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Original article

# Unfavorable short-term outcome indicators in young people at clinical high risk for psychosis: preliminary results from the "Parma At-Risk Mental States" (PARMS) program

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## SUMMARY

### Objective

*Despite advances in the implementation of "Early Intervention in Psychosis" (EIP) services, people at Clinical High Risk (CHR) are still difficult to identify and follow up. Moreover, outcomes other than psychosis conversion are relatively under-estimated and were not systematically reported, thereby compromising further, more sophisticated, prognostic stratifications. Thus, the aims of this study were: (1) to investigate unfavorable short-term outcome indicators (i.e. drop-out rate, psychosis conversion rate, hospital admission rate, longitudinal functioning decline, persistence of CHR-P criteria) in an Italian CHR sample across a 1-year follow-up period, and (2) to examine any significant associations with sociodemographic and clinical characteristics.*

### Methods

*All participants completed a sociodemographic/clinical schedule, the "Health of Nation Outcome Scale" (HoNOS) and the Global Assessment of Functioning (GAF) scale. Inter-group comparisons, Kaplan-Meier survival analysis and Cox regression analysis were performed.*

### Results

*A total of 57 CHR-P subjects was enrolled in this study. At the end of the follow-up, 14% of them transitioned to psychosis, 24% dropped out, 36% had a persistence of CHR-P criteria, 22% were hospitalized and 23%s showed a significant longitudinal functioning decline.*

### Conclusions

*As 1/4 of our participants remitted overtime, sustained clinical attention for CHR people should be provided in the longer term, also to monitor unfavorable outcomes and to improve prognosis.*

**Key words:** clinical high risk, early psychosis, outcome, early intervention, follow-up

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## Introduction

Prevention interventions in specialized programs for individuals at "Clinical High Risk for Psychosis" (*CHR-P*) potentially decrease presenting symptoms, delay/prevent psychosis transition, significantly reduce the duration of untreated psychosis and improve specialist healthcare access [1]. Individuals meeting CHR-P criteria are more often help-seeking adolescents and young adults (aged 14-25 years) manifesting their first psychological suffering during adolescence and frequently accessing Child/Adolescent Mental Health Services (CAMHS) [2].

Despite advances in the development of early detection tools and spe-

cialized "Early Intervention in Psychosis" (EIP) services, CHR-P subjects are hard to identify and follow up, especially in real word care settings [3], with the consequent risk of under-investigating clinical outcomes. Indeed, together with psychosis transition, other *unfavorable clinical trajectories* are service disengagement ("drop-out"), hospitalization, functioning decline, persistence of attenuated psychotic symptoms, poor quality of life and psychiatric comorbidity (e.g., substance misuse, anxiety, depression) [4]. In this respect, outcomes other than conversion to psychosis are still relatively underestimated, especially in Italy and were not systematically reported, thereby compromising further, more sophisticated, prognostic stratifications [5].

### CHR-P programs in Italy

Based on the pilot experience of the "Programma 2000" in Milan [6], several EIP programs are spreading within Italian mental health service networks, albeit often with protocols providing generalist (not evidence-based) interventions and targeting young adults (aged 18-35 years) mostly affected by "First Episode Psychosis" (FEP) [7]. However, there was no lack of interesting Italian experiences of early intervention in CHR-P people within specialized EIP programs.

The "*Programma 2000*", developed as centralized EIP service in Milan, also recruited CHR-P individuals, but without using specific psychometric criteria. In ten years of clinical activity, 71 at-risk subjects (aged 14-35 years) were detected. No detailed outcome analysis was specifically performed. Only 7% of them showed a small symptom improvement during the first 6 months of treatment, followed by a worsening of their clinical status at 12 months [8].

The "Reggio Emilia At-Risk Mental States" (*ReARMS*) program [9] was the first Italian EIP protocol developed as a diffused infrastructure involving both CAMHS and Adult Mental Health Services (AMHS) and specifically addressing adolescents meeting well-defined CHR-P criteria (together with FEP patients). Given that adolescents have the topmost lifetime prevalence of severe mental illness, albeit having the lowest admission in CAMHS compared to the other age groups, with serious consequences in terms of under-treatment, care discontinuation and unmet needs [10], one of the main ReARMS aims was to quickly plan personalized care programs also for favoring continuity of treatment during the transition between CAMHS and AMHS [11]. After five years of clinical activity, 79 CHR-P subjects (aged 13-35 years) were identified. No specific outcome investigation was carried out. However, 9% of them refused the treatment protocol after the enrollment and 15% dropped out during the first year of intervention. A 1-year psychosis transition rate of 9% was also observed.

More recently, an "ITAlian partnership for Psychosis Prevention" (*ITAPP*) [12] was developed to implement large-scale collaborations among specialized CHR-P services in Italy, with the specific intent that using adequate sample sizes and follow-ups for achieving a stronger statistical power could advance knowledge on treatment benefits for young people at-risk for psychosis. The ITAPP is a CHR-P clinical research partnership also aimed at favoring preventive intervention, at improving prognosis and at transferring innovative research findings into clinical practice. It includes 5 academic centers for psychosis prevention in Italy (Pavia, Naples, Perugia, Milan and Bari), all incorporating as EIP centralized services into their community mental health departments. To date, no detailed outcome analysis on CHR-P ITAPP individuals was specifically performed. Only a cumulative risk of psychosis increasing from 8.7% at 1 year to 15.9% at 2 years, 21.8% at 3 years and 34.8% at 4 years was reported.

Given poor information on outcomes in CHR-P people enrolled within specialized EIP services (especially in Italy), the aims of the current research was (1) to investigate specific unfavorable short-term outcome indicators (i.e., drop-out rate, psychosis conversion rate, hospital admission rate, longitudinal functioning decline, persistence of CHR-P criteria and incidence of suicide/self-harm thinking and behavior) in an Italian CHR-P sample across a 1-year follow-up period, and (2) to examine any significant associations with sociodemographic and clinical characteristics of the CHR-P total group at entry.

## Methods

### Subjects and setting

All *participants* were CHR-P adolescents and young adults enrolled in the first 5 years of activity of the "Parma At-Risk Mental States" (PARMS) program between January 2013 and December 2017. The *PARMS* program was a specialized EIP protocol for CHR-P subjects developed as a diffused infrastructure involving all CAMHS and AMHS of the Parma department of mental health in Northern Italy [13]. Among its main objectives, there were to bridge the gap between CAMHS and AMHS, and to disseminate the CHR-P paradigm and its prevention principles in all the Parma community mental health centers. The PARMS program is a remarkable Italian EIP experience aimed at involving CAMHS and adolescents meeting well-defined CHR-P criteria, and at promoting a real continuity of treatment between CAMHS and AMHS [14].

