

# Characterization of young people with first episode psychosis or at ultra-high risk: the Reggio Emilia At-Risk Mental States (ReARMS) program

## *Caratterizzazione dei pazienti con primo episodio di psicosi o stato mentale a ultra-high risk: il programma ReARMS (Reggio Emilia At-Risk Mental States)*

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**SUMMARY. Aim.** Twenty years of research on the Ultra-High Risk (UHR) paradigm have shown the importance of early intervention in psychosis (EIP) in reducing its severity and persistence. From September 2012, the Reggio Emilia Department of Mental Health developed a specific care pathway (the Reggio Emilia At-Risk Mental States [ReARMS] protocol) as an diffused, “liquid” EIP infrastructure branched within the network of all its adult and child/adolescent mental health service, aimed to offer an evidence-based, expertise-driven protocol of care to young people with a First Episode Psychosis (FEP) or an UHR mental state. Aim of the current study was to investigate patterns of referral to the ReARMS protocol during the first five years of clinical activity. **Methods.** All participants (n=300) were help-seeking adolescents and young adults, aged 13-35 years, who completed an ad-hoc socio-demographic/clinical schedule and the Comprehensive Assessment of At-Risk Mental States (CAARMS). **Results.** Among individuals who completed the baseline assessment, 95 (31.7%) did not comply with UHR/FEP defined criteria (UHR- subgroup), while 205 (68.3%) were offered the ReARMS protocol: of them, 154 (75.1%) accepted and were enrolled in the program, 19 (9.3%) refused, and 32 (15.6%) dropped out during the first year of treatment. In comparison with UHR- and UHR, FEP patients showed higher percentages of history of substance abuse and previous hospitalization, as well as higher levels of psychopathology and functioning. Individuals entering the ReARMS protocol were mainly referred by emergency room/general hospital, general practitioners, or they were self-referred. **Conclusions.** EIP on young subjects at UHR of psychosis (together with FEP patients) in Italian public mental health services is clinically relevant, feasible, and recommended, also in adolescence, where there is a specific high risk of falling through the child adult service gap.

**KEY WORDS:** early intervention psychosis, early psychosis, ultra-high risk, mental health services, referral procedures.

**RIASSUNTO. Scopo.** Vent'anni di ricerca sul paradigma dell'Ultra-High Risk (UHR) hanno mostrato l'importanza dell'intervento precoce nel ridurre la severità e la persistenza delle psicosi. Dal settembre 2012, il Dipartimento di Salute Mentale di Reggio Emilia ha sviluppato uno specifico percorso di cura (il protocollo ReARMS [Reggio Emilia At-Risk Mental States]) come infrastruttura “liquida” di intervento precoce ramificata all'interno di tutta la rete dei centri di salute mentale per adulti e dei servizi di neuropsichiatria infantile, al fine di offrire un programma di cura basato sulle evidenze a giovani affetti da primo episodio di psicosi (PEP) o con stato mentale UHR. Scopo del presente studio è analizzare le modalità di invio al protocollo ReARMS nei primi 5 anni di attività clinica. **Metodi.** Tutti i partecipanti (n=300) sono giovani help-seeker, di età compresa fra i 13 e i 35 anni, che hanno completato una scheda socio-demografica e il Comprehensive Assessment of At-Risk Mental States (CAARMS). **Risultati.** Tra i soggetti che hanno completato l'assessment, 95 (31,7%) non hanno soddisfatto i criteri diagnostici di UHR/PEP (sottogruppo UHR-), mentre a 205 (68,3%) è stato offerto il protocollo ReARMS: di questi ultimi, 154 (75,1%) sono stati arruolati nel programma, 19 (9,3%) hanno rifiutato e 32 (15,6%) hanno abbandonato il percorso durante il primo anno di trattamento. In confronto ai soggetti UHR- e UHR, i pazienti PEP hanno percentuali più elevate di storia d'abuso di sostanze e di pregressa ospedalizzazione, così come livelli più severi di psicopatologia e decremento del funzionamento. Le modalità di invio principali sono avvenute tramite i medici di medicina generale e il pronto soccorso. **Conclusione.** L'intervento precoce nelle psicosi è fattibile e clinicamente rilevante nei servizi pubblici di salute mentale adulta e infantile, soprattutto in adolescenza, dove il rischio di abbandono dei percorsi di cura è particolarmente elevato.

**PAROLE CHIAVE:** intervento precoce nelle psicosi, psicosi precoce, ultra-high risk, servizi salute mentale, modalità di invio.

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### INTRODUCTION

In the last 20 years, since the seminal work of McGorry<sup>1</sup>, the paradigm of Early Intervention in Psychosis (EIP) has gained increased attention in the scientific community. Specifically, it has germinated focused protocols of care that have been implemented in EIP programs, as well as in autonomous EIP services within the mental health care network of different countries<sup>2</sup>. Systematic review of the evidence for service models delivering EIP suggested that early detection and intervention on individuals with First Episode Psychosis (FEP) reduced inpatient care, treatment drop-out, morbidity and related disability, also improving both short-term and long-term outcomes<sup>3-5</sup>. As psychoses are one of the main determinants to the global burden of disease in the world, leaving these patients untreated may have serious consequences in terms of health, functioning, and quality of life, as well as in costs for the society related to lost opportunities, unemployment, and long-term treatment<sup>6</sup>.

### 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)<sup>7</sup>. This community mental health care system appears to be particularly favorable for the implementation of the EIP paradigm within the Italian public psychiatric services<sup>2</sup>.

Since the innovative boost of Programma 2000 (1999), the first service in Italy specifically targeting the early detection and intervention on young individuals with FEP<sup>8</sup>, 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 evidence-based protocols<sup>9</sup>. In September 2012, after being involved in the GET-UP trial (a study protocol aimed to evaluate the 9-month effectiveness and 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)<sup>10</sup>, the General Direction of the Emilia-Romagna region financed a project (Progetto Regionale Esordi Psicotici [PREP]) in order to implement innovative protocols of intervention based on the EIP model within all the regional departments of mental health<sup>11</sup>.

Under the aegis of PREP, 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 (stand-alone) departmental service, but through a diffused ("liquid") infrastructure within the network of all the Reggio Emilia Adult and Child/Adolescent Mental Health Services (a semi-urban catchment area of approximately 550.000 inhabitants, in the northern Italy)<sup>12-14</sup>. ReARMS program was established in order to offer a dedicated, evidence-based and expertise-driven protocol of care to adolescents and young adults with FEP or in the prodromal phase of psychosis<sup>15</sup>.

