

Early detection of psychosis: positive effects on 5-year outcome

T. K. Larsen^{1,2*}, I. Melle^{3,4}, B. Auestad⁵, U. Haahr⁶, I. Joa¹, J. O. Johannessen¹, S. Opjordsmoen^{3,4}, B. R. Rund⁷, J. I. Rossberg^{3,4}, E. Simonsen⁶, P. Vaglum⁸, S. Friis^{3,4} and T. McGlashan⁹

¹ Stavanger University Hospital, Psychiatric Clinic, Stavanger, Norway

² Department of Clinical Medicine, Section Psychiatry, University of Bergen, Norway

³ Oslo University Hospital, Oslo, Norway

⁴ Institute of Psychiatry, University of Oslo, Norway

⁵ Faculty of Science and Technology, University of Stavanger, Norway

⁶ Psychiatric Research Unit and University of Copenhagen, Zealand Region Psychiatry Roskilde, Denmark

⁷ Vestre Viken Hospital Trust/Department of Psychology, University of Oslo, Norway

⁸ Department of Behavioral Sciences in Medicine, University of Oslo, Norway

⁹ Yale University School of Medicine, New Haven, Connecticut, USA

Background. During the last decades we have seen a new focus on early treatment of psychosis. Several reviews have shown that duration of untreated psychosis (DUP) is correlated to better outcome. However, it is still unknown whether early treatment will lead to a better long-term outcome. This study reports the effects of reducing DUP on 5-year course and outcome.

Method. During 1997–2000 a total of 281 consecutive patients aged >17 years with first episode non-affective psychosis were recruited, of which 192 participated in the 5-year follow-up. A comprehensive early detection (ED) programme with public information campaigns and low-threshold psychosis detection teams was established in one healthcare area (ED-area), but not in a comparable area (no-ED area). Both areas ran equivalent treatment programmes during the first 2 years and need-adapted treatment thereafter.

Results. At the start of treatment, ED-patients had shorter DUP and less symptoms than no-ED-patients. There were no significant differences in treatment (psychotherapy and medication) for the 5 years. Mixed-effects modelling showed better scores for the ED group on the Positive and Negative Syndrome Scale negative, depressive and cognitive factors and for global assessment of functioning for social functioning at 5-year follow-up. The ED group also had more contacts with friends. Regression analysis did not find that these differences could be explained by confounders.

Conclusions. Early treatment had positive effects on clinical and functional status at 5-year follow-up in first episode psychosis.

Received 15 June 2010; Revised 16 September 2010; Accepted 16 September 2010; First published online 14 October 2010

Key words: Early intervention, first-episode psychosis, outcome.

Introduction

Schizophrenia remains a devastating disorder, often emerging during the final neurobiological push toward mature human brain structure and function. The consequence of its expression at this critical juncture is all too often an ablation of capacities for productivity, creativity and relatedness that lasts for the entire

adult lifespan. Given the resistance of this disorder to ameliorative treatments, the last two decades have seen an emerging interest in prevention through early detection (ED) and intervention (McGlashan & Johannessen, 1996; McGorry *et al.* 2010).

One of the first preventive strategies to become popular targets the initial emergence of psychosis and attempts to identify and treat this ‘first episode’ as early as possible, i.e. to reduce the duration of untreated psychosis (DUP). Two meta-analytical reviews document a significant correlation between reduced or shorter DUP and better outcome (Marshall *et al.* 2005; Perkins *et al.* 2005). However, as noted in a prior

* Address for correspondence: T. K. Larsen, M.D., Stavanger University Hospital, Division of Psychiatry, Armauer Hansensv 20, p.b. 8100, N-4068 Stavanger, Norway.
(Email: tkmaclarsen@mac.com)

communication (Melle *et al.* 2008), while the significance of this correlation is clear, the underlying direction is not (McGlashan, 1999). We do not know whether untreated psychosis generates poorer prognosis or whether persons who are at risk for a poor prognosis enter treatment via pathways generating longer DUP (Bosanac *et al.* 2010). The only way of disentangling the causal direction is to manipulate the DUP and then measure the outcome. Delaying treatment through a randomized clinical trial would be unethical in acute first episode psychosis. The best possible way to isolate the influence of DUP at this point is through a quasi-experimental 'service-systems' design intended to reduce DUP in one healthcare area (experimental) but not in another (control) and to track the outcomes of the ED *versus* no-ED groups.

