Unfinished business: Functional outcomes in a randomized controlled trial of a three-year extension of early intervention versus regular care following two years of early intervention for psychosis.

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Data availability statement
Data available on request due to privacy/ethical restrictions.

Conflict of interest
Dr Malla, the study PI, reports no conflict of interest related to any aspect of this study. However, for full disclosure of activities unrelated to this study he has received honoraria for lectures delivered at conferences sponsored by Lundbeck Global; and research consulting activities with Lundbeck Canada in the last 3 years. Dr. Joober served as speaker and member of advisory board committees for Pfizer, Janssen, BMS, Sunovian, Myelin, Otsuka, Lundbeck, shire and Perdue. He also received grants from Janssen, BMS, Otsuka, Lundbeck, Astra Zeneca and HLS. Dr. Margolese reports to be a paid speaker and/or consulting committee member and/or to have received honoraria from: AbbVie, HLS Therapeutics, Janssen, Lundbeck, Otsuka, Sunovion; Research Support: Acadia, Amgen, and SyneuRx. All mentioned conflicts of interest are unrelated to the present article. Authors Iyer, Mustafa, Latimer, Schmitz, Jarvis, Abadi, Casacalenda and Abdel-Baki have no conflicts of interest."

Abstract

Objective

To investigate whether first-episode psychosis patients receiving extended early intervention (EI) had better functional outcomes than those in regular care and to examine the predictors of functional outcomes.

Methods

This is a randomized controlled single-blind trial of 220 patients randomized after two years of EI to receive EI or regular care for the subsequent three years. Outcomes included cumulative time in functional recovery during the three-year trial assessed using the Social and Occupational Functioning Assessment Scale (SOFAS); and employment/education at last assessment which were respectively analysed using multiple linear regression and logistic regression, accounting for well-known predictors. Linear mixed and generalized linear models were also used to examine the course of SOFAS and employment/education over the three-year period.

Results

The extended EI and regular care groups did not differ on time in functional recovery (Mean=50.17 weeks; SD=46.62 vs. Mean=46.18 weeks; SD=51.54); percent employed/in school (60.4% vs. 68.8%) or change in SOFAS or employment/education status over time**.** SOFAS scores were stable between Years 2 and 5. Individuals with longer periods of total symptom remission experienced significantly longer periods of functional recovery and were likelier to be employed/in school. Those who had completed high school were nine times likelier to be employed/studying.

Conclusion

Most individuals maintained functional gains accrued from two years of EI with no further improvement whether in extended EI or regular care. There was a gap between symptomatic and functional recovery and one-third were unemployed/not in school at Year 5. The lack of additional progress even in extended EI suggests that specific interventions addressing functional roles need to be provided beyond the first two years of EI. Sustaining symptom remission and high-school completion may be additional avenues for targeting functional recovery.

Key words

Extended early intervention, first-episode psychosis, functional recovery, employment/education, symptom remission

Significant Outcomes

1. Gains made in social and occupational functioning and employment/school roles after two years of early intervention are maintained but do not further improve between Years 2 and 5 for individuals continuing to receive EI or those transferred to regular care.
2. There is a substantial gap between symptomatic improvements and functional recovery and around one-third of patients do not participate in employment or education even after five years of treatment, underscoring the need for effective interventions specifically designed to impact functional outcomes.
3. Effective vocational interventions should be provided to all early on in treatment and later for those not achieving good functional outcomes. Also, preventative and intervention strategies should target symptom remission, substance use and high-school completion for improving functional outcomes.

Limitations

1. There was a higher rate of attrition and non-completion of assessments in the regular care arm, which may have affected the validity of our findings.

2. The present analysis did not include some known predictors of functioning such as verbal memory.
3. Even in the early intervention arm, only a minority of patients may have had access to evidence-based employment support, which may have contributed to our negative findings. This also highlights critical implementation gaps even in early intervention for psychosis.

Introduction

FEP patients have better employment or educational prospects when they receive specialized early intervention (EI) services compared to regular psychiatric care [RR = 1.13 (1.03-1.24); 52.5% versus 45.3% based on 6 trials].[1] Despite the relative advantage that specialized EI offers, optimal longer-term occupational and psychosocial functioning remains a challenge.[2] The pooled prevalence of recovery (of symptoms *and* social, occupational and educational functioning) was only 38% in a meta-analysis of 9,642 patients with first-episode psychosis followed for a mean of 7.2 years.[3] Not all patients included in this meta-analysis had received EI services. Even among those receiving EI, the Bond et al. systematic review reported an employment rate during follow-up of 49% for those also receiving employment support and 29% for those receiving only EI.[4]

Concern about sustaining the initial therapeutic gains achieved by EI services and the notion that longer-lasting enriched care may be needed to further improve functional outcomes prompted investigations of the benefits of extending EI beyond the usual one-to-two years to the entire five-year critical period. A randomized controlled trial (RCT) in Hong Kong reported that extending EI by one year, i.e., offering a three-year EI service, produced a significant increase in social and occupational functioning, although there was no gain in full-time employment.[5] The OPUS-II RCT,[6] however, did not detect a difference in global assessment of functioning or labour market participation between patients receiving EI for five years versus those receiving EI for two years followed by regular care for three years. Finally, in a naturalistic study reporting that gains made at two years after EI were generally maintained at year 5, 59% of patients achieved good global functioning; however, only 18% were in full employment at five years.[7] Overall, findings about whether extending EI improves functional

outcomes are inconsistent. Further, functional outcomes seem to be better when measured using global rating scales, rather than in terms of employment/school status.

The present study is a randomized controlled single-blind trial comparing an extension of EI by three years to cover the entire five-year critical period with two years of EI followed by three years of regular care. Symptom remission was the trial's primary outcome and functioning, the focus of the current report, a secondary outcome.[8]

We hypothesized that individuals receiving EI for five years would have better functional outcomes compared to those in the regular care group. This hypothesis is also supported by our previous finding that total symptom remission, which is a well-established independent predictor of functional outcomes,[9] was better in the extended EI group.[10] Functional outcomes studied were cumulative time spent in functional recovery as assessed by the Social and Occupational Functioning Assessment Scale (SOFAS);[11] and employment/education status at last assessment. Functional recovery was defined as scoring more than 60 on the SOFAS. This widely adopted cut-off[7, 12-14] represents individuals who are, at the very least, "generally functioning well, with some meaningful interpersonal relationships" although they may have "some difficulty in social, occupational, or school functioning." We used cumulative time spent in functional recovery because it was consistent with length of symptom remission (the trial's primary outcome) and provided an index of the course of functioning, rather than a single-timepoint measure. We also looked at the longitudinal course of SOFAS scores and education/employment status over the three-year period, examining time and group effects.