For the purposes of this study, *inclusion criteria* were: (1) specialist help-seeking request; (2) age 12-25 years; and (c) CHR-P mental state as defined by the "Comprehensive Assessment of At-Risk Mental States"

(CAARMS) criteria [15]. This narrow age range was selected to focus our therapeutic effort on a mean age at the turn of the CAMHS/AMHS transition. In accordance with the CAARMS criteria, *CHR-P status* included "Brief Limited Intermittent Psychotic Symptoms" (BLIPS), "Attenuated Psychotic Symptoms" (APS) and "Genetic Risk and Functioning Deterioration" (GRFD) syndrome.
*Exclusion criteria* were: (1) past DSM-IV-TR affective or non-affective psychosis [16]; (2) past exposure to antipsychotic medication; (3) current DSM-IV-TR substance dependence; (4) known severe/moderate intellectual disability (i.e. IQ < 50); and (5) neurological disease or any other medical condition manifesting with psychiatric symptoms. In this study, we considered past exposure to antipsychotics (i.e. at any dosage and time before the PARMS enrollment) as an equivalent of a past psychotic episode, in accordance with what was established in the CAARMS criteria for psychosis [15], which defined the psychometric threshold for a full-blown psychotic episode as essentially that at which antipsychotic medication would probably be started in the common clinical practice.
All participants and their parents (if minors) agreed to participate to the research and gave their written informed consent prior to their inclusion in this study. Local relevant ethical approvals were obtained for the study (AVEN Ethics Committee: protocol n. 36102/09.09.2019). The current research has been also carried out in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Instruments and assessment

For the purpose of this study, a *sociodemographic/clinical schedule* collecting information on age, gender, years of education, ethnic group, employment status, source of referral, past hospitalization, previous specialist contact, current substance misuse, "Duration of Untreated Illness" (DUI, defined as the time interval [in months] between the onset of a prominent psychiatric symptom and the first pharmacological/psychosocial treatment) [17] and PARMS treatment proposals was completed at entry. The *axis-I diagnosis* was formulated in accordance with the DSM-IV-TR diagnostic criteria using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [18].
The *CHR-P status* was detected in accordance with the CAARMS psychometric criteria using the authorized Italian version of the CAARMS (CAARMS-ITA) [19]. The CAARMS-ITA showed excellent interrater reliability and validity in Italian CHR-P populations [20].
As outcome assessment tool, the "Health of Nation Outcome Scale" (*HoNOS*) [21] was completed to assess levels of health and socio-occupational functioning. Structurally, the HoNOS includes 12 items, each one rated on a 4-point Likert scale (from 0 = "no problem" to 4 = "very severe problems"). We clustered HoNOS items in the following 4 main domains: "Behavioral Problems" (items 1-3), "Impairment" (items 4-5), "Psychiatric Symptoms" (items 6-8) and "Social Problems" (items 9-12) [22]. Furthermore, the presence of suicidality (i.e. suicide/self-harm thinking and behavior) was defined by an at least HoNOS "Non-accidental self-injury" item subscore of ≥ 1 (i.e. "...occasional thoughts about death or of self-harm not leading to injury")[23]. In the present investigation, we used the Italian version of the HoNOS, which was commonly administered in Italian samples with early psychosis [24].
Finally, the "Global Assessment of Functioning" (*GAF*) scale [16] was also completed to further assess clinical, social and occupational functioning. It showed good psychometric properties in Italian populations of young subjects with early psychosis [25].

## Procedures

All assessment instruments were completed by trained PARMS team members both at baseline and after the 1-year follow-up period. Regular scoring workshops and supervision sessions were used to ensure the interrater reliability. At the end of the follow-up, information on drop-out condition and hospitalization were also collected.
Based on their symptom severity, CHR-P subjects were provided with a comprehensive *intervention* package including a multi-element psychosocial intervention (combining individual psychotherapy inspired by cognitive-behavioral principles, psychoeducational sessions for family members and an early recovery-oriented case management) and a psychopharmacological treatment (as appropriate), in accordance with the current guidelines on the topic [26]. Specifically, *antipsychotic* prescription was avoided unless CHR-P individuals (1) were overwhelmed by abruptly worsening overt psychotic symptoms, (2) had an imminent risk of suicide or severe violence, (3) were rapidly deteriorating in functioning, or (4) did not adequately respond to any other intervention. Low-dose atypical antipsychotic was used as first-line treatment. Selective serotonin re-uptake inhibitors could also be used in case of depression or anxiety. *Individual psychotherapy* was based on the model by van der Gaag and co-workers [27] for psychosis-risk syndrome. *Family intervention* was developed on the cognitive-behavioral model proposed by Kuipers and colleagues [28]. As for *case management*, each individual/family received a dedicated case manager coordinating all the planned interventions, especially those aimed at an early recovery-oriented early rehabilitation (also promoting social and job inclusion) [29].
In the current investigation, we specifically examined the following *unfavorable outcome indicators* across the

follow-up period: (1) 1-year drop-out rate (i.e. after having accepted the PARMS treatment proposal), (2) 1-year psychosis transition rate, (3) 1-year hospital admission rate, (4) 1-year incidence of functioning decline, (5) 1-year incidence of persistence of CHR-P status and (6) 1-year incidence of suicidal thinking and behavior. For each condition, we also investigated any significant association with acceptance of PARMS treatment proposal, sociodemographic and clinical characteristics of the CHR-P total sample at baseline.

### Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 [30]. Categorical parameters were described as frequencies and percentages, while continuous measures as mean ± standard deviations. Statistical analyses were two-tailed, with a significance level set at 0.05. Due to non-normality in all explorations (i.e. Kolmogorov-Smirnov test with Lilliefors significance correction: $p < 0.05$), nonparametric statistics were used [31]. Cumulative incidence rates of unfavorable outcome indicators were also calculated using the Kaplan-Meier survival analysis, taking into account the time of survival (in days) among the patients entered in our 1-year follow-up period [32]. Finally, significant associations of outcome parameters with PARMS therapeutic proposals, sociodemographic and clinical characteristics in the CHR-P total sample were explored through between-group comparisons (using Chi-squared or Mann-Whitney test [as appropriate]) and a multivariate Cox regression analysis considering parameters previously having a statistical significance.

## Results

Fifty-seven CHR-P subjects were enrolled in this study. Clinical and sociodemographic characteristics of the CHR-P total sample are shown in the Table I.

At baseline, 33 (57.9%) CHR-P participants met APS criteria and 23 (40.4%) met BLIPS criteria. Schizotypal personality disorder was the most common diagnosis (n = 23; 40.4%), followed by brief psychotic disorder (n = 11; 19.3%) and borderline personality disorder (n = 10; 17.5%).