The early Treatment and Intervention in Psychosis (TIPS) investigation used this design to study whether DUP could be reduced and, if so, what effect it would have upon the course of the disorder (Johannessen *et al.* 2001). A comprehensive ED system based on low-threshold psychosis-detecting teams and public information campaigns was created in one area (ED area). First-episode patients from this area were compared with first-episode patients from a parallel area without ED (no-ED area). The chosen areas had nearly indistinguishable sociodemographic and treatment service characteristics. Both ran equivalent 2-year comprehensive first-episode treatment programmes consisting of antipsychotic medication, assertively oriented individual out-patient treatment and psycho-educational family work.

The study was designed to test the following core hypotheses: (1) ED programmes can reduce DUP; (2) reducing DUP will be related to a comparative reduction in positive and negative symptoms displayed at the beginning of the first treatment; (3) the initial ED area *versus* no-ED area differences in these variables will be maintained for the first 2 years of standardized treatment, indicating ED-related secondary prevention.

The TIPS study of 2 years confirmed all of these hypotheses except for positive symptoms, where the two groups had nearly identical levels from 3 months and beyond (Melle *et al.* 2005, 2006, 2008; Larsen *et al.* 2006). This report tests the additional hypothesis that the initial ED/no-ED differences will have a long-term effect. The 5-year follow-up aims to test whether the 2-year advantage in outcome of the ED group survives beyond the cessation of the standardized study treatment. This would suggest that ED and treatment has a lasting effect on outcome of first episode psychosis that is significantly independent of ongoing treatment.

Method

Setting

Four Scandinavian specialized psychiatric healthcare service sectors or areas participated in the study. The ED sectors were located in Rogaland County on the west coast of Norway, which is divided into a north and a south healthcare sector. The ED sectors had a total population of 370 000 inhabitants. The control (no-ED) sectors were located at Ullevaal healthcare sector in Oslo, Norway and Roskilde mid-sector in Denmark. The combined population for the control sites was 295 000 inhabitants. The four sectors were regarded as similar since they had no differences in age and gender distribution, mean income levels and unemployment rates. All four sectors are mainly urban or suburban, but in the no-ED sector 96% lived in urban areas compared with 84% in the ED sector (for details, see Melle *et al.* 2005, 2008). All sectors served all possible cases with first episode psychosis since the participant treatment systems were catchment area-based, publicly funded and organized within national healthcare systems.

During 1997–2000 all cases with possible psychosis were referred to the healthcare system, rapidly assessed and, if meeting intake criteria, were offered treatment within the public healthcare systems either at out-patients' clinics or hospital wards. All four sites utilized the same treatment algorithm during the first 2 years, consisting of three elements: antipsychotic medication; supportive individual psychotherapy at least once per week; multi-family psycho-education groups twice per month. After 2 years the study treatment package was terminated, but sectorized psychiatric care was available, which included individual psychotherapy, medication and hospitalization if necessary.

In the ED sector an elaborate system for ED of psychosis was established using information campaigns about the signs and symptoms of psychosis, its treatment and phone numbers to call for rapid evaluation. The campaigns were directed at the general population, general practitioners, schools and primary health providers (for details, see Johannessen *et al.* 2001; Melle *et al.* 2005; Joa *et al.* 2008).

Participants

The study included all patients with a first episode psychosis who came for treatment in one of the four catchment areas from 1 January 1997 to 31 December 2000. Inclusion criteria were as follows: living in one of the four healthcare sectors; aged 18–65 years; meeting the DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder (core),

brief psychotic episode, delusional disorder, affective psychosis with mood-incongruent features or psychotic disorder not otherwise specified; being actively psychotic, as measured by a Positive and Negative Syndrome Scale (PANSS) score of ≥ 4 on at least one of the positive subscale items, 1 (delusions), 3 (hallucinatory behaviour), 5 (grandiosity) or 6 (suspiciousness/persecution) or general subscale item 9 (unusual thought content) for at least 7 days; not having received previous adequate treatment for psychosis (defined as antipsychotic medication >3.5 haloperidol equivalents for >12 weeks or until remission of the psychotic symptoms); having no neurological or endocrine disorders with relationship to the psychosis; having no contraindications to antipsychotic medication; speaking a Scandinavian language; having an IQ score >70 ; being willing and able to give informed consent.

