**Research Paper**

Real-world long-term outcomes in individuals at clinical risk for psychosis: The case for extending duration of care

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**ABSTRACT**

**Background:** Most services for individuals at Clinical High Risk for Psychosis (CHR-P) provide short-term clinical care. This study determines the real-world and long-term clinical outcomes beyond transition to psychosis in a large cohort of CHR-P individuals.

**Method:** Retrospective RECORD-compliant real-world Electronic Health Records (EHR) cohort study in secondary mental health care (the South London and the Maudsley -SLaM- NHS Foundation Trust). All CHR-P patients accessing the CHR-P service at SLaM in the period 2001–2018 were included. Main outcomes were long-term cumulative risk of first: (i) developing an ICD-10 psychotic disorder (primary outcome), receiving a treatment with (iia) antipsychotic medication, (iib) benzodiazepines, (iic) other psychotropic medications, (iid) psychotherapy, receiving an (iiia) informal or (iiib) compulsory admission into a mental health hospital, and the time to these events; (iii) number of days spent in hospital and (iv) cumulative risk of death for any reason and age/gender Standardised Mortality Ratio (SMR). Data were extracted from the EHR and analysed with Kaplan Meier failure functions, Cox and zero-inflated negative binomial regressions.

**Findings:** 600 CHR-P patients (80.43% Attenuated Psychotic Symptoms, APS; 18.06%, Brief and Limited Intermission Psychotic Symptoms, BLIPS, 1.51% Genetic Risk and Deterioration Syndrome) were included (mean age 22.63 years, range 13–36; 55.33% males; 46.44% white, mean duration of untreated attenuated psychotic symptoms 676.32 days, 1105.40 SD). The cumulative risk to first psychosis was 0.365 (95%CI 0.302–0.437) at 11 years; first antipsychotic 0.777 (95%CI 0.702–0.844) at 9 years; first benzodiazepine 0.259 (95% CI 0.183–0.359) at 12 years; those admitted spent on average 94.84 (SD=169.94) days in hospital; the cumulative risk of death for any reason was 0.036 (95%CI 0.012–0.083) at 9 years, with an SMR of 3.9 (95%CI 1.20–6.6). Compared to APS, BLIPS had a higher risk of developing psychosis, being admitted compulsorily into hospital, receiving antipsychotics and benzodiazepines and lower probability of receiving psychotherapy. Other prognostic factors of long-term outcomes included age, symptoms severity, duration of untreated attenuated psychotic symptoms, ethnicity and employment status.

**Interpretation:** Duration of care provided by CHR-P services should be expanded to address long-term real-world outcomes.

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Research in context

Evidence before this study

Preventive interventions implemented in specialised mental health services for young individuals at clinical high risk for psychosis improve outcomes of the most severe psychiatric disorder. To address the real-world long-term outcomes of this population we conducted a systematic Web of Knowledge literature search from inception to 1 January 2020. We only found a few long-term studies limiting their focus on transition to psychosis, transition and clinical/functional remission or symptomatic persistence, neurocognition, employment or brain structure, while other relevant real-world clinical outcomes such as utilisation of mental health resources have not been investigated in the long-term.

Added value of this study

Overall, broader long-term real-world clinical outcomes in this patient population are not fully characterised. In this clinical register-based Electronic Health Record real-world cohort study, 600 individuals accessing the Outreach and Support in South-London specialised service for individuals at clinical high risk for psychosis showed a substantial long-term risk of developing the disorder, being treated with medications, admitted to mental health hospitals and spending several days in hospitals. Some of them may be at risk of premature death in the long-term.

Implications of all the available evidence

This study demonstrates that the current short-term duration of care offered by specialised mental health services is unlikely to capture most real-world clinical outcomes presented by individuals at clinical high risk of psychosis. The available evidence indicates that specialised services for individuals at clinical high risk for psychosis should extend the duration of the care offered to capture the real-world, long-term outcomes of this vulnerable group. These findings should inform clinical guidelines and health service research in the field of preventive psychiatry.