Aim of the current study was to examine socio-demo-

graphic, clinical, and psychopathological characteristics of young help-seeking individuals entering the ReARMS protocol in the first five years from its implementation, as well as to investigate their patterns of referrals.

### METHODS

#### Participants

Data were collected during the baseline routine assessment of help-seeking adolescents and young adults recruited in the ReARMS protocol between September 2012 and December 2017. All participants (n=311) and their parents (if minors) agreed to participate to the research and gave their written 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 experimental 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 Comprehensive Assessment of At-Risk Mental States (CAARMS)<sup>16</sup> or (d) a Duration of Untreated Psychosis (DUP, defined as the period of treatment delay [in weeks] between the onset of psychotic symptoms and pharmacotherapy initiation)<sup>17</sup> <2 years in case CAARMS-defined FEP criteria are detected at baseline assessment. Indeed, within the EIP paradigm, a DUP less than 24 months is considered the limit to start a specific EIP protocol of care<sup>18</sup>.

According to CAARMS operational criteria<sup>16</sup>, UHR status is defined as follows: (a) Attenuated Psychotic Symptoms (APS), including individuals with sub-threshold positive psychotic symptoms during the past year; (b) Brief, Limited, and Intermittent Psychotic Symptoms (BLIPS), comprising subjects 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 people 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<sup>16</sup>, the threshold of full-blown psychotic episode 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 psychosis, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR)<sup>19</sup>; (b) history of previous exposure to antipsychotics; (c) current substance dependence, according to the DSM-IV-TR<sup>19</sup>; (d) known intellectual disability (IQ <70); and (e) neurological disorders, head injury or any other medical condition associated with psychiatric symptoms. In this protocol, 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<sup>16</sup>, 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<sup>12,20</sup>. In the current study, the following standardized instruments were considered:

- An *ad hoc* 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 enrollment), previous specialist contact (both as single consultation and taking charge at Child/Adolescent or Adult Mental Health Services [CAMHS and AMHS]), DUP, 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)<sup>21</sup>. DUI and DUP were based on interviews with the patient and of at least one key informant (in this population, generally a parent).
- 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)<sup>16</sup>. 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]) that can be clustered in seven 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<sup>16</sup>. CAARMS interviews were conducted by clinical psychologists, psychiatrists, and neuropsychiatrists trained by the main author of the approved Italian translation (CAARMS-ITA)<sup>22</sup>, 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<sup>23</sup>.

The axis-I diagnosis was made according to DSM-IV-TR criteria<sup>19</sup> by two trained ReARMS team members, using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I)<sup>24</sup>. After CAARMS interviews, participants were divided into three groups according to UHR/psychosis criteria<sup>16</sup>: (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-seekers referred to the ReARMS protocol were assigned to a multi-professional team, generally within 2-3 weeks. 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 (for details, see also Supplementary Materials published online only at [www.rivistadipsichiatria.it](http://www.rivistadipsichiatria.it)).

According to their symptoms, FEP and UHR individuals were then provided with a comprehensive two-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), according

to current guidelines<sup>11,25,26</sup>. 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<sup>25,26</sup>. Low-dose atypical antipsychotics were used. Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depressive symptoms, anxiety, and insomnia. Interventions provided to all individuals/relatives were supervised by a team of departmental experts.

As the specific aim of this study was to characterize young people entering the ReARMS program, it is necessary to underline that in this protocol early identification of individuals with FEP or UHR mental states was a 2-step procedure. The first screening step included a triage service using the Screening Schedule for Psychosis (SS)<sup>27</sup>, performed by general service staff members (for details, see also Supplementary Materials). The second step consisted of the CAARMS interview to investigate the clinical status (i.e. psychosis risk, psychosis, or neither)<sup>16</sup>, 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<sup>12</sup>.

## Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0<sup>28</sup>. 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 variables. 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 variables 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  $\leq 5$ ) were employed for categorical data. Pearson's  $r$  or Spearman's  $\rho$  correlation coefficients were used to examine associations between two variables.

## RESULTS

A total of 311 subjects (175 males [56.3%]; mean age at entry =  $21.26 \pm 5.83$  years) have been consecutively referred to the ReARMS protocol since its establishment (available data were from September 2012 to December 2017). Among these, 11 did not complete the baseline assessment (Figure 1).

Among those who completed the baseline assessment ( $n=300$ ), 95 (31.7%) individuals did not meet UHR/FEP defined criteria (12) and were grouped as UHR-. Therefore, 205 (68.3%) participants were offered a dedicated protocol of care: of them, 154 (75.1%) 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). However, the UHR- cases and those who refused the ReARMS intervention received appropriate advice for future treatment (Figure 2).

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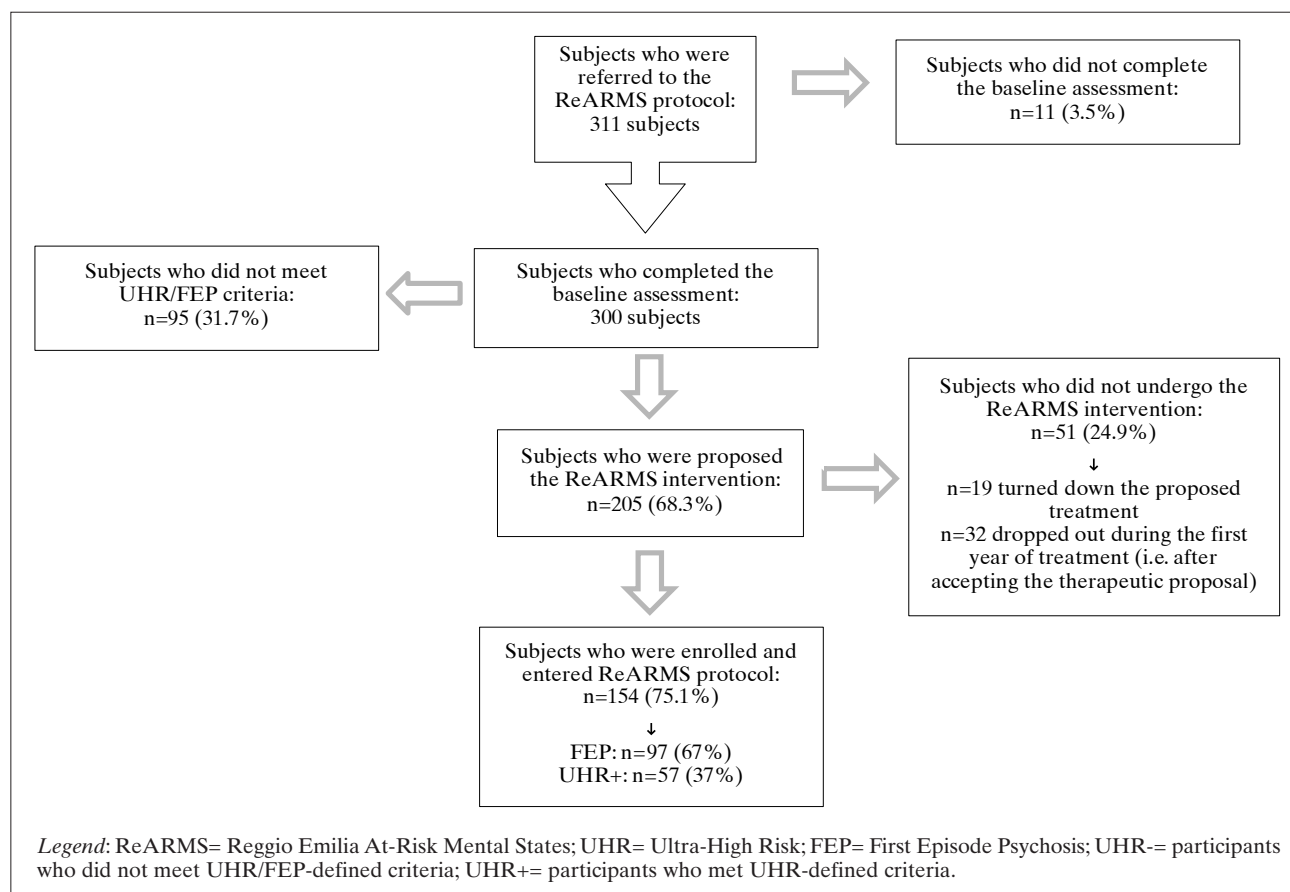