Baseline sample

Power analysis estimated the need for 300 patients in order to ascertain clinically significant outcome differences between ED and no-ED sites (Friis *et al.* 2003). Over 4 years of recruitment, we identified 179 patients from the ED area and 194 from the no-ED area. Informed consent was obtained from 281 patients; 141 in the ED area and 140 in the no-ED area. The refuser rate was thus 24%. Patients who did not enter the study had significantly longer DUP than patients who entered [median 26 weeks (range 0–936 weeks) and 10 weeks (range 0–1196 weeks), respectively; $p < 0.001$]. This finding was replicated in both areas when they were examined separately. No other significant differences between patients who did and did not enter the study were found (for details, see Friis *et al.* 2003.) The sample was reassessed at 3 months, 1, 2 and 5 years after intake.

Follow-up sample

At the 5-year follow-up, 13 patients (5%) of the original 281 had died and we collected complete datasets for 195 cases of the 268 who were still alive (73%). Out of the 76 cases, we lacked data on 28 who refused, 36 who did not show up, nine who could not be found and three who had incomplete datasets. Compared with the group with complete data, the 89 (33%) cases with no PANSS scores at 5-year follow-up were generally more symptomatic at earlier follow-up points. For example, they had higher scores on drug abuse at 2 years (1.70 *v.* 1.38, $p = 0.047$), more severe PANSS general symptoms at 3 months (29.2 *v.* 25.5, $p = 0.007$), higher PANSS total scores at 3 months (56.4 *v.* 50.4, $p = 0.018$), higher PANSS depressive scores at

3 months (10.5 *v.* 9.2, $p = 0.011$), higher PANSS excitative scores both at 3 months (7.9 *v.* 6.7, $p = 0.009$) and 1 year (7.7 *v.* 6.5, $p = 0.024$). No additional significant differences for PANSS or global assessment functioning (GAF) scores at baseline, 3 months, 1 or 2 years were found and there were also no differences for age, gender distribution, pre-morbid adjustment, drug or alcohol use at baseline, 1 or 2 years, suicidality before or at baseline or at 1 or 2 years, DUP or the proportion of patients with core schizophrenia spectrum disorder at baseline and 1 or 2 years.

Overall, however, subjects dropping out of the study were more symptomatic. For most variables, this tendency was the same for both ED and no-ED patients. However, while the ED patients who were lost at 5 years had a slightly lower level of negative symptoms at 2 years (PANSS negative component score 14.8 *v.* 15.7), the no-ED sites lost patients with higher levels of negative symptoms (22.1 *v.* 18.3). The tendency to lose more high negative symptom no-ED patients is close to statistically significant ($F = 3.54$, degrees of freedom = 1, $p = 0.06$ for the interaction). Therefore, we used linear mixed effect modelling as the statistical method when we compared ED with no-ED groups. For details see the section regarding statistics.

At baseline and at follow-up it is noteworthy that the ED group was younger, more often of Nordic origin, had shorter DUP and more substance abuse (Table 1).

After a complete description of the study to the subjects, written informed consent was obtained. The regional ethical research committees approved the study.

Assessments

The assessment teams at all sites consisted of clinically experienced and trained research personnel. The Structured Clinical Interview for the DSM-IV Axis I disorders was used for diagnostic purposes (First *et al.* 1995). Pre-morbid functioning was measured by the Premorbid Adjustment Scale (PAS), which describes four pre-morbid periods in life: childhood (<12 years); early adolescence (12–15 years); late adolescence (16–18 years); adulthood (>18 years) (Cannon-Spoor *et al.* 1982). Previous analyses identified two pre-morbid dimensions: (a) social, consisting of the PAS items social isolation and peer relationships; (b) academic, containing school performance and school adaptation. Two parameters for each dimension were rated, childhood level of adjustment and degree of change of level of adjustment over post-childhood developmental phases (for details about this modification, see Larsen *et al.* 2004; Haahr *et al.*

Table 1. Baseline demographic and clinical characteristics of early versus usual detected first episode psychosis patients

Characteristics	Subjects from communities with no early detection programme (n=91)		Subjects from early detection communities (n=104)		Significant between group differences <i>p</i>
	<i>n</i>	%	<i>n</i>	%	
Male	51	58	64	62	
Nordic origin	78	89	104	100	<0.0001
Schizophrenia spectrum disorders	52	59	68	65	
Drug or alcohol abuse	22	25	39	38	<0.04
	Mean	S.D.	Mean	S.D.	
Age at study entrance (years)	31.8	10.3	26.1	7.1	<0.0001
Years of education	12.3	2.9	12.1	2.0	
	Median	Range	Median	Range	
Duration of untreated psychosis (weeks)	16	0–555	4	0–1196	<0.002