Introduction

Young individuals at Clinical High-Risk for Psychosis (CHR-P) [1,2] accumulate risk factors for the disorder [3–5], attenuated psychotic symptoms [6] and functional impairments [7], and seek help [8] at specialised CHR-P clinical services [9–11]. The preventive care (termed primary indicated prevention) implemented in these CHR-P services has the potential to maximise the benefits of early interventions for psychosis [12]. The accomplishments and challenges of the CHR-P paradigm, two decades since being first conceived [13,14], have been recently appraised in this journal [15,16] by the European College of Neuropsychopharmacology Network for the Prevention of Mental Disorders and Mental Health Promotion [17]. The study found that a core limitation of knowledge is that, to date, research has mostly focused on prediction of transition to psychosis in the short term [15]. The broad clinical and long-term fate of CHR-P individuals beyond transition to psychosis is relatively undetermined because tracking these real-world outcomes is logistically challenging. A few studies followed up CHR-P individuals for more than 10 years but limited their focus on transition to psychosis (baseline sample: n = 416 [18]), transition and clinical/functional remission or symptomatic persistence (n = 702 [19], 363 [20], 255 [21], 246 [22]), neurocognition (n = 325 [23], 80 [24]), employment (n = 268 [25]) or brain structure (n = 109 [26]). Other relevant real-world clinical outcomes such as utilisation of mental health resources (formal and informal admission to mental health units, numbers of days spent in hospital, exposure to treatments) have been investigated only in the short term (n = 432 [27]). Because of the limited knowledge of long-term outcomes, preventive interventions have similarly targeted the short-term period [28]. Accordingly, most CHR-P services worldwide limit the duration of care to the short-term (median 2 years [11]) period since the initial presentation. Another limitation of knowledge is that factors predicting long term outcomes are not completely clear. In the short-term, CHR-P subgroups (Attenuated Psychosis Symptoms, APS; Brief and Limited Intermittent Psychotic Symptoms, BLIPS; Genetic Risk and Deterioration syndrome, GRD) have been demonstrated to be associated with differential risk to psychosis [29,30]. Other short-term prognostic factors include sociodemographic and clinical features that characterise the CHR-P state [3–5].

This study fills in this gap of knowledge describing as primary aim the long-term and broad real-world clinical outcomes in a large sample of CHR-P individuals. As secondary step we explored potential prognostic factors predicting long term outcomes in this population.

Methods

Design

Clinical real-world, long-term prospective cohort study using Electronic Health Records (EHRs).

Data source

Real-world EHR data on routine mental healthcare [31] from all patients managed by the South London and Maudsley (SLaM) National Health Service Foundation Trust, UK (eMethods 1).

Study population

OASIS [10] is an early detection service which was set up in 2001, and it is one of the oldest CHR-P services in the UK [10]. The level of risk enrichment observed at OASIS (pretest risk [32]: 14.6% at more than 3 years [33]) aligns with that observed in CHR-P services worldwide (meta-analytical pretest risk 15% at more than 3 years [34]), indicating that OASIS population is representative of the general CHR-P samples. OASIS focuses on the identification, prognostic assessment and treatment of help-seeking CHR-P individuals aged 14–35 years, serving the SLaM catchment area. The OASIS team offers focused interventions spanning pharmacological, psychological [35] (i.e. cognitive behavioural therapy, the only recommended first-line preventive treatment for CHR-P individuals [35]) and psychoeducational activities for a period of two years [36]. Clinical follow-up is usually performed as part of the standard care. OASIS is integrated into the Pan-London Network for Psychosis-prevention (PNP) [9].
The study population included a convenience sample of all individuals accessing OASIS in the period January 2001 to June 2018, assessed with the CHR-P instrument and meeting Comprehensive Assessment of At Risk Mental State (CAARMS) [37] criteria: BLIPS, APS, GRD. All OASIS staff undergo extensive psychometric training as part of numerous research studies (EUGEI, PSYSCAN, HARMONY) to ensure high reliability in the designation of at-risk cases.