Along with examining differences in functional outcomes between the extended EI and regular care groups, we sought to examine the predictors of functional outcomes. Given the strong evidence for the contribution of symptom remission to functioning,[9, 15-18] we hypothesized that longer durations of symptom remission would be associated with longer periods in functional recovery and higher odds of being employed or studying at the

end of follow-up, while controlling for other known predictors, such as age upon first entering EI, sex, education, diagnosis, duration of untreated psychosis (DUP), baseline functioning, and substance use.[13,9,19]

Aims of the Study

Our primary aim was to examine whether individuals randomized to an additional three years of early intervention for psychosis after an initial two years would have better functional recovery and employment/education outcomes compared to those receiving two years of early intervention followed by three years of regular care. A second objective was to examine the predictors of functional outcomes, particularly symptom remission, while controlling for other known predictors, such as age, sex, education, diagnosis, duration of untreated psychosis, baseline functioning, and substance use.

Material and Methods

Study design, setting and participants:

This report is based on data derived from a single-blind randomized controlled trial conducted at three Canadian EI services within the McGill University network. The main EI service in this study was the Prevention and Early Intervention Program for Psychosis (PEPP- Montréal), established in 2003. The other two sites were the First-episode Psychosis Program at the Jewish General Hospital, established in 2007, and the PEPP program at the McGill University Health Centre, established in 2009. Both sites were modelled after the largest site (PEPP-Montréal) and provided the same set of services.

At the initiation of treatment in the EI services, participants were 14-35 years old, had an IQ of more than 70, had affective or non-affective psychosis and had been treated with antipsychotic medication for less than 30 days. Inclusion criteria for the trial, following 2 years of EI, were the same except for restricting the age to ≥18 years. Remission status at randomization and co-morbid substance use were not reasons for exclusion from the

trial. At the end of the second year (+/-3 months), RCT participants were randomized to receive either a three-year extension of EI or regular care. This study was approved by McGill University's Faculty of Medicine Institutional Review Board and the Douglas Institute Research Ethics Board. All participants provided informed consent.

A detailed account of the interventions, the randomization process, and the protocol of the trial has been previously reported.[8, 10] The experimental and control interventions are also briefly described here.

Trial interventions:

Extended EI:

The EI arm followed international guidelines for EI services for psychosis[20, 21] and an earlier publication details implementation of these guidelines in the specific study context.[22] In the extended EI group, modified assertive case management remained the main service delivery mode, ensuring caseloads of 20-22 per case manager. Reintegration into employment and/or education and promoting autonomy were emphasized by case managers along with encouraging treatment adherence for maintaining remission, and providing psychoeducation, crisis intervention and relapse prevention. The same psychiatrist and case manager assigned to the patient during their initial two years followed them for the three years of EI post-randomization, and a minimum frequency of follow-up (at least monthly meetings) was established and monitored throughout the study. During monthly meetings, the case manager reviewed with each patient their early warning signs profile[23] which facilitated relapse prevention and increased patient understanding of their illness and its management. The frequency and severity of alcohol and drug use was assessed repeatedly with the timeline follow-back procedure,[24] and case managers were trained in providing brief motivational interviewing that integrated personalized feedback based on these ongoing assessments. Booster sessions of family psychoeducation, multiple family group therapy[25], cognitive-behavior therapy (CBT), substance use management, Individual Placement and Support and a family peer support group[26] were also offered. Barring

individual placement and support for which there was a waitlist, these individual interventions were available to all patients who needed them. All interventions also had in-built quality assurance mechanisms (e.g., weekly supervision sessions for CBT). Fidelity to EI was also established through regular review of work done at each site and case review meetings once a month by the study coordinator and often the principal investigator and/or additional investigators.

Regular Care:

In the regular care group, patients were transferred to either primary care, which includes family physicians and community health and social service centres with some psychiatric support, *or* to secondary care, i.e., hospital-attached outpatient clinics where care was provided mainly by psychiatrists along with nurses or other allied professionals. For those randomized to regular care, the choice of primary vs. secondary care was made before randomization in collaboration with patients and their families. Patients judged to need a higher intensity care based on a more complex course during the initial two years were transferred to secondary care, whereas those who enjoyed longer periods of remission and functioning were transferred to primary care.

Outcome measures:

The main outcome measures in this study were cumulative time in functional recovery over the entire three years of follow-up; and employment/education at the last assessment. In accordance with previous reports on functional outcomes in FEP,[7, 12-14] participants were considered to be in functional recovery if they scored 61 or above on the SOFAS,[11] wherein scores range from 0 to 100 with higher scores indicating better functioning. The total duration of functional recovery during the three-year period was calculated for each participant on the basis of repeated SOFAS ratings which was administered every six months. Using data from the Productivity Interview[27] administered every three months, patients were considered employed if they were engaged in part or full-time study or employment. We also examined change in overall functioning (SOFAS score and education/employment status) over the three-year period. As in the primary outcome paper,[10] the length of

time patients were in total (positive and negative) symptom remission was calculated according to Andreasen et al.'s consensus criteria.[28] Patients scoring 2 (mild) or less on all the global (subscale) items on both the Scale for Assessment of Positive Symptoms[29] (SAPS) and the Scale for Assessment of Negative Symptoms[30] (SANS) were considered to be in total remission. Symptom remission was assessed every three months.

About 90% of the ratings were conducted by the same rater over the entire study period, and hence, inter-rater reliability (IRR) for SOFAS was not pertinent to calculate. However, we conduct inter-rater reliability sessions at least once a year in our larger EI research program in which all raters participate (intra-class coefficients for symptom and SOFAS ratings have ranged from 0.75 to 0.92). In addition to rating the same cases, raters also participate in discussion with senior clinician-scientists. This serves to ensure that all raters are similarly, continuously, and rigorously trained.

