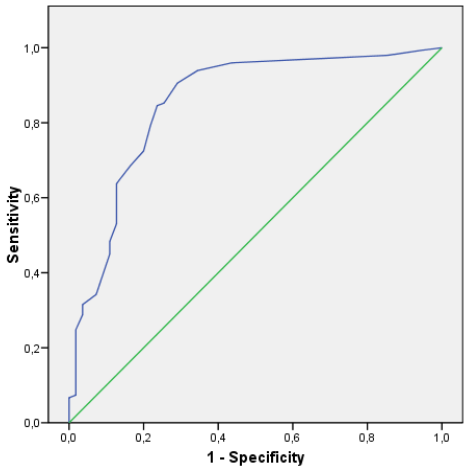
ROC curve was plotted for the ASI total score to predict CAARMS diagnosis (i.e. UHR/FEP vs CAARMS-) (Figure 10). The AUC was excellent (0.854, SE = 0.033, 95% CI = 0.789-0.918, p = 0.0001) [226]. Accuracy measures of different thresholds for the ASI total score showed that the ≥ 5 cut-off performed best in terms of distance (d) of points on ROC curve closest to the point (0,1) and Youden index (J) (Table 41), balancing the best sensitivity (0.906) and specificity (0.709).

Table 40 – Associations of the ASI total score with sociodemographic and clinical characteristics, CAARMS and SPQ-B subscale scores.

Variables		ASI total score (ρ)
CAARMS		
Positive Symptoms		0.525[a]
Unusual Thought Content		0.476[a]
Non Bizarre Ideas		0.407[a]
Perceptual Abnormalities		0.378[a]
Disorganized speech		0.348[a]
Anhedonia		0.166[b]
SPQ-B		
Cognitive-Perceptual Deficits		0.542[a]
Interpersonal Deficits		0.274[a]
Disorganizations		0.484[a]
Age		-0.052
Years of education		0.096
DUI (in weeks)		0.350[a]
Males (n = 122)	Females (n = 82)	z
11.66 ± 7.20	10.70 ± 7.97	-1.06

Legend – ASI = Aberrant Salience Inventory, CAARMS = Comprehensive Assessment of At-Risk Mental States; SPQ-B = Schizotypal Personality Questionnaire – Brief version; DUI = Duration of Untreated Psychosis; [a]Holm-Bonferroni corrected p-value < 0.001; [b]Holm-Bonferroni corrected p-value < 0.05. Spearman's rank correlation coefficient (ρ) and Mann-Whitney U test (z) values are reported.

Figure 10 - Receiver Operating Characteristic (ROC) curves of ASI total score predicting UHR/FEP vs CAARMS- diagnosis.



Legend – ASI = Aberrant Salience Inventory.

Compared to the ≥ 5 cut-off of the ASI total score, the ≥ 4 threshold increased sensitivity value up to 0.940, in spite of a decrease in specificity (0.654). Regarding likelihood ratios, in accordance with Jaeschke et al. (1994) [225], the ASI cutoff of ≥ 5 showed a 0.13 LR- value, generating

moderate shifts in pretest to posttest probability, despite a 3.11 LR+, which only changed post-test probabilities to a small degree.

Table 41 - CAARMS diagnostic classification accuracy by ASI cut-off scores.

ASI cut-offs	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (%) (95% CI)	J	d
ASI ≥ 3	95.97 (91.44-98.51)	56.36 (42.32-69.70)	85.63 (81.50-88.96)	83.78 (69.52-92.13)	2.20 (1.63-2.98)	0.07 (0.03-0.16)	0.523	0.231
ASI ≥ 4	94.00 (88.84-97.20)	65.45 (51.42-77.76)	88.05 (83.63-91.40)	80.00 (67.36-88.58)	2.72 (1.89-3.92)	0.09 (0.05-0.18)	0.594	0.180
ASI ≥ 5	90.60 (84.74-94.77)	70.91 (57.10-82.37)	89.40 (84.77-92.75)	73.58 (62.20-82.51)	3.11 (2.05-4.72)	0.13 (0.08-0.22)	**0.615**	**0.179**
ASI ≥ 6	85.23 (78.50-90.51)	74.55 (61.00-85.33)	90.07 (85.17-93.48)	65.08 (55.16-73.85)	3.35 (2.12-5.29)	0.20 (0.13-0.30)	0.598	0.212
ASI ≥ 7	84.56 (77.74-89.96)	76.36 (62.98-86.77)	90.65 (85.71-94.00)	64.62 (54.95-73.22)	3.58 (2.21-5.78)	0.20 (0.14-0.30)	0.609	0.210
ASI ≥ 8	79.19 (71.79-85.40)	78.18 (64.99-88.19)	90.77 (85.55-94.23)	58.11 (49.61-66.15)	3.63 (2.19-6.03)	0.27 (0.19-0.37)	0.574	0.256

Legend - CAARMS = Comprehensive Assessment of At-Risk Mental States; ASI = Aberrant Salience Inventory; 95% CI = 95% Confidence Intervals; PPV = Positive Predictive Value; NPV = Negative Predictive value; LR+ = Positive Likelihood Ratio; LR- = Negative Likelihood Ratio; J = Youden index; d = distance between the point (0,1) at each cut-off point on the ROC curve. The most promising ASI cut-off threshold balancing the best sensitivity and specificity (and their related diagnostic accuracy measures) is reported in bold.

Considering removal of ASI items 8 and 15, ROC curve was also plotted for the remaining ASI-27 item total score to predict CAARMS diagnosis (i.e. UHR/FEP vs CAARMS-). The AUC was slightly less significant, but still acceptable compared to that of the original ASI (29-item) total score (0.865, SE = 0.033, 95% CI = 0.801-0.929, p = 0.0001) [226]. Accuracy measures of different thresholds for 27-item ASI total score showed that, overall, the ≥ 3 cut-off performed best in terms of Youden index and d value, increasing sensitivity up to 0.926 with a still acceptable specificity of 0.691 (Table 42).

Table 42 - CAARMS diagnostic classification accuracy by 27-item ASI cut-off scores.

ASI cut-offs	Sensitivity (%)	Specificity (%)	J	d
ASI ≥ 2	94.60	63.60	0.585	0.186
ASI ≥ 3	92.60	69.10	**0.626**	**0.169**
ASI ≥ 4	89.90	72.70	0.617	0.175
ASI ≥ 5	85.90	76.40	0.623	0.197

Legend - CAARMS = Comprehensive Assessment of At-Risk Mental States; 27-item ASI = 27-item version of the Aberrant Salience Inventory; J = Youden index; d = distance between the point (0,1) at each cut-off point on the ROC curve. The most promising ASI cut-off threshold balancing the best sensitivity and specificity (and their related diagnostic accuracy measures) is reported in bold.