Figura 1. Flowchart of referrals to the ReARMS protocol (available data from September 2012 to December 2017) (n=311).

Among the UHR+ group (n=79; 26.3% of the total sample who completed the baseline assessment), 72 met APS criteria (91.1% of the UHR+ subgroup), 3 met BLIPS criteria, and 4 met GRFD criteria. Major depression was the most frequent diagnosis (n=40; 50.6%) at initial examination, followed by anxiety disorders (n=22; 27.8%), schizotypal personality disorder (n=14; 17.7%), and brief psychotic disorder (n=3; 3.9%).

The FEP group (n=126; 42% of the total sample) consisted of patients with DSM-IV-TR schizophrenia (n=56; 44.4%), psychotic disorder not otherwise specified (n=31; 24.6%), affective (bipolar or major depressive) psychosis (n=30; 23.8%), and substance-induced psychotic disorder (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%), anxiety disorders (n=29; 30.5%), and non-schizotypal personality disorder (n=27; 28.4%) (specifically borderline, avoidance, or narcissistic personality disorder).

The socio-demographic and clinical variables and the mean ratings of SOFAS and CAARMS subscales in the total sample who completed the baseline assessment (n=300) and in the three subgroups are reported in Table 1.

## Sociodemographic and clinical data

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

FEP subjects had also significantly higher percentages of history of substance abuse, previous hospitalization, and previous compulsory mental health treatment than the other two subgroups. Moreover, in comparison with UHR- individuals, FEP patients showed a significantly higher frequency of family psychiatric history. However, although a family psychiatric history was more frequent in the FEP group than in UHR+ subjects and in the UHR+ sample than in UHR- individuals, these differences were not significant (respectively,  $\chi^2=1.99$ ,  $p=0.183$  and  $\chi^2=1.34$ ,  $p=0.247$ ). No between-group difference in terms of DUI and percentages of first-degree relative with psychosis, history of attempted suicide, and previous specialist contact was found.

## Psychopathology and functioning

There was a significant between-group difference in SOFAS scores (Table 1). In details, following a dimensional gra-



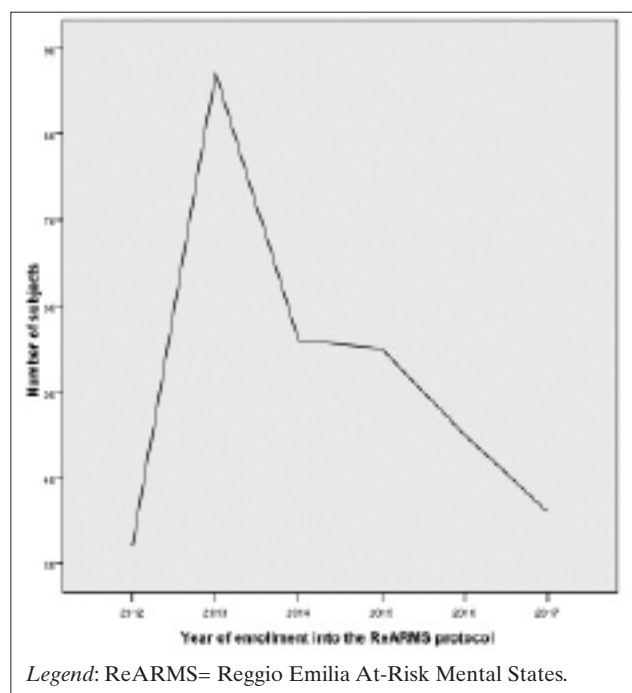


Figure 2. Enrollment into the ReARMS protocol (available data from September 2012 to December 2017) (n=311).

dient of severity, SOFAS scores of the FEP group were significantly lower than those in UHR+ individuals, who had significantly lower SOFAS scores than UHR- subjects.

As expected, CAARMS “Positive Symptoms” dimension scores in the UHR+ group were significantly higher than those in UHR- individuals, but significantly lower than those in FEP patients (Table 1). The same significant increasing trend of severity in CAARMS “Cognitive Change”, “Emotional Disturbance”, and “Behavioral Change” subscale scores was also found.

Differently, CAARMS “Negative Symptoms” and “General Psychopathology” subscores of FEP and UHR+ individuals were significantly higher than those in the UHR- group (Table 1). However, although negative symptoms and general psychopathology were slightly higher in FEP patients than in the UHR+ sample, these differences were not significant (respectively,  $Z=-0.74$ ,  $p=0.456$  and  $Z=-0.64$ ,  $p=0.520$ ). Moreover, the FEP group showed significantly higher CAARMS “Motor/Physical Changes” subscale scores only than UHR- individuals. Indeed, although FEP patients had more severe motor/physical changes than UHR+ subjects, this difference was not significant ( $Z=-1.35$ ,  $p=0.176$ ). Finally, no significant between-group difference in CAARMS “Motor/Physical Changes” subscores between UHR+ and UHR- subgroups was found ( $Z=-1.51$ ,  $p=0.131$ ).

