

Optimal duration of an early intervention programme for first-episode psychosis: randomised controlled trial

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Background

Numerous early intervention services targeting young people with psychosis have been established, based on the premise that reducing treatment delay and providing intensive treatment in the initial phase of psychosis can improve long-term outcome.

Aims

To establish the effect of extending a specialised early intervention treatment for first-episode psychosis by 1 year.

Method

A randomised, single-blind controlled trial (NCT01202357) compared a 1-year extension of specialised early intervention with step-down care in patients who had all received a 2-year intensive early intervention programme for first-episode psychosis.

Results

Patients receiving an additional year of specialised intervention had better outcomes in functioning, negative and depressive symptoms and treatment default rate than those managed by step-down psychiatric care.

Conclusions

Extending the period of specialised early intervention is clinically desirable but may not be feasible in lower-income countries.

Declaration of interest

None.

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Psychotic disorders including schizophrenia are severe mental illnesses that affect approximately 3% of the population¹ and constitute one of the highest disease burdens globally.² Numerous early intervention services targeting young people with psychosis have been established worldwide in the past two decades, based on the premise that reducing treatment delay and providing intensive phase-specific interventions in the initial few years of psychosis can improve long-term illness outcome.³ Superiority of early intervention services over standard care in improving clinical and functional outcomes in people with early psychosis has been consistently demonstrated by recent meta-analytic reviews.^{4,5} A summary of studies that evaluated the effectiveness of specialised early intervention services for patients with first-episode or recent-onset psychosis given in online Table DS1. However, the initial therapeutic benefits achieved by such programmes may not be maintained after the service is withdrawn. In the OPUS trial, the largest randomised controlled trial (RCT) thus far evaluating the effectiveness of integrated early intervention services for psychosis, the findings of better symptom outcome and treatment adherence for early intervention over standard care at 2 years were no longer significant after 5 years of follow-up.⁶ Similarly, the Lambeth Early Onset (LEO) study found that improved 18-month outcomes on functioning, quality of life and hospital admission resulting from early intervention were not sustained at 5 years.⁷ Considerable concern is thus raised regarding the durability of beneficial effects of early intervention and how long specialised intervention should be provided to consolidate and optimise these initial treatment gains.^{8,9} The lack of empirical data determining the optimal duration of early intervention (usually provided for the first 1–2 years of illness) emphasises the need for research to evaluate the effectiveness of longer-term early intervention programmes for psychosis.^{6,8,9} It is also worth noting that both the early intervention service model and evidence supporting its effectiveness in treating psychosis

were mainly derived from Western populations, particularly in Australia, Canada, the UK and Scandinavia. There is substantial variation across different regions regarding the content and intensity of early intervention services and the characteristics of patients enrolled, including age range and diagnostic distribution.¹⁰ This limits generalisability of results and precludes direct adoption of early intervention services by non-Western countries where mental healthcare is often underresourced and sociocultural contextual factors are markedly different from those of Western populations.

Hong Kong is among the few cities in Asia to implement early intervention services for psychosis. The intervention programme Early Assessment Service for Young People with Psychosis (EASY) was launched in 2001 and comprises community awareness programmes, an open referral system and a 2-year specialised intervention for young people presenting with first-episode psychosis, followed by 1-year step-down care with preserved medical follow-up but no provision of case-management service.¹¹ Evaluation of the EASY programme using historical-control methods showed that patients receiving early intervention had better functioning, milder symptom severity, fewer suicides and hospital admissions and a lower disengagement rate than those in standard care, despite a lack of significant between-group difference in duration of untreated psychosis (DUP).¹² However, consistent with increasing evidence indicating that a significant proportion of patients with early psychosis exhibit persistent functional impairment even in the presence of clinical remission,^{13,14} we found that only approximately a quarter of patients treated in the EASY programme fulfilled criteria for functional remission and less than half of those achieving symptomatic remission were also in functional remission.¹⁵ The existing data thus highlight an inadequacy of current early intervention services in addressing patients' functional disability. In this regard, it is suggested that extending the duration of early intervention services may be

necessary to promote recovery, as a longer period is required for sustained and progressive functional improvement to take place after stabilisation of the initial psychotic episode with medication treatment.^{8,9}

Our study compared a 1-year extension of a specialised early intervention service, comprising continuing phase-specific case management, with step-down psychiatric care without provision of case management in a representative cohort of Chinese patients who had received 2-year intensive treatment in the EASY programme for their first psychotic episode. To the best of our knowledge, this is the first reported RCT to examine the effectiveness of a specialised early intervention programme for psychosis with its treatment period extended beyond 2 years; currently, there are two ongoing RCTs evaluating the effectiveness of 5-year specialised early intervention services, namely the OPUS II study in Denmark and the Prevention and Early Intervention Program for Psychoses study in Canada.^{16,17} We predicted that, over 12 months, patients receiving the additional year of specialised early intervention would have better functional and symptom outcomes and lower default rate in out-patient treatment than patients receiving step-down treatment.

Method

A single-blind RCT was used to compare a 1-year extension of specialised early intervention (i.e. a 3-year early intervention programme) with step-down care (i.e. a 2-year early intervention programme) in patients who had received 2 years of care from the intensive early intervention service for first-episode psychosis in Hong Kong. Participants were recruited from the EASY programme between November 2010 and August 2011 and were followed up for 12 months. The EASY programme is a publicly funded, territory-wide service providing comprehensive assessment and early intervention for individuals aged 15–25 years presenting with first-episode psychosis.¹¹ The service consists of five clinical teams, each covering a geographically defined catchment area and comprising two psychiatrists, three case managers and one social worker. The programme adopts a phase-specific, case-management approach in which each patient is assigned a case manager who provides protocol-based psychosocial interventions, namely the Psychological Intervention Programme in Early Psychosis (PIPE),¹⁸ with reference to the International Clinical Practice Guidelines for Early Psychosis,¹⁹ with local cultural adaptations. The PIPE comprises three main modules of intervention:

- (a) enhancing psychological adjustment to early psychosis through in-depth engagement, comprehensive psychoeducation, adherence to medication treatment, coping and stress management, and relapse prevention (PIPE-I);
- (b) psychotherapy for secondary psychiatric morbidity (PIPE-II);
- (c) cognitive-behavioural therapy (CBT) for treatment-resistant psychotic symptoms (PIPE-III).¹⁸

A standardised PIPE-I module is offered by case managers to all patients and their family caregivers. As case-loads of EASY case managers (approximately 1:80) are much heavier than those of well-established early intervention services in the West, rather than providing intensive intervention such as CBT or specialised family therapy, case management of the EASY programme focuses on psychoeducation and supportive care.^{11,18} Emphasis is also placed on enhanced support and communications with family caregivers, who have a critical role in patient management in Hong Kong, as most patients enrolled in the programme live with their families.¹¹ Family counselling and carer support groups are

arranged if indicated. Patients with additional treatment needs such as the presence of residual symptoms or secondary depressive symptoms are referred to clinical psychologists for provision of PIPE-II and PIPE-III modules as appropriate. The programme also closely collaborates with non-governmental organisations (NGOs) which organise community-based rehabilitation programmes and vocational training for patients recovering from early psychosis. Multidisciplinary case reviews are held on a regular basis to monitor the patients' clinical progress and treatment outcomes. Patients are assertively followed up for 2 years, after which they are managed by a transitional step-down clinic in the third year of treatment, whereby medical follow-up is offered by psychiatrists who have been responsible for their care in the 2-year programme but no case management is provided (i.e. equivalent to standard psychiatric care but with 1-year continuous out-patient follow-up by psychiatrists from the EASY programme). They are then transferred to generic psychiatric services for continuous care.

Consecutive cases of patients who had received 2 years of treatment in the EASY programme following their first episode of psychosis, with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, delusional disorder, psychosis not otherwise specified, bipolar disorder with psychotic symptoms or depressive disorder with psychotic symptoms according to DSM-IV criteria,²⁰ were included in the study. Exclusion criteria were intellectual disability, substance-induced psychosis, psychotic disorder due to a general medical condition or an inability to speak Cantonese Chinese for the research interview. The study was approved by the local institutional review boards. All participants provided written informed consent. For those aged under 18 years, consent was also obtained from a parent or guardian. The trial was registered with ClinicalTrials.gov (NCT01202357).

Randomisation

Following baseline assessment participants were randomly assigned in a 1:1 ratio to either extended early intervention (early intervention group) or step-down care (control group) for the next 12 months. An allocation sequence was computer-generated with a fixed block size of four. Randomisation and concealment procedures were conducted by an independent research staff member who was not involved in recruitment, clinical management or research assessment of the study participants.

Treatment

Participants in both treatment conditions were managed by psychiatrists from their respective EASY clinical teams.

Extended early intervention

Specialised early intervention was continued in the form of an additional year of case management. A trained case manager took over cases from the EASY programme and was responsible for providing care and coordinating treatment with clinicians, allied health professionals and NGOs to all participants in this group ($n=82$) (i.e. a case-load comparable to the EASY programme). Case management closely aligned with the EASY treatment protocols, focusing specifically on functional enhancement by assisting participants to re-establish supportive social networks, resume leisure pursuits and return to work. Additionally, continuous supportive care, psychoeducation, and coping and stress management were delivered to family caregivers of each participant in the extended intervention group by the case manager. Each participant in this group received on average 16 intervention

sessions, which were defined as case-management contacts each lasting for a minimum of 30 min with either clinical assessment conducted or psychosocial treatment delivered by the case manager, over 1 year. Biweekly clinical supervision was provided to case managers by senior psychiatrists who had extensive experience in early intervention for psychosis.

Step-down care

Step-down care provided out-patient medical follow-up with limited community support which focused mainly on crisis intervention. The two treatment groups did not differ from each other with respect to the intensity of medical follow-up by psychiatrists, prescription of antipsychotic medications and availability of various psychosocial interventions and community-based services.

Assessment

Trained research assistants masked to treatment allocation administered all assessments. Diagnosis of each participant was ascertained in consensus meetings attended by a senior psychiatrist and research assistants using all available information encompassing the entire follow-up period, including the Chinese-bilingual Structured Clinical Interview for DSM-IV,²¹ informant histories and medical records. The Interview for the Retrospective Assessment of the Onset of Schizophrenia was employed to determine DUP, age and mode of onset of psychosis.²² Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale (CDS).^{23,24} Symptomatic remission was measured and defined according to the operational criteria formulated by the Remission in Schizophrenia Working Group based on PANSS ratings.²⁵ In this study we applied the symptom severity criterion in defining remission status attained at the end of 12-month follow-up. Psychopathological evaluation was conducted at baseline and at 12 months.

Psychosocial functioning was measured with the Social and Occupational Functioning Assessment Scale (SOFAS) and the Role Functioning Scale (RFS).^{26,27} The SOFAS provided a global functioning estimate of the individual participants, whereas the RFS, comprising four subscales, was used to assess functional levels of various domains including independent living and self-care, work productivity, and immediate and extended social networks. Good functioning status was operationalised as simultaneous fulfilment of the following criteria: the participant attained a score above 60 (achieving functional level of 'generally functioning well though with some difficulty in social or occupational functioning' or above) in SOFAS,²⁶ a score above 5 (achieving 'adequate' functional level or above) in RFS independent living and immediate social network subscales,²⁷ a score above 4 in RFS work productivity (at least 'moderately functional' in independent employment, at home or in school) and extended social network subscales (at least 'moderately effective and independent' in community interactions),²⁷ and was engaged in competitive employment (as opposed to employment in a supported or sheltered environment) at 12 months of follow-up. Functioning was assessed at baseline, at 6 months and at 12 months after study entry.