### 1-year drop-out rate

During the follow-up, 13 (22.8%) CHR-P participants dropped out the PARMS protocol. Kaplan-Meier analysis results confirmed a 1-year cumulative incidence rate of 24.6%. In comparison with CHR-P individuals who did not drop out, those with drop-out condition showed shorter DUI at entry, lower baseline prevalence of previous specialist contact and antipsychotic prescription, lower acceptance of all PARMS psychosocial treatment,

**TABLE I.** *Clinical and sociodemographic data of the CHR-P total sample (n = 57).*

| Variables | |
|---|---|
| Age at entry (in years) | 22.14 ± 3.02 |
| Adolescent/adult ratio | 1/5.7 (17.5%) |
| Gender (males) | 36 (63.2%) |
| Education (in years) | 10.96 ± 2.61 |
| Ethnic Group (White Caucasians) | 49 (86.0%) |
| Unemployed | 28 (49.1%) |
| Previous specialist contact | 23 (40.4%) |
| Past hospitalization | 11 (19.3%) |
| Current substance misuse (at entry) | 12 (21.1%) |
| DUI (in months) | 5.70 ± 4.93 |
| CHR-P group | 33 (57.9%) |
| *APS* | 23 (40.4%) |
| *BLIPS* | 1 (1.8%) |
| *GRFD syndrome* | 23 (40.4%) |
| DSM-IV-TR diagnosis | 11 (19.3%) |
| *Schizotypal personality disorder* | 10 (17.5%) |
| *Brief psychotic disorder* | 7 (12.3%) |
| *Borderline personality disorder* | 6 (10.5%) |
| *Depressive disorder* | 25 (43.9%) |
| *Anxiety disorder* | 14 (24.6%) |
| Sources of referral | 6 (10.5%) |
| *General practitioner* | 6 (10.5%) |
| *School/Social services* | 6 (10.5%) |
| *Family members* | 33 (57.9%) |
| *General Hospital/Emergency room* | 2.01 ± 1.34 |
| *Self-referral* | 9 (15.8%) |
| Baseline antipsychotic prescription rate | 20.00 ± 7.81 |
| Baseline equivalent dose of risperidone (mg/day) | 14 (24.6%) |
| Baseline antidepressant prescription rate | 8 (14.0%) |
| Baseline equivalent dose of fluoxetine (mg/day) | 13 (22.8%) |
| 1-year drop-out rate | 13 (22.8%) |
| 1-year psychosis transition rate | 21 (36.8%) |
| 1-year hospitalization rate | 19 (33.3%) |
| 1-year functioning decline (GAF score decrease) | |
| 1-year persistence of CHR-P criteria | |
| 1-year Suicide/Self -Harm thought and behavior | |

*Legend – CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness; APS = Attenuated Psychotic Symptoms; BLIPS = Brief Limited Intermittent Psychotic Symptoms; GRFD = Genetic Risk Functioning Deterioration; DSM-IV-TR = Diagnostic and Statistical Manual for mental disorders, IV Edition, Text Revised, GAF = Global Assessment of Functioning. Frequencies (and percentages) and mean ± standard deviation are reported.*

and higher baseline prevalence of BLIPS and emergency room/general hospital as source of referral (Tab. II). In Cox regression analysis, no statistically significant predictive factor was found.

### 1-year psychosis conversion rate

During the follow-up, 8 (14%) CHR-P individuals psychometrically transitioned to full-blown psychotic disorder. Kaplan-Meier analysis found a 1-year cumulative

**TABLE II.** *Associations of 1-year drop-out condition with sociodemographic and clinical features in the CHR-P total sample (n = 57).*

| Variable (inter-group comparisons) | CHR-P with 1-year drop-out condition (n = 13) | CHR-P without 1-year drop-out condition (n = 43) | $X^2$/z |
|---|---|---|---|
| Gender (male) | 8 (61.5%) | 28 (65.1%) | 0.289 |
| Age at entry (in years) | 22.86 ± 2.28 | 21.91 ± 3.21 | -0.949 |
| Adolescent/adult ratio | 1/13 (7.7%) | 9/43 (20.9%) | 1.388 |
| Education (in years) | 11.07 ± 2.37 | 10.93 ± 2.71 | -0.445 |
| Ethnic group (white Caucasian) | 10 (76.9%) | 39 (90.7%) | 3.250 |
| Unemployment | 6 (46.1%) | 22 (51.2%) | 0.292 |
| Past hospitalization | 3 (23.1%) | 8 (18.6%) | 0.054 |
| Previous specialist contact | 2 (15.4%) | 21 (48.8%) | **5.238*** |
| Current substance misuse (at entry) | 3 (23.1%) | 9 (20.9%) | 0.002 |
| DUI (in months) | 3.43 ± 2.21 | 6.44 ± 5.35 | **-2.084*** |
| BLIPS group at baseline | 9 (68.2%) | 14 (32.6%) | **4.417*** |
| APS group at baseline | 4 (30.8%) | 29 (67.4%) | **6.546*** |
| Emergency room/General hospital (as source of referral) | 4 (30.8%) | 2 (4.7%) | **6.416*** |
| Antipsychotic prescription at baseline | 4 (30.8%) | 29 (67.6%) | **6.546*** |
| Antidepressant prescription at baseline | 0 (0.0%) | 9 (20.9%) | 3.480 |
| Baseline Individual Psychotherapy proposal acceptance | 1 (7.7%) | 33 (76.7%) | **12.528**** |
| Baseline Family Psychoeducation proposal acceptance | 0 (0.0%) | 33 (76.7%) | **17.395**** |
| Baseline Case Management proposal acceptance | 0 (0.0%) | 41 (95.3%) | **38.902**** |
| Baseline GAF score | 51.00 ± 8.77 | 48.95 ± 8.48 | -1.431 |
| Baseline HoNOS "Behavioral Problems" domain score | 2.86 ± 2.41 | 3.33 ± 2.38 | -0.515 |
| Baseline HoNOS "Impairment" domain score | 3.00 ± 2.48 | 3.53 ± 2.11 | -0.851 |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 8.21 ± 3.64 | 8.28 ± 3.91 | -0.195 |
| Baseline HoNOS "Social Problems" domain score | 6.57 ± 4.62 | 9.21 ± 4.16 | -1.757 |

| Variable (Cox regression analysis) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | 95% CI for HR Upper |
|---|---|---|---|---|---|---|---|---|
| Previous specialist contact | 0.338 | 75.774 | .000 | | 0.996 | 0.713 | 0.000 | 0.940 |
| DUI (in months) | -0.041 | 0.095 | 0.190 | 1 | 0.663 | 0.959 | 0.797 | 1.156 |
| BLIPS group at baseline | -0.878 | 1.243 | 0.499 | 1 | 0.480 | 0.416 | 0.036 | 4.745 |
| General hospital/Emergency room (as source of referral) | -2.569 | 1.598 | 2.582 | 1 | 0.108 | 0.077 | 0.003 | 1.758 |
| Antipsychotic prescription at baseline | 1.460 | 1.593 | 0.839 | 1 | 0.360 | 4.305 | 0.190 | 4.100 |
| Baseline Individual Psychotherapy proposal acceptance | -2.759 | 1.806 | 2.332 | 1 | 0.127 | 0.063 | 0.002 | 2.254 |
| Baseline Family Psychoeducation proposal acceptance | -0.345 | 114.798 | 0.000 | 1 | 0.998 | 0.708 | 0.000 | 3.750 |
| Baseline Case Management proposal acceptance | 12.640 | 119.106 | 0.011 | 1 | 0.915 | 308.229 | 0.000 | 301.342 |

Overall score → -2 Log Likelihood = 20.843, $X^2$ = 48.374, df = 8, p = 0.287.