Demographic and clinical characteristics included age at entry to EI; sex; education (completed or did not complete high-school); DUP measured with the Circumstances of Onset and Relapse Schedule[31] and diagnosis (including substance use) according to the Structured Clinical Interview for *DSM-IV-Tr* Axis I disorders (SCID-I).[32]

Data analysis

Descriptives

For the total sample and separately for the extended EI and regular care groups, we calculated means and standard deviations for total SOFAS scores and length of functional recovery over the entire three-year follow-up. We also calculated the frequency and percentage of participants in school or employment at randomization and last assessment and the percentage duration of employment.

Analyses to address study aims

Multiple linear regression with length of time in functional recovery as the dependent variable and logistic regression with employment/education status at last assessment as the dependent variable were conducted, with group (EI vs. regular care) as the main independent variable. These analyses controlled for site, and included well-known predictors of functioning: symptom remission; age at EI entry; sex; education; diagnosis; DUP; baseline functioning and substance use.[9] Each predictor was also tested in univariate analyses (supplementary tables 1 & 2) to understand its relationship with the outcome. Multicollinearity was evaluated (by calculating tolerance and variance inflation factor; VIF) and established to be not a concern before carrying out the regression analyses.

Linear mixed model analysis was used to assess the three-year longitudinal course of functioning (SOFAS scores) examining time effect, group (extended EI vs. regular care) effect and time-by-group interaction. Generalized linear model was used to assess the three-year longitudinal course of employment/education status. These statistical approaches allowed the use of all available data (participants with incomplete data were not excluded), with maximum likelihood-based inference.[33]

In an earlier report,[10] within the regular care arm, we found better symptom outcomes among patients transferred to primary care (vs. secondary care). To examine if the same pattern is true for functional outcomes, we performed exploratory analyses comparing those randomized to primary vs. secondary care within the regular care group for time spent in functional recovery, SOFAS scores and employment/school status at last assessment using unpaired *t* test and χ^2 test for continuous and categorical variables, respectively.

Consistently with this trial's previous publications,[10, 34-36] this was an intent to treat analysis where participants who provided at least one post-baseline assessment, were included. Missing data secondary to missing assessments at some time-points were retrospectively reconstructed for 75 (34.1%) participants from clinical records, if available. This was significantly more possible for extended EI [n=47 (42.7%)] than regular care [n=28 (25.5%)]; $\chi 2$ (1) = 7.30, p = 0.007. Data which were still missing were not imputed. Data for SOFAS scores were

available for a median of 5 from a total of 7 possible assessments. Data for employment were available for a median of 7 from a total of 13 possible assessments. For employment/education status at the end of the trial, if month 36 data were missing, the latest post-baseline values, hereby called "last assessment"[37] were taken instead for the logistic regression analyses. The median month of last assessment was 33 and the mode was 36. Participants included in the analyses were compared to those who were not included because of not having a single post-randomization baseline assessment on demographic and clinical variables and values of the primary outcomes at baseline. Moreover, individuals who were included but missing 50% or more of their repeated individual assessments were compared to those missing less than 50% on the same variables. We also examined functioning (SOFAS and employment/education status) at the time of dropout between the two treatment conditions. Finally, as sensitivity analyses, we compared functional outcomes of the extended EI and regular care groups but only including those who completed the study and excluding data from those who dropped out. The software used was SPSS, version 23. All tests were 2-tailed and *p* values of ≤ 0.05 were considered significant.

Results

A total of 220 patients were recruited, 110 of whom were randomized to extended EI and the other 110 to regular care. Of the 220 patients, 178 patients had been treated for the first two years in the study's main EI program, PEPP-Montreal. A detailed consort flow diagram is available in the original paper.[10] At the time of randomization, there were no significant differences between the two groups on any demographic or clinical variables, including symptom remission, functioning (SOFAS score) and proportion employed/in school (Table 1). Significantly more individuals in the EI group completed the trial than in the regular care group (87 versus 53; χ^2 (1) = 22.71, p < 0.001). As previously reported,[10, 38] the patients in the EI group also received significantly more physician and nonphysician interventions than the regular care group, suggesting a higher intensity of care as was expected.

We compared individuals whose data were included in the estimates of length of functional recovery (n = 168, 76.4%) and those who were randomized but whose data on length of functional recovery was not available (n = 52, 23.6%). These two groups were not different on any randomization baseline parameters: age at EI entry, sex, education, schizophrenia spectrum versus affective psychoses primary diagnosis, substance use secondary diagnosis, DUP, positive symptoms, negative symptoms or SOFAS. Individuals from the regular care group were significantly more likely to not be included in length of functional recovery analysis (Missing cases: extended EI: 7 (6.4%), regular care: 45 (40.9%); χ^2 (1) = 36.36, p < 0.001). For participants who are included but missing SOFAS assessments at some time point(s) during the three-year time period, we compared those missing more than 50% of assessments (n=36, 21.4%) to those who were not (n=132, 78.6%) and found no significant difference in age at EI entry, sex, education, diagnosis, substance use, DUP, positive symptoms, negative symptoms or SOFAS at baseline. This was true for both the extended EI and the regular care groups, although the proportion of patients missing more than 50% of their SOFAS assessments was significantly higher in the regular care group (n=23, 35.4%) compared to the extended EI arm (n=13, 12.6%); χ^2 (1) = 12.27, p < 0.001.