2008). Symptom levels were measured by means of the PANSS (Kay *et al.* 1987). Symptom domains are represented by the corresponding PANSS components (positive, negative, excitement, cognitive and depressive) (Bentsen *et al.* 1996). The cognitive factor consists of the PANSS items P2: Conceptual disorganization, N5: Abstract thinking and G10: Disorientation and does not represent a full neuropsychological testing. Global functioning was measured by the GAF scale (DSM-IV) and the scores were split into symptom (GAFs) and function (GAFf) scores to improve psychometric properties (Pedersen *et al.* 2007). Quality of life was measured with the Lehman Quality of Life Interview, brief version (Lehman, 1988). Misuse of alcohol and drugs was measured by the Drake Scale (Drake *et al.* 1990). If patients abused drugs, we would initiate a longer period (>4 weeks) of drug-free observation (mostly involuntarily) before a diagnostic conclusion was made. The DUP was measured as the time from onset of psychosis until the start of adequate treatment (for details, see Melle *et al.* 2005).

After 3 months, we repeated PANSS and GAF measurements. At 1-, 2- and 5-year follow-ups, all assessments were repeated including the Structured Clinical Interview for DSM-IV. For each follow-up, a separate summary interview was conducted, in which we gathered information regarding three different outcome domains: (1) psychosis course: time to remission, duration and number of relapses and remission status at follow-up; (2) treatment utilization as weeks of participation for hospitalizations, individual supportive psychotherapy (at least weekly sessions), family work and use of antipsychotic medication; (3) participation in working activities.

The definition of stable remission was at least 2 months with no positive symptoms defined as a

rating <4 on specific PANSS items. The definition of relapse was that the patient had a score >3 on the PANSS items for >1 week. Patients who were psychotic at follow-up, but not continuously psychotic, were labelled as being in relapse (for details, see Friis *et al.* 2003).

Assessment reliability

All major baseline assessments such as diagnosis, PANSS, GAF, drug abuse and DUP underwent tests of intra- and inter-site reliability with satisfactory results. Raters trained in reliability for DUP and PANSS made assessments of remission and relapse at follow-up.

Regarding reliability for the follow-up, 31 vignettes were randomly selected from 1 and 2 years follow-up and rated by two experienced psychiatrists on the following variables: diagnosis; GAFs; GAFf; alcohol and drug use scores. For all dimensions, the reliability was clearly satisfactory. For diagnosis, $\kappa=0.81$, for the other dimension intra-class correlations (ICCs) (1.1), GAFf=0.86; GAFs=0.91, alcohol use=0.75 and illicit drug use=0.86. No new reliability tests were carried out at 5 years since the same raters did the assessments.

Statistical method

Statistical analyses were conducted with the use of SPSS 15.0 (SPSS Inc., USA) and R 2.9.0 (R Development Core Team, 2005). All tests are two-tailed with a level of significance of 0.05. For the bivariate group comparisons, the *p* values are corrected for multiple testing. Non-significant findings are marked N.S. For skewed data, we used non-parametric tests or transformed the variable in order to achieve normal distribution; DUP was substituted in the linear mixed-effects and regression models with $\ln(\text{DUP} + 1)$.

To account for missing data and confounding variables, we used a linear mixed model, which has been the recommended method for repeated measures (Pinheiro & Bates, 2000). As opposed to performing *t* tests for the 5-year data only, a longitudinal approach, which utilizes data for a longer period, will generally have more power. The linear mixed-effects model is strongly recommended and a standard way to handle the dependencies of the longitudinal data at hand and the model with maximum likelihood estimation has the advantage of coping with drop-outs in an efficient way (Gueorguieva & Krystal, 2004). To fit the linear mixed-effects models, baseline scores were excluded since all symptom measures had a clear non-linearity during the first months of treatment. Otherwise, the average time trends seem fairly linear. We used a random intercept model with expected score at month *j* conditional on individual *i*:

$$\beta_0 + b_{0i} + \beta_1 \text{ed}_i + \beta_2 \text{month}_j + \beta_3 (\text{ed} : \text{month})_{ij} + \text{covariates},$$

with β_0 being the main level, β_1 the deviation from the main level for group ED=1, β_2 the average level change per month and β_3 the deviation from the average level change for group ED=1. The b_{0i} is the random intercept term for individual *i*. The covariates represent the variables age, gender, ethnicity (i.e. being Nordic or not), change in pre-morbid academic performance, DUP (log transformed) and substance abuse or not at baseline. The main focus in the analysis was on the estimates of the β_1 term, which represents a difference in level between the two groups in the linear predicting time trends. In order to ascertain that group differences are not caused by possible confounding variables, we first fitted models with the covariates only. Then the two terms representing group differences were included and checked for significant improvement (likelihood ratio test). For the negative, depressive and cognitive factors in the PANSS and for symptom and functioning GAF scores, the improvement was significant. Except for GAFs, the group \times time interaction term β_3 was non-significant and the models were refit without this term.