Data on sociodemographic characteristics, occupational status, hospital admission, defaults in psychiatric out-patient appointments, suicide attempts, relapse and treatment characteristics including use of second-generation antipsychotic, dose of antipsychotic medication (chlorpromazine equivalent doses were computed for analysis),²⁸ and medication adherence of each participant were also obtained through systematic record review using out-patient and in-patient case notes as well as

computerised clinical information from the hospital database. Relapse was operationally defined as recurrence or exacerbation of positive symptoms necessitating either hospital admission or adjustment of antipsychotic medication. Participants were considered as having good treatment adherence if they took more than 75% of prescribed medication (assessed on the basis of reports from patients and relatives as well as medical record review). Complete clinical record data for the follow-up year were available for all participants for analysis.

Training in the use of study instruments was provided to research assistants prior to participant recruitment. Videotaped interviews of 10 cases selected at baseline were independently rated by all research assistants for the purpose of interrater reliability evaluation. Intraclass correlation coefficients (ICCs) for PANSS general psychopathology, positive and negative symptom subscales and CDS total score were 0.92, 0.96, 0.91 and 0.89 respectively, indicating good interrater reliability. Satisfactory levels of concordance were also observed in functional measures, with ICCs for SOFAS and RFS total scores being 0.93 and 0.88 respectively.

Statistical analysis

Statistical analyses were performed on an intention-to-treat basis. Primary outcome was psychosocial functioning as measured by SOFAS and RFS. Secondary outcome measures included symptom severity, service use and other clinical variables. We estimated sample size based on SOFAS as this was a key outcome measure of the study. To detect a clinically meaningful 5-point difference in SOFAS, with a power of 0.8 and $\alpha=0.05$, and to allow for a withdrawal rate of 20%, 160 participants were required for the study. To test whether the two treatment groups were comparable at intake after randomisation, between-group differences in sociodemographic factors, baseline clinical profiles, treatment characteristics, symptom and functioning scores at entry were examined using the chi-squared test and independent *t*-test, as appropriate. To determine group differences in functional and symptom outcome measures, a series of linear mixed model (LMM) analyses with random intercepts and slopes were employed,²⁹ using R version 3.02 for Windows. The final models were optimised by defining the covariance structure with assessment time-points as within-individual factors (i.e. repeated effects) and treatment group as between-individual factors to estimate longitudinal changes of outcome variable across follow-up period, in particular the presence of any significant group \times time interactions, followed by the specific intervals (i.e. baseline to 6 months or 6–12 months) in which the two groups differed in functioning score change. Between-group comparisons of symptom and functional outcomes at follow-up were performed. Implementation of LMM analysis is recommended as a preferred statistical method of outcome analysis in clinical trials, as these models can address missing outcome data by allowing the analysis of all available data on the assumption that data are missing at random, conditional on adjustment for covariates and baseline observed scores.²⁹ Rates of attaining symptomatic remission and good functional status at 12 months were compared between the two groups. To address potential effects of attrition bias, sensitivity analysis was conducted based on a worst-case scenario, i.e. participants lost to follow-up were considered not to be in remission and to have poor functional status. Treatment characteristics at follow-up and other outcome variables were compared between the two groups. Duration of untreated psychosis was log-transformed owing to its skewed distribution. All statistical analyses were two-tailed with level of significance set at $P<0.05$.

Results

A total of 160 patients were enrolled and randomly assigned to the extended early intervention group ($n=82$) or the stepped-care (control) group ($n=78$). The 160 participants were predominantly single (96%) and 51% were male. The mean age of the sample at intake was 22.9 years (s.d.=3.2). The median DUP of the sample was 13 weeks (mean=36, s.d.=52.5). Diagnoses of the cohort were schizophrenia spectrum disorder ($n=131$), affective psychosis ($n=15$) and other non-affective psychoses ($n=14$). Four participants withdrew from the study (Fig. 1). There was no significant between-group difference in discontinuation rate ($P=0.62$), sociodemographic profile or baseline clinical, functional and treatment characteristics (Tables 1 and 2).

Functional outcomes

There was no significant difference between the two groups in functional outcomes at 6 months (Table 2). After 12 months, participants in the extended intervention group had significantly better global functioning, as revealed by higher SOFAS and RFS total scores, and more favourable outcomes in independent living skills, work productivity, and relationships of both immediate and extended social networks as measured by RFS subscales, than those in control group (Table 2). A significantly greater proportion of participants in the intervention group achieved good functional status compared with those in control group at 12 months (Table 3). No significant between-group difference was noted in attainment of full-time work at the 12-month follow-up.

The longitudinal analysis showed significant group \times time interactions in SOFAS score, with significant changes in functioning between baseline and 6 months as well as between 6 months and 12 months (Table 4). Participants in the intervention group had significant improvement in SOFAS score from baseline to 6 months ($P<0.001$) and from 6 months to 12 months ($P<0.001$), whereas there was no significant change in SOFAS score across the study period in the control group (Fig. 2). No significant main between-individual effect of treatment allocation on SOFAS rating was observed. Regarding the change in RFS ratings over time, LMM analyses indicated significant group \times time interactions in total score and scores on work productivity, independent living, and immediate and extended social network subscales (Table 4). Significant changes between baseline and 6 months in work productivity and immediate social network subscale scores, and significant changes between 6 months and 12 months in RFS total score, work productivity, independent living, immediate and extended social network subscale scores were observed. The intervention group was found to have significant improvements in RFS total score ($P<0.001$), work productivity ($P<0.001$), immediate ($P<0.01$) and extended ($P<0.01$) social network subscale scores from baseline to 6 months and from 6 months to 12 months of follow-up. A significant increase in independent living subscale score ($P<0.01$) was found in the intervention group from baseline to 6 months (Fig. 2). Conversely, participants in the control group failed to show significant improvement in RFS total and any of the subscale scores from 6 months to 12 months. The RFS total ($P<0.01$), independent living ($P<0.01$) and extended social network subscale ($P<0.01$) scores were significantly improved in the control group from baseline to 6 months (Fig. 2). Otherwise, there was no significant main between-individual effect of treatment allocation on any of the RFS ratings. Taken

together, participants in the early intervention group had ongoing functional gains across 12 months whereas those in the control group failed to attain any sustained functional improvement after study entry.