Similarly, we compared individuals whose data were included (n = 173, 78.6%) in the estimates of employment/school status at last assessment and those who were randomized but whose data on employment/school status at last assessment were not available (n = 47, 21.4%). Compared to the included participants [Means SAPS total severity score = 7.23 (9.95) and Mean SOFAS score = 57.95 (14.21)], individuals whose data were not available were significantly more likely to have lower positive symptoms [Mean SAPS total severity score = 4.02 (8.26); t (214) = 2.03, p = 0.044] and higher SOFAS scores [Mean = 65.48 (17.86); t (32) = 2.08, p = 0.046] at randomization baseline. They were not different regarding baseline employment [Employed/at school: included: 107 (65.6%), excluded: 28 (77.8%); χ^2 (1) = 1.99, p = 0.158]. Again, individuals from the regular care group were significantly more likely to not have data for employment/school status at last assessment (Missing cases: extended EI: 14 (12.7%), regular care: 33 (30.0%); χ^2 (1) = 9.77, p = 0.002). We compared participants who were missing more than 50% of the thirteen employment assessments (n=98,

46.9%) to those who were not (n=111, 53.1%). There was no significant difference in age at EI entry, sex, education, diagnosis, substance use, DUP, positive symptoms, negative symptoms or employment at baseline. This was the same for both the extended EI and regular care groups with the latter being significantly more likely to be missing more than 50% of employment assessments; extended EI: n=36, 34.0%, regular care: n=62, 60.2%; χ^2 (1) = 14.43, p < 0.001.

For those who dropped out from the study, there were no significant differences in functioning at the time of drop-out between the two treatment conditions [Mean SOFAS scores = 53.88 (18.84) and 56.05 (14.79) for extended and regular care dropouts, respectively; t (33) = 0.38, p = 0.704; percent employed/in education = 50% and 56% among extended EI and regular care drop-outs, respectively; χ^2 (1) = 0.13, p=0.718].

Functional outcomes

Table 2 describes the functional outcomes measured for the total sample, the extended EI and regular care groups at randomization and last assessment and also presents their cumulative time spent in positive, negative and total symptom remission.

Time spent in functional recovery and change in functioning over time

The mean time spent in functional recovery over the three-year trial period was 50.17 weeks (46.62) and 46.18 (51.54) weeks for the extended EI and regular care groups, respectively. There was no significant difference between the groups; t (166) = 0.52, p = 0.604.

Multiple linear regression analysis (Table 3) showed that, while controlling for site, there was no significant difference in time spent in functional recovery between the extended EI and regular care groups (t = 0.07, p = 0.942). Functional recovery at randomization baseline, which corresponds to month-24 of EI, and time in total symptom remission were the factors significantly associated with time spent in functional recovery. The other tested predictors of functioning – age, sex, education, diagnosis, substance use and DUP –were not significant.

Linear mixed model analysis showed that SOFAS scores did not change over time [F (279.76) = 0.58, p = 0.446]; and did not differ between groups [F (274.14) = 1.93, p = 0.166]. The time x group interaction was also not significant [F (279.76) = 0.50, p = 0.481]. This indicates that extended EI and regular care were not different and were both stable with respect to SOFAS over the three-year follow-up (Figure 1a). At all time-points from randomization baseline to month-36, mean SOFAS total scores were around the cut-off point for functional recovery, for both the extended EI and regular care groups (Figure 1a).

Employment/Education

Nearly two-thirds of the sample was engaged in employment/school at randomization and at the time of the last assessment (Table 2), with no significant difference in the proportion employed/in school between randomization baseline and month-36 for extended EI (McNemar's test; p = 0.458) or regular care (McNemar's test; p = 0.711) arms. Extended EI and regular care participants were employed for 68.01% (34.42) and 66.1% (37.82) of the trial duration, respectively, with no difference between the groups; t (207) = 0.39, p = 0.697. At both time-points, the majority of those employed, irrespective of arm, were engaged in part- or full-time employment or education, with only a minority in non-competitive employment such as volunteering [Randomization: 8 (4.0%); Last assessment: 17 (9.8%)].

The binary logistic regression model (Table 4) indicated that, while controlling for site, employment/education status at last assessment was not statistically different between the two treatment conditions. The three significant correlates of being employed/in school were longer durations of total symptom remission; having completed high-school; and not having a substance use diagnosis. Each additional week spent in total symptom remission increased the likelihood of being employed/in school at the last assessment by 2.6%. Completing high-school or above predicted an impressive 9-fold increase in the likelihood of being employed/at school at the last assessment. Upon consenting to the trial, all participants were at least 18 years old (mean = 25.22

years), the age by which most youths in Quebec are expected to have completed high school. Having a substance use diagnosis decreased the odds of being employed/in school by 76%.

Generalized linear model analysis showed that employment/education status did not change over time [randomization baseline to month 36: OR 1.02, 95% CI 1.00 - 1.04, χ^2 (1) = 3.08, p = 0.079] and did not differ between groups [extended EI vs. regular care, OR 1.18, 95% CI 0.79 – 1.76, χ^2 (1) = 0.64, p = 0.424]. The time x group interaction was only marginally significant [OR 0.98, 0.96 – 1.00, χ^2 (1) = 4.01, p = 0.045] (Figure 1b). Similar to SOFAS ratings, the proportion of individuals employed/in school was stable over the three-year follow-up period.

As expected, individuals who were employed/in school at the last assessment were functionally recovered as per the SOFAS>60 definition for longer periods [Mean = 61.34 (51.45) weeks] than those who were not employed/not in school [Mean = 24.09 (33.43) weeks; t (143) = 5.38, p<0.001).

Sensitivity analyses

Even when including only those who completed the study, there was no difference in main outcomes between the extended EI and regular care groups [Last assessment: mean SOFAS scores = 60.17 (12.40) and 63.30 (13.64) for extended EI and regular care, respectively; t (131) = 1.34, p = 0.183; percent employed/in education = 62.2% and 75% in extended EI and regular care, respectively; χ^2 (1) = 2.37, p = 0.124].

Comparing outcomes of primary and secondary care settings within the regular care group

Of those transferred to regular care, 51 were transferred to primary care and 48 to secondary care, with 11 dropping out following randomization but before transfer. Mean length of time from randomization to transfer was 23.05 (14.12) and 28.63 (17.68) weeks for primary and secondary care, respectively; t (97) = 1.74, p = 0.085. Compared to those transferred to secondary care, patients transferred to primary care spent longer

times in functional recovery, had higher SOFAS scores at last assessment and were more likely to be employed/in school at the last assessment (see supplementary Table 3). Notably, the primary care group had higher SOFAS scores and a higher likelihood of being employed/in school even at the time of randomization. This is consistent with what we reported earlier with respect to symptom remission.[10]

Discussion

Contrary to what was hypothesized, patients who received a three-year extension of EI did not enjoy longer periods of functional recovery than their counterparts who received EI for two years followed by three years of regular care. Nearly equal proportions of individuals were employed/in school at the last assessment in both arms, with extended EI producing no additional advantage. Irrespective of treatment condition, the overall level of social and occupational functioning (whether assessed in terms of SOFAS or employment/education status) was maintained and did not change significantly over the three-year follow-up.