Results

Treatment utilization data revealed no statistically significant differences between the groups regarding participation in psychotherapy or use of medication (Table 2). However, the ED group was more often hospitalized during year 5 and had more weeks in hospital during all 5 years of follow-up.

A large majority of the patients were in stable remission at follow-up and most of these had been in remission for the whole of the previous year (no-ED 62 of 68; ED 61 of 74). Only a small proportion of the

patients (10% in the no-ED group and 12% in the ED group) were continuously psychotic. No significant differences between the groups were found on this variable. The same goes for total duration of psychosis during all 5 years and total number of relapses.

No difference between the groups was found regarding participation in work. Overall, approximately 25% of patients worked >20 h per week. The ED group had more contacts with friends; 76% saw friends more than twice per month compared with 59% in the no-ED group.

Regarding levels of symptoms, the ED group had better scores for PANSS cognitive and depressive components.

The linear mixed-effects modelling indicates that the outcome was significantly better for the ED group compared with the no-ED group for the negative, depressive and cognitive component scores in the PANSS. Figs. 1–3 show average values at 0, 3, 12, 24 and 60 months. The lines show lapse at 3–60 months as estimated by the linear mixed effects model.

Similar profiles were found for the GAF social functioning scores (not reported in the figures).

Discussion

This is the first study showing that ED may have a positive impact on long-term outcome, i.e. 5 years. We have already shown in the TIPS study that ED is clinically beneficial, since patients from the ED sector enter treatment with a lower level of symptoms (Melle *et al.* 2005), less suicidality (Melle *et al.* 2006) and shorter total duration of their first episode (Larsen *et al.* 2007). We have also reported previously that the ED group had a persistently lower level of negative symptoms throughout the first 2 years of follow-up (Melle *et al.* 2008). That finding has now been extended to 5 years. Furthermore, the difference at 5 years is significant for depressive and cognitive component symptoms in addition to negative symptoms. We also see an effect on social functioning since ED patients have more contact with friends.

Both groups were provided with the same treatment package consisting of antipsychotic medication, supportive psychotherapy and multi-family groups focusing on psycho-educational approaches. Treatment utilization for medication and psychotherapy was the same. The ED group had more hospitalizations despite the fact that they did not have more relapses or a greater total time as psychotic. This discrepancy, in turn, suggests that hospitalization may be more policy driven than psychopathology driven, thus rendering it less valid as a treatment-related dependent variable.

Table 2. Functional status at 5-year follow-up of early versus usual detected first episode psychosis patients

Characteristics	Subjects from communities with no early detection programme (<i>n</i> = 91)		Subjects from early detection communities (<i>n</i> = 104)		Significant between group differences <i>p</i>
	<i>n</i>	%	<i>n</i>	%	
Hospitalized during last year	28	20	39	37	<0.01
Remission status at 5-year follow-up					
In remission (at least 2 months)	69	76	74	71	
In relapse	13	14	17	16	
Continuous psychotic	9	10	13	12	
Working >20 hours/week	20	23	26	25	
Seeing friends at least twice/month	51	59	80	76	<0.01
Participation in treatment (weeks)	Mean	S.D.	Mean	S.D.	
Psychotherapy twice per week	168.8	83.6	158.5	86.8	
Use of medication	153.1	91.6	157.1	89.0	
Hospitalization (weeks)					
During last year	4.1	11.4	8.3	16.8	0.04
During all 5 years	30.8	42.4	45.3	59.7	0.03
Total duration of psychosis during 5 years (weeks)	76.4	91.0	80.1	90.2	
Total number of relapses during 5 years	1.4	1.6	1.2	1.6	
PANSS					
Positive component	8.6	4.4	9.0	5.0	0.5
Negative component	17.0	7.0	15.8	7.2	0.3
Excitement component	6.6	2.4	6.5	3.2	0.7
Depressive component	9.0	3.3	7.8	3.1	0.01
Cognitive component	5.4	2.5	4.2	1.9	0.0001
GAF					
Symptoms	53.5	14.1	54.5	17.3	0.7
Functioning	51.0	13.6	53.9	16.6	0.2

PANSS, Positive and Negative Syndrome Scale; GAF, global assessment of functioning.