Predictive validity

Fourteen out of 55 participants scoring ≥ 5 on the ASI total score, who did not meet the CAARMS psychosis criteria at baseline, did not finish the 1-year follow-up period. Eleven of these individuals had a follow-up period of < 1 year; the other three subjects went out of the ReARMS protocol catchment area and they could not be contacted for the follow-up assessment. After 1 year of follow-up, 8 (19.5%) of the 41 remaining individuals developed a FEP. No other psychosis conversion was found among ASI negative screen individuals. Considering a cut-off of ≥ 4 on ASI total score at the baseline assessment, 8 transitions to psychosis have been equally detected (i.e. 8 [17.0%] of the 47 participants who had a ≥ 4 cut-off on the ASI total score at baseline, who did not meet the CAARMS psychosis criteria at the initial assessment and who finished the 1-year follow-up period).

DISCUSSION

Aim of the current study was to validate the approved Italian version of the ASI in a clinical sample of adolescent and young adult community help-seekers recruited within the ReARMS program. In comparison with CAARMS-, both UHR and FEP participants had significantly higher ASI total scores, indicating more severe levels of AS not only at the onset of psychosis, but also in its prodromal phase. These findings confirm what hypothesized by Kapur (2003) [297], who suggested that the unusual or incorrect assignment of salience or significance to innocuous stimuli is a central mechanism in the development of psychotic disorders. These results are also in line with what reported in studies on the ASI in psychosis-proneness individuals. Specifically, Cicero et al. (2010) [158] showed higher ASI total scores in nonclinical individuals (aged 18-24 years) scored two standard deviations above the mean on the Social Anhedonia Scale [318] or scored 1.96 standard deviations above the mean on either the Magical Ideation Scale [141] or the Perceptual Aberration Scale [319], compared to a control group (i.e. subjects scored less than 0.5 standard deviations above the mean on the Perceptual Aberration Scale, the Magical Ideation Scale and the Social Anhedonia Scale). Moreover, Cicero et al. (2010) [158] reported a significantly higher mean of the ASI total score in clinically-stable forensic inpatients with a history of psychosis (identified by a review of their charts) in comparison with a psychiatric control group including clinically-stable forensic inpatients with nonpsychotic diagnoses. Moreover, Raballo et al. (2019) [298] reported the highest ASI total scores in a group of undergraduate students (aged 18-22 years) with SPQ scores in the schizotypy range.

In the current study, the mean of the ASI total score was 13.93 ± 7.00 in FEP patients and 12.96 ± 6.24 in UHR participants. Although similar to results reported by both Cicero et al. (2010) [158] in stable forensic patients with a history of psychosis and Lelli et al. (2015) [307] in Italian psychiatric subjects (aged 18-65 years) with psychotic symptoms, these findings are definitely lower than those observed by Cicero et al. (2010) [158] in a nonclinical sample of psychosis-proneness subjects (i.e. 22.26 ± 5.40) and by Raballo et al. (2019) [298]in their "High Aberrant Salience" class of Italian undergraduate students (i.e. 20.20 ± 2.90). Therefore, the ASI seems to be particularly suitable for early detection of young individuals with a specific vulnerability to psychosis (such as those highly scoring in schizotypy scales) and/or in the psychosis prodromes. The privileged link of measures of AS with schizotypy and pre-psychotic symptoms appears to reinforce its value as potential catalyzer of the development of full-blown psychosis [298].

Although FEP and CAARMS- participants were older than UHR individuals, and FEP patients had a greater percentage of males than CAARMS- subjects, our findings overall confirm what previously reported by Cicero et al. (2010) [158] and by Raballo et al. (2019) [298], who showed a substantial independence of ASI scores from gender, ethnic group, mother language, age at entry and years of education. Only DUI, which was significantly longer in FEP than CAARMS- participants, had a positive correlation with the ASI total score. This result could be intrinsically related to the FEP condition, which often delays the first help-seeking contact with mental health services, also due to a catastrophic fear relating to going mad, to fears of stigma or to the risk of a possible hospitalization [173].

Reliability

The approved Italian version of the ASI showed a high short-term test-retest reliability, consistently with what reported by Lelli et al. (2015) [307], who observed a correlation coefficient of 0.96 in a clinical sample of Italian adult psychiatric patients using an unofficial, non-authorized version of the questionnaire. Likewise, strong Spearman's correlation coefficients (ranging from 0.611 to 0.815) for each ASI item in our total sample were observed. During this short span of time (i.e. approximately 2 weeks), pharmacotherapy was not substantially modified in order to exclude a drug-induced interference with the dopamine system linked to salience.

Moreover, we found an excellent internal consistency of the Italian version of the ASI in our total sample (i.e. Cronbach's alpha = 0.925), in line with what reported by Cicero et al. (2010) in both native-English speaking college students (α = 0.890) and clinically-stable forensic inpatients with a history of psychosis (α = 0.910), by Raballo et al. (2014) [306] in a nonclinical population of Italian undergraduate students (α = 0.900) and by Lelli et al. (2015) [307] in a clinical sample of Italian

psychiatric patients, aged 18-65 years (α = 0.890). Thus, the ASI appears to be reliably good in different samples and cultures. However, as item-total correlations of ASI items 8 and 15 were lower than 0.30 in the current research, resulting in a decrease in the alpha value if they were deleted, their removal from the instrument should be reasonably considered.

CFA

Our CFA results on the original ASI 5-factor model proposed by Cicero et al. (2010) are contradictory and controversial. Indeed, although CFI, TLI and RMSEA were adequate in the total sample, SRMR had a poor fit value. In particular, factor loading analysis showed values of < 0.45 for the items 8 and 15, further supporting the usefulness of their removal from the Italian version of the ASI.

Concurrent validity

As expected, the ASI total score showed highly significant positive correlations with CAARMS "Positive Symptoms" subscores and the positive dimensions of schizotypy (i.e. SPQ-B "Cognitive-Perceptual Deficits" and "Disorganization"). These findings support a good concurrent validity of the approved Italian version of the ASI and are a further confirmation of its construct validity, as reported in the original validation study by Cicero et al. (2010) [158]. Specifically, the instrument shows to be related with specific measures that have been hypothesized to be associated with dopamine functioning and to comprise the nomological network of AS [158, 297].

As predicted, the ASI total score was also positively correlated with CAARMS "Anhedonia" item and SPQ-B "Interpersonal Deficits" subscores, but not as strongly as with the above mentioned positive symptom dimensions. According to Cicero et al. (2010) [158], these results provide further evidence for the discriminant validity of ASI scores.