Our results are in alignment with the Danish OPUS II trial which did not find a difference in terms of global assessment of functioning or labour market participation between individuals receiving EI for five years and those receiving EI for two years followed by regular care.[6] According to the OPUS II study authors, the high quality of their regular care, which in some respects was similar to EI, may have contributed to the lack of difference. As in our case and OPUS II, a Hong Kong RCT[5] found that extending EI from two to three years did not yield any additional benefits with respect to the rate of full-time employment at the end of the trial when compared to only two years of EI followed by regular care, with similar proportions being vocationally engaged (full-time employment at the end of the trial in the Hong Kong study: extended EI=56%, regular care=47%; employment/education at last assessment in this study: extended EI=60%, regular care=69%). It is noteworthy that the rates of competitive employment and education in OPUS II (extended EI=23.4%, regular care=25.1%) were much lower than in the Hong Kong study and ours. Some of these differences in employment rates may be methodological artefacts, as our data were based on interviews whereas OPUS II obtained theirs from a

national registry and the Hong Kong study from a systematic review of case records. In addition, we did not restrict our definition of employment to only full-time work or study. Economic-political factors such as unemployment rates in the general population, and the ease of obtaining state benefits such as welfare, disability pension, employment insurance, etc. and their magnitude may have also contributed to differences.

Unlike the OPUS II trial and ours, the Hong Kong RCT found a significant increase in social and occupational functioning in the extended EI arm.[5] Like in our study, however, the Hong Kong study's mean SOFAS scores were around the functional recovery cut-off of 61 and spanned only two categories from 51 to 70, with scores from 51-60 indicating "'moderate difficulties" in social and occupational/school functioning in contrast to 61-70 which represents "some difficulty" in these areas.

Symptom remission, functional recovery and disability

Those who were in total (positive and negative) symptom remission for longer periods during the three-year follow-up also experienced longer periods of functional recovery and were more likely to be employed or in school at the five-year mark. Our finding that symptom remission plays an important role in functional outcomes in early psychosis echoes what has consistently been reported previously.[9, 17, 18, 39]

Our findings also clearly highlight a gap between symptomatic and functional recovery in early psychosis. Our primary outcomes publication found the extended EI group to have significantly longer durations of positive, negative and total symptom remission during the three-year follow-up compared to the regular care group. This differential advantage of extended EI did not reach length of functional recovery. Moreover, irrespective of whether patients received extended EI or regular care, they spent substantially less time in functional recovery than they did in positive, negative or total symptom remission. For instance, we found that individuals in EI had 42, 23 and 16 fewer weeks of functional recovery during the three-year follow-up than of positive, negative and total symptom remission, respectively. While it is somewhat heartening that about two-thirds of

the sample were employed/in school at the two- and five-year marks and throughout the three-year follow-up period in both arms, the roughly 30+% prevalence of NEET (not in education, employment or training) status even after five years of follow-up was strikingly higher than the 12% prevalence of NEET status in the general Canadian youth population aged 16 to 29[40] and the 6-7% unemployment rate in the general Canadian population over the duration of the study.[41] Prior FEP research has similarly reported the presence of a substantial patient sub-population with poor functioning[2] and pointed to such psychosocial disability being stable, and often beginning early in the illness course and even before the formal onset of psychosis.[13, 17, 19, 42, 43]

In our study, functional recovery status at randomization (the two-year mark) continued to be a significant predictor of time spent in functional recovery over the subsequent three years. The stability in SOFAS scores, with average scores being around the functional recovery point, and employment/education status between Years 2 and 5 suggests a plateauing of gains in functioning that are well known to occur in the first two years after initiation of EI.[1] There was also no significant difference in the numbers of patients productively engaged at the two- and five-year marks. Furthermore, those who had not completed high-school were about nine times less likely to be engaged in education/employment at the five-year mark. This aligns with previous findings that level of education was a determinant of functional outcomes in FEP.[19, 44] Overall, our findings are also suggestive of functional outcomes being relatively stable, being set early during treatment and being influenced by prior levels of disability and functioning.

In our primary outcomes paper, we found that individuals who were in symptom remission for shorter total durations during follow-up received more interventions from their clinical team.[10] Post-hoc analyses revealed similar findings that individuals who were functionally recovered for shorter total durations during their follow-up also had a higher number of contacts with their clinical team during their three-year follow-up, in both the EI and regular care arms (Pearson correlation coefficient = - 0.31, $p < 0.001$). This is suggestive of clinical teams

augmenting contact for individuals who were not experiencing clinical and functional improvements. While this appears justifiable, our findings suggest that more of the same may not yield benefits in terms of functioning.

In fact, targeted educational and employment interventions may be needed to enable more young people with psychosis to attain and maintain functional roles before psychosocial disability takes root.[45, 46] Unfortunately, only a relatively small proportion of patients even in our EI service (30%) receive individual placement and support, for which there is a long waiting list. We were unable to examine if better access to individual placement and support would have contributed to our extended EI group having better vocational outcomes than the regular care group. Nonetheless, given the strength of evidence for individual placement and support,[46, 47] we recommend that it be offered as a core intervention in EI.

Knowing the markers of poor functional outcomes can also help identify who needs such targeted interventions and can inform the design of effective interventions. Our findings indicate that absence of symptom remission; not having completed high-school; and having a substance use diagnosis may serve as markers of poorer functional outcomes. These factors are also likely linked with each other. For example, those with substance use disorder may be less likely to finish high-school and to have ongoing symptoms. While these factors have been previously implicated in influencing functional outcomes in psychosis,[19, 48] our study adds to this literature base from the vantage point of a well-designed RCT of an extension of EI for the entire critical period of five years. It also suggests that interventions to improve and sustain symptom remission, increase high-school completion[49] and reduce substance use are likely to positively influence functional recovery and reduce NEET status.