The null hypothesis of this study is that the ED/no-ED differences seen at 2 years would not be extended to 5 years after the cessation of the study treatment package. That hypothesis has been disconfirmed. Our results stand in contrast with those of the recently completed and published 5-year follow-up of the OPUS study in Denmark (Bertelsen *et al.* 2008). There, first episode psychotic patients were openly randomized to intensive *versus* standard treatment. No attempt was made to treat either sample earlier and, in fact, the median DUP for each sample was around 1 year. In contrast, even the no-ED group of the TIPS study had a considerably shorter DUP (median = 4 months) than the OPUS sample.

The TIPS study also differed from the OPUS study in that the same treatment package was applied to both ED and no-ED samples. TIPS was designed to test whether different timing of the same treatment makes a difference in outcome, whereas OPUS was designed

to test whether similar timing of different treatments makes a difference in outcome.

Both studies found that their unique manipulations did make a significant difference in outcome 2 years after intake (Petersen *et al.* 2005; Melle *et al.* 2008). For TIPS, however, this difference continued to the 5-year follow-up, whereas for OPUS the difference did not (Bertelsen *et al.* 2008). The *prima facie* interpretation of these contrasting findings between OPUS and TIPS is that the (earlier) timing of treatment has a lasting effect on course but that the complexity and intensity of the treatment does not, at least when treatment initiation is as late as in the OPUS study.

Strengths and limitations

Our study has several strengths. First, the sample is large and from a well-defined catchment area. We assume that nearly every first episode case has been

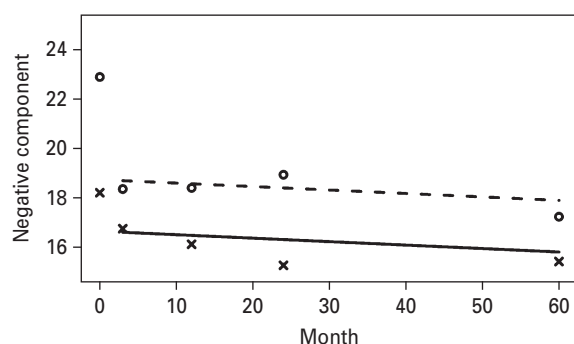


Fig. 1. Linear mixed-effects models for Positive and Negative Syndrome Scale negative component for early versus usual detected first episode psychosis patients over the 5-year period. ○, average values for no-early detection (ED) group; ×, average values for the ED group at 0, 3, 12, 24 and 60 months. Lines indicate lapse at 3 and 60 months as estimated by the linear mixed effects model: ---, no-ED group; —, ED group.

identified and we regard our sample as being highly representative. Second, our sample is from Scandinavia, in which all healthcare is free and provided by the State. Third, we report outcome results from an early detected sample. The study also had a number of limitations. Although the sample was large, 24% refused to participate at baseline and we were able to collect full datasets at 5-year follow-up for only 68% of the original sample.

It certainly can be argued that the drop-out and refuser rate may threaten the validity of the findings. However, the refusers had a longer DUP than the participants and the no-ED drop-outs had a higher level of negative symptoms than the ED drop-outs. If attrition might have affected our results, it would be in the direction of reducing the ED/no-ED difference. Consequently, the loss of patients due to refusal and drop-out seems to have reduced the chance of finding significant differences in outcome between ED and no-ED patients. Therefore, we think that our results represent an underestimate rather than an overestimate of the true differences. However, since our study has a quasi-experimental design it is difficult to rule out selection biases. We believe our study needs to be replicated in order to strengthen our findings.

Possible mechanisms

Overall, our study could not disconfirm the hypothesis that the 2-year differences between ED and no-ED first episode samples would be carried forward to 5 years. The mechanism(s) by which this ED and/or intervention advantage is generated and maintained is unknown. The finding, nevertheless, raises the question/hypothesis that earlier recognition and/or

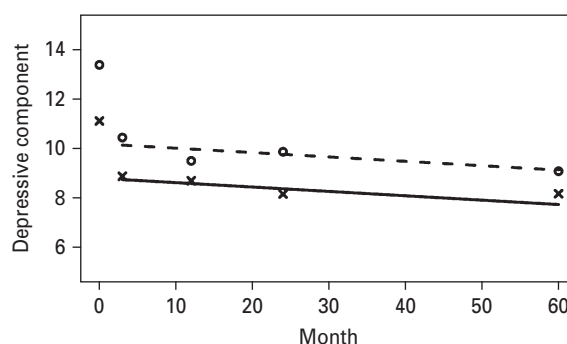


Fig. 2. Linear mixed-effects models for the Positive and Negative Syndrome Scale depressive component for early versus usual detected first episode psychosis patients over the 5-year period.