**Study measures**

**Variables**

Baseline descriptive variables included sociodemographic (age, sex, ethnicity, marital status, employment status, accommodation status, SLaM borough) and clinical characteristics (severity of CHR-P symptoms, type of CHR-P subgroup, Duration of Untreated Attenuated Psychotic Symptoms [DUAPS]; Social and Occupational Functioning Assessment Scale [SOFAS] [38]; Health Of the Nation Outcome Scale [HoNOS] [39], for details see eMethods 2).

**Follow-up**

Follow-up started at the time of acceptance to OASIS and ended when an outcome was recorded, or when the patient dropped out of the EHR (as documented by the last entry on the EHR).

**Outcomes**

The real-world outcomes of the current study were the long-term cumulative risk of first: (i) developing an ICD-10 psychotic disorder (primary outcome), receiving a treatment with (iia) antipsychotic medication (complemented by type of molecule and chlorpromazine equivalent), (iib) benzodiazepines (complemented by type of molecule), (iic) other psychotropic medications (i.e. excluding antipsychotics and benzodiazepines, type of molecules were described), (iid) psychotherapy (complemented by the number of psychotherapy sessions), receiving an (iiia) informal or (iiib) compulsory admission to a mental health hospital (involving a Mental Health Act [MHA] assessment), and the time to these events. Additional outcomes included (iii) number of days spent in mental health hospital and (iv) risk of death for any reason, with age/gender Standardised Mortality Ratio (SMR).

**Statistical analysis**

This clinical register-based cohort study was conducted according to the REPorting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [40] (see eTable 1). Sociodemographic and clinical characteristics of the sample (including missing data), were described with mean and SD for continuous variables, and absolute and relative frequencies for categorical variables. The cumulative probability of developing a (i) first episode of psychosis (primary outcome), (iia-d) receiving a first treatment or a (iia-b) first informal or compulsory admission to a mental health hospital and (iv) risk of death were described through Kaplan Meier [41] failure functions (1-survival) [41] and Greenwood 95% CIs [42]. For each outcome, we reported the numbers of those at risk and truncate the failure function when less than 10 patients were still at risk (50 for risk of death). Therefore, the follow-up time reported in the Kaplan Meier failure functions varied across each outcome. Counts and relative frequencies were used to describe the type of molecules; mean and SD and percentiles were used to describe the chlorpromazine equivalents and the number of psychotherapy sessions. Counts were reported to describe the (iii) number of days spent in hospital. The SMR was defined as the ratio between the number of deaths observed in the OASIS cohort at the end of follow-up and the annualised number of deaths expected in a similar size general population. The expected deaths were estimated using the Office for National Statistics [43] death rates in the OASIS catchment area, stratified for individuals aged 15–34 (the 15–35 stratum was not available) and weighted by OASIS gender. We then conducted two types of sensitivity complete-case analyses (missing variables were not imputed). First, we described the association between CHR-P subgroups (BLIPS, APS, GRD) and the outcomes (i-iv). As an additional exploratory outcome, we analysed the number of psychotherapy sessions. Second, we described the multivariable association between putative prognostic factors (age, CAARMS severity, DUAPS, gender, ethnicity, employment status) selected a priori on the basis of clinical knowledge and outcomes i-iv. For each sensitivity analysis, the association between predictors and the time-dependent outcomes (i, iia-d and iv) was explored using Cox regression models, after checking for edge and outcomes i-iv. For each sensitivity analysis, the association was described with mean and SD for continuous variables, and absolute and relative frequencies for categorical variables. The cumulative probability of developing a (i) first episode of psychosis (primary outcome), (iia-d) receiving a first treatment or a (iia-b) first informal or compulsory admission to a mental health hospital and (iv) risk of death were described through Kaplan Meier [41] failure functions (1-survival) [41] and Greenwood 95% CIs [42]. For each outcome, we reported the numbers of those at risk and truncate the failure function when less than 10 patients were still at risk (50 for risk of death). Therefore, the follow-up time reported in the Kaplan Meier failure functions varied across each outcome. Counts and relative frequencies were used to describe the type of molecules; mean and SD and percentiles were used to describe the chlorpromazine equivalents and the number of psychotherapy sessions. Counts were reported to describe the (iii) number of days spent in hospital. The SMR was defined as the ratio between the number of deaths observed in the OASIS cohort at the end of follow-up and the annualised number of deaths expected in a similar size general population. The expected deaths were estimated using the Office for National Statistics [43] death rates in the OASIS catchment area, stratified for