### Patterns and correlates of referral

The vast majority of individuals enrolled in the ReARMS protocol were mainly referred by general practitioners

(33.3%), emergency room/general hospital (24%), or they were self-referred (15%) (Table 2). In particular, compared to 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 (respectively,  $\chi^2=8.21$ ,  $p=0.040$  and  $\chi^2=15.95$ ,  $p=0.001$ ). Differently, in comparison with UHR+ and UHR-, FEP subjects were significantly less often self-referred (respectively,  $\chi^2=4.61$ ,  $p=0.032$  and  $\chi^2=5.86$ ,  $p=0.015$ ) or referred by school/social services (respectively,  $\chi^2=5.52$ ,  $p=0.035$  and  $\chi^2=4.28$ ,  $p=0.049$ ) to the ReARMS protocol. However, no between-group differences in terms of referral by general practitioners, family members, and private/public mental health care professionals were found (Table 2).

Referrals to the ReARMS protocol exponentially increased during the first year of implementation of the program in the Reggio Emilia Department of Mental Health (n=86 subjects enrolled per year in 2013). Then, it decreased in the following years and settled down to an enrollment rate value of 36 subjects per year in 2017 (Figure 1).

In details, referral rate decrease was statistically significant for referral by school/social services in UHR+/FEP sample (i.e. year versus number of referrals: Spearman’s  $\rho=-0.999$ ;  $p=0.033$ ) and for referral by general practitioners only in the FEP group (Spearman’s  $\rho=-0.964$ ;  $p=0.002$ ). Moreover, although DUP and DUI decreased over time, this change was not statistically significant neither in FEP (i.e. year versus DUP: Spearman’s  $\rho=-0.024$ ;  $p=0.781$ ) nor in UHR+ individuals (i.e. year versus DUI: Spearman’s  $\rho=-0.014$ ;  $p=0.791$ ) (see also supplementary materials [Table S1]).

FEP patients who joined ReARMS protocol through emergency room/general hospital (i.e. the most FEP subjects enrolled) showed significantly higher CAARMS “Negative Symptoms” subscore than those who contacted it via other referral sources or by self-referral ( $10.32\pm3.99$  vs  $8.56\pm4.64$ ;  $Z=-1.99$ ;  $p=0.049$ ). However, no between-group difference in terms of DUI, DUP, SOFAS and the other six CAARMS subscale scores was found (see also supplementary materials [Table S2]).

UHR+ individuals who were self-referred or referred by school/social services to the ReARMS protocol (i.e. the most UHR+ subjects enrolled that significantly differed from FEP patients in terms of source of referral) had significantly lower SOFAS scores ( $38.81\pm8.45$  vs  $46.87\pm8.70$ ;  $Z=-2.24$ ;  $p=0.025$ ) and higher CAARMS “Cognitive Change” subscores ( $5.63\pm2.34$  vs  $4.62\pm2.33$ ;  $Z=-1.96$ ;  $p=0.049$ ) than those who joined it through other referral sources. However, no between-group difference in terms of DUI and the other six CAARMS subscale scores was found (see supplementary materials [Table S3]).

Finally, family involvement was not related to DUP, DUI, SOFAS and CAARMS dimension subscale scores in either sample.

### DISCUSSION

The ReARMS protocol is the first example of diffused (“liquid”) EIP program in Italy that specifically involved CAMHS and recruited adolescents and young people meeting specific (CAARMS-defined) diagnostic criteria for an

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Table 1. Demographic, clinical, functional, and psychopathological 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/ 2)	Post hoc test
Gender (males)	165 (55.5%)	45 (47.4%)	36 (45.6%)	84 (66.7%)	12.00b	FEP>UHR+=UHR-
Ethnic group (Caucasian)	259 (86.3%)	80 (84.2%)	69 (87.3%)	110 (87.3%)	0.53	-
Marital status					8.75	-
<i>Unmarried</i>	277 (92.3%)	83 (87.4%)	78 (98.7%)	116 (92.1%)		
<i>Married</i>	20 (6.7%)	11 (11.3%)	1 (1.3%)	8 (6.3%)		
<i>Separated/divorced</i>	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 <sup>a</sup>	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 <sup>c</sup>	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	-
<i>DUP (in weeks)</i>	-	-	-	46.98±48.49		
History of substance abuse	94 (31.3%)	24 (25.3%)	14 (17.7%)	56 (44.4%)	18.50 <sup>a</sup>	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 (48.4%)	43.14 <sup>a</sup>	FEP>UHR+=UHR-
<i>Previous compulsory mental health treatment</i>	22 (7.3%)	1 (1.1%)	1 (1.3%)	20 (15.9%)	23.32 <sup>a</sup>	FEP>UHR+=UHR-
Previous specialist contact	145 (48.3%)	51 (53.7%)	39 (49.4%)	55 (43.7%)	2.23	-
SOFAS	48.37±11.45	58.25±9.75	46.18±8.97	42.77±9.18	122.29 <sup>a</sup>	UHR->UHR+>FEP
CAARMS						
<i>Positive Symptoms</i>	10.76±6.53	3.89±3.19	10.28±4.08	16.29±4.16	197.41 <sup>a</sup>	FEP>UHR+>UHR-
<i>Cognitive Change</i>	4.73±2.61	2.89±1.61	4.92±2.37	6.01±2.57	81.11 <sup>a</sup>	FEP>UHR+>UHR-
<i>Emotional Disturbance</i>	5.42±3.94	2.80±2.63	5.86±3.29	7.14±4.12	69.37 <sup>a</sup>	FEP>UHR+>UHR-
<i>Negative Symptoms</i>	7.39±4.58	4.14±3.55	8.68±3.66	9.04±4.52	70.92 <sup>a</sup>	FEP=UHR+>UHR-
<i>Behavioral Change</i>	10.32±5.48	6.12±4.93	11.28±4.18	12.92±4.57	87.78 <sup>a</sup>	FEP>UHR+>UHR-
<i>Motor/Physical Changes</i>	3.92±3.99	2.84±2.98	3.78±3.73	4.82±4.60	9.56 <sup>b</sup>	FEP>UHR-
<i>General Psychopathology</i>	15.08±6.42	12.48±6.34	16.13±6.32	16.54±5.77	23.52 <sup>a</sup>	FEP=UHR+>UHR-
<i>Legend:</i> DUI= Duration of Untreated Illness (in weeks); DUP= Duration of Untreated Psychosis (in weeks); SOFAS= Social and Occupational Functioning Assessment Scale; 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 ( $\chi^2$ ), and Chi-squared test ( $\chi^2$ ) values are reported; ap<0.001; bp<0.01; cp<0.05.						