Diagnostic accuracy measures

In the present study, diagnostic accuracy measures overall confirm that the approved Italian version of the ASI has good concurrent validity with interview-based CAARMS diagnoses. Indeed, it effectively differentiated between UHR/FEP individuals versus CAARMS- (i.e. nonpsychotic spectrum) patients. Specifically, in our help-seeking sample of adolescents and young adults, a cut-off threshold of ≥ 5 on the ASI total score appears to be a promising cutoff, especially in terms of d value (0.179) and Youden index (0.615), balancing 91% sensitivity with 71% specificity. This cut-off value is definitely lower than that (≥ 14) suggested by Lelli et al. (2015) [307] and based on

mean values of the ASI total score observed in an Italian clinical sample of psychotic patients, aged 18-65 years.

However, as for screening purposes greater weighting should be given to sensitivity over specificity, especially if part of a 2-step diagnostic process (e.g. screening tool followed by in-depth interview) [156], an alternative, equally promising cut-off is a threshold of ≥ 4 on the ASI total score, which increased sensitivity value up to 94%, in spite of a slight decrease in specificity (65%). Indeed, in most cases, having a few more false positives during a screening process is less of an issue than missing appropriate individuals from a clinical perspective [320]. However, in our UHR/FEP-enriched clinical sample, a higher sensitivity implies that full assessment burden can be considerably reducing with little impact on missing UHR/FEP individuals [256]. According to Jaeschke et al. (1994) [225], the ASI cutoff of both ≥ 5 and ≥ 4 showed LR- values that generated moderate shifts in pretest to posttest probability (despite LR+ values that only changed post-test probabilities to a small degree). Thus, at these thresholds, the ASI total score appears to be better in ruling out than in ruling in possible UHR/FEP status.

As an alternative, considering removal of ASI items 8 and 15, a cut-off threshold of ≥ 3 on the 27-item ASI total score performed best in terms of d value and Youden index, increasing sensitivity up to 93% with a specificity of 69%.

Predictive validity

After 12 months of follow-up, a percentage ranging from 17% to 19.5% of participants who at baseline scored above the most suitable ASI cut-off thresholds identified in our total sample (i.e. respectively ≥ 4 and ≥ 5 on the ASI total score) and who did not meet CAARMS psychosis criteria at the initial assessment, developed a FEP. Considering these results, some methodological peculiarities of the present research should be considered. Indeed, ReARMS program is a clinical protocol providing evidence-based interventions that are shown to be effective in UHR/FEP individuals (i.e. pharmacotherapy, intensive case management, psychoeducation for family members, individual CBT within the framework of an assertive community treatment) [170]. Precisely because providing the optimal treatment for help-seekers was the main ethical mandate in ReARMS clinical setting, our interventions were not controlled (e.g. against placebo group or other treatments), but evenly delivered to all UHR/FEP participants [171]. This could therefore affect current psychosis transition rates.

Limitations

In the present research, there are some methodological limitations to be acknowledged. First, a possible weakness is that CAARMS- and UHR total sample sizes were relatively small. Thus, further studies on larger populations of people at UHR of psychosis and nonpsychotic psychiatric controls are needed in order to confirm these promising psychometric properties of the approved Italian version of the ASI.

Second, another limitation of this research is that the ASI was completed in a population "enriched" for the target diagnoses (i.e. adolescent and young adult help-seekers with clinical features of early psychosis and a decline in social functioning). Therefore, our results are not perfectly comparable with those expected in the general population, where psychotic-like experiences occur commonly, although transiently in most cases and not necessarily accompanied by distress or treatment seeking [298].

Third, a further weakness is that the ASI seems to be not sensitive enough to discriminate between UHR mental states and FEP. However, because the ASI is proposed in this context as a screening tool followed in the second phase of assessment by the CAARMS interview that can perform this discrimination well, such issue appears to be less relevant.

Fourth, another limitation of this research is that our findings on the ASI total score were not checked for antipsychotic dosage. Thus, further research involving specific measures on the use of antipsychotics are needed.

Finally, as the "Screening Schedule for psychosis" [185] was used before the ASI administration in all individuals entered the ReARMS protocol [170, 171], this is likely to impact the generalizability of our findings. Indeed, the ASI is ideally indicated for being used as the first step in a 2-stage screening process. Therefore, by excluding a certain amount of true negative cases in the pre-ASI step, this could further reduce the specificity of the screener.

CONCLUSIONS

Findings of this research indicate that the approved Italian version of the ASI is reliable and valid, showing satisfactory psychometric properties in a clinical sample of adolescent and young adult community help-seekers. Specifically, this instrument appears to be a suitable self-report screener for routine use in mental health care services within specialized, evidence-based programs of early detection/intervention in psychosis.

CONCLUSIONS

One the major concerns of modern psychiatry remains the implementation of efficient prevention models. Primary and secondary prevention strategies have been addressed in several fields of medicine, but early detection in psychiatry still remains a grey zone. Serious mental illnesses share an early presentation, with a typical beginning during adolescence for the 75% of them [321]. The personal and societal impact of such disorders makes early detection and intervention a crucial issue, in the attempt to prevent significant consequences on individual functioning [322].

Staging models have been developed in order to use a preventative approach, targeted at avoiding the onset and/or progression of serious mental disorders, with treatment regimens selected according to stage and individual profile risk factors [332, 324]. Staging allows the introduction of effective treatment in early illness phases, by means of placing individuals on a continuum in the context of the disorder progression. This goes along with the assumption that administering treatments during early illness stages could also modify the individual risk of disease progression [325]. Although the first models were mainly applied to psychosis, the concept of staging has been progressively applied to severe psychiatric disorders, in the attempt to define early clinical phenotypes showing an enhanced risk of progression into chronic and recurrent phases of such disorders.

In this research, our interest was focalized on early detection of psychosis (specifically, of adolescents and young adults with FEP or at UHR of psychotic disorder). A 2-step identification procedure was proposed. For the first ("*screening*") step, different instruments were described and were analyzed in their psychometric characteristics. These screeners can also be used in different settings (e.g. the CVEP in general medical practice; the PQ-B, the PQ-16 and the ASI in triage services allocated in general child/adolescent and adult mental health centers). The second step included an in-depth assessment using clinical interviews specifically developed for the early detection of psychosis and the psychosis risk stratification (such as the CAARMS).