**Table 1**

Clinical and sociodemographic characteristics of the CHR-P sample.

| Variable                        | N   | Mean | SD  |
|---------------------------------|-----|------|-----|
| Age (years)                     | 598 | 22.63| 4.94|
| CAARMS severity                 | 470 | 34.35| 15.83|
| DUAPS (days)                    | 522 | 676.32| 1105.40|
| Baseline SOFAS                  | 527 | 54.09| 13.02|
| HONOS (adjusted total)          | 379 | 11.68| 6.95|
| Type of CHR-P subgroup           |     |      |     |
| APS                             | 481 | 80.43|     |
| BLIPS                           | 108 | 18.06|     |
| GRD                             | 9   | 1.51 |     |
| Gender                          | 600 |      |     |
| Females                         | 268 | 44.67|     |
| Males                           | 332 | 55.33|     |
| Borough                         | 567 |      |     |
| Lambeth                         | 250 | 44.09|     |
| Southwark                       | 178 | 31.39|     |
| Lewisham                        | 75  | 13.23|     |
| Croydon                         | 56  | 9.88 |     |
| Homeless                        | 8   | 1.41 |     |
| Ethnicity                       | 590 |      |     |
| White                           | 274 | 46.44|     |
| Asian                           | 42  | 7.12 |     |
| Black                           | 191 | 32.37|     |
| Other                           | 83  | 14.07|     |
| Marital status                  | 583 |      |     |
| Married                         | 24  | 4.12 |     |
| Separated or divorced           | 13  | 2.23 |     |
| Single                          | 464 | 79.59|     |
| In a relationship               | 82  | 14.07|     |
| Employment status               | 589 |      |     |
| Employed                        | 151 | 25.64|     |
| Student                         | 207 | 35.14|     |
| Unemployed                      | 231 | 39.22|     |
| Accommodation status            | 561 |      |     |
| Living with own family          | 278 | 49.55|     |
| Owner                           | 7   | 1.25 |     |
| Rental                          | 146 | 26.02|     |
| Council flat or hostel          | 98  | 17.47|     |
| Homeless                        | 17  | 3.03 |     |
| Other                           | 15  | 2.67 |     |

(a) range 13–36 (although the OASIS age range is typically 14–35 there are a few exceptions).

(b) sum of CAARMS severity by frequency across each P1-P4 CAARMS domains; CAARMS: Comprehensive Assessment of At Risk Mental State; SOFAS: Social and Occupational Functioning Assessment Scale; DUAPS: Duration of Untreated Attenuated Psychotic Symptoms; HONOS: Health Of the Nation Outcome Scale; APS: Attenuated Psychotic Symptoms; BLIPS: Brief and Limited Interimittent Psychotic Symptoms; GRD: Genetic Risk and Deterioration syndrome.
For all analyses, statistical tests were two-sided and statistical significance was defined as \( p < 0.05 \). All analyses were conducted in STATA 14 (STATA Corp., TX, USA).

**Role of funding**

The founders had no influence on the analysis of the data, interpretation of the results and drafting of the current manuscript.

**Ethics**

Approval for the study was granted by the Oxfordshire Research Ethics Committee C.