High-school completion (which occurred before entering the EI service in most cases) conferred a strong advantage with respect to future functional roles. Even in the general population, high school completion is associated with better vocational trajectories.[49] An emerging body of research[50] and our own prior work[44] suggest that for a considerable number of patients with psychosis, not having completed high-school is

indicative of psychosocial disability that began before the onset of psychosis and coincided with other mental health and/or substance use problems. Although the current study does not directly support this recommendation, broad prevention and EI efforts in youth mental health may reduce the risk of becoming NEET and developing long-term disability.

The stability of functioning from years 2 to 5 suggests that interventions targeting attainment of functional roles such as individual placement and support should be offered from the very outset of EI. When EI is extended for longer, interventions designed specifically for those who do not achieve good functional outcomes at the end of two years, whether or not they are in symptom remission, may need to be added, along with a conscious rejection of any nihilism that may creep up on the part of providers and patients.

Among the patients randomized to regular care, those who were transferred to primary care fared better than those transferred to psychiatric care in terms of time spent in functional recovery, SOFAS scores and employment/education status at the five-year mark. These very differences were present even at randomization. This indicates that the EI service carefully matched patients to the right type of post-EI care, considering their progress over the first two years of EI. Our findings also show that at least a sub-group of patients can maintain relatively high levels of social and occupational functioning, and work/school roles (for over 80%) even after transitioning out of EI. Future analyses are needed to elucidate the mechanisms driving these positive outcomes for this patient sub-group.

Limitations and conclusion

A major limitation of our study is that a considerable proportion of patients were excluded due to not having even one post-baseline assessment. Those who were transferred to regular care were substantially more likely to have been lost to follow up. This indicates that data were likely not missing at random and thus could bias and affect the validity of our findings. Future work is therefore needed to discern the robustness of our

findings. The higher drop-out rate in regular care is indicative of EI being more successful in engaging patients in services and research.[51] In a previous publication from this trial, we found that patients randomized to extended EI were more likely to express satisfaction with their group assignment than those randomized to regular care (88.2% vs 31.5%, $p < 0.001$) and were likelier to continue seeing their case manager for the entire follow-up period.[51] Data was not available at all time-points even among those who did not drop out, highlighting the challenges of implementing longitudinal services research trials, and the need for innovative strategies to mitigate these (e.g., administrative data, e-data collection).

Our assessment protocol also precludes comment on other well-known predictors (e.g., verbal memory) and other functional outcomes (e.g., productive use of time, full- versus part-time employment). While several mechanisms were in place to ensure fidelity to the EI service delivery model, such as case manager-to-patient ratios, minimum number of clinical contacts per month, availability of a range of psychosocial interventions, regular monitoring meetings, etc., we did not use a fidelity scale[52] in our study. Nonetheless, our detailed review of service utilization pointed to a higher intensity of follow-up as expected in the EI compared to the regular care arm.

Nonetheless, this study provides useful information based on a rigorous, longitudinal three-year randomized controlled design with multiple assessments of functional outcomes and their correlates. While some of our findings (e.g., the associations of symptom remission and prior functioning) reinforce previous research, others make novel contributions to the literature. For instance, prior research found males to be at particularly higher risk for poorer functional outcomes.[2, 19, 53, 54] We, however, did not find significant differences between males and females, suggesting that sex and gender differences in functional outcomes may vary according to the larger sociocultural context and the job/school opportunities that may be available.

In conclusion, our findings suggest that most individuals maintain the initial gains in psychosocial functioning accrued after the first two years of EI, with no further improvements between Years 2 and 5, whether

individuals received extended EI or regular care in the follow-up period. Furthermore, there was a substantial gap between symptomatic and functional improvements and around one third of the sample were not employed or in school even after five years of treatment, including patients assigned to extended EI. This suggests that specific interventions targeting functional recovery need to be prioritized beyond the first two years of EI. More broadly, our study adds to the call for effective interventions throughout the critical period to enable all young people with psychosis to maximise their life potential.[55]

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Tables:

Table 1. Demographic and clinical characteristics at randomization

	Total sample (N=220)	**Extended EI (N=110)**	**Regular care (N=110)**
Age at onset of psychosis [years, M (SD)]	22.39 (4.42)	21.87 (4.12)	22.90 (4.66)
Age at EI entry [years, M (SD)]	23.18 (4.38)	22.62 (4.28)	23.73 (4.42)
Age at signing RCT consent [years, M (SD)]	25.22 (4.33)	24.68 (4.24)	25.76 (4.38)
Male (N, %)	151 (68.6%)	75 (68.2%)	76 (69.1%)
Single (N, %)	200 (90.9%)	103 (93.6%)	97 (88.2%)
Completed high school (N, %)	149 (68.3%)	76 (69.1%)	73 (67.6%)
Duration of untreated psychosis [weeks, M (SD)]	49.33 (123.61); median=11.6 weeks	52.39 (148.82); median=8.3 weeks	46.29 (92.71); median=12.7 weeks
Schizophrenia spectrum primary diagnosis (N, %)	143 (65.3%)	74 (67.3%)	69 (63.3%)
Substance use secondary diagnosis (N, %)	105 (57.4%)	52 (55.9%)	53 (58.9%)
Antipsychotic dose in chlorpromazine equivalents [mg, M (SD)]	311.85 (345.61)	299.94 (350.12)	329.70 (342.88)
SAPS total score (M, SD)	6.53 (9.68)	7.07 (10.39)	6.00 (8.95)
SANS total score (M, SD)	13.80 (11.63)	13.58 (10.43)	14.03 (12.79)
In positive symptom remission (N, %)	161 (73.2%)	81 (73.6%)	80 (72.7%)
In negative symptom remission (N, %)	107 (48.6%)	53 (48.2%)	54 (49.1%)
In total symptom remission (N, %)	92 (41.8%)	45 (40.9%)	47 (42.7%)
SOFAS [M (SD)]	59.09 (15.01)	57.20 (15.48)	61.40 (14.16)
Employed/in school (N, %)	135(67.8%)	70 (69.3%)	65 (66.3%)