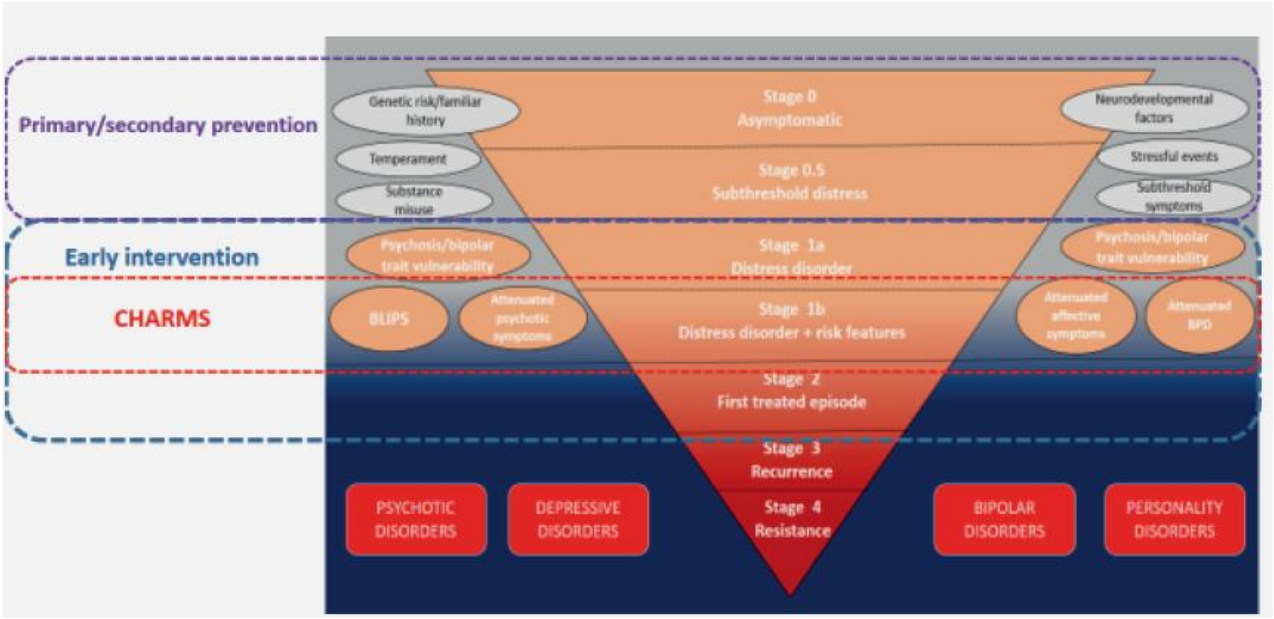
Future direction

A more recent conceptualization of At Risk Mental States (ARMS) is represented by the Clinical High At-Risk Mental State (CHARMS), a broader definition of a syndrome that deserves treatment due to help-seeking and distress associated with presenting symptoms, albeit below threshold for canonical categorical diagnoses. Such criteria were developed on the basis of available evidence and expert clinical experience and are applied using a combination of validated instruments [326]. The CHARMS approach was aimed at identifying the sub-syndromal population at risk of severe

psychopathology, providing an operational definition of a broad-spectrum pluripotent state. This requires a broadening of at-risk states for psychosis and their operationalization into a trans-diagnostic ARMS, which is also in line with evidence regarding the non-specific nature of emerging psychopathology. In fact, the majority of subjects at risk for psychosis fulfill diagnostic criteria for one or more mood, anxiety, substance use and personality disorders, and the criteria capture markedly elevated risk for exit syndromes other than psychosis [327-329]. This may reflect an "early shared pathway" or a form of pluripotency of the early clinical phenotypes of mental disorders [330].

In consideration of this, observed early signs and symptoms may not indicate a fixed trajectory to particular diagnoses and may evolve into a range of different psychiatric syndromes [160, 331]. Noteworthy, subthreshold (stage 1b) states include attenuated psychotic symptoms, subthreshold bipolar states, mild-moderate depression and borderline personality features of reduced range and shorter duration than full diagnostic threshold (Figure 11).

Figure 11 - Trans-diagnostic staging model and possible relationship with risk syndromes and CHARMS paradigm [326].



The trait vulnerability is then expanded to include history of serious mental disorders in a first degree relative, in addition to functional decline or chronic low functioning in the young person. Data show about 30% transition rate to stage 2 over a 6-12 month period in young people meeting these criteria and receiving treatment in mental health services, as opposed to <5% transition rate in help-seeking young people below this threshold (stage 1a). Furthermore, since CHARMS target is any stage 2 "exit syndrome" rather than a specific disorder outcome, the observation that evolution

of symptoms from stage 1 do not necessarily follow a homotypic course (i.e. sub-threshold psychosis evolving into full threshold psychosis), but possibly heterotypic ones (i.e. attenuated mood spectrum symptoms without psychotic elements evolving into first episode psychosis), gives even more consistency to the CHARMS pluripotent model. Such broader input-output approach can include and detect a wider sample of sub-threshold conditions, allowing researchers to trace trans-diagnostic trajectories of emerging mental disorders and tailoring more efficient preventive interventions.

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CONFLICT OF INTEREST

The author declares to have no conflict of interests.

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Appendix S1 - The "Reggio Emilia At-Risk Mental States" (ReARMS) protocol: processes and procedures

PROCESS 1 - Identification

Procedures	Setting	Professionals	Timing	
			Procedure duration	**Process scheduling**
1.1 Compilation of the screening questionnaire (*Screening Schedule for Psychosis [SS]*) (**T0***)	Child/Adolescent or Adult Mental Health service Emergency room/general hospital/psychiatric ward	Psychiatrist Neuropsychiatrist Psychologist	30 minutes	Usually within 7 days from the individual's first contact with Reggio Emilia

*T0 = date of compilation of the screening questionnaire (SS)

** ReARMS team psychologist = psychologist specifically trained in early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

***ReARMS multi-professional team members = psychiatrist or neuropsychiatrist, psychologist, nurse, professional educator, social assistant and psychiatric rehabilitation therapist specifically trained for early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

1.2 Communication of the positive outcome of the screening to the patient (and parents, if minor) and obtaining of a written informed consent to the depth psychopathological and diagnostic assessment ("Reggio Emilia At-Risk Mental States [ReARMS] battery)	Child/adolescent or adult mental health service Emergency room/general hospital/psychiatric ward	Psychiatrist Neuropsychiatrist Psychologist	30 minutes	mental health services
1.3 Communication of the positive outcome of the screening to a ReARMS team psychologist** and planning of the first clinical interview with the patient	Child/adolescent or adult mental health service Emergency room/general hospital/psychiatric ward	Psychiatrist Neuropsychiatrist Psychologist ReARMS team psychologist	30 minutes	Usually within 1 week from T0*
1.4 Constitution of a multi-professional team for early intervention in psychosis	Team meeting in Child/adolescent or adult mental health service	Psychiatrist Neuropsychiatrist Psychologist ReARMS multi-professional team members***	30 minutes	Usually within 3 weeks from T0*

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Screening Schedule (SS) for Psychosis

In addition to provide evidence-based interventions that are supposed to be effective in UHR/FEP subjects, the ReARMS protocol aimed also to an early identification of young people with FEP or at UHR of psychosis through a 2-step procedure. The first screening step included a triage service using the "Screening Schedule" for Psychosis (SS) (Jablensky et al., 1992), performed by service staff (see also supplementary materials). The second step consisted of the CAARMS interview to investigate the clinical status (i.e. psychosis risk, psychosis, or neither) (Yung et al., 2005), which was carried out by trained clinicians. Indeed, the ReARMS team is specialized in detecting young people at UHR of psychosis as measured by the CAARMS.