**Results**

**Baseline characteristics of the sample**

As shown in Table 1, 600 CHR-P individuals (55.33% males) attended the OASIS service from its set up until June 2018 across all SLaM boroughs (mostly Lambeth, [44.09%] and Southwark [31.39%]). At presentation, their mean age was 22.63 years (range 13/0–36); 79.59% of them were single, 39.22% unemployed and about one-third (35.14%) were students. Half of CHR-P individuals lived with their own family (49.55%); 17.47% lived in supported accommodations (council flats or hostels) and 3.03% were homeless. The proportion of white (46.44%) and non-white (black 32.37%, Asian 7.12%, other 14.07%) ethnicities was similar. The baseline severity of the total CAARMS symptoms was 34.35; baseline functional level was rather low (SOFAS=54.09) and reflected by an average HONOS score of 11.68. The onset of attenuated psychotic symptoms occurred on average about 1.85 years ahead of the CHR-P designation (DUAPS=676.32 days). DUAPS was 202.42 days in the GRD (SD 125.27), 302.03 days in the BLIPS (SD=896.06) and 773.88 days in the APS (SD=1139.69) subgroups. At OASIS, 80.43% CHR-P individuals met APS criteria, followed by a substantial proportion of BLIPS (18.06%), while GRD cases were rarer (1.51%).

**Real-world, long-term clinical outcomes in CHR-P patients**

**Cumulative risk of developing a first ICD-10 psychotic disorder**

The cumulative risk to psychosis was 0.133 (95%CI 0.107–0.165) at 1 year, 0.191 (95%CI 0.158–0.229) at 2 years, 0.247 (95%CI 0.208–0.291) at 3 years, 0.273 (95%CI 0.231–0.321) at 4 years, 0.288 (95%CI 0.244–0.337) at 5 years, 0.298 (95%CI 0.252–0.349) at 6 years, 0.324 (95%CI 0.275–0.379) at 7 and 8 years, 0.333 (95%CI 0.282–0.392) at 9 years, 0.365 (95%CI 0.302–0.437) at 10 and 11 years (Fig. 1).

**Cumulative probability of receiving a first psychotropic or psychotherapeutic treatment**

The cumulative risk to first receiving antipsychotic medication was 0.427 (95%CI 0.378–0.478) at 1 year, 0.530 (95%CI 0.477–0.585) at 2 years, 0.622 (95%CI 0.561–0.683) at 3 years, 0.672 (95%CI 0.607–0.736) at 4 years, 0.729 (95%CI 0.657–0.796) at 5 years, 0.740 (95%CI 0.668–0.808) at 6 years, 0.777 (95%CI 0.702–0.844) at 8 and 9 years (Fig. 2). Most of those treated with antipsychotics received quetiapine (38.25%) followed by olanzapine (18.43%), risperidone (18.89%), aripiprazole (14.75%), amisulpride (3.69%) and promethazine (5.99%) (eTable 2). The mean chlorpromazine equivalent was 156.94 mg (SD 148.92, 25%–75% percentiles 25mg-675 mg).

The cumulative risk to first receiving benzodiazepines was 0.077 (95%CI 0.056–0.105) at 1 year, 0.121 (95%CI 0.093–0.156) at 2 years, 0.139 (95%CI 0.108–0.180) at 3 years, 0.147 (95%CI 0.113–0.189) at 4 years, 0.161 (95%CI 0.124–0.209) at 5 years, 0.191 (95%CI 0.114–0.249) at 6 years, 0.227 (95%CI 0.171–0.299) at 7–9 years, 0.259 (95%CI 0.183–0.359) at 10–12 years (Fig. 2). The most frequently prescribed benzodiazepines are reported in eTable 3.

The cumulative risk to first receiving other medications was 0.242 (95%CI 0.203–0.288) at 1 year, 0.316 (95%CI 0.271–0.367) at 2 years, 0.407 (95%CI 0.351–0.467) at 3 years, 0.463 (95%CI 0.401–0.529) at

![Fig. 1. Real-world cumulative risk of transition to psychosis in CHR-P individuals in the long-term. The dotted line indicates the median duration of care provided by CHR-P services (such as OASIS) worldwide [11].](image-url)
4 years, 0.514 (95%CI 0.440–0.588) at 5 years, 0.560 (95%CI 0.484–0.640) at 6 years, 0.587 (95%CI 0.506–0.669) at 7 and 8 years, 0.630 (95%CI 0.538–0.772) at 9 years (Fig. 2). The most frequently prescribed other medications are reported in eTable 4.