Symptoms and other secondary outcomes

Table 3 summarises the differences between treatment groups in 12-month outcomes on symptom severity as well as other clinical and service use variables. The intervention group had significantly fewer negative and depressive symptoms, lower PANSS general psychopathology scores and fewer defaults in psychiatric out-patient appointments than the control group. Significant group \times time interactions were noted in outcomes on negative symptoms ($t=2.4$, $P<0.05$), depressive symptoms ($t=3.0$, $P<0.01$) and PANSS general psychopathology scores ($t=2.9$, $P<0.01$). No significant between-group difference was observed with respect to medication treatment characteristics, positive symptom level, length of in-patient stay or rates of symptomatic remission, relapse and attempted suicide (Table 3).

Discussion

We found that patients receiving an additional year of specialised early intervention had significantly better functioning, fewer negative and depressive symptoms and a lower default rate in out-patient treatment than the control group. With regard to functional outcome, two important findings emerged: first, patients in both treatment groups exhibited a moderate degree of functional disability at baseline (i.e. after completing the 2-year

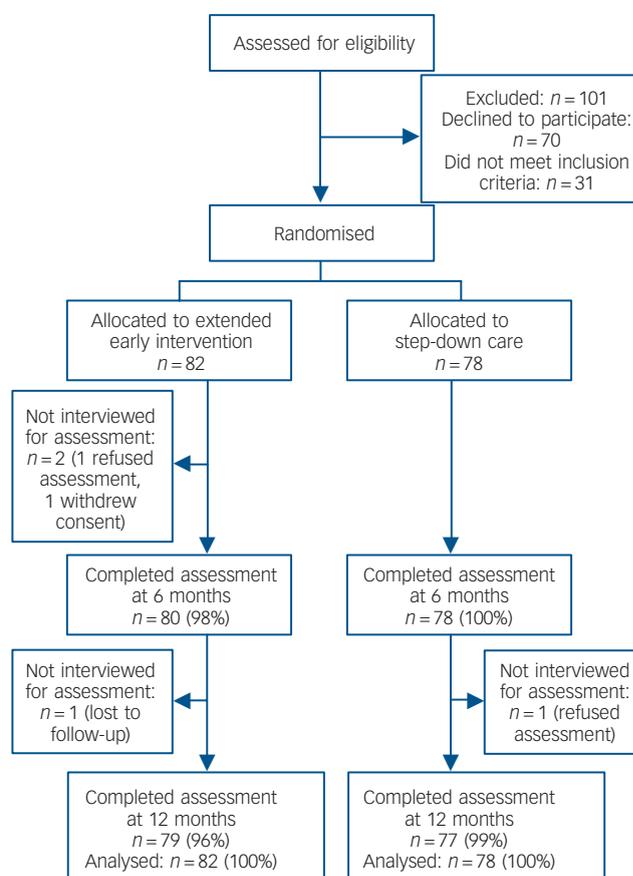


Fig. 1 Flow of patients through the study.

Table 1 Baseline demographic, clinical and treatment characteristics of the sample

	Extended intervention group (n = 82)	Control group (n = 78)	t or χ^2	P
Demographic characteristics				
Age at study entry, years: mean (s.d.)	23 (3.0)	22.8 (3.3)	0.31	0.756
Male gender, % (n)	50 (41)	51 (40)	0.03	0.871
Marital status: single, % (n)	94 (77)	97 (76)	1.19 ^a	0.444
Education: tertiary level or above, % (n)	24 (20)	27 (21)	0.14	0.714
Employed at baseline, % (n)	60 (50)	65 (51)	0.33	0.563
Illness onset characteristics				
Age at onset of psychosis, years: mean (s.d.)	20.2 (2.9)	20.3 (3.3)	-0.17	0.863
Gradual onset of psychosis < 1 month, % (n)	66 (54)	56 (44)	1.50	0.220
Duration of untreated psychosis, weeks				
Median	9	16		
LogDUP: mean (s.d.) ^b	1.9 (0.7)	2.0 (0.8)	-0.74	0.459
Three-year longitudinal diagnosis, % (n)				
Schizophrenia spectrum disorder ^c	84 (69)	80 (62)	1.48	0.476
Affective psychosis ^d	10 (8)	9 (7)		
Other non-affective psychosis ^e	6 (5)	12 (9)		
Past clinical and treatment parameters, % (n)				
Psychiatric hospital admission	66 (54)	60 (47)	0.54	0.463
Default of psychiatric follow-up	43 (35)	40 (31)	0.14	0.706
History of suicide attempt	6 (5)	4 (3)	0.43 ^a	0.720
Baseline symptom severity: mean (s.d.)				
PANSS positive symptom score	9.3 (3.3)	9.1 (2.9)	0.60	0.551
PANSS negative symptom score	11.7 (5.2)	12.3 (5.6)	-0.74	0.464
PANSS general psychopathology score	24.5 (7.4)	24.5 (6.3)	-0.01	0.990
CDS total score	2.8 (3.4)	2.9 (3.5)	-0.06	0.956
Baseline treatment characteristics				
Antipsychotic treatment				
Not taking antipsychotic, % (n)	7 (6)	5 (4)	0.37 ^a	0.833
Use of SGA, % (n)	82 (67)	85 (66)		
CPZ equivalent dose, mg: mean (s.d.)	307 (256)	300 (253)	0.17	0.869
CDS, Calgary Depression Scale; CPZ, chlorpromazine; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; SGA, second-generation antipsychotic.				
a. Fisher's exact test was applied.				
b. Duration of untreated psychosis was log-transformed for parametric analysis owing to its skewed distribution.				
c. Schizophrenia, schizoaffective disorder or schizophreniform disorder.				
d. Includes bipolar affective disorder and depressive disorder with psychotic symptoms.				
e. Includes brief psychotic disorder, delusional disorder and psychosis not otherwise specified.				