The SS for psychosis (Jablensky et al., 1992) is a checklist containing demographic, history, symptomatological and behavioral items, all dichotomous (yes/no), which constituted inclusion and exclusion criteria for ReARMS protocol eligibility (Raballo et al., 2014). Those were: (a) age between 13-35 years; (b1) presence, in the preceding 12 months, of at least one of the following psychotic symptoms: hallucinations or pseudo-hallucinations in any modality; delusions and/or ideas of reference; qualitative thought or speech disorder; qualitative psychomotor disorder; or gross behavioral abnormalities representing a break in the person's previous patterm; or (b2) at least one of the following abnormalities indicative of a substantial modification of personality or behavior and suggestive of psychotic disorder: loss of interest, initiative, and drive leading to deterioration of daily performance; onset of social withdrawal; episodic severe excitement, purposeless destructiveness or aggression; episodic or persistent states of overwhelming fear or anxiety; or gross and persistent self-neglect; (c) first-in-lifetime contact with any "helping agency" within the last three months, occasioned by the above mentioned symptoms and behaviors; (d) presence of a "Duration of Untreated Psychosis" (DUP) < 2 years; (e) absence of clinical evidence of organic cerebral disorder, including central nervous system damage due to alcohol or drug abuse, and manifest in either delirium or dementia, with or without peripheral neuropathy; and (f) presence of an Intelligence Quotient (IQ) ≥ 50.

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Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures, a World Health Organization ten-country study. Psychol Med Monogr 1992; 20 (suppl.): 1-97.
Raballo A, Chiri LR, Pelizza L, Fontana F, Favazzo R, Pensieri L, Paterlini F, Scazza I, Semrov E. Field-testing the early intervention paradigm in Emilia-Romagna: the Reggio Emilia At Risk Mental State (ReARMS) Project. Early Interv Psychiatry 2014; 8, 88.
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Process 2 - ASSESSMENT

Procedures	Setting	Professionals	Timing	
			Procedure duration	Process scheduling
2.1 First clinical interview: presentation of the assessment process and compilation of the ad-hoc socio-demographic/clinical schedule	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team Psychologist	45 minutes	Usually within 3 weeks from T0*
2.2 Administration and scoring of the ReARMS assessment battery: psychopathological and diagnostic evaluation	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team psychologist	10 hours	Usually within 8 weeks from T0*
ReARMS assessment Battery: Comprehensive Assessment of At-Risk Mental States (CAARMS), Positive And Negative Syndrome Scale (PANSS), Schizophrenia Proneness Inventory (SPI –Adult or Child/Youth version), Structured Clinical Interview for DSM-IV-TR axis I Mental Disorder (SCID-I), Schizotypal Personality Questionnaire – Brief version (SPQ-B) Health of Nation Outcome Scale (HONOS – Adult or Child/Adolescent version), Beck Depression Inventory- II Edition (BDI-II), Premorbid Social Adjustment scale (PSA), Aberrant Salience Inventory (ASI), World Health Organization Quality Of Life – Brief version (WHOQOL-Brief), Millon Clinical Multiaxial Inventory (MCMI), Beck Cognitive Insight Scale (BCIS), and Autism Questionnaire (AQ).				

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2.3 Assessment outcome: - Sharing with the other ReARMS team referent members for the patient - CAARMS-defined criteria for: 1) First-Episode Psychosis (FEP) 2) Ultra-High Risk (UHR) mental states (i.e. Brief Limited Intermittent Psychotic Symptoms [BLIPS], Attenuated Psychotic Symptoms [APS], Genetic Risk and Functioning Deterioration [GRFD] syndrome) - No FEP/UHR criteria: exit from the ReARMS protocol - Drawing of a psychodiagnostic report	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members	2 hours	Usually within 9 weeks from T0*
2.4.1 Return of the assessment outcome to the patient and family members, and case formulation	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members	2 hours	

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PROCESS 3 – INTERVENTION IN FIRST-EPISODE PSYCHOSIS: ACUTE PHASE OR RELAPSE

Procedures	Setting	Professionals	Timing	
			Procedure duration	Process scheduling
3.1 Identification of a case manager within the ReARMS multi-professional team, according to the need analysis	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	30 minutes	Usually within 10 weeks from T0* (no application, if relapse)
3.2 Psychopharmacological therapy	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team Psychiatrist or Neuropsychiatrist***	30 minutes	Promptly, according to the symptom severity

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***ReARMS multi-professional team members = psychiatrist or neuropsychiatrist, psychologist, nurse, professional educator, social assistant and psychiatric rehabilitation therapist specifically trained for early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

3.3.1 Co-planning of a personalized pathway of treatment that can include all or only some of the interventions provided by the ReARMS protocol	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members***	2-3 hours	Usually within 12 weeks from T0* (no application, if relapse)
3.3.2 Drafting of a project signed and shared by patient, family and ReARMS multi-professional team members				
3.4 Individual Cognitive-Behavioral Therapy	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team psychologist**	**In the first year:** at least 20 sessions (each lasting 60 minutes	Usually within 13 weeks from T0* If relapse: re-planning of the intervention according to the need analysis

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***ReARMS multi-professional team members = psychiatrist or neuropsychiatrist, psychologist, nurse, professional educator, social assistant and psychiatric rehabilitation therapist specifically trained for early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

3.5 Psychoeducation for family members	Child/adolescent or adult mental health service	ReARMS multi-professional team members*** (i.e. psychologist, nurse educator, psychiatric rehabilitation therapist)	**In the first year**: at least 10 sessions (each lasting 60 minutes)	Usually within 15 weeks from T0* If relapse: re-planning of the intervention according to the need analysis
3.6 Early psychosocial rehabilitation	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members*** (i.e. nurse, educator, social assistant, psychiatric rehabilitation therapist)	**In the first year**: at least 24 sessions (each lasting 60 minutes)	Usually within 1 year from T0*
3.7 Monitoring of metabolic parameters in patients receiving pharmacological treatment, and promotion of physical health	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members*** (i.e. psychiatrist, neuropsychiatrist, nurse)	20 minutes	Both at T0* and every 6 months