The cumulative risk of receiving a first psychotherapeutic treatment was of 0.670 (95%CI 0.637–0.720) at 1 year, 0.746 (0.704–0.787) at 2 years, 0.758 (95%CI 0.715–0.793) at 3 years, 0.763 (95%CI 0.719–0.803) at 4 years, 0.787 (95%CI 0.742–0.829) at 5 years, 0.786 (95%CI 0.742–0.829) at 6 years, 0.805 (95%CI 0.756–0.849) at 7 years, 0.814 (95%CI 0.764–0.859) at 8 and 9 years (Fig. 2). On average CHR-P individuals received 10.42 sessions of psychotherapy (SD=11.74); among those who received it, the mean number of sessions was 15.09 (SD=11.39).

Cumulative probability of being admitted into a mental health hospital and days spent in hospital

The cumulative risk to the first informal admission to a mental health hospital was 0.607 (95%CI 0.543–0.672) at 1 year, 0.746 (0.704–0.787) at 2 years, 0.758 (95%CI 0.715–0.793) at 3 years, 0.763 (95%CI 0.719–0.803) at 4 years, 0.787 (95%CI 0.742–0.829) at 5 years, 0.786 (95%CI 0.742–0.829) at 6 years, 0.805 (95%CI 0.756–0.849) at 7 years, 0.814 (95%CI 0.764–0.859) at 8 and 9 years (Fig. 2). On average CHR-P individuals received 10.42 sessions of psychotherapy (SD=11.74); among those who received it, the mean number of sessions was 15.09 (SD=11.39).

The cumulative risk of death for any reason (n = 8) was 0.004 (95%CI 0.001–0.025) at 3–4 years, 0.009 (95%CI 0.002–0.040) at 5–8 years, 0.036 (95%CI 0.012–0.103) at 9 years: 3 committed suicide, 2 died of other causes, and in 2 cases the cause of death was unknown. The SMR standardised for age/sex was 3.9 (95%CI 1.20–6.60).

Sensitivity analyses

Sensitivity analyses (eTable 5) showed that, compared to APS, BLIPS individuals had a higher risk of developing psychosis, being compulsorily admitted into mental health hospitals, receiving antipsychotics and benzodiazepines treatments, lower likelihood of receiving other medications, a comparable likelihood of receiving psychotherapy but fewer psychotherapy sessions, a comparable
Multivariable sensitivity analyses (eTable 6) showed that age, CAARMS severity and black ethnicities were associated with an increased risk of psychosis; age, CAARMS severity and unemployment with an increased risk of antipsychotic treatment; age and DUAPS with an increased and decreased risk of benzodiazepines treatment respectively; female gender female and black ethnicity with an increased and decreased risk of other medications respectively; CAARMS severity, DUAPS with an increased likelihood of receiving psychotherapy: CAARMS severity and DUAPS with an increased risk of informal admission; age, CAARMS severity, male gender, black ethnicities with an increased risk of formal admission; DUAPS and unemployment with a decreased and increased number of days spent in hospital respectively.

Discussion

To our best knowledge, this is the largest cohort study addressing the broadest real-world outcomes for CHR-P individuals beyond psychosis onset in the long-term. In 600 individuals accessing OASIS, there was a substantial long-term risk of developing psychosis, being treated with psychotropic medications, admitted formally or compulsorily into mental health hospitals and spending several days in hospitals. Some CHR-P individuals may be at risk of premature death in the long-term.

This study advances clinical knowledge on several lines. Firstly, it suggests that the real-world risk of psychosis in CHR-P individuals almost double from the short-term (0.191 at 2 years) to the long-term (0.365 at 10–11 years). CHR-P individuals have about a 50-fold increase in the probability of developing a psychotic disorder, compared to the local general population (South London, risk of psychosis: 0.72 at 10 years, estimated as in Fig. 3 in [46]). This finding contradicts the criticisms that the group of CHR-P patients only display a negligible risk of psychosis and that prevention of psychosis in this group should, therefore, be dismissed [47]. This result also suggests that the real-world risk of psychosis in CHR-P individuals may be higher than that observed in research studies or trials, which typically filter their participants through additional entry criteria or sampling biases. This finding is relevant to inform ongoing large-scale international consortia (e.g. PSYSCAN [48, 49], PRONIA [50], NAPLS [51], PNC [52], HARMONY) that are developing and validating risk prediction models in this group. Furthermore, the notion of declining transition risk in CHR-P samples over the most recent years may also represent –at least partially- an artefact of research recruitment [33] and insufficient duration of follow-up.