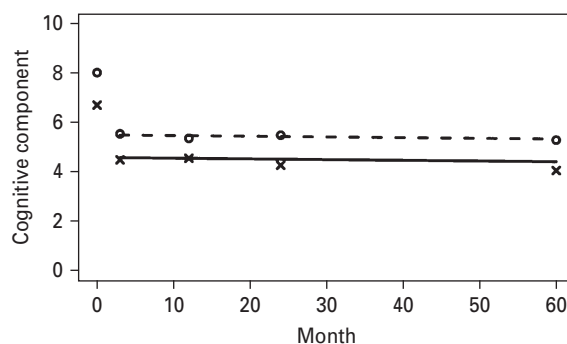


Fig. 3. Linear mixed-effects models for the Positive and Negative Syndrome Scale cognitive component for early versus usual detected first episode psychosis patients over the 5-year period.

treatment of psychosis somehow prevents or at least slows the neurobiological processes leading to greater severity and chronicity of psychosis. The nature of these processes remain largely unknown (McGlashan & Hoffman, 2000) and they require further theoretical elaboration and empirical testing. Our results, however, do suggest that these processes can be influenced with the earlier application of existing interventions, the result being lasting secondary prevention of psychotic deficits.

To our knowledge, a 5-year follow-up of differences in the outcome of earlier treatment of first episode psychosis has never been reported. Our findings clearly require further follow-up to determine the permanence of these differences. They also require replication by independent investigators. In the meantime, however, our findings continue to suggest that the timing of illness detection and illness treatment has a powerfully mutative effect on the development and/or expression of psychotic psychopathology.

Acknowledgments

Supported by the Norwegian National Research Council (no. 133897/320 and no. 154642/320), the Norwegian Department of Health and Social Affairs, the National Council for Mental Health/Health and Rehabilitation (no. 1997/41 and no. 2002/306), Rogaland County and Oslo County (Drs Vaglum, Johannessen, Friis, Larsen, Melle, Opjordsmoen). Also funded by the Theodore and Vada Stanley Foundation, the Regional Health Research Foundation for Eastern Region, Denmark; Roskilde County, Denmark, Helsefonden Lundbeck Pharma, Eli Lilly and Janssen-Cilag Pharmaceuticals (Drs Simonsen and Haahr). Also supported by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Distinguished Investigator Award and NIMH grant MH-01654 (Dr McGlashan) and a NARSAD Young Investigator Award (Dr Larsen).

Declaration of Interest

Melle, Larsen and Joa have received a speaker's fee from Jansen Cilag. Simonsen has received a speaker's fee from Boehringer Ingelheim, Eli Lilly and Bristol-Myers Squibb. Haahr has received a speaker's fee from Bristol-Myers Squibb. Opjordsmoen has received a speaker's fee from Bristol-Myers Squibb, has been a member of a Nordic expert group concerning antipsychotics sponsored by Janssen Cilag and is currently PI for an investigation sponsored by Janssen Cilag.