Table 2 Functional outcomes

	Extended intervention group (n = 82)	Control group (n = 78)	P
Baseline scores: mean (s.d.)			
SOFAS	57.5 (14.3)	57.9 (13.6)	0.867
RFS total score	19.2 (4.2)	19.8 (3.9)	0.354
RFS work productivity score	4.1 (1.8)	4.6 (1.5)	0.096
RFS independent living score	6.1 (1.0)	6.2 (0.8)	0.220
RFS immediate social network score	4.9 (2.1)	5.0 (1.3)	0.665
RFS extended social network score	4.1 (1.4)	4.0 (1.5)	0.663
Scores at 6-month follow-up: mean (s.d.)			
SOFAS	62.3 (13.3)	58.7 (11.1)	0.203
RFS total score	21.1 (3.7)	20.7 (3.3)	0.537
RFS work productivity score	4.8 (1.6)	4.7 (1.4)	0.727
RFS independent living score	6.3 (0.8)	6.5 (0.6)	0.110
RFS immediate social network score	5.3 (0.9)	5.1 (1.0)	0.111
RFS extended social network score	4.6 (1.2)	4.5 (1.3)	0.352
Scores at 12-month follow-up: mean (s.d.)			
SOFAS	64.8 (13.1)	57.9 (12.7)	0.001**
RFS total score	22.1 (3.2)	20.3 (3.7)	0.002**
RFS work productivity score	5.1 (1.4)	4.7 (1.5)	0.045*
RFS independent living score	6.5 (0.6)	6.2 (1.0)	0.036*
RFS immediate social network score	5.5 (0.9)	5.1 (1.0)	0.002**
RFS extended social network score	4.9 (1.0)	4.3 (1.3)	0.004**
RFS, Role Functioning Scale; SOFAS, Social and Occupational Functioning Assessment Scale.			
a. Endpoint analyses were based on planned comparison t-tests derived from linear mixed models.			
*P < 0.05, **P < 0.01.			

Table 3 Clinical outcomes and treatment characteristics of the two study groups

	Extended early intervention group (n = 82)	Control group (n = 78)	t or χ^2	P
Symptom severity at 12 months ^a				
Subscale scores: mean (s.d.)				
PANSS positive symptoms	8.3 (2.5)	8.6 (2.8)	-0.68	0.50
PANSS negative symptoms	8.5 (2.5)	9.8 (3.8)	-2.5	0.013*
PANSS general psychopathology	19.2 (3.7)	21.1 (5.0)	-2.6	0.01*
CDS total score	0.9 (1.6)	1.8 (2.7)	-2.5	0.008*
Symptomatic remission, % (n) ^a	78 (64)	68 (53)	2.7	0.150
Global functioning at 12 months				
Good functioning status, % (n)	35 (29)	19 (15)	5.2	0.022*
Other outcome measures during follow-up				
Psychiatric hospital admission, % (n)	16 (13)	10 (8)	0.3	0.353
Length of hospital stay, days: mean (s.d.) ^b	7.4 (20.6)	3.5 (12.8)	1.5	0.146
Default in out-patient appointment, % (n)	18 (15)	33 (26)	4.7	0.029*
Suicide attempt, % (n)	0 (0)	0 (0)		
Relapse of psychotic episode, % (n)	16 (13)	19 (15)	0.3	0.574
Full-time work at 12 months, % (n)	56 (46)	47 (37)	1.2	0.273
Treatment characteristics at follow-up				
Antipsychotic treatment at 6 months				
Not taking antipsychotic, % (n)	8 (7)	6 (5)	0.5 ^c	0.796
Use of SGA, % (n)	79 (65)	83 (65)		
Antipsychotic treatment at 12 months				
Not taking antipsychotic, % (n)	10 (8)	8 (6)	0.4	0.815
Use of SGA, % (n)	78 (64)	82 (64)		
CPZ equivalent dose, mg: mean (s.d.)				
At 6 months	302 (238)	323 (300)	-0.5	0.640
At 12 months	322 (276)	301 (295)	0.4	0.618
Good treatment adherence, % (n)	83 (68)	79 (62)	0.2	0.694

CDS, Calgary Depression Scale; CPZ, chlorpromazine; PANSS, Positive and Negative Syndrome Scale; SGA, second-generation antipsychotic.
a. Symptom assessments were completed by 79 participants in the intervention group and 77 participants in the control group at 12 months.
b. Non-parametric Mann-Whitney *U*-test revealed no significant difference between the two groups ($P=0.33$).
c. Fisher's exact test was applied.
* $P<0.05$.

Table 4 Linear mixed model analyses: treatment conditiontime interactions for functional outcomes

	Group \times time interaction (overall model)			Baseline to 6 months	6 to 12 months
	t	s.e.	P	P	P
SOFAS score	4.49	0.128	<0.0001	0.023*	<0.0001
RFS total score	4.15	0.039	<0.0001	0.068	<0.0001
RFS work productivity score	3.58	0.016	0.0004***	0.033*	0.0003***
RFS independent living score	1.98	0.010	0.0481*	0.302	0.0129*
RFS immediate social network score	3.60	0.012	0.0004***	0.019*	0.0003***
RFS extended social network score	2.69	0.014	0.0076**	0.497	0.0027**

RFS, Role Functioning Scale; SOFAS, Social and Occupational Functioning Assessment Scale.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$.

early intervention programme). Our results thus concur with accumulating evidence showing that people with early psychosis still experience significant functional impairment even when clinical stabilisation and remission have been achieved.^{13–15} Second, different functional trajectories were observed between treatment groups across the study period; although there was no significant between-group difference in functioning either at intake or at 6-month follow-up, patients in the intervention group displayed progressive functional improvement, whereas those in the control group failed to show any significant enhancement of functioning over 12 months. Hence, these results support our primary hypothesis that the extended early intervention service would be superior to step-down care in improving the functional outcome of patients with early psychosis. In fact, promoting recovery and facilitating uptake of educational, social and vocational opportunities are identified as key elements in early

intervention for young people with psychosis.³⁰ One recent study further indicated that functional recovery status achieved in the early illness course strongly predicted long-term outcomes on social functioning and negative symptoms.³¹ Longer-term early intervention services may thus be crucial to consolidation and sustained improvement of initial functional gains. This also aligns with stage-specific processes regarding the course of illness, wherein symptom resolution and clinical stabilisation take place at an earlier stage followed by gradual functional improvement which occurs later and requires substantially longer to achieve.