UHR mental state (together with FEP patients)<sup>12-14</sup>. Specifically, main reasons that supported the decision to implement the ReARMS protocol within the network of all the CAMHS and AMHS of the Reggio Emilia Department of Mental Health were: (a) to improve the quality of treatments and outcomes, establishing a specialized EIP program aimed to early detection and intervention in UHR and FEP young

people, according to well-defined, state-of-art guidelines on the topic; (b) to reduce the variability of treatments; (c) to shorten DUP and DUI, as well as the time between the onset of relevant psychiatric symptoms and an integrated case management by local mental health services in order to promote a clinical, social, and personal recovery as wide and as early as possible; and (d) to reduce personal and social stig-

Table 2. Patterns of referral to the ReARMS protocol 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 ( $\chi^2$ )	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 <sup>a</sup>	FEP>UHR+=UHR-
Self-referral	45 (15.0%)	19 (20.0%)	15 (19.0%)	11 (8.7%)	6.73 <sup>c</sup>	UHR-=UHR+>FEP
Family involvement	37 (12.3%)	12 (12.6%)	8 (10.1%)	17 (13.5%)	0.52	-
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 <sup>c</sup>	

UHR+=UHR->FEP Legend: ReARMS= Reggio Emilia At-Risk Mental States; 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 ( $\chi^2$ ) values are reported; ap<0.001; bp<0.01; cp<0.05.

ma associated with psychosis, promoting social and interpersonal inclusion<sup>29</sup>. In this regards, a “liquid” infrastructure was preferred to ensure the best possible local dissemination of ReARMS interventions, as well as their highest supply to the users.

Approximately 300 young individuals, aged 13-35 years, have been consecutively referred to the ReARMS protocol in the five years following its establishment. In comparison with referral rates reported in Programma 2000 studies (i.e. about 400 subjects, aged 17-30 years, in 11 years of clinical activity)<sup>2,9,18</sup>, our finding is clearly higher, suggesting that a diffused (“liquid”) infrastructure, specifically involving all 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, the Programma 2000 was developed as centralized (stand-alone) service within the Department of Mental Health of the Niguarda Ca’ Granda Hospital (a catchment area catering to approximately 200.000 inhabitants)<sup>18</sup>.

However, it is also important to emphasize a progressive decrease of ReARMS referral rates over time, after a definitely high peak occurred during the first year from its establishment. This temporal reduction appears to be statistically significant for referral by school/social services in UHR+/FEP mixed sample and for referral by general practitioners exclusively in the FEP group. Therefore, more attention should be paid to all the potential sources of referral to EIP services (e.g., general practitioners, emergency room, general hospitals, family members, school, and social agencies) through awareness campaigns and professional training courses. However, in comparison with Programma 2000 findings (i.e. a mean of 20 subjects enrolled per year), ReARMS enrollment rates remained overall higher, even in 2017, when it has been reached a value of 36 individuals enrolled per year.

Among subjects who completed the ReARMS assessment battery at baseline, about one third (31.7%) did not

meet UHR/FEP-defined criteria. Therefore, 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 et al.<sup>18</sup> in Programma 2000 11-year longitudinal study (i.e. 25.4% = subjects who were rejected because they did not comply with UHR 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). Our findings confirm that EIP programs are commonly well accepted by adolescent and young adult help-seekers, with a low 1-year rate of dropped-out individuals<sup>4</sup>.

The baseline prevalence of UHR diagnosis among individuals entering the ReARMS protocol was 26.3%. This is similar to what observed in Italian comparable studies (24.7%; 18.9%)<sup>18,30</sup>. In line with other findings reported in the literature<sup>31,32</sup>, 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%). These results confirm that persons who merit clinical care within the UHR paradigm have multiple psychopathology issues apart from attenuated psychotic symptoms<sup>33,34</sup>. Therefore, 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<sup>35</sup>.

Similarly, the baseline prevalence of FEP diagnosis (42%) among patients entering the ReARMS protocol was consistent with what reported (46.2%) in the first eleven years of activity of Programma 2000<sup>18</sup>, with schizophrenia as markedly prevalent DSM-IV-TR diagnosis (approximately 45%).

### *Characterization of young people with first episode psychosis or at ultra-high risk*

In line with findings reported in other Italian comparable studies<sup>18,36</sup>, FEP patients assessed in the ReARMS protocol showed a preponderance of males and a significantly higher mean age at entry than UHR+ and UHR- subgroups. This confirms the well-known earlier onset of psychosis in males, especially in early adulthood<sup>37</sup>.

Differently, UHR mental states occur more frequently in adolescence: hence the importance of overcoming the child-adult service gap and implementing reformed service models that are specifically geared to meeting the unique needs of adolescents, are not strictly aligned to chronology and rigid diagnostic boundaries, and provide high quality, evidence-based early interventions that promote a secondary prevention of psychosis<sup>38,39</sup>.

FEP patients entering the ReARMS protocol had also significantly higher percentages of history of substance abuse, previous hospitalization, and previous compulsory mental health treatment than UHR+ and UHR- groups. In line with what reported by Cocchi et al.<sup>18</sup> and together with evidence of a significantly poorer social and occupational functioning in FEP subjects (for details, see also Table 1), our findings confirm the greater clinical severity of individuals with first episode psychosis. FEP onset probably 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 self-treatment<sup>40</sup>.

Notably, in addition to a significantly poorer social and occupational functioning than UHR- individuals, UHR subjects assessed in the ReARMS protocol showed negative symptoms and general psychopathology profiles that share similarities in severity with that of FEP patients. In line with what reported in other studies<sup>33,41</sup>, high levels of negative symptoms and general psychopathology (such as anxiety and depression) could significantly limit psychosocial functioning of people at UHR of psychosis, leading to a severe impairment of academic or occupational performance, as well as to difficulties with interpersonal relationships<sup>42,43</sup>. Moreover, these findings also confirm that negative symptoms and multiple aspects of general psychopathology could represent earlier features which mark the prodromal phase of psychosis, especially in adolescence and adulthood<sup>44</sup>.

Finally, from a strictly psychopathological point of view, in addition to positive symptoms (as expected), also cognitive change, emotional disturbance, and behavioral change in the UHR+ and FEP groups were significantly higher than those in the UHR- individuals, showing an increasing trend of severity. This suggests their further specific sensitivity in signaling an imminent risk of psychosis and in making an in-depth risk stratification<sup>15,20,45,46</sup>.