Secondly, this study demonstrates that CHR-P individuals display several poor mental health outcomes beyond transition to psychosis with about one-third of them (informal admission 0.378 at 12 years; formal admission 0.251 at 12 years) being admitted into mental health hospitals. This is also the first study to indicate that CHR-P individuals have a threefold risk (SMR=3.9) of death compared to age and sex matched individuals living in the local general population (cumulative risk of death for any cause 0.036 at 9 years). The magnitude of the SMR in the CHR-P state is comparable to that observed in young people from the same geographical area for severe mental disorders (4.47, 95%CI 3.49–5.64 [53]) such as established psychosis or affective disorders. Another proxy of poor mental health outcomes is indexed by the high exposure to psychotropic medications that do not typically represent the recommended first-line treatment for this group (antipsychotics: 0.777 at 9 years, benzodiazepines 0.259 at 10–12 years, other medications 0.630 at 9 years), although these findings should be interpreted with caution. For example, the average chlorpromazine equivalent is lower than the minimum effective dose (200mg [54]), and the most frequently used antipsychotic was quetiapine; this suggests that low-dosage antipsychotics may have been used to treat comorbid disorders as opposed to primarily treating emerging psychosis. This is substantiated by the relatively high proportion of those receiving benzodiazepines or antidepressants, which again may reflect the substantial prevalence of comorbid affective disorders in this group [55].

Interpretation of these outcomes in the context of a non-randomised naturalistic study is not straightforward. OASIS fully aligned with the current clinical recommendations, and by the end of their care, most CHR-P individuals (0.746 at 2 years) had been offered the recommended preventive cognitive behavioural therapy. The hypothesis that cognitive behavioural therapy is substantially effective to prevent psychosis conflicts with the substantial transition risk observed in this cohort. Furthermore, the number of sessions provided to individuals accepting cognitive behavioural therapy is close to the recommended standard for efficacy [56]. Alternatively, a possibility may be that cognitive behavioural therapy is only effective to delay the onset of the disorder and that its effect vanishes over the long-term. A further possibility is that the magnitude of the putative preventive effects of cognitive behavioural therapy is too small to be observed across the heterogeneous CHR-P group. The latter
hypothesis is supported by recent evidence synthesis studies that
indicated no robust evidence to favour cognitive behavioural therapy
over other treatments for preventing psychosis in CHR-P individuals
[28, 57–59].

Thirdly, this study is also the first to stratify broad, long-term out-
comes beyond transition to psychosis across CHR-P subgroups. Since
in SLaM there is one of the highest rates of psychosis in the world
[60] (and therefore a large proportion [18%] of BLIPS [61]), this study
was also best placed on demonstrating that BLIPS individuals have a
higher risk than APS of developing psychosis, being compulsorily
admitted into mental health hospitals, being exposed to non-recom-
manded treatments (antipsychotics and benzodiazepines) and
receiving lower intensity of the recommended treatments (i.e. a
lower number of psychotherapy sessions). Conversely, they had a
lower likelihood of receiving antidepressants or mood stabilizers,
presumably in the light of the lower prevalence of affective or per-
sonality comorbidities in this subgroup [62]. This implies that pre-
ventive treatments should be stratified across APS and BLIPS
subgroups [1]. To date, only 3% of BLIPS individuals receive the appro-
ropriate “dose” of the recommended preventive treatment (cognitive
behavioural therapy) [56], because it primarily targets attenuated
psychotic symptoms and not their specific needs.

This study is also the first one to investigate the potential signifi-
cance of several prognostic factors for long-term outcomes in this
population. We found that age, baseline symptoms severity, duration
of untreated attenuated psychotic symptoms, ethnicity and employ-
ment status are consistently associated with various long-term
clinical outcomes in CHR-P individuals. Although subsequent inde-
pendent studies are needed to replicate these findings, our results
could be used to inform the building of new clinical prediction mod-
els to forecast various long-term clinical outcomes beyond the onset
of psychosis.