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3.8 Hospitalization: if necessary, the hospitalization setting should be the least coercive and restrictive as possible	Psychiatric ward	Psychiatrist Neuropsychiatrist	Not definable	Not definable

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PROCESS 4 – INTERVENTION IN ULTRA-HIGH RISK MENTAL STATES (BLIPS, APS, GRFD)	

Procedures	Setting	Professionals	Timing	
			Procedure duration	Process scheduling
4.1 Identification of a case manager within the ReARMS multi-professional team, according to the need analysis	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	30 minutes	Usually within 10 weeks from T0*
4.2.1 Co-planning of a personalized pathway of treatment that can include all or only some of the interventions provided by the ReARMS protocol 4.2.2 Drafting of a project signed and shared by patient, family and ReARMS multi-professional team members	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	2-3 hours	Usually within 12 weeks from T0*

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4.3 Psychopharmacological therapy, according to risk stratification and symptom severity	Child/adolescent or adult mental health service	ReARMS team psychiatrist or neuropsychiatrist	30 minutes	Promptly, according to the symptom severity
4.4 Individual Cognitive-Behavioral therapy	Child/adolescent or adult mental health service	ReARMS team psychologist**	**In the first year:** at least 20 sessions (each lasting 60 minutes) **In the second year:** Eventually booster sessions	Usually within 13 weeks from T0*
4.5 Psychoeducation for family members	Child/adolescent or adult mental health service	ReARMS multi-professional team members*** (i.e. psychologist, nurse, educator, psychiatric rehabilitation therapist)	**In the first year:** at least 6 sessions (each lasting 60 minutes) **In the second year:** Eventually booster sessions	Usually within 13 weeks from T0*

*T0 = date of compilation of the screening questionnaire (SS)

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4.6 Early psychosocial rehabilitation (according to the need analysis)	Child/adolescent or adult mental health service	ReARMS multi-professional team members (i.e. psychologist, nurse, educator, social assistant, psychiatric rehabilitation therapist)	According to social and occupational functioning	Usually within 6 months from T0*
4.7 Monitoring of metabolic parameters in patients receiving pharmacological treatment, and promotion of physical health	Child/adolescent or adult mental health service	ReARMS team psychiatrist or neuropsychiatrist	If medicaions	Both at T0* and every 6 months
4.8 If transition to psychosis, go to the procedures of the process 3	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	Not definable	Not definable

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4.9 Hospitalization: it should not be a standard procedure in UHR mental states, but should be recommended in cases of high risk of suicide, severe aggression or hostility that puts the safety of the subject at risk, and a depressive condition that has not responded to antidepressants.	Psychiatric ward	ReARMS team psychiatrist or neuropsychiatrist	Not definable	Not definable

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PROCESS 5 – INTERVENTION IN FIRST-EPISODE PSYCHOSIS: MAINTENANCE TREATMENT

Procedure	Setting	Professionals	Timing	
			Procedure duration	Process Scheduling
5.1 Redefining recovery-oriented goals by maintaining psycho-social interventions and also through annual follow-up assessments (see ReARMS assessment battery).	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	2-3 hours	Usually within 12 months from T0*
5.2 Psychopharmacological therapy	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team psychiatrist or neuropsychiatrist***	30 minutes	In continuity from T0*, according to the symptom severity

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5.3 Individual Cognitive-Behavioral Therapy	Child/adolescent or adult mental health service	ReARMS team psychologist**	**In the second year:** at least 10 sessions (each lasting 60 minutes) **From third to fifth year**: eventually booster sessions on specific symptomatic areas	Usually within 12 months from T0*
5.4 Psychoeducation for family members	Child/adolescent or adult mental health service	ReARMS multi-professional team members*** (i.e. psychologist, nurse, educator, psychiatric rehabilitation therapist)	**From second to fifth year**: eventually booster sessions	Usually within 12 months from T0*

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5.5 Early psychosocial rehabilitation (according to the need analysis)	Child/adolescent or adult mental health service	ReARMS multi-professional team members*** (i.e. nurse, educator, social assistant, psychiatric rehabilitation therapist)	**From second to fifth year**: at least 50 sessions (each lasting 60 minutes), according to patient's social and occupational functioning	Usually within 12 months from T0*
5.6 Monitoring of metabolic parameters in patients receiving pharmacological treatment and promotion of physical health	Child/adolescent or adult mental health service Psychiatric ward	ReARMS team psychiatrist or neuropsychiatrist***	20 minutes	Both at T0* and every 6 months
5.7 Hospitalization: if necessary, the hospitalization setting should be the least coercive and restrictive as possible.	Psychiatric ward	ReARMS team psychiatrist or neuropsychiatrist	Not definable	Not definable

*T0 = date of compilation of the screening questionnaire (SS)

** ReARMS team psychologist = psychologist specifically trained in early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

***ReARMS multi-professional team members = psychiatrist or neuropsychiatrist, psychologist, nurse, professional educator, social assistant and psychiatric rehabilitation therapist specifically trained for early detection/intervention in psychosis, locally present in each child/adolescent or adult mental health service of the Reggio Emilia Department of Mental Health.

Appendix S2. The “Checklist per la Valutazione dell’Esordio Psicotico” (CVEP) [211].