The majority (about 33%) of individuals enrolled in the ReARMS protocol were mainly referred by general practitioners. Differently, in the Programma 2000, patients were more likely to contact EIP program through the referral of a mental health care professional (68.9%)<sup>18</sup>. This finding reflects the close relationship built up over time between CAMHS/AMHS of the Reggio Emilia Department of Mental Health and general practitioners. This historical collaboration is probably further strengthened by the establishment of a "liquid" EIP infrastructure rather than a centralized departmental service. Indeed, this model could be more capable of creeping widely into the depth of local health care

services 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, especially in a target population of adolescents and young adults.

Compared to other subgroups, FEP patients entering the ReARMS protocol contacted significantly more often emergency room and general hospital (36.5%) as specific settings where formulating their first request for specialist help. This result is in line with what reported by Cocchi et al.<sup>18</sup>, suggesting that FEP patients were more often referred to the Programma 2000 by a public/private mental health care professional. In the current study, FEP subjects who joined ReARMS protocol through emergency room/general hospital showed specifically higher levels of negative symptoms than those who contacted it via other sources of referral or by self-referral. This probably suggests the additional importance of negative dimension (in addition to the positive one) on clinical severity of psychosis, functioning impairment, and hospitalization risk.

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<sup>18,30</sup>. In particular, 62% of UHR subjects joined the Programma 2000 through the referral of a public/private mental health professional<sup>18</sup>. Moreover, UHR+ individuals who were self-referred or referred by school/social services to the ReARMS protocol had a poorer social and occupational functioning, as well as higher cognitive deficits than those who joined it through other sources of referral.

### **LIMITATION OF THE STUDY**

A major methodological limitation of the present study was the sample size, which prevented the execution of multivariate analyses and, in all likelihood, limited the chance of finding associations for some occurrence. Indeed, the lack of between-group differences in some psychopathological and clinical variables (such as DUI or DUP) among different sources of referral most likely could be because each diagnostic subgroup was too small to reliably detect these links.

Furthermore, in the current study we had no control data, either for a site that does not have an established EIP program 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 protocol were the result of changes in public attitudes or in awareness of mental health issue unrelated to the establishment of the EIP service.

### **CONCLUSIONS**

Early detection and intervention on young people at UHR of psychosis or with FEP in Italian CAMHS and AMHS are feasible and clinically relevant, also in adolescence<sup>33,34</sup>. In particular, it is necessary to define evidence-based, individualized pathway of care between CAMHS and AMHS as soon as possible<sup>38</sup>. 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, or experience poor care, leading to high risk of disengagement from services and discontinuity of care<sup>45</sup>. In this context, EIP programs could be an important driving factor for the organizational reform of Italian CAMHS and AMHS.

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 medicine and the other community agencies (i.e. school and social services).

*Conflict of interest:* the authors declare that they have no conflict of interest. This research did not receive any specific grant from funding agency, commercial or not-for-profit sector. ReARMS program is partly financed through a special regional fund: Progetto Esordi Psicotici della Regione Emilia-Romagna.

*Acknowledgments:* the ReARMS technical-scientific multi-professional steering committee was established in 2012 and included in alphabetical order: Azzali Silvia (psychologist), Cioncolini Leonardo (head nurse), Chiri Luigi Rocco (psychologist), Fabiani Michela (child-adolescent psychiatrist), Favazzo Rosanna (psychiatrist), Fontana Francesca (psychiatrist), Garlassi Sara (psychologist), Paterlini Federica (psychologist), Pelizza Lorenzo (psychiatrist), Pensieri Luana (child-adolescent psychologist), Raballo Andrea (psychiatrist), Scazza Ilaria (psychologist), and Semrov Enrico (senior psychiatrist). We wish to thank the all the patients and family members who actively participated to the ReARMS program, and we gratefully acknowledge the facilitating support of Dr. Enrico Semrov and all the other colleagues of the Reggio Emilia Department of Mental Health and Pathological Addiction for their technical and administrative support. Further to that, we wish to thank Dr. Eva Gebhardt that acted as external advisor insuring wide-spread educational training and clinical-supervision support.

*Ethical standards:* the authors declare that relevant ethical approvals were sought for the study and the current research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## REFERENCES