*Legend - CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness, BLIPS = Brief Limited Intermittent Psychotic Symptoms, APS = Attenuated Psychotic Symptoms, GAF = Global Assessment of Functioning, HoNOS = Health of Nation Outcome Scale. B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degrees of freedom, HR = hazard ratio, 95% CI = 95% confidence intervals for HR, $X^2$ = Chi-squared value, $R^2$ = R-squared or coefficient of determination, p = statistical significance. Frequencies (and percentages), mean ± standard deviation, Chi-squared ($X^2$) and Mann-Whitney (z) test values are reported. *p < 0.05, **p < 0.001. Statistically significant p value are in bold. No association with specific DSM-IV-TR diagnosis was found.*

incidence rate of 18.2%. Compared to non-converter CHR-P subjects, those with psychosis transition showed higher adolescent/adult ratio at entry and greater baseline prevalence of APS (Tab. III). In Cox regression analysis, no statistically significant predictor for psychosis transition was observed.

### 1-year hospital admission rate

During the follow-up, 13 (22.8%) CHR-P participants were hospitalized. Kaplan-Meier analysis found a 1-year cumulative incidence rate of 29.5%. Compared to non-hospitalized CHR-P individuals, those hospitalized had longer DUI at entry and higher baseline

**TABLE III.** *Associations of 1-year psychosis conversion and 1-year hospitalization conditions with sociodemographic and clinical features in CHR-P participants who concluded the 1-year follow-up period (n = 44).*

| Variable | CHR-P with 1-year psychosis conversion condition (n = 8) | CHR-P without 1-year psychosis conversion condition (n = 36) | $X^2$/z |
|---|---|---|---|
| (Inter-group comparisons) | | | |
| Gender (male) | 5 (62.5%) | 23 (63.9%) | 0.005 |
| Age at entry (in years) | 20.13 ± 4.09 | 22.19 ± 2.95 | -1.098 |
| Adolescent/adult ratio | 5/8 (62.5%) | 5/36 (13.9%) | **8.807**** |
| Education (in years) | 10.25 ± 1.67 | 11.14 ± 2.87 | -0.838 |
| Ethnic group (white Caucasian) | 7 (87.5%) | 33 (91.7%) | 0.138 |
| Unemployment | 2 (25.0%) | 22 (61.1%) | 2.200 |
| Past hospitalization | 2 (25.0%) | 6 (16.7%) | 0.306 |
| Previous specialist contact | 2 (25.0%) | 19 (52.8%) | 2.024 |
| Current substance misuse (at entry) | 3 (37.5%) | 7 (19.4%) | 1.215 |
| DUI (in months) | 6.50 ± 9.81 | 6.28 ± 3.98 | -1.230 |
| BLIPS group at baseline | 0 (0.0%) | 15 (41.7%) | **5.057*** |
| APS group at baseline | 8 (100.0%) | 21 (58.3%) | **5.057*** |
| Antipsychotic prescription at baseline | 3 (37.5%) | 26 (72.2%) | 3.512 |
| Antidepressant prescription at baseline | 0 (0.0%) | 9 (25.0%) | 2.514 |
| Baseline Individual Psychotherapy proposal acceptance | 6 (75.0%) | 27 (75.0%) | 0.000 |
| Baseline Family Psychoeducation proposal acceptance | 7 (87.5%) | 26 (72.2%) | 0.815 |
| Baseline Case Management proposal acceptance | 7 (87.5%) | 34 (94.4%) | 0.497 |
| Number of 1-year Individual Psychotherapy sessions | 10.50 ± 8.07 | 8.50 ± 7.53 | -0.676 |
| Number of 1-year Family Psychoeducation sessions | 6.25 ± 3.24 | 4.44 ± 4.81 | -1.350 |
| Number of 1-year Case Management sessions | 16.25 ± 11.67 | 16.33 ± 11.34 | -0.030 |
| Baseline GAF score | 45.88 ± 7.26 | 48.31 ± 8.74 | -0.911 |
| Baseline HoNOS “Behavioral Problems” domain score | 4.00 ± 1.77 | 3.19 ± 2.46 | -1.200 |
| Baseline HoNOS “Impairment” domain score | 4.25 ± 1.58 | 3.42 ± 2.18 | -1.199 |
| Baseline HoNOS “Psychiatric Symptoms” domain score | 10.13 ± 3.00 | 8.03 ± 4.08 | -1.420 |
| Baseline HoNOS “Social Problems” domain score | 10.50 ± 3.89 | 8.97 ± 4.17 | -0.855 |
| 1-year Hospitalization | 3 (37.5%) | 10 (27.8%) | 0.297 |
| 1-year Functioning (GAF) decline | 1 (12.5%) | 12 (33.3%) | 1.365 |
| 1-year Suicide/Self-Harm condition | 4 (50.0%) | 15 (41.7%) | 0.185 |

| Variable (Cox regression) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| Adolescent/adult ratio | -0.127 | 0.101 | 1.598 | 1 | 0.206 | 0.881 | 0.723 | 1.072 |
| BLIPS group at baseline | 4.238 | 98.426 | 0.002 | 1 | 0.966 | 69.252 | 0.000 | 150.175 |
| Overall model score → -2 Log Likelihood = 33.563, $X^2$ = 16.503, df = 16, p = 0.418 | | | | | | | | |

*continue*

**TABLE III.** *Follows.*

| Variable (inter-group comparisons) | CHR-P with 1-year hospitalization condition (n = 13) | CHR-P without 1-year hospitalization condition (n = 31) | $X^2$/z |
|---|---|---|---|
| Gender (male) | 8 (61.5%) | 20 (64.5%) | 0.035 |
| Age at entry (in years) | 22.77 ± 3.27 | 21.42 ± 3.18 | -0.975 |
| Adolescent/adult ratio | 1/13 (7.7%) | 9/31 (29.0%) | 2.375 |
| Education (in years) | 11.31 ± 2.36 | 10.84 ± 2.85 | -0.818 |
| Ethnic group (white Caucasian) | 12 (92.3%) | 28 (90.3%) | 0.044 |
| Unemployment | 7 (53.8%) | 16 (51.6%) | 0.018 |
| Past hospitalization | 6 (46.2%) | 2 (6.5%) | **9.705**** |
| Previous specialist contact | 2 (46.2%) | 15 (48.4%) | 0.018 |
| Current substance misuse (at entry) | 3 (23.1%) | 7 (22.6%) | 0.001 |
| DUI (in months) | 8.85 ± 7.46 | 5.26 ± 3.85 | **-1.728*** |
| BLIPS group at baseline | 3 (23.1%) | 12 (38.7%) | 0.996 |
| APS group at baseline | 10 (76.9%) | 19 (61.3%) | 0.996 |
| Self-referral (as source of referral) | 3 (23.1%) | 1 (3.2%) | **4.367*** |
| Antipsychotic prescription at baseline | 10 (76.9%) | 19 (61.3%) | 0.996 |
| Antidepressant prescription at baseline | 3 (33.3%) | 6 (19.4%) | 0.078 |
| Baseline Individual Psychotherapy proposal acceptance | 11 (84.6%) | 22 (71.0%) | 0.910 |
| Baseline Family Psychoeducation proposal acceptance | 10 (76.9%) | 23 (74.2%) | 0.036 |
| Baseline Case Management proposal acceptance | 12 (92.3%) | 29 (93.5%) | 0.022 |
| Baseline GAF score | 46.92 ± 8.92 | 48.26 ± 8.39 | -0.248 |
| Baseline HoNOS "Behavioral Problems" domain score | 2.46 ± 2.70 | 3.71 ± 2.13 | -1.913 |
| Baseline HoNOS "Impairment" domain score | 3.15 ± 1.52 | 3.74 ± 2.29 | -1.001 |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 7.31 ± 3.45 | 8.87 ± 4.12 | -1.174 |
| Baseline HoNOS "Social Problems" domain score | 9.08 ± 3.35 | 9.32 ± 4.45 | -0.155 |
| 1-year Psychosis Conversion | 3 (23.1%) | 5 (16.1%) | 0.297 |
| 1-year Functioning (GAF) decline | 5 (38.5%) | 8 (25.8%) | 0.705 |
| 1-year Persistence of CHR-P criteria | 3 (21.3%) | 18 (58.1%) | 2.705 |
| 1-year Suicide/Self-Harm condition | 6 (46.2%) | 13 (41.9%) | 0.066 |