ITEM	PUNTEGGIO	DOMANDE ESPLORATIVE SUGGERITE
1 punto ciascuno		
Trascorre più tempo per conto proprio	___	Pensi di essere diventato più solitario e introverso o meno espansivo e loquace?
Litiga con gli amici o i familiari	___	Preferisci passare il tempo per conto tuo? Hai iniziato a ridurre i contatti col tuo gruppo di amici?
La famiglia è preoccupata	___	Eviti di fare le cose in compagnia?
		Qualcuno ha mai detto di essere stato preoccupato per te?
Consumo eccessivo di alcool	___	Sei insolitamente irritabile o arrabbiato o finisci per trovarti più spesso a litigare con parenti e amici?
Consumo di sostanze stupefacenti (cannabis inclusa)	___	Recentemente, ti è capitato di esagerare nel bere?
		Hai fatto uso di droghe recentemente? Se sì, ricordi il tipo di droga e quando l’hai assunta l’ultima volta?
2 punti ciascuno		
Difficoltà nel sonno	___	Come hai dormito recentemente?
		Com’è stato l’appetito?
Perdita di appetito	___	Hai avuto meno voglia di mangiare del solito? Per quanto tempo?
		Ti sei sentito giù o abbattuto?
Umore depresso	___	Ti sei sentito in ansia o in preda al panico? Per quanto tempo?
Ridotta concentrazione	___	Ti succede che diversi pensieri si mescolino nella tua mente, fai fatica a mettere ordine ed organizzare i pensieri?
		Ti senti teso, agitato o inquieto?
Irrequietezza/agitazione	___	Ti senti irrequieto e reattivo o così sembri agli altri che te lo hanno fatto notare?
Tensione o nervosismo	___	Ti sei sentito meno interessato e coinvolto nel lavoro, nello studio, nelle attività quotidiane, nello stare con gli altri?
Ridotto piacere, interesse o coinvolgimento nelle cose	___	
3 punti ciascuno		
Sensazione di essere osservato o guardato dagli altri *	___	Hai la sensazione che la gente ti osservi o stia provando ad approfittarsi di te?
Sentire o vedere cose che gli altri non possono sentire o vedere *	___	A volte riesci a vedere, udire, avvertire cose che gli altri non possono percepire? Ti è capitato di sentire rumori o voci mentre eri da solo, per conto tuo?
5 punti ciascuno		
Idee di riferimento *	___	Ti è mai capitato di pensare che eventi o azioni di altre persone abbiano un significato speciale, in qualche modo destinato a te?
Credenze bizzarre *	___	Hai mai la sensazione che gli altri ridano o parlino di te? O cogli messaggi che ti riguardano trasmessi dalla TV, giornali, radio, computer? (idee di riferimento)
Stranezza nel pensiero o nell’eloquio	___	Hai qualche opinione o credenza che gli altri trovano inconsueta, peculiare o strana? (credenze bizzarre)
Affettività inappropriata o incongrua	___	Ti è mai capitato di avvertire che le persone o le cose intorno a te sembravano essere cambiate all’improvviso?
Stranezza nel comportamento o nell’aspetto	___	Qualcuno, recentemente, ti ha fatto notare che hai detto cose inconsuete o confuse?
Storia familiare di psicosi (parenti di primo grado) e aumentato carico di sollecitazioni o deterioramento nel funzionamento *	___	Qualcuno nella tua famiglia ha mai avuto problemi psicologici o di salute mentale?
TOTALE		
Se il punteggio globale supera 20, valutare l’invio per un approfondimento in ambito specialistico. Se sono soddisfatti gli item contrassegnati con l’asterisco *, prendere in considerazione l’invio anche se il punteggio globale è inferiore a 20.		

Appendix S3 – The Italian version of the 16-item Prodromal Questionnaire [157].

PQ-16

Nome .....
Data di nascita .....
Data .....

Se hai un' età compresa tra 12 e 35, per favore compila il questionario

Il questionario esplora aspetti dei tuoi pensieri, sentimenti ed esperienze. Per cortesia, leggi attentamente ogni affermazione e indica se sei d'accordo o in disaccordo cerchiando "vero" o "falso" sulla destra. Cerca di rispondere ad ogni domanda. Nel caso tu risponda VERO, indica nell'ultima colonna il livello di disagio associato. Per favore, rispondi a tutte le domande.

				Se hai risposto "Vero", quanto disagio hai provato?			
				Nessuno	*Lieve*	*Medio*	*Grave*
1.	Ho perso interesse per cose che prima mi piacevano.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
2.	Spesso mi sembra di vivere degli eventi esattamente come mi fossero già capitati prima (déjà vu)	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
3.	A volte sento l'odore o il sapore di cose che gli altri non riescono a sentire.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
4.	Spesso sento suoni insoliti come esplosioni, schiocchi, sibili, schianti o squilli nelle orecchie	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
5.	A volte mi sono sentito confuso sulla natura reale o immaginaria di una esperienza	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
6.	Guardandomi allo specchio o guardando un'altra persona, ho visto il volto cambiare davanti ai miei occhi.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
7.	Divento estremamente ansioso quando incontro qualcuno per la prima volta.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
8.	Ho visto cose che altri apparentemente non riescono a vedere	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
9.	I miei pensieri sono talvolta così forti che posso quasi udirli	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
10.	A volte colgo un significato speciale nelle pubblicità, nelle vetrine dei negozi o nel modo in cui sono disposti gli oggetti intorno a me.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
11.	A volte mi sono sentito come se non avessi controllo sulle mie idee o pensieri	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
12.	Talvolta mi capita di essere distratto all'improvviso da suoni distanti ai quali normalmente non presto attenzione	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
13.	Ho sentito cose che gli altri non riescono a sentire, come voci di gente che bisbiglia o che parla.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
14.	Ho spesso la sensazione che gli altri ce l'abbiano con me.	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
15.	Ho avuto la sensazione che qualche persona o forza mi stia accanto anche se non posso vederla	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3
16.	Ho l'impressione che parti del mio corpo siano cambiate in qualche modo, o che funzionino in modo diverso da prima	☐ Vero	☐ Falso	☐ 0	☐ 1	☐ 2	☐ 3

Hai risposto a tutti gli item? Grazie per aver compilato il questionario

Adattamento italiano a cura di Andrea Raballo, Giorgio D. Kotzalidis, Valeria Savoja, Andrea Solfanelli, Antonio Preti, Università di Roma "Sapienza", 2012.
Italian version based on:
PQ–92 Rachel Loewy, Adrian Raine, Tyrone Cannon © UCLA 2002
Authorized Italian version by Giorgio D. Kotzalidis, Valeria Savoja, Andrea Solfanelli, University of Rome "La Sapienza",2011
PQ–B Rachel Loewy, Tyrone D. Cannon, © University of California 2010
Authorized Italian version by Antonio Preti, Andrea Raballo, Studio CAPIRE: Cagliari – Psychosis: Investigation on Risk Emergence, 2011.

Appendix S4

The Italian version of the Brief (21-item) Prodromal Questionnaire (iPQ-B)

(Source: Loewy RL, Pearson R, Vinogradov S, et al. *Psychosis risk screening with the Prodromal Questionnaire-Brief version (PQ-B)*. Schizophr Res 2011;129:42-6).
(Authorized Italian version by Preti A, Raballo A. Studio CAPIRE. *Cagliari Psychosis: Investigation on Risk Emergence*, 2011).

Per cortesia, indica se hai avuto i seguenti pensieri, sentimenti ed esperienze nel corso dell'ultimo mese segnando "Sì" o "No" per ciascuna domanda. **Non tenere conto di esperienze che si verificano sotto influenza di alcol, droghe o farmaci che non ti erano stati prescritti**. Se rispondi "Sì" a una domanda indica anche quanto disagio ti ha causato quell'esperienza [quanto spiacevole è stata per te quell'esperienza].