EI: Early intervention, SAPS: Scale for the Assessment of Positive Symptoms, SANS: Scale for the Assessment of Negative Symptoms, SOFAS: Social and Occupational Functioning Assessment Scale

Table 2. Functional characteristics of the sample at randomization and last assessment

	Total Sample (N=220)		Extended EI (N=110)		Regular care (N=110)	
	Randomization	**Last assessment**	**Randomization**	**Last assessment**	**Randomization**	**Last assessment**
SOFAS [M (SD)]	59.09 (15.01)	59.96 (13.90)	57.20 (15.48)	59.19 (13.68)	61.40 (14.16)	61.18 (14.26)
Education, competitive or non-competitive employment (N, %)	135 (67.8%)	111 (64.2%)	70 (69.3%)	58 (60.4%)	65 (66.3%)	53 (68.8%)
Time* in positive symptom remission [weeks, M (SD)]	78.23 (46.58)		92.55 (41.95)		63.62 (46.74)	
Time* in negative symptom remission [weeks, M (SD)]	66.79 (45.72)		73.41 (43.72)		59.61 (47.00)	
Time* in total symptom remission [weeks, M (SD)]	61.95 (43.39)		66.52 (41.60)		56.73 (45.06)	
Time* in functional recovery [weeks, M (SD)]	48.63 (48.47)		50.17 (46.62)		46.18 (51.54)	
Time* in employment/education [weeks, M (SD)]	65.43 (49.85)		63.90 (47.33)		67.62 (53.51)	

EI: Early intervention, SOFAS: Social and Occupational Functioning Assessment Scale

***Time is counted from randomization until Month 36**

Table 3. Linear regression with time spent in functional recovery as the outcome

	Time spent in functional recovery (weeks)						
	B	SE	Standardized Beta	t	p	95% CI for B	
						Lower Bound	Upper Bound
Group	-0.46	6.31	0.00	-0.07	0.942	-12.99	12.06
Site	10.39	11.59	0.06	0.90	0.372	-12.61	33.39
Functional recovery at baseline	21.24	6.64	0.22	3.20	**0.002**	8.05	34.43
Time in total symptom remission	0.80	0.08	0.72	10.42	**<0.001**	0.65	0.95
Age at EI entry	0.03	0.86	0.00	0.04	0.969	-1.68	1.74
Sex	-3.48	6.41	-0.03	-0.54	0.588	-16.20	9.24
Education	-5.64	7.68	-0.05	-0.73	0.465	-20.88	9.61
Diagnosis	-8.04	6.85	-0.08	-1.17	0.244	-21.63	5.56
Substance use	-6.86	6.28	-0.07	-1.09	0.277	-19.34	5.61
Log DUP	0.30	5.13	0.00	0.06	0.953	-9.89	10.49

EI=Early intervention, DUP=duration of untreated psychosis, SOFAS=Social and Occupational Functioning Scale
Group = extended EI or regular care
Functional recovery is defined as SOFAS score > 60
$F(10, 95) = 17.76$, $p < 0.001$, adjusted $R^2 = 0.62$
Time in total symptom remission and functional recovery at baseline were significantly associated with longer time in functional recovery.

Table 4: Binary logistic regression with employment/school status at last assessment as the outcome

	Employment/school at last assessment			
	Odds ratio	95% CI	χ^2	P
Extended EI group[a]	0.29	0.08-1.03	3.64	0.056
Site	0.54	0.05-5.97	0.26	0.613
Employed/in school at randomization[b]	1.73	0.47-6.37	0.69	0.408
Time in total symptom remission	1.03	1.01-1.04	9.63	**0.002**
Age at EI entry	0.96	0.81-1.13	0.29	0.593
Female[c]	1.09	0.30-3.88	0.02	0.899
Completed high school[d]	9.34	2.32-37.51	9.91	**0.002**
Affective psychosis[e]	0.88	0.24-3.22	0.04	0.847
Substance use[f]	0.24	0.06-0.88	4.60	**0.032**
Log DUP	1.03	0.38-2.78	0.00	0.956

EI=Early intervention, DUP=duration of untreated psychosis.
[a]Reference: Regular care, [b]Reference: Unemployed/not in school at randomization, [c]Reference: Male, [d]Reference: Did not complete high school, [e]Reference: schizophrenia spectrum primary diagnosis; [f]Does *not* have substance use secondary diagnosis.
$\chi^2(10) = 41.71$, $p < 0.001$, Nagelkerke $R^2 = 0.47$

Figures:

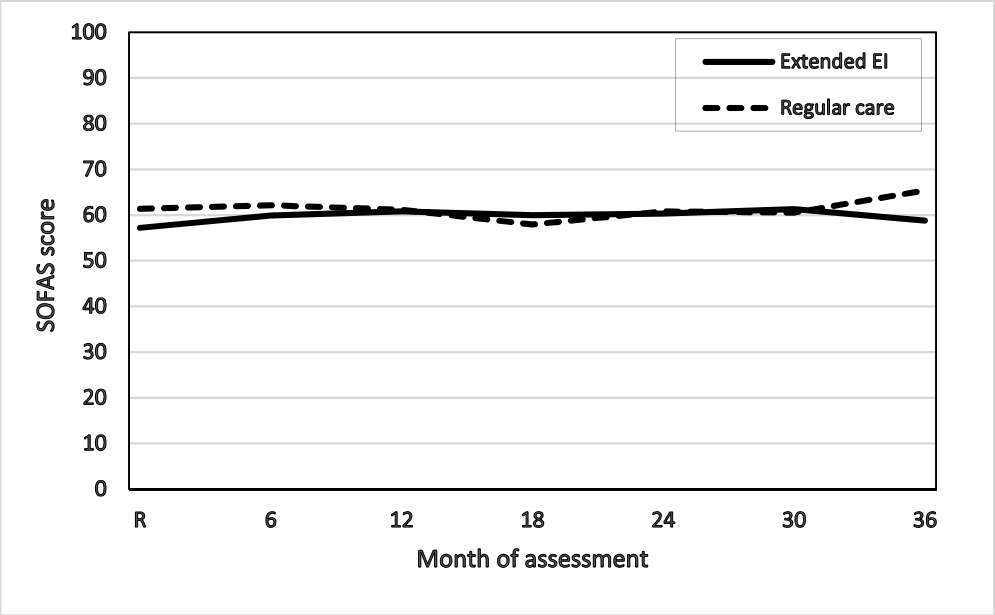

Figure 1a. Social and occupational functioning scores over the three-year follow-up.
EI=Early intervention, SOFAS=Social and Occupational Functioning Scale, R=Randomization baseline.
SOFAS scores range from 0 to 100 with higher scores indicating better functioning. SOFAS score>60 is the cut-off for functional recovery.