Secondary outcomes

An additional year of specialised early intervention was relatively effective in reducing negative symptoms, which nonetheless remained an unmet therapeutic need and were associated with poor

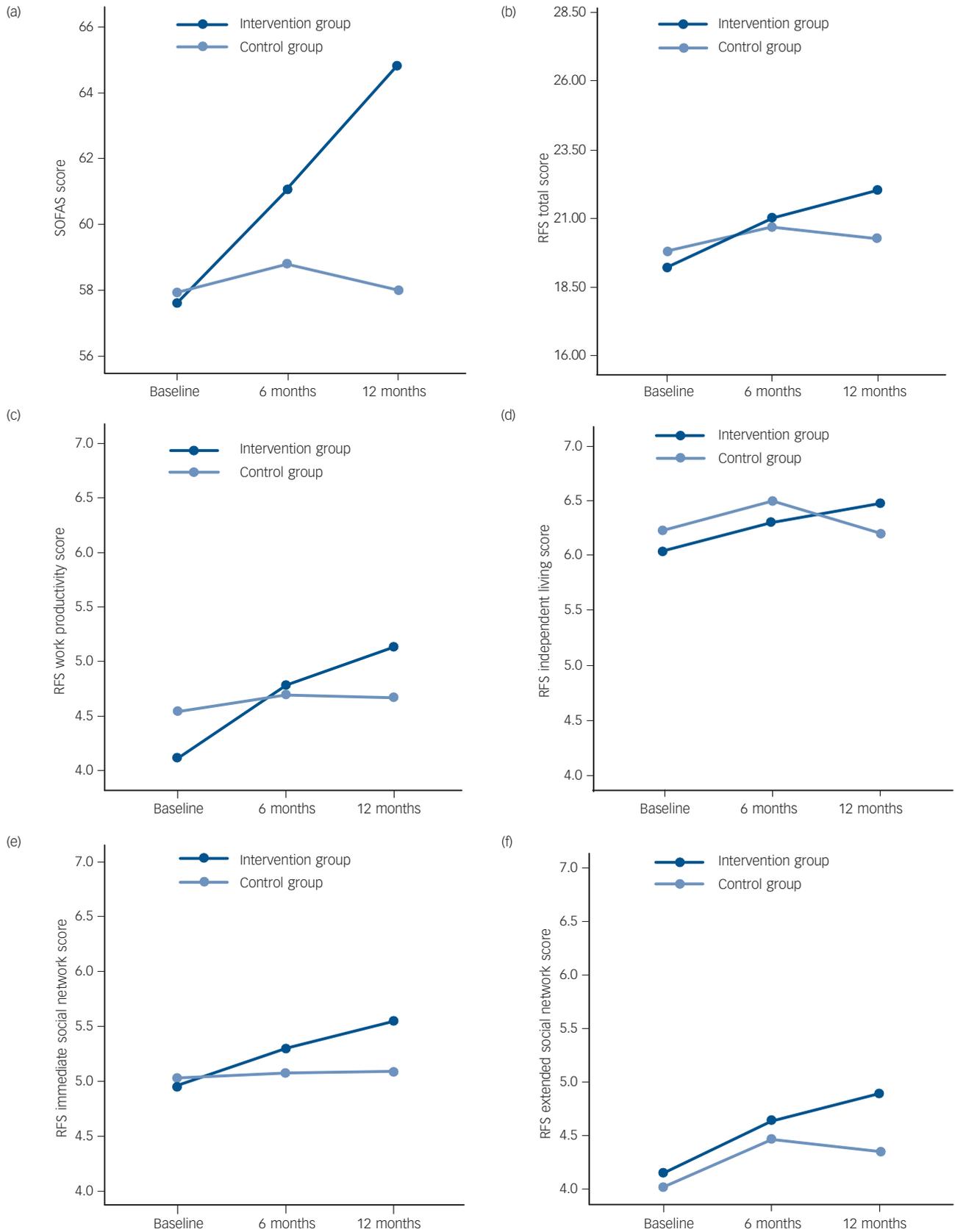


Fig. 2 Longitudinal change in functioning scores across 12-month follow-up in the extended early intervention and step-down care groups: (a) change in Social and Occupational Functioning Assessment Scale (SOFAS) score; (b) change in Role Functioning Scale (RFS) total score; (c) change in RFS work productivity score; (d) change in RFS independent living score; (e) change in RFS immediate social network score; (f) change in RFS extended social network score. Significant group \times time interactions were noted in all functional outcome scores as revealed by repeated-measures analyses of variance except RFS extended social network domain (see Table 4 for detailed results of longitudinal analyses of functioning scores).

functional outcome and limited response to pharmacotherapy.^{32,33} The intervention also compared favourably with step-down treatment in ameliorating depressive symptoms at 12-month follow-up. This is of critical clinical significance, as research has repeatedly demonstrated that depressive symptoms frequently occur in people with psychotic disorders and are closely associated with heightened suicide risk,^{34,35} particularly in the early stage of the illness.^{36,37} Consistent with previous reports, we found that patients in the intervention group had a significantly lower out-patient default rate than those receiving standard care;^{4,5} on the other hand, we failed to demonstrate any additional benefit of the intervention in relation to positive symptom severity, attainment of symptomatic remission or rate of relapse. Our findings thus concurred with some,^{38–40} but not all,⁴¹ prior RCTs evaluating the effectiveness of phase-specific, service-level intervention for early psychosis. One possible explanation for the lack of significant between-group differences in positive symptom outcome and relapse rate was that extended early intervention focused primarily on improving psychosocial functioning by means of specialised case management, and there was no difference between the intervention and control groups with respect to pharmacological treatment. It is also possible that as our patients were mostly clinically stabilised at entry after completion of the EASY programme, it was unlikely that a significant further reduction of positive symptoms could be observed. In agreement with previous RCTs comparing early intervention services with standard care in patients with early psychosis,^{38–41} we found that the two treatment groups did not differ in the rate of suicide attempt. Our result of lack of significant difference between early intervention and control groups in hospital admission rates was, however, contrary to a number of past RCTs,^{41,42} and historical case–control comparison studies,^{12,43,44} which demonstrated that patients who received early intervention services had fewer admissions than those in standard care. It is plausible that an absence of group difference in relapse rates during follow-up may partly explain the null finding on rate of in-patient treatment. The discrepant result may also be attributable to the difference in case-loads between our extended early intervention and the early intervention services of some Western countries, with the former having a significantly higher patient-to-case manager ratio, which might lower the capacity of the service to reduce the risk of readmission to hospital. Alternatively, the modest sample size and short follow-up duration of our study may have limited its power to examine the treatment effects of extended early intervention on readmission, as well as the suicide risk.