- McGorry PD. Preventive strategies in early psychosis: verging on reality. *Br J Psychiatry* 1998; 172 (suppl. 33): 1-2.
- Cocchi A, Balbi A, Corlito G, et al. Early intervention in psychosis: a feasibility study financed by the Italian Center on Control of Maladies. *Early Interv Psychiatry* 2015; 9: 163-71.
- McGorry PD. Early intervention in psychosis: obvious, effective, overdue. *J Nerv Ment Dis* 2015; 203: 310-8.
- Behan C, Masterson S, Clarke M. Systematic review of the evidence for service models delivering early intervention in psychosis outside the stand-alone centre. *Early Interv Psychiatry* 2017; 11: 3-13.
- Michel C, Toffel E, Schmidt SJ, et al. Detection and early treatment of subjects at high risk of clinical psychosis: definitions and recommendations. *Encephale* 2017; 43: 292-7.
- McEvoy JP. The costs of schizophrenia. *J Clin Psychiatry* 2007; 68 (suppl. 14): 4-7.
- De Girolamo G, Cozza M. The Italian psychiatric reform: a 20-year perspective. *Int J Law Psychiatry* 2000; 23: 197-214.
- Cocchi A, Meneghelli A, Preti A. “Programma 2000”: celebrating 10 years of activity of an Italian pilot programme on early intervention in psychosis. *Aust N Z J Psychiatry* 2008; 42: 1003-12.
- Cocchi A, Cavicchini A, Collavo M, et al. Implementation and development of early intervention in psychosis services in Italy: a national survey promoted by the Associazione Italiana Interventi Precoci nelle Psicosi. *Early Interv Psychiatry* 2015; 12: 37-44.
- Ruggeri M, Bonetto C, Lasalvia A, et al.; the GET-UP group. A multi-element psychosocial intervention for early psychosis (GET UP PIANO TRIAL) conducted in a catchment area of 10 million inhabitants: study protocol for a pragmatic cluster randomized controlled trial. *Trials* 2012; 13: 73.
- Regione Emilia-Romagna. Raccomandazioni regionali per la promozione della salute e del benessere in persone all'esordio psicotico. Bologna: Centro stampa della Regione Emilia-Romagna, 2016.
- Raballo A, Chiri LR, Pelizza L, et al. Field-testing the early intervention paradigm in Emilia-Romagna: the Reggio Emilia At Risk Mental State (ReARMS) project. *Early Interv Psychiatry* 2014; 8: 88.
- Poletti M, Pelizza L, Azzali S, et al. Clinical high risk for psychosis in childhood and adolescence: findings from the 2-year follow-up of the ReARMS project. *Eur Child Adolesc Psychiatry* 2019; 28: 957-71.
- Pelizza L, Poletti M, Azzali S, et al. Suicidal thinking and behavior in adolescents at Ultra-High Risk of psychosis: a two-year longitudinal study. *Suicide Life Threat Behav* 2019; Apr 1; doi: 10.1111/sltb.12549.
- Pelizza L, Raballo A, Semrov E, et al. Validation of the “early detection Primary Care Checklist” in an Italian community help-seeking sample: the “checklist per la Valutazione dell'Esordio Psicotico”. *Early Interv Psychiatry* 2019; 13: 86-94.
- Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry* 2005; 39: 964-71.
- Ran MS, Xiao Y, Chui CHK, et al. Duration of untreated psychosis (DUP) and outcome of people with schizophrenia in rural China: 14-year follow-up study. *Psychiatry Res* 2018; 267: 340-5.
- Cocchi A, Meneghelli A, Erlicher A, Pisano A, Cascio MT, Preti A. Patterns of referral in first episode schizophrenia and ultra-high risk individuals: results from an early intervention program in Italy. *Soc Psychiatry Psychiatr Epidemiol* 2013; 48: 1905-16.
- American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders, IV edition, text revised (DSM-IV-TR). Washington DC: APA Press, 2000.
- Pelizza L, Azzali S, Paterlini F, et al. 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. *Early Interv Psychiatry* 2019; 13: 1513-24.
- Rapp C, Canela C, Studerus E, Walter A, Aston J, Borgwardt S, Riecher-Rössler A. Duration of untreated psychosis/illness and brain volume changes in early psychosis. *Psychiatry Res* 2017; 255: 332-7.
- Raballo A, Semrov E, Bonner Y, Simmons MB. Traduzione e adattamento italiano della CAARMS (the Comprehensive Assessment of At-Risk Mental States). Bologna: Centro Stampa della Regione Emilia-Romagna, 2013.
- Pelizza L, Paterlini F, Azzali S, et al. The approved Italian version of the comprehensive assessment of at-risk mental states (CAARMS-ITA): field test and psychometric features. *Early Interv Psychiatry* 2019; 13: 810-7.
- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I). New York: New York State Psychiatric Institute, 2002.
- National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in children and young people: recognition and management. Leicester: British Psychological Society, 2013.
- Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *Eur Psychiatry* 2015; 30: 388-404.

*Characterization of young people with first episode psychosis or at ultra-high risk*

27. Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures, a World Health Organization ten-country study. *Psychol Med Monogr* 1992; 20 (suppl. 1): 1-97.
28. SPSS Inc. Statistical Package for Social Science (SPSS) for Windows, version 15.0. Chicago (IL): SPSS Inc Press, 2010.
29. Semrov E, Pelizza L, Barbanti Silva V, et al. Percorso Diagnostico-Terapeutico-Assistenziale (PDTA) per la promozione della salute e del benessere nelle persone con disturbo psicotico all'esordio ed in quelle ad alto rischio di esordio. Reggio Emilia: Centro Stampa dell'Azienda USL-IRCCS di Reggio Emilia, 2017.
30. Masillo A, Brandizzi M, Nelson B, et al. Youth mental health services in Italy: an achievable dream? *Early Interv Psychiatry* 2018; 12: 433-43.
31. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. *JAMA Psychiatry* 2016; 73: 113-20.
32. Fusar-Poli P, Raballo A, Parnas J. What is an attenuated psychotic symptom? On the importance of the context. *Schizophr Bull* 2017; 43: 687-92.
33. Pelizza L, Azzali S, Garlassi S, et al. Adolescents at ultra-high risk of psychosis in Italian neuropsychiatry services: prevalence, psychopathology and transition rate. *Eur Child Adolesc Psychiatry* 2018; 27: 725-37.
34. Pelizza L, Azzali S, Paterlini F, et al. The Italian version of the 16-item prodromal questionnaire (iPQ-16): field-test and psychometric features. *Schizophr Res* 2018; 199: 353-60.
35. Raballo A, Poletti M, Carpenter WT. Rethinking the psychosis threshold in clinical high risk. *Schizophr Bull* 2019; 45: 1-2.
36. Ruggeri M, Bonetto C, Lasalvia A, et al.; the GET UP Group. Feasibility and effectiveness of a multi-element psychosocial intervention for first-episode psychosis: results from the cluster-randomized controlled "Get Up Piano" trial in a catchment area of 10 million inhabitants. *Schizophr Bull* 2015; 41: 1192-203.
37. Golay P, Alameda L, Mebdouhi N, et al. Age at the time of onset of psychosis: a marker of specific needs rather than a determinant of outcome? *Eur Psychiatry* 2017; 45: 20-6.
38. Raballo A, Poletti M, McGorry P. Architecture of change: rethinking child and adolescent mental health. *Lancet Psychiatry* 2017; 4: 656-8.
39. McGorry PD, Mei C. Ultra-high-risk paradigm: lessons learnt and new directions. *Evid Based Ment Health* 2018; 21: 131-3.
40. Kraan T, Velthorst E, Koenders L, et al. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. *Psychol Med* 2016; 46: 673-81.
41. Rocca P, Galderisi S, Rossi A, et al. Disorganization and real-world functioning in schizophrenia: results from the multicenter study of the Italian Network for Research on Psychoses. *Schizophr Res* 2018; 201: 105-12.
42. Spada G, Molteni S, Pistone C, et al. Identifying children and adolescents at ultra-high risk of psychosis in Italian neuropsychiatry services: a feasibility study. *Eur Child Adolesc Psychiatry* 2016; 25: 91-106.
43. Bucci P, Galderisi S, Mucci A, et al. Premorbid academic and social functioning in patients with schizophrenia and its associations with negative symptoms and cognition. *Acta Psychiatrica Scandinavica* 2018; 138: 253-66.
44. McGorry PD, Nelson B, Amminger GP, et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. *J Clin Psychiatry* 2009; 70: 1206-12.
45. Pelizza L, Azzali S, Paterlini F, et al. 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. *Early Interv Psychiatry* 2019; 13: 752-60.
46. Singh SP, Toumainen H. Transition from child to adult mental health services: needs, barriers, experiences and new models of care. *World Psychiatry* 2015; 14: 358-61.