1. Capita talvolta che gli ambienti abituali ti sembrino strani, confusi, minacciosi o irreali?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

2. Hai mai sentito suoni insoliti come esplosioni, schiocchi, sibili, schianti o squilli nelle tue orecchie?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

3. Le cose che vedi ti appaiono differenti dal modo in cui sono abitualmente (più luminose o più scure, più larghe o più piccole, comunque cambiate in qualche modo)?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

4. Hai avuto esperienze con la telepatia, le forze psichiche o la predizione del futuro?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

5. Ti sei sentito come se non avessi controllo sulle tue idee o pensieri?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

6. Hai difficoltà a spiegarti, perché fai troppe digressioni o devi dal filo del discorso quando parli?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

7. Hai l'impressione o la convinzione di essere dotato in modo particolare o di possedere un talento speciale?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

8. Hai l'impressione che altre persone ti stiano tenendo d'occhio o parlino di te?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

9. Hai talvolta sensazioni strane sulla pelle o appena al di sotto, come insetti che camminano?
☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo

10. Ti capita talvolta di essere distratto all'improvviso da suoni distanti dei quali generalmente non sei consapevole? [ai quali normalmente non presti attenzione]

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

11. Hai la sensazione che qualche persona o forza ti stia accanto anche se tu non puoi vederla?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

12. Ti preoccupi talvolta del fatto che qualcosa nella tua mente non funzioni correttamente?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

13. Hai mai avuto la sensazione di non esistere, o che il mondo non esiste, o di essere morto?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

14. Qualche volta ti sei sentito confuso sulla natura reale o immaginaria di un'esperienza?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

15. Hai delle idee o delle convinzioni che altre persone troverebbero insolite o bizzarre?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

16. Senti che parti del tuo corpo sono cambiate in qualche modo, o che funzionano in modo diverso?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

17. I tuoi pensieri sono talvolta così forti che puoi quasi udirli?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

18. Ti capita di provare sfiducia o essere sospettoso riguardo alle altre persone?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

19. Hai visto oggetti insoliti come bagliori, fiamme, lampi accecanti o figure geometriche?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

20. Hai visto cose che altri non riescono a vedere o non sembrano notare?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

21. Capita talvolta che le persone abbiano difficoltà a capire quello che stai dicendo?

☐ **SI** ☐ **NO** ***Se Sì:*** Quando capita, mi sento spaventato, preoccupato, o comunque la cosa mi crea problemi: ☐ Fortemente in disaccordo ☐ In disaccordo ☐ Indifferente ☐ D'accordo ☐ Fortemente d'accordo

Appendix S5 – The approved Italian version of the ASI (Preti and Raballo, 2011).

Cognome ……..Nome…….……Data…….

Siamo interessati a studiare il tipo di atteggiamento e le esperienze di vita che le persone hanno. Il seguente questionario contiene delle domande su atteggiamenti ed esperienze di vita. Per cortesia, risponda "sì" oppure "no" facendo un cerchio attorno alla risposta corrispondente. Quando fa riferimento alle sue personali esperienze, non tenga conto di atteggiamenti, sensazioni, o esperienze vere e proprie che potrebbe avere avuto sotto l'effetto dell'alcool o di altre droghe (ad esempio, marijuana, LSD, cocaina).

1) Ti succede mai che certe cose, anche banali e quotidiane, acquistino improvvisamente un significato o un´importanza particolare per te?	Si	No
2) Ti capita a volte di sentirti come se fossi sull'orlo di qualcosa di veramente grande o magnifico, ma che non riesci a definire?	Si	No
3) Ti capita a volte di avere l´impressione che i tuoi sensi siano diventati particolarmente acuti o recettivi?	Si	No
4) Ti capita mai di sentirti come se stessi rapidamente raggiungendo la massima acutezza o intensità delle tue capacità mentali?	Si	No
5) Ti succede di fare talvolta caso a dettagli minori o a particolari cui prima non facevi attenzione e che ora ti sembrano importanti?	Si	No
6) A volte, senti il bisogno di fare chiarezza su qualcosa, anche se non sei sicuro di che cosa si tratta?	Si	No
7) Ti capita mai di attraversare periodi in cui ti senti particolarmente religioso o interessato ad esperienze di tipo mistico?	Si	No
8) Ti capita mai di avere difficoltà a distinguere se sei inquieto, impaurito, preoccupato o in ansia?	Si	No
9) Hai mai delle fasi o dei periodi durante i quali la tua coscienza ti pare dilatata o particolarmente intensa?	Si	No
10) Senti mai il bisogno di dare un senso a situazioni o eventi apparentemente casuali, come coincidenze o incontri occasionali?	Si	No
11) Ti capita a volte di sentirti come se stessi sul punto di trovare il pezzo mancante di un puzzle?	Si	No
12) A volte hai la sensazione di poter udire o avvertire i suoni in modo più distinto del solito?	Si	No
13) Ti capita mai di cogliere un significato insolitamente importante in cose a cui abitualmente non presti particolare attenzione?	Si	No
14) Ti capita talvolta che osservazioni o frasi normalmente di scarso rilievo, assumano un significato sfavorevole, quasi di malaugurio?	Si	No
15) Ti capitano delle fasi o dei periodi in cui, talvolta, certe canzoni sembrano contenere un significato importante per la tua vita?	Si	No
16) A volte, attribuisci un´importanza particolare a cose o oggetti che normalmente trascuri?	Si	No
17) A volte, hai l´impressione di essere sul punto di scoprire qualcosa di realmente grande o importante, ma di non sapere esattamente di cosa si tratta?	Si	No
18) Ti è mai successo di sentire i sapori più intensamente, come se il tuo senso del gusto si fosse fatto più acuto?	Si	No
19) Ti succede mai di avere l´impressione che i misteri del cosmo si stiano rivelando a te?	Si	No
20) Hai delle fasi o dei periodi in cui ti senti eccessivamente eccitato da cose o esperienze che sono normalmente gestibili?	Si	No
21) Ti capita spesso di essere affascinato o attratto dalle piccole cose intorno a te?	Si	No
22) Ti capita mai che i tuoi sensi sembrino eccezionalmente acuti, chiari o penetranti?	Si	No
23) Ti capita mai di sentire come se un intero mondo ti si stesse rivelando?	Si	No
24) Avverti mai la sensazione che i confini tra il tuo mondo interno e quello esterno siano svaniti?	Si	No
25) Ti capita di avere a volte la sensazione che il mondo stia	Si	No

cambiando e te ne domandi il motivo?		
26) Ti capita mai di avere una sensazione di urgenza inesprimibile, e di non sapere bene cosa fare?	Si	No
27) Ti è successo di essere talvolta particolarmente incuriosito da persone, eventi, luoghi, o idee che normalmente non avrebbero alcun interesse per te?	Si	No
28) Ti succede mai che i tuoi pensieri e percezioni diventino così rapidi da non riuscire più a seguirli o assimilarli?	Si	No
29) Ti capita di notare, talvolta, cose cui prima non avevi fatto caso e che assumono un significato particolare?	Si	No

Legend – ASI = Aberrant Salience Inventory.