References

- Bentsen H, Munkvold OG, Notland TH (1996). The interrater reliability of the Positive and Negative Syndrome Scale. *International Journal of Methods in Psychiatric Research* 6, 1–9.
- Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, Christensen TO, Krarup G, Jorgensen P, Nordentoft M (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of General Psychiatry* 65, 762–771.
- Bosanac P, Patton GC, Castle DJ (2010). Early intervention in psychotic disorders: faith before facts? *Psychological Medicine* 40, 353–358.
- Cannon-Spoor HE, Potkin SG, Wyatt RJ (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin* 8, 470–484.
- Drake RE, Osher FC, Noordsy DL, Hurlbut SC, Teague GB, Beaudett MS (1990). Diagnosis of alcohol use disorders in schizophrenia. *Schizophrenia Bulletin* 16, 57–67.
- First MB, Spitzer RL, Gibbon M, Williams JB (1995). *The Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID I/P, version 2.0)*. New York: State Psychiatric Institute Biometrics Research Department: New York.
- Friis S, Larsen TK, Melle I, Opjordsmoen S, Johannessen JO, Haahr U, Simonsen E, Rund BR, Vaglum P, McGlashan T (2003). Methodological pitfalls in early detection studies – the NAPE Lecture 2002. Nordic Association for Psychiatric Epidemiology. *Acta Psychiatrica Scandinavica* 107, 3–9.
- Gueorguieva R, Krystal JH (2004). Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Archives of General Psychiatry* 61, 310–317.
- Haahr U, Friis S, Larsen TK, Melle I, Johannessen JO, Opjordsmoen S, Simonsen E, Rund BR, Vaglum P, McGlashan T (2008). First episode psychosis: diagnostic stability over one and two years. *Psychopathology* 41, 322–329.
- Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I, Opjordsmoen S, Simonsen E, Vaglum P, Larsen TK (2008). The key to reducing duration of untreated first psychosis: information campaigns. *Schizophrenia Bulletin* 34, 466–472.
- Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S, Kvebaek R, Friis S, Melle I, Opjordsmoen S, Simonsen E, Ulrik H, Vaglum P (2001). Early detection strategies for untreated first-episode psychosis. *Schizophrenia Research* 51, 39–46.
- Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13, 261–276.
- Larsen TK, Friis S, Haahr U, Johannessen JO, Melle I, Opjordsmoen S, Rund BR, Simonsen E, Vaglum PV, McGlashan TH (2004). Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *British Journal of Psychiatry* 185, 108–115.
- Larsen TK, Melle I, Auestad B, Friis S, Haahr U, Johannessen JO, Opjordsmoen S, Rund BR, Simonsen E, Vaglum P, McGlashan T (2006). Early detection of first-episode psychosis: the effect on 1-year outcome. *Schizophrenia Bulletin* 32, 758–764.
- Larsen TK, Melle I, Friis S, Joa I, Johannessen JO, Opjordsmoen S, Simonsen E, Vaglum P, McGlashan TH (2007). One-year effect of changing duration of untreated psychosis in a single catchment area. *British Journal of Psychiatry (Suppl.)* 51, s128–s132.
- Lehman AF (1988). A quality of life interview for the chronically mental ill. *Evaluation and Program Planning* 11, 51–62.
- McGlashan TH (1999). Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biological Psychiatry* 46, 899–907.
- McGlashan TH, Hoffman RE (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry* 57, 637–648.
- McGlashan TH, Johannessen JO (1996). Early detection and intervention with schizophrenia: rationale. *Schizophrenia Bulletin* 22, 201–222.
- McGorry P, Johannessen JO, Lewis S, Birchwood M, Malla A, Nordentoft M, Addington J, Yung A (2010).

- Early intervention in psychosis: keeping faith with evidence-based health care. *Psychological Medicine* **40**, 399–404.
- Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T** (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry* **62**, 975–983.
- Melle I, Haahr U, Friis S, Hustoft K, Johannessen JO, Larsen TK, Opjordsmoen S, Rund BR, Simonsen E, Vaglum P, McGlashan T** (2005). Reducing the duration of untreated first-episode psychosis – effects on baseline social functioning and quality of life. *Acta Psychiatrica Scandinavica* **112**, 469–473.
- Melle I, Johannesen JO, Friis S, Haahr U, Joa I, Larsen TK, Opjordsmoen S, Rund BR, Simonsen E, Vaglum P, McGlashan T** (2006). Early detection of the first episode of schizophrenia and suicidal behavior. *American Journal of Psychiatry* **163**, 800–804.
- Melle I, Larsen TK, Haahr U, Friis S, Johannesen JO, Opjordsmoen S, Rund BR, Simonsen E, Vaglum P, McGlashan T** (2008). Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Archives of General Psychiatry* **65**, 634–640.
- Pedersen G, Hagtvedt HA, Karterud S** (2007). Generalizability studies of the Global Assessment of Functioning – split version. *Comprehensive Psychiatry* **48**, 88–94.
- Perkins DO, Gu H, Boteva K, Lieberman JA** (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry* **162**, 1785–1804.
- Petersen L, Jeppesen P, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO, Krarup G, Jorgensen P, Nordentoft M** (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *British Medical Journal* **331**, 602.
- Pinheiro JC, Bates DM** (2000). *Mixed Effect Models in S- and S-PLUS*. Springer: New York.
- R Development Core Team** (2005). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing: Vienna, Austria (<http://www.R-project.org/>).