Supplementary

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 ( <i>Screening Schedule for Psychosis [SS]</i> ) ( <b>T0*</b> )	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 mental health services
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	
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*

**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 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.

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.

Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry* 2005; 39 (11-12): 964-971.

\*T0= date of compilation of the screening questionnaire

\*\* 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.

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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 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*
<b>ReARMS assessment Battery:</b> 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).				
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 to the patient and family members of the assessment outcome and case formulation	Child/adolescent or adult mental health service Psychiatric ward	ReARMS multi-professional team members	2 hours	
*T0= date of compilation of the screening questionnaire ** 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.				



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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
3.3.1 Co-planning of a personalized treatment path 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
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 recovery-oriented	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
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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 \*\* 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.

*Characterization of young people with first episode psychosis or at ultra-high risk*

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 treatment path that can include all or only some of the interventions provided by the ReARMS protocol	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	2-3 hours	Usually within 12 weeks from T0*
4.2.2 Drafting of a project signed and shared by patient, family and ReARMS multi-professional team members				
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**	<i>In the first year:</i> at least 20 sessions (each lasting 60 minutes)	Usually within 13 weeks from T0*
			<i>In the second year:</i> Eventually booster sessions	
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)	<i>In the first year:</i> at least 6 sessions (each lasting 60 minutes)	Usually within 13 weeks from T0*
			<i>In the second year:</i> Eventually booster sessions	
4.6 Early psychosocial rehabilitation recovery-oriented, 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 psychopharmacological therapy	Both at T0* and every 6 months
4.8 If transition to psychosis (FEP), go to the procedures of the process 3	Child/adolescent or adult mental health service	ReARMS multi-professional team members***	Not definable	Not definable
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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 \*\*\*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.

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 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
5.3 Individual Cognitive-Behavioral Therapy	Child/adolescent or adult mental health service	ReARMS team psychologist**	<i>In the second year:</i> at least 10 sessions (each lasting 60 minutes)	Usually within 12 months from T0*
			<i>From third to fifth year:</i> eventually booster sessions on specific symptomatic areas	
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)	<i>From second to fifth year:</i> eventually booster sessions	Usually within 12 months from T0*
5.5 Early psychosocial rehabilitation recovery-oriented, 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)	<i>From second to fifth year:</i> 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  
 \*\* 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.

*Characterization of young people with first episode psychosis or at ultra-high risk*

Table S1. Correlations between number of referrals/DUI or DUP, and year of enrollment in the ReARMS protocol (available data from September 2012 to December 2017) (n=205).

Variables	UHR+/FEP (n=205) Year of enrollment (ρ)	UHR+ (n=79) Year of enrollment (ρ)	FEP (n=126) Year of enrollment (ρ)
General practitioners	-0.300	0.643	-0.964b
Emergency room/general hospital	-0.277	-0.350	-0.229
Self-referral	-0.108	-0.213	0.207
Family involvement	-0.390	-0.632	-0.545
Mental health care professional	-0.384	-0.255	-0.357
School/Social services	-0.999c	-0.886	-0.349
DUI (in weeks)	-0.043	-0.014	–
DUP (in weeks)	–	–	-0.024

Legend: ReARMS= Reggio Emilia At-Risk Mental States; DUI= Duration of Untreated Illness; DUP= Duration of Untreated Psychosis; ReARMS= Reggio Emilia At-Risk Mental States; FEP= First-Episode Psychosis; UHR= Ultra-High Risk; UHR+= individuals who met CAARMS-defined UHR criteria; CAARMS= Comprehensive Assessment of At-Risk Mental States; Spearman's rho correlation coefficients (ρ) values are reported; ap<0.001; bp<0.01; cp<0.05.

Table S2. Correlates of referral in FEP patients enrolled in the ReARMS protocol (n=126).

Variables	Emergency room/general hospital (n=46)	Other sources of referral or self-referral (n=80)	Statistics (Z)
DUP (in weeks)	53.31±48.24	43.33±48.40	-1.48
DUI (in weeks)	106.32±66.54	92.78±66.35	-0.84
SOFAS CAARMS	41.85±9.01	43.64±9.33	-0.73
Positive Symptoms	16.35±4.30	16.26±4.13	-0.31
Cognitive Change	6.35±2.64	5.88±2.55	-1.15
Emotional Disturbance	7.50±4.07	7.01±4.15	-1.05
Negative Symptoms	10.32±3.99	8.56±4.64	-1.99 <sup>a</sup>
Behavioral Change	12.94±4.22	12.91±4.72	-0.26
Motor/Physical Changes	5.32±4.46	4.64±4.66	-0.92
General Psychopathology	17.21±5.58	15.73±6.56	-1.34

Legend: FEP= First-Episode Psychosis; ReARMS= Reggio Emilia At-Risk Mental States; DUP= Duration of Untreated Psychosis; DUI= Duration of Untreated Illness (in weeks); SOFAS= Social and Occupational Functioning Assessment Scale; CAARMS= Comprehensive Assessment of At-Risk Mental States. Mean±standard deviation and Mann-Whitney test (Z) values are reported; <sup>a</sup>p<0.001; <sup>b</sup>p<0.01; <sup>c</sup>p<0.05.

Table S3. Correlates of referral in UHR+ individuals enrolled in the ReARMS protocol (n=79).

Variables	School/Social services or Self-referral (n=23)	Other sources of referral (n=56)	Statistics (Z)
DUI (in weeks)	78.73±39.07	69.36±52.17	-1.60
SOFAS CAARMS	38.81±8.45	46.87±8.70	-2.24c
Positive Symptoms	10.79±4.06	10.05±4.10	-0.76
Cognitive Change	5.63±2.34	4.62±2.33	-1.96 <sup>c</sup>
Emotional Disturbance	5.33±2.70	6.09±3.52	-1.09
Negative Symptoms	9.29±2.98	8.42±2.91	-0.63
Behavioral Change	11.29±3.93	11.27±4.33	-0.19
Motor/Physical Changes	4.00±3.57	3.69±3.82	-0.45
General Psychopathology	17.00±5.52	16.35±5.91	-0.44

Legend: UHR= Ultra-High Risk; UHR+= individuals who met CAARMS-defined UHR criteria; CAARMS= Comprehensive Assessment of At-Risk Mental States; ReARMS= Reggio Emilia At-Risk Mental States; DUP= Duration of Untreated Psychosis; DUI= Duration of Untreated Illness; SOFAS= Social and Occupational Functioning Assessment Scale; Mean±standard deviation and Mann-Whitney test (Z) values are reported; <sup>a</sup>p<0.001; <sup>b</sup>p<0.01; <sup>c</sup>p<0.05.