The above findings converge towards the most important clinical
implication of the current study: the short-term duration of care cur-
rently offered by CHR-P services [11] worldwide is unlikely to be suf-
ficient to capture the complex and broad long-term outcomes of this
group, and should, therefore, be extended. The likelihood of severe
real-world outcomes almost doubles from the short-term to the
long-term; psychosis risk from 0.191 at 2 years to 0.365 at 10–11
years; risk of informal hospital admission from 0.115 at 2 years to
0.316 at 10–11 years, risk of compulsory admission from 0.080 at
2 years to 0.251 at 10–12 years. This is paralleled by a similar
increase in psychotropic treatments, which is a proxy of long-term
mental health problems: risk of a first antipsychotic from 0.530 at
2 years to 0.777 at 8–9 years; risk of a first benzodiazepine from
0.121 at 2 years to 0.259 at 10–12 years, risk to first receiving other
medications from 0.316 at 2 years to 0.630 at 9 years. This is further
aggravated by the fact that the median duration of follow-up assess-
ment offered to CHR-P individuals after being discharged from CHR-P
services is only 12 months [11]. Monitoring for broad clinical out-
comes in the long-term is extremely challenging. This study further
advances knowledge by demonstrating that a possible way of over-
coming these challenges may be to leverage EHRs, which are increas-
ingly adopted across several primary and secondary health care
systems. EHR not only represent real-world clinical information but
can incorporate automatic detection or prognostic algorithms
[63–66], translating stratified and precision medicine approaches in
this field. Overall, these results will inform future studies such as the
proposed 26-site ProNET cohort study and global health policies
relating to CHR-P service development as well as worldwide clinical
guidelines.

The main limitation of this study is that it did not employ struc-
tured psychometric interviews to ascertain the onset of outcomes at
follow-up including the diagnostic stability of psychotic onset [67].
Therefore, while the current EHR findings have high ecological valid-
ity (i.e. they represent real-world clinical practice), they have not
been subjected to formal validation with research-based criteria.
However, the aim of the present study was to assess real-world cli-
nical outcomes rather than psychometric outcomes in this cohort.
The use of structured diagnostic interviews in research settings can itself
lead to the selection of white, more highly educated and “squeak-
clean” [68] patient subsamples [69], further exaggerating sampling
biases that are already affecting this field [34]. Additionally, some of
the current results should be interpreted cautiously because of the
limited counts, in particular the SMR. Another limitation is that
patients moving outside the SLAM catchment area may not have been
followed up.

A final important limitation is that the current study simply
described outcomes in the long-term without addressing the effec-
tiveness of CHR-P clinics (or interventions), given the naturalistic
design. Testing the effectiveness of CHR-P clinics would require rand-
omised designs, which are ethically and logistically difficult to imple-
ment.

In conclusion, this study suggests that duration of care provided
by CHR-P services should be expanded to better capture the long-
term real-world outcomes displayed by this group.

Declaration of Competing Interest

Dr. Fusar-Poli reports grants and personal fees from Lundbeck,
personal fees from Menarini, personal fees from Angelini, outside the
submitted work. Dr. Salazar de Pablo reports grants from Fundación
Alicia Koplowitz, outside the submitted work. The other authors have
nothing to disclose.

Author contribution

PFP conceived and led the study. ADM, LS, HB, GSDP, PM gave sub-
stantial contributions to the acquisition and interpretation of data.
PFP drafted the work and conducted the analyses. PM gave sub-
stantial contributions to the interpretation of the results.

ADM, LS, HB, GSDP, PM revised it critically for important intellec-
tual content. All authors approved the final version to be published
and agreed to be accountable for all the aspects of the work. PFP had
full access to all the data in the study and can take responsibility for
the integrity of the data and the accuracy of the data analysis.

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founders had no influence on the analysis of the data, interpretation
of the results and drafting of the current manuscript.

Data sharing statement

There is no ethical permission for data sharing.

Supplementary materials

Supplementary material associated with this article can be found
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