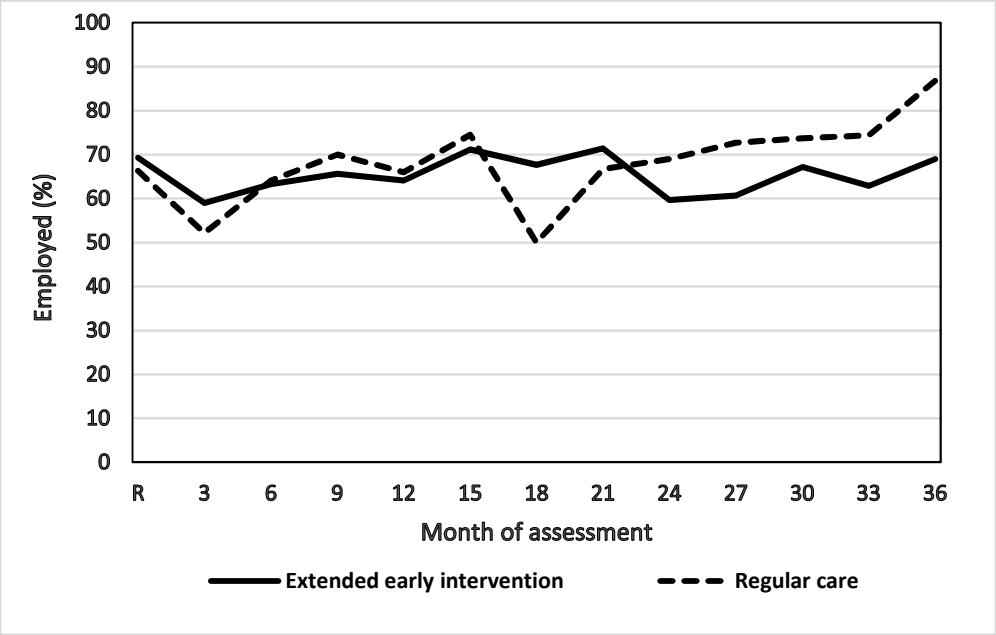

Figure 1b. Employment status over the three-year follow-up.

Supplementary material:

Supplementary Table 1. Univariate analyses for time spent in functional recovery:

		Length of functional remission (weeks)			
		M (SD)	**Df**	**Test**	**p**
Group	**Extended EI**	50.17 (46.62)	166	t=0.52	0.604
	Regular care	46.18 (51.54)			
Sex	**Male**	48.00 (49.56)	166	t=0.26	0.80
	Female	50.11 (46.22)			
Completed high school	**No**	36.93 (41.09)	164	t=2.11	***0.036***
	Yes	53.82 (50.94)			
Primary diagnosis	**Schizophrenia spectrum**	45.96 (49.73)	165	t=1.02	0.311
	Affective psychosis	54.13 (46.15)			
Substance use secondary diagnosis	**No**	52.64 (46.96)	142	t=1.01	0.316
	Yes	44.43 (49.09)			
Pearson correlations					
Age at EI entry			r= 0.03		0.70
Log DUP			r= - 0.13		0.11
Length of symptom remission (weeks)			***r= 0.77***		***<0.001***

EI=early intervention, DUP=duration of untreated psychosis

Supplementary Table 2. Differences between unemployed/not in school and employed/in school at last assessment: univariate analyses

	Employed/in school at last assessment	**Unemployed/not in school at last assessment**	**df**	***t***	**p**
Continuos variables [M (SD)], t					
Age at EI entry	23.50 (4.45)	22.03 (4.06)	171	2.15	***0.033***
Log DUP	1.13 (0.68)	1.21 (0.71)	169	0.75	0.455
Length of total remission (weeks)	75.88 (43.13)	44.00 (34.54)	130	3.94	***<0.001***
Binary variables [n (%)], χ^2					
	Employed/in school	**Unemployed/not in school**	**Φ**	**χ^2**	**p**
Group: Extended EI	58 (52.3%)	38 (61.3%)		1.32	0.251
Sex: Male **Female**	72 (64.9%) 39 (35.1%)	49 (79.0%) 13 (21.0%)	0.15	3.80	***0.051***
Completed high school	90 (82.6%)	25 (40.3%)	0.43	32.03	***<0.001***
Schizophrenia spectrum	67 (60.4%)	47 (77.0%)	0.17	4.91	***0.027***
Substance use	47 (49.5%)	36 (73.5%)	0.23	7.62	***0.006***
Employed/in school at randomization	77 (73.3%)	30 (51.7%)	0.22	7.74	***0.005***

EI=early intervention, DUP=duration of untreated psychosis

Supplementary Table 3. Comparing patients transferred to primary or secondary care

	Primary (N=51)	**Secondary (N=48)**	**Test**	**p**

Time spent in functional recovery [weeks, M (SD)]	67.11 (53.45)	21.75 (36.96)	t=4.02	***<0.001***
Sofas [M (SD)] at randomization	68.37 (13.18)	53.30 (10.58)	t=5.67	***<0.001***
Sofas [M (SD)] at last assessment	67.91 (14.16)	53.33 (9.77)	t=4.88	***<0.001***
Education, competitive or non-competitive employment at randomization (N, %)	37 (84.1%)	23 (50.0%)	χ^2=11.76	***0.001***
Education, competitive or non-competitive employment at last assessment (N, %)	32 (82.1%)	21 (55.3%)	χ^2=6.44	***0.011***

SOFAS=Social and Occupational Functioning Scale