| Variable (Cox regression) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| Past hospitalization | 1.308 | 0.565 | 5.367 | 1 | **0.021** | 0.270 | 0.089 | 0.818 |
| Current substance misuse (at entry) | 0.149 | 0.669 | 0.049 | 1 | 0.824 | 1.161 | 0.313 | 4.310 |
| Self-referral (as source of referral) | -0.950 | 0.669 | 2.013 | 1 | 0.156 | 0.387 | 0.104 | 1.437 |

Overall score → -2 Log Likelihood = 91.223, $X^2$ = 9.610, df = 3, p = **0.022**.

*Legend - CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness, BLIPS = Brief Limited Intermittent Psychotic Symptoms, APS = Attenuated Psychotic Symptoms, GAF = Global Assessment of Functioning, HoNOS = Health of Nation Outcome Scale, B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degrees of freedom, HR = hazard ratio, 95% CI = 95% confidence intervals for HR, $X^2$ = Chi-squared value, R2 = R-squared or coefficient of determination, p = statistical significance. Frequencies (and percentages), mean ± standard deviation, Chi-squared ($X^2$) and Mann-Whitney (z) test values are reported. *p < 0.05, **p < 0.01. Statistically significant p value are in bold. No association with specific DSM-IV-TR diagnosis was found.*

prevalence of self-referral and past hospitalization (Tab. III). In Cox regression analysis, 1-year hospitalization condition was significantly predicted by past hospitalization at baseline (Tab. III).

### 1-year functioning decline

At the end of the follow-up, 13 (22.8%) CHR-P subjects had a significant longitudinal functioning decline (as defined by a decrease in GAF scores). Kaplan-Meier anal-

ysis found a 1-year cumulative incidence rate of 29.5%. Compared to CHR-P participants with functioning improvement, those with functional deterioration had higher baseline prevalence of past hospitalization, lower baseline GAF score and higher baseline HoNOS "Behavioral Problems", "Psychiatric Symptoms" and "Social Problems" domain subscores (Tab. IV). In Cox regression analysis, no significant predictive parameter was observed.

**TABLE IV.** *Associations of 1-year functioning (GAF) decline condition with sociodemographic and clinical features in CHR-P participants who concluded the 1-year follow-up period (n = 44).*

| Variable (inter-group comparisons) | CHR-P with 1-year GAF decline condition (n = 13) | CHR-P without 1-year GAF decline condition (n = 31) | $X^2$/z |
|---|---|---|---|
| Gender (male) | 10 (76.9%) | 18 (58.1%) | 1.408 |
| Age at entry (in years) | 21.23 ± 3.92 | 22.06 ± 2.93 | -1.027 |
| Adolescent/adult ratio | 3/13 (23.1%) | 7/31 (22.6%) | 0.001 |
| Education (in years) | 11.46 ± 2.93 | 10.77 ± 2.62 | -0.790 |
| Ethnic group (white Caucasian) | 12 (92.3%) | 28 (90.3%) | 0.044 |
| Unemployment | 6 (46.2%) | 17 (54.8%) | 0.277 |
| Past hospitalization | 5 (38.5%) | 3 (9.7%) | **5.101*** |
| Previous specialist contact | 6 (46.2%) | 15 (48.4%) | 0.018 |
| Current substance misuse (at entry) | 1 (7.7%) | 9 (29.0%) | 2.375 |
| DUI (in months) | 6.77 ± 3.32 | 6.13 ± 6.04 | -1.273 |
| BLIPS group at baseline | 4 (30.8%) | 11 (35.5%) | 0.091 |
| APS group at baseline | 9 (69.2%) | 20 (64.5%) | 0.091 |
| Antipsychotic prescription at baseline | 10 (76.9%) | 19 (61.3%) | 0.996 |
| Antidepressant prescription at baseline | 2 (15.4%) | 7 (22.6%) | 0.291 |
| Baseline Individual Psychotherapy proposal acceptance | 12 (92.3%) | 21 (67.7%) | 2.948 |
| Baseline Family Psychoeducation proposal acceptance | 101(84.6%) | 22 (71.0%) | 0.910 |
| Baseline Case Management proposal acceptance | 13 (100.0%) | 28 (90.3%) | 1.350 |
| Baseline GAF score | 46.32 ± 8.97 | 51.54 ± 5.92 | **-2.102*** |
| Baseline HoNOS "Behavioral Problems" domain score | 3.84 ± 2.42 | 2.15 ± 1.72 | **-2.251*** |
| Baseline HoNOS "Impairment" domain score | 3.97 ± 1.97 | 2.62 ± 2.14 | -1.820 |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 9.39 ± 4.05 | 6.08 ± 2.63 | **-2.736**** |
| Baseline HoNOS "Social Problems" domain score | 10.52 ± 3.62 | 6.23 ± 3.74 | **-3.032**** |
| 1-year Psychosis Conversion | 1 (7.7%) | 7 (22.6%) | 1.365 |
| 1-year Hospitalization | 5 (38.5%) | 8 (25.8%) | 0.705 |
| 1-year Persistence of CHR-P criteria | 8 (61.5%) | 13 (41.9%) | 1.914 |
| 1-year Suicide/Self-Harm condition | 3 (23.1%) | 16 (51.6%) | 3.040 |

| Variable (Cox regression) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | 95% CI for HR Upper |
|---|---|---|---|---|---|---|---|---|
| Past hospitalization | -0.742 | 0.612 | 1.469 | 1 | 0.225 | 0.476 | 0.144 | 1.581 |
| Baseline GAF score | -0.042 | 0.057 | 0.538 | 1 | 0.463 | 0.959 | 0.859 | 1.072 |
| Baseline HoNOS "Behavioral Problems" domain score | -0.139 | 0.152 | 0.843 | 1 | 0.358 | 0.870 | 0.646 | 1.171 |
| Baseline HoNOS "Psychiatric Symptoms" domain score | -0.093 | 0.117 | 0.637 | 1 | 0.425 | 0.911 | 0.724 | 1.146 |
| Baseline HoNOS "Social Problems" domain score | -0.171 | 0.105 | 2.671 | 1 | 0.102 | 0.843 | 0.686 | 1.035 |
| Overall score → -2 Log Likelihood = 87.176, $X^2$ = 10.964, df = 5, p = 0.052. | | | | | | | | |