It is, however, important to note that our study compared an early intervention service with low resources and high case-loads with well-established early psychosis programmes implemented in some Western countries; our results therefore should be generalised to other populations with caution. Extending the early intervention service from 2 years to 5 years, to encompass the entire hypothetically critical period of psychosis,⁴⁵ might improve our patients' prognosis. However, in the context of competing demands and budgetary constraints, lengthening the intervention to 5 years might not be feasible or affordable in most non-Western regions, even in some relatively affluent Asian communities. Three-year specialised early intervention programmes may thus represent an economically viable alternative.

The strengths of the study included successful randomisation, lack of differential attrition between treatment groups, masking of the research staff assessing outcomes to treatment allocation, low withdrawal rate, comprehensive evaluation of functional outcomes encompassing both global functioning and various specific functional dimensions, and availability of complete

clinical record data regarding medication treatment, follow-up defaults and hospital admission for all participants. Several methodological limitations, however, warrant consideration in interpreting the study results. First, as the sample was recruited from the EASY programme, which treated patients aged 15–25 years only, our results may not be generalisable to people who were older at onset of psychosis. Second, the short follow-up period precluded us from addressing the question of whether therapeutic benefits attained from an additional year of specialised early intervention could be maintained after service withdrawal. Reassessment at a later time is required to examine this issue.

Further research

This was the first RCT to provide evidence of the efficacy of extending an early intervention service for psychosis beyond 2 years. Our results indicated that patients receiving an additional year of specialised early intervention had better outcomes in functioning, negative symptoms and depressive symptoms, and lower treatment default rates, than those managed by step-down psychiatric care. Further follow-up is required to clarify the sustainability of treatment effects of this extended intervention.

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First received 17 Apr 2014, final revision 11 Jul 2014, accepted 6 Aug 2014

Funding

The study was supported by a grant from the Commissioned Research on Mental Health Policy and Services (SMH-29) of the Food and Health Bureau, Government of Hong Kong Special Administrative Region. The funding body had no involvement in any aspect of the study or manuscript preparation. E.Y.H.C has been a member of the paid advisory board for Otsuka and has received educational grant support from Janssen-Cilag, Eli Lilly, Sanofi-Aventis and Otsuka. E.H.M.L has been a member of the paid advisory boards for Eli Lilly and AstraZeneca.

Acknowledgements

The authors thank all the coordinating clinicians and staff from the psychiatric units involved in the study. We thank Dr H.C. So for his kind assistance in statistical analysis using R software. We are also grateful to the individuals who participated in the study.

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Table DS1 Summary of studies evaluating the effectiveness of specialised early intervention service^a for early psychosis

Study	N	Age at Entry	DUP (median)	FEP Status	Diagnostic Scope	Follow-up	Attrition Rate	Early Intervention	Comparison Group	Outcomes
<u>Studies which adopted an experimental design (i.e., randomised controlled trial)</u>										
LEO Craig et al 2004 ⁴	144 EI: 71 SC: 73	16-40	EI: 10.5 months SC: 7.6 months ^b	Recent-Onset ^c	ICD10 non-affective psychosis	18 months	EI: 8.4% SC: 11%	Specialised team providing 18-month service included assertive outreach, CBT, family counseling and vocational support	Community mental health team with no training in managing early psychosis patients	-EI group had fewer admissions and lower dropout rate than SC group over 18-month follow-up period
Garety et al 2006 ⁷						18 months	EI: 23% SC: 40%			-EI group had better treatment adherence, social and vocational functioning, and quality of life than SC group over 18 months
Gafoor et al 2010 ¹⁴	99 EI: 45 SC: 54					5 years	EI: 37% SC: 26%			-No difference between the two groups in rate and length of admissions over 5 years
COAST Kuipers et al 2004 ⁵	59 EI: 32 SC: 27	18-65	Not reported	Recent-onset ^d	Both affective and non-affective psychosis Diagnostic criteria not reported	9 months	66.1%	Specialised team providing case management, family intervention, psychotherapy for residual symptoms and vocational support (caseload: 1:12)	Community mental health team with no specialised psychosocial intervention (caseload: 1:35)	-No difference between the two groups in symptom severity, functioning, quality of life, unmet needs and length of admissions at 9 months
OPUS Petersen et al 2005 ⁶	547 EI: 275 SC: 272	18-45	EI: 46 weeks SC: 53 weeks	FEP	ICD10 non-affective psychosis	2 years	EI: 25% SC: 40%	2-year integrated service with assertive community treatment, family intervention and social skills training (caseload: 1:10)	Community mental health team with psychosocial treatment available but on a less frequent basis (caseload: 1:20 to 1:30)	-EI group had fewer positive and negative symptoms, better treatment adherence and greater satisfaction with treatment than SC group at 2 years
Bertelsen et al 2008 ¹³	301 EI: 151 SC: 150					5 years	EI: 44% SC: 43%			-EI patients were less likely to live in supported housing and had fewer inpatient days over 5 years -No difference between the two groups in symptom level, global functioning, depression and suicidal behaviour at 5 years
OTP Grawe et al 2006 ⁸	50 EI: 30 SC: 20	18-35	Not reported	Recent-onset ^e	DSM-IV schizophrenia	2 years	EI: 10% SC: 20%	2-year integrated treatment providing home-based case management and structured psychosocial interventions (caseload: 1:10)	Clinic-based case management with no specialised psychosocial intervention (caseload: 1:10)	-EI group had fewer negative symptoms at 2 years than SC group -EI group had fewer minor psychotic episodes and better overall clinical outcome over 2 years than SC group
<u>Studies which adopted a quasi-experimental design (i.e., non-randomised treatment group allocation e.g. historical controlled study)</u>										
EPICC McGorry et al 1996 ¹	102 EI: 51 HC ^f : 51	EI: 16-30 HC: 16-45	EI: 52 days HC: 30 days	FEP	DSM-III-R affective and non-affective psychosis	1 year	EI: 27.5% HC: 33.3%	Specialised team providing 2-year service including case management, psychosocial interventions and specialized inpatient unit (caseload: 1:40)	Inpatient unit specialised for FEP but without community case management	-EI group had fewer admissions and inpatient days over 1 year than SC group -EI group had better global functioning than SC group at 1 year follow-up