*Legend - CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness, BLIPS = Brief Limited Intermittent Psychotic Symptoms, APS = Attenuated Psychotic Symptoms, GAF = Global Assessment of Functioning, HoNOS = Health of Nation Outcome Scale, B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degrees of freedom, HR = hazard ratio, 95% CI = 95% confidence intervals for HR, X2 = Chi-squared value, R2 = R-squared or coefficient of determination, p = statistical significance. Frequencies (and percentages), mean ± standard deviation, Chi-squared (X2) and Mann-Whitney (z) test values are reported. *p < 0.05, **p < 0.01. Statistically significant p value are in bold. No association with specific DSM-IV-TR diagnosis and source of referral was found.*

### 1-year persistence of CHR-P criteria

At the end of our follow-up, 21 (36.8%) CHR-P participants had a prolonged persistence of CHR-P criteria. Kaplan-Meier analysis found a higher 1-year cumulative incidence rate of 47.7%. Compared to CHR-P individuals not meeting FEP/CHR-P criteria, those with persistence of CHR-P status had fewer years of education at entry, higher baseline HoNOS "Impairment" and "Psychiatric Symptoms" domain scores, lower baseline acceptance of individual psychotherapy, and higher 1-year incidence of suicide/self-harm thinking and behavior (Tab. V). In Cox regression analysis, no significant predictor was observed.

**TABLE V.** *Associations of 1-year persistence of CHR-P criteria with sociodemographic and clinical features in CHR-P participants who concluded the 1-year follow-up period, excluding those with psychosis conversion (n = 36).*

| Variable (inter-group comparisons) | CHR-P with 1-year persistence of CHR-P criteria (n = 21) | CHR-P without 1-year persistence of CHR-P criteria (n = 15) | $X^2$/z |
|---|---|---|---|
| Gender (male) | 14 (66.7%) | 9 (60.0%) | 0.169 |
| Age at entry (in years) | 21.81 ± 2.96 | 22.73 ± 2.93 | -0.503 |
| Adolescent/adult ratio | 4:17 (19.0%) | 1:14 (6.7%) | 1.121 |
| Education (in years) | 10.19 ± 2.81 | 12.33 ± 2.58 | **-2.265*** |
| Ethnic group (white Caucasian) | 18 (85.7%) | 15 (100.0%) | 2.338 |
| Unemployment | 12 (57.1%) | 10 (66.6%) | 0.334 |
| Past hospitalization | 5 (23.8%) | 1 (6.7%) | 1.851 |
| Previous specialist contact | 9 (42.9%) | 10 (66.7%) | 1.990 |
| Current substance misuse (at entry) | 3 (14.3%) | 4 (26.7%) | 0.856 |
| DUI (in months) | 6.62 ± 4.18 | 5.80 ± 3.78 | -0.054 |
| BLIPS group at baseline | 10 (47.6%) | 5 (33.3%) | 0.735 |
| APS group at baseline | 11 (52.4%) | 10 (66.7%) | 0.735 |
| Antipsychotic prescription at baseline | 15 (71.4%) | 11 (73.3%) | 0.016 |
| Antidepressant prescription at baseline | 6 (28.6%) | 3 (20.0%) | 0.343 |
| Baseline Individual Psychotherapy proposal acceptance | 13 (61.9%) | 14 (93.3%) | **4.610*** |
| Baseline Family Psychoeducation proposal acceptance | 15 (71.4%) | 11 (73.3%) | 0.016 |
| Baseline Case Management proposal acceptance | 19 (90.5%) | 15 (100.0%) | 1.513 |
| Baseline GAF score | 49.10 ± 7.20 | 47.20 ± 7.20 | -0.567 |
| Baseline HoNOS "Behavioral Problems" domain score | 3.57 ± 2.29 | 2.67 ± 2.66 | -1.542 |
| Baseline HoNOS "Impairment" domain score | 4.10 ± 2.34 | 2.47 ± 1.55 | **-2.252*** |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 9.14 ± 4.46 | 6.47 ± 2.95 | **-1.916*** |
| Baseline HoNOS "Social Problems" domain score | 9.38 ± 4.84 | 8.40 ± 3.06 | -0.805 |
| 1-year Hospitalization | 3 (14.3%) | 7 (46.7%) | 4.753 |
| 1-year Functioning (GAF) decline | 8 (38.1%) | 4 (26.7%) | 0.514 |
| 1-year Suicide/Self-Harm condition | 12 (57.1%) | 3 (20.0%) | **4.967*** |

| Variable (Cox regression) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| Education (in years) | -0.096 | 0.150 | 0.406 | 1 | 0.524 | 0.909 | 0.677 | 1.220 |
| Baseline Individual Psychotherapy proposal acceptance | -0.394 | 0.967 | 0.166 | 1 | 0.684 | 0.675 | 0.101 | 4.491 |
| Baseline HoNOS "Impairment" domain score | 0.020 | 0.262 | 0.006 | 1 | 0.940 | 1.020 | 0.610 | 1.705 |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 0.102 | 0.132 | 0.604 | 1 | 0.437 | 1.108 | 0.856 | 1.434 |
| 1-year Suicide/Self-Harm condition | -0.112 | 0.898 | 0.015 | 1 | 0.901 | 0.894 | 0.154 | 5.196 |
| Overall score → -2 Log Likelihood = 58.410, $X^2$ = 2.210, df = 5, p = 0.821. | | | | | | | | |

*Legend - CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness, BLIPS = Brief Limited Intermittent Psychotic Symptoms, APS = Attenuated Psychotic Symptoms, GAF = Global Assessment of Functioning, HoNOS = Health of Nation Outcome Scale, B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degrees of freedom, HR = hazard ratio, 95% CI = 95% confidence intervals for HR, X2 = Chi-squared value, R2 = R-squared or coefficient of determination, p = statistical significance. Frequencies (and percentages), mean ± standard deviation, Chi-squared (X2) and Mann-Whitney (z) test values are reported. *p < 0.05, **p < 0.01. Statistically significant p value are in bold. No association with specific DSM-IV-TR diagnosis and source of referral was found.*

**TABLE VI.** *Associations of 1-year Suicide/Self-Harm condition with sociodemographic and clinical features in CHR-P participants who concluded the 1-year follow-up period (n = 44).*

| Variable (inter-group comparisons) | CHR-P with 1-year Suicide/Self-Harm condition (n = 19) | CHR-P without 1-year Suicide/Self-Harm condition (n = 25) | $X^2$/z |
|---|---|---|---|
| Gender (male) | 12 (63.2%) | 16 (64.0%) | 0.003 |
| Age at entry (in years) | 23.53 ± 2.24 | 20.52 ± 3.00 | **-3.100**** |
| Adolescent/adult ratio | 2:17 (10.5%) | 8:17 (32.0%) | 2.835 |
| Education (in years) | 10.95 ± 2.91 | 11.00 ± 2.58 | -0.176 |
| Ethnic group (white Caucasian) | 16 (84.2%) | 24 (96.0%) | 1.816 |
| Unemployment | 12 (63.2%) | 11 (44.0%) | 1.588 |
| Past hospitalization | 3 (15.8%) | 5 (20.0%) | 0.129 |
| Previous specialist contact | 9 (47.4%) | 12 (48.0%) | 0.002 |
| Current substance misuse (at entry) | 5 (26.3%) | 5 (20.0%) | 0.245 |
| DUI (in months) | 7.68 ± 6.91 | 5.28 ± 3.58 | -0.922 |
| BLIPS group at baseline | 6 (31.6%) | 9 (36.0%) | 0.094 |
| APS group at baseline | 13 (68.4%) | 16 (64.0%) | 0.094 |
| Borderline personality disorder at baseline | 7 (36.8%) | 2 (8.0%) | **5.519*** |
| Antipsychotic prescription at baseline | 12 (63.2%) | 17 (68.0%) | 0.113 |
| Antidepressant prescription at baseline | 3 (15.8%) | 6 (24.0%) | 0.447 |
| Baseline Individual Psychotherapy proposal acceptance | 9 (47.4%) | 24 (96.0%) | **13.617***** |
| Baseline Family Psychoeducation proposal acceptance | 14 (73.7%) | 19 (76.0%) | 0.031 |
| Baseline Case Management proposal acceptance | 16 (84.2%) | 25 (100.0%) | **4.236*** |
| Baseline GAF score | 47.21 ± 8.21 | 48.36 ± 8.79 | -0.673 |
| Baseline HoNOS "Behavioral Problems" domain score | 4.53 ± 2.39 | 2.44 ± 1.92 | **-3.032**** |
| Baseline HoNOS "Impairment" domain score | 4.58 ± 1.92 | 2.80 ± 1.91 | **-2.694**** |
| Baseline HoNOS "Psychiatric Symptoms" domain score | 9.74 ± 4.33 | 7.40 ± 3.40 | -1.759 |
| Baseline HoNOS "Social Problems" domain score | 10.53 ± 4.52 | 8.28 ± 3.58 | -1.700 |
| 1-year Psychosis conversion | 4 (21.1%) | 4 (16.0%) | 0.185 |
| 1-year Hospitalization | 6 (31.6%) | 7 (28.0%) | 0.066 |
| 1-year Functioning (GAF) decline | 3 (15.8) | 10 (40.0%) | 3.040 |
| 1-year Persistence of CHR-P criteria | 12 (63.2) | 9 (36.0%) | **4.967*** |

| Variable (Cox regression) | B | SE | Wald | df | p | HR | 95% CI for HR Lower | 95% CI for HR Upper |
|---|---|---|---|---|---|---|---|---|
| Age at entry (in years) | 0.286 | 0.135 | 4.480 | 1 | 0.054 | 1.331 | 1.021 | 1.735 |
| Borderline personality disorder at baseline | -0.917 | 0.580 | 2.497 | 1 | 0.114 | 0.400 | 0.128 | 1.247 |
| Baseline Individual Psychotherapy proposal acceptance | 0.685 | 0.731 | 0.877 | 1 | 0.349 | 1.983 | 0.473 | 8.310 |
| Baseline Case Management proposal acceptance | 0.492 | 0.903 | 0.297 | 1 | 0.586 | 1.635 | 0.279 | 9.590 |
| Baseline HoNOS "Behavioral Problems" domain score | -0.059 | 0.275 | 0.046 | 1 | 0.829 | 0.942 | 0.549 | 1.617 |
| Baseline HoNOS "Impairment" domain score | 0.085 | 0.117 | 0.531 | 1 | 0.466 | 1.089 | 0.866 | 1.369 |
| 1-year Persistence of CHR-P criteria | -0.703 | 0.846 | 0.690 | 1 | 0.406 | 0.495 | 0.094 | 2.599 |

Overall score → -2 Log Likelihood = 94.112, $X^2$ = 12.240, df = 7, p = 0.093.

*Legend - CHR-P = Clinical High Risk for Psychosis; DUI = Duration of Untreated Illness, BLIPS = Brief Limited Intermittent Psychotic Symptoms, APS = Attenuated Psychotic Symptoms, GAF = Global Assessment of Functioning, HoNOS = Health of Nation Outcome Scale, B = regression coefficient, SE = standard error, Wald = Wald statistic value, df = degrees of freedom, HR = hazard ratio, 95% CI = 95% confidence intervals for HR, $X^2$ = Chi-squared value, R2 = R-squared or coefficient of determination, p = statistical significance. Frequencies (and percentages), mean ± standard deviation, Chi-squared (X2) and Mann-Whitney (z) test values are reported. *p < 0.05, **p < 0.01, ***P < 0.001. Statistically significant p value are in bold. No association with specific source of referral was found.*

### 1-year incidence of suicidal thinking and behavior

At the end of the follow-up, 19 (33.3%) CHR-P subjects had a HoNOS "Non-accidental self injury" item subscore of ≥ 1. Kaplan-Meier analysis found a higher 1-year cumulative incidence rate of 43.2%. Compared to CHR-P participants without suicide risk, those with self-harm/suicidal thinking and behavior had older age at entry, higher baseline prevalence of borderline personality disorder, higher baseline HoNOS "Behavioral Problems" and "Impairment" domain scores and lower baseline acceptance of individual psychotherapy and case management (Tab. VI). In Cox regression analysis, no significant predictive parameter was observed.

## Discussion

The aim of the current research was to investigate unfavorable short-term outcome indicators in young people at CHR-P treated within an EIP program (also involving CAMHS). To the best of our knowledge, no Italian study systematically assessing outcome trajectories in a CHR-P sample has been reported in the literature to date. Indeed, outcomes other than psychosis conversion are still relatively under-investigated, also in Europe[4].

As for clinical characteristics at entry, the notable prevalence of participants with BLIPS (approximately 40%) was unexpected. Indeed, previous meta-analytic works highlighted a BLIPS prevalence of 10% in the CHR-P population [33]. Brief psychotic episodes represent an intriguing paradox in clinical psychiatry because they defy the standard knowledge that applies to persisting psychotic disorders, such as schizophrenia [34]. However, given the preliminary nature of this investigation that involved the first years of implementation of the PARMS program, it is possible that mental health clinicians had less familiarity in identifying attenuated psychotic symptoms and paid more clinical attention to BLIPS (i.e., full-blown psychotic symptoms) than APS [35,36]. In this respect, in the same years, the Parma mental health department also implemented an early intervention program for patients with FEP [37].

### 1-year drop-out rate

About 1/4 of CHR-P subjects entered the PARMS protocol *dropped out* during the first year of treatment. This result is higher than those reported in other Italian EIP services (7% in the "Programma 2000", 11% in the ReARMS program) [7,11] and in comparable international programs. In the prospective "Früherkennung von Psychosen" (FePsy) study, the risk of dropping out within 1 year of follow-up was 0.13 [38]. In the North American Prodrome Longitudinal Study (NAPLS-2), a 1-year drop-our incidence rate of 16.9% was observed [39]. The reasons for this higher rate are not immediately inferable and will be the subject of future analysis, also extending the CHR-P sample size.

However, our CHR-P individuals with drop-out condition showed *lower duration of psychological suffering* (i.e. shorter DUI at entry and lower prevalence of previous specialist contact), but *more severe current psychopathology* (i.e. higher prevalence of BLIPS and access to emergency room). In this respect, Minichino and co-workers [40] reported that patients with acute and transient psychotic features had higher cumulative incidence of service disengagement (60% at 1 year). In this research, the 1-year drop-out condition was also related to lower baseline antipsychotic prescription and lower acceptance of PARMS psychosocial interventions, suggesting a *poor predisposition/motivation to treatment* already at the enrollment in the PARMS program. Information on predictors of drop-out in CHR-P people within EIP services is still very poor. Only severe baseline disorganized symptoms seem to be significantly associated to service disengagement [38].