Mihalopoulos et al 2009 ¹¹	65 EI: 32 HC ^f :33					8 years	EI: 37.3% HC:35.3%				-EI group had fewer positive symptoms, higher symptom remission rate at the end of follow-up than HC group -EI group had more favourable course of illness (without active psychosis) in the last 2 years of follow-up
Carbone et al 1999 ²	347 EI:147 HC ^f :200					1 year	EI: 25.2% HC: 30%				-For patients with DUP ranged between 4 weeks and 6 months, EI group had better functional outcome than HC group at 1 year
Parachute project Cullberg et al 2002 ³	388 EI: 253 PC ^g : 64 HC ^h : 71	18-45	Schizophrenia-Spectrum ^h : EI: 21 weeks PC: 12 weeks Non-schizophrenia spectrum: EI: 2.3 weeks PC: 2 weeks DUP data not reported in HC	FEP	DSM-IV non-affective psychosis and affective disorder with mood-incongruent psychosis (affective psychosis not included in HC)	1 year	EI: 31% PC: 20% HC: 0%	Integrated, need-specific treatment including home-based community care, family intervention with some centres providing overnight crisis home as an alternative for inpatient treatment	PC: inpatient and outpatient care provided by Uppsala research unit without specialised intervention for FEP HC: intervention focused mainly on pharmacological and supportive treatment without specialised intervention for FEP		-EI and PC groups had better global functioning at 1 year than HC group -No significant difference between EI and PC in functional and symptom outcomes at 1 year
Cullberg et al 2006 ⁹	143 EI: 71 PC ^g : 29 HC ^h : 43				DSM-IV schizophrenia-spectrum disorders	3 years	EI: 14% PC: 14% HC: 5%				-EI and PC groups had better global functioning at 3 years than HC group -No significant difference between EI and PC in functional and symptom outcomes at 3 years
PEPP Goldberg et al. 2006 ¹⁰	305 EI: 159 HC ⁱ : 146	16-50	Not reported	FEP ^j	DSM-IV non-affective psychosis	2 years	EI: 0% HC: 0%	Specialised team providing 2-year service including case management and protocol-based psychosocial interventions	Generic psychiatric service without specialised interventions for FEP		-EI group had fewer admissions and attendances to Emergency Department than HC group over 2 years
EASY Chen et al 2011 ¹²	1400 EI: 700 HC ^k :700	15-25	EI: 239.8 days HC: 232 days ^l	FEP	ICD10 affective and non-affective psychosis	3 years	EI: 23% HC: 30%	Specialised team providing 2-year service including case management and protocol-based psychosocial interventions (caseload: 1:80)	Generic psychiatric service with limited community support and no specialised psychosocial interventions		-EI group had less severe positive and negative symptoms, fewer suicides, fewer inpatient days, lower disengagement rate and longer full-time employment than HC group over 3 years

CBT, Cognitive-behavioural therapy; COAST, Croydon Outreach and Assertive Support Team; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised 3rd edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DUP, Duration of untreated psychosis; EASY, Early Assessment Service for Young people with psychosis; EI, Early intervention; EPICC, Early Psychosis Prevention and Intervention Centre; FEP, First-episode psychosis; HC, Historical control; ICD10, International Statistical Classification of Diseases, 10th Revision; LEO, Lambeth Early Onset team; OTP, Optimal Treatment Project; PC, Prospective control; PEPP, Prevention and Early Intervention Program for Psychosis; SC, Standard care.

^aOnly randomised controlled trials and other non-randomised case-control comparison studies focusing on evaluation of phase-specific, service-level intervention for early psychosis were included in this summary. Studies that only examined the impact of early detection program on treatment delay or the effectiveness of individual specialised psychosocial intervention for early psychosis were excluded from this review.

^bMean DUP was reported.

^cRecent-onset psychosis in LEO study included patients presenting with first or second psychotic episode, with 86% of EI sample and 71% of SC sample was FEP.

^dRecent-onset psychosis in COAST study included patients having first psychiatric service contact within 5 years due to psychosis from study entry.

^eRecent-onset psychosis in OTP included patients presenting with their first psychotic episode within 2 years from study entry.

^fHC sample was recruited from 1989 to 1992, while EI sample was recruited in 1993. HC sample was interviewed at follow-up for assessment.

^gHC, PC and EI samples were recruited in periods of 1991-1992, 1995-1997 and 1996-1997, respectively. Data of HC were based on retrospective medical record review without face-to-face interview.

^bSchizophrenia-spectrum in Parachute project included schizophrenia, schizoaffective disorder and schizophreniform disorder based on DSM-IV diagnostic criteria.

ⁱHC sample was recruited from 1993 to 1995, while EI sample was recruited from 1997 to 1999. Data of both HC and EI were based on retrospective medical record review without face-to-face interview.

^jFirst-admission sample.

^kHC sample was recruited from 1998 to 2001, while EI sample was recruited from 2001 to 2003. Data of both HC and EI were based on retrospective medical record review without face-to-face interview.

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Optimal duration of an early intervention programme for first-episode psychosis: randomised controlled trial

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BJP 2015, 206:492-500.

Access the most recent version at DOI: [10.1192/bjp.bp.114.150144](https://doi.org/10.1192/bjp.bp.114.150144)

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Supplementary material can be found at:
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