### 1-year psychosis conversion

In line with what was observed in other Italian and European comparable studies, we observed a 1-year incidence rate of psychosis conversion of 14%. In this respect, a recent meta-analysis found that the risk of developing psychosis continued increasing after 3 years, cumulating from 15% at 1 year to 25% at 3 years and reaching 35% at 10 years [41].

Our CHR-P individuals with psychosis transition were more likely *adolescents*. This suggests the crucial importance of paying special attention to CHR-P subjects under the age of 18, providing early, timely and intensive EIP interventions and favoring their stable retention in care within specialized services (also during the CAMHS/AMHS transition), especially if they are suffering from *attenuated psychotic symptoms*. Indeed, unlike what was reported by Salazar de Pablo and colleagues [42], who found that a greater proportion of BLIPS was associated with higher transition risk, all our converter CHR-P individuals met APS criteria. Although controversial and unexpected, this finding suggests that psychosis conversion in our CHR-P subjects could not be related to a greater psychometric severity at baseline. Perhaps, individuals with overt, but transient psychotic symptoms attract more clinical attention than those with attenuated psychotic features (which are often considered as relatively common experiences, also in the general population and especially in adolescence) [43]. This could induce less efforts in clinical monitoring of APS subjects by mental healthcare professionals, with a consequent increased risk of psychosis transition. In this respect, compared to APS participants, those with BLIPS showed significantly higher baseline prevalence of antipsychotic prescription (16 [48.5%] VS 17 [73.9%]; X2 = 3.721; p = 0.047). No other intergroup differences in treatment components were also

observed. However, no significant predictor of 1-year psychosis conversion was found in our Cox regression analysis, perhaps even for the small sample size of our converter CHR-P individuals. Therefore, it is crucial to implement clinical research collaborations in the CHR-P field (also in Italy) to replicate our unexpected results.

### Other adverse outcomes

Just over a fifth of our CHR-P participants were *hospitalized* during the follow-up. This results is in line with what was reported in two Australian EIP services (17% in the "Personal Assessment and Crisis Evaluation" [PACE] clinic in Melbourne, 21% in the "Psychological Assistance Service" [PAS] in Newcastle) [44,45]. Differently, in a recent register-based cohort study conducted in the "Outreach and Support in South London" (OASIS) service, the cumulative risk to admission to a mental health hospital was lower (i.e., 7% at 1 year) [3]. In this study, hospitalization was associated with *longer lasting symptom suffering and experience* (i.e., higher baseline prevalence of previous hospitalization and longer DUI at entry) and self-referral to the PARMS program (rather than a greater severity of psychopathology). In this respect, *self-motivation to treatment* could lead young people at CHR-P to feel more reassured in a hospital setting that may potentially provide a closer clinical monitoring and more intensive interventions. The predictive importance of previous hospitalization was also confirmed by our Cox regression analysis results.

At the end of our follow-up, more than 20% of CHR-P participants showed a relevant longitudinal *functioning decline*. A 6-year perspective research conducted in the OASIS center reported that among non-transitioned CHR-P individuals, 45.3% remained functionally impaired at follow-up [46]. Differently, in a 2-year follow-up research on CHR-P subjects enrolled within the "Support for Wellness Achievement Program" (SWAP) in Singapore, 29.9% was unable to attain functional recovery at 24 months [47]. In this investigation, longitudinal functioning deterioration in people at CHR-P was associated with a history of past hospitalization and higher baseline levels of psychopathology and socio-occupational functioning decline. This further supports the clinical importance of severity of the psychopathological and functioning picture at entry as indicators of poorer short-term functional recovery [48].

After 1 year of follow-up, more than 1/3 of CHR-P individuals had a *persistence of CHR-P criteria* (all experienced as attenuated psychotic symptoms). This is in line with what was reported in the "Cologne Early Recognition and Intervention Centre for mental crises" (FETZ) service (27.6%) [49], but much lower that that was observed in the FOCUS trial (63.7%) [50]. In this research, the 1-year persistence of CHR-P criteria was associated with lower level of education, higher baseline severity levels of current psychiatric symptoms and cognitive functioning, and lower acceptance of individual psychotherapy. Therefore, psychological intervention and high degree of education should be further examined as predictive factors for longitudinal CHR-P criteria remission. Differently from what was reported in the literature, no relationship with male gender, younger age and worsening in social and role functioning was found [41,47,50]. Finally, we notably observed an association between persistence of APS criteria and 1-year incidence of suicide/self-harm thinking and behavior. This confirms the need of a special clinical attention on CHR-P people experiencing prolonged, attenuated psychotic symptoms, also in terms of prevention of suicide risk [51].

At the end of our follow-up, a third of CHR-P participants showed *suicide/self-harm thinking and behavior*. This further supports that suicidality and self-harm are highly prevalent in people at CHR-P [52], also after a 1-year treatment within specialized EIP programs. Appropriate, prolonged (and routinely) managing and monitoring of suicide risk should thus be crucial for services working with CHR-P populations. Moreover, the results of this investigation suggest that suicidality monitoring in CHR-P populations should pay special attention to older age at entry, presence of borderline personality disorder, and people manifesting behavioral disturbances (such as aggression and substance misuse) or having cognitive impairment and physical suffering. Finally, acceptance of individual psychotherapy and case management seems to be an important factor contrasting the 1-year suicidality incidence. Other relevant predictive factors for suicidality in CHR-P individuals reported in the literature are depression severity and anhedonia [53].

### Limitations

A first weakness of this research was the absence of previous control data. Thus, we cannot exclude that the changes observed over time were due to changes in awareness of mental health issue unrelated to the establishment of the PARMS program.

Second, when comparing our results with those reported in other Italian or international studies, it should be considered any national/regional difference in terms of catchment area size and local organization of mental healthcare services. Indeed, national healthcare in Italy is financed and provided by regional political organisms. Therefore, there could be relevant functional and structural divergences among different mental healthcare departments, both in Italy and in other countries.

Finally, when considering our follow-up results, it should also be taken into account the small sample size of the examined conditions (especially 1-year psychosis transition). Future studies on larger CHR-P populations to confirm our findings are thus needed.

## Conclusions

The results of this investigation suggested that just over 1/4 (26.3%) of our CHR-P participants remitted over time. At the end of the follow-up, 14% of them transitioned to psychosis, 36.8% had a persistence of CHR-P criteria and 24.5% dropped out the PARMS protocol. Therefore, sustained clinical attention for CHR-P populations should be provided in the longer term, also to monitor these unfavorable outcomes and to improve prognosis.

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### Conflicts of interest statement

The authors declare to have no conflicts of interest.

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### Ethical consideration

All participants and their parents (if minors) agreed to participate to the research and gave their written informed consent prior to their inclusion in this study. Local relevant ethical approvals were obtained for the study (AVEN Ethics Committee: protocol n. 36102/09.09.2019). The current research has been also carried out in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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