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ORIGINAL ARTICLE

The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis

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Background. The association between the duration of untreated psychosis (DUP) and outcome of schizophrenia may be confounded by other factors such as poor pre-morbid adjustment. The aim of the present study was to examine the independent contributions of DUP and of pre-morbid adjustment to the clinical and social outcomes of schizophrenia.

Method. A longitudinal, prospective, 2-year follow-up study of 423 patients with first-episode schizophrenia-spectrum psychosis was conducted. Patients were comprehensively assessed at entry, 1-year and 2-year follow-up. At entry, DUP was measured by IRAOS (an instrument for the assessment of onset and early course of schizophrenia) and pre-morbid adjustment was measured by the Pre-morbid Adjustment Scale (PAS) as 'pre-morbid social adaptation' and 'pre-morbid school adaptation'. Outcome measures included the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Social Network Schedule and social information. Multiple linear regression models were used for data analysis.

Results. The median DUP was 48 weeks, which is long compared to other studies. Longer DUP was independently associated with more psychotic symptoms at entry, 1-year and 2-year follow-up. Poorer pre-morbid social adaptation was independently associated with more negative symptoms and smaller social network at entry and 1-year follow-up. Poorer pre-morbid school adaptation was independently associated with poor vocational outcome at 1-year and 2-year follow-up.

Conclusions. Longer DUP is associated with poorer 2-year outcome of psychosis in schizophrenia-spectrum disorders, when pre-morbid functioning and other prognostic factors are controlled for. Impaired pre-morbid development is independently associated with more negative symptoms and poorer social outcome.

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Key words: Duration of untreated psychosis, first-episode psychosis, premorbid adjustment, schizophrenia, treatment outcome.

Introduction

Studies from around the world have consistently revealed that patients with a first episode of schizophrenia experience an alarming delay between the onset of first psychotic symptoms and the initiation of treatment. This duration of untreated psychosis (DUP) averages 1–2 years (McGlashan, 1999). Wyatt (1991) was the first to hypothesize that a longer period of untreated psychosis has a biological toxic effect, causing a poorer outcome of illness due to deterioration of brain function.

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The hypothesized toxic effect of the psychotic state is still under debate. Follow-up magnetic resonance imaging (MRI) studies demonstrated a progressive decrease in global grey matter volume in adolescents with childhood-onset schizophrenia (Sporn *et al*. 2003) and in patients in the early stages of schizophrenia (Cahn *et al*. 2002). In a 5-year longitudinal MRI study, excessive decreases in grey matter density in the left superior frontal area and the left superior temporal gyrus (van Haren *et al*. 2007) were associated with an increased number of psychotic episodes, with atypical antipsychotic medication (clozapine and olanzapine) possible attenuating these changes. Several cross-sectional MRI studies have found associations between long DUP and more marked grey matter reductions in specific regions (Keshavan *et al*. 1998; Lappin *et al*.

2006; Crespo-Facorro *et al*. 2007; Takahashi *et al*. 2007). However, the longitudinal studies can be interpreted in two ways. First, the regional progressive pathological processes may represent neuronal damage induced by a toxic effect of untreated psychosis in the early stages of illness. Second, patients with progressive brain abnormalities may have a more severe illness and therefore a later presentation to first treatment.

A systematic review of the existing follow-up studies of first-episode cohorts concluded that there is convincing evidence of an association between longer DUP and poorer outcome (Marshall *et al*. 2005). The clearest evidence was seen in the meta-analysis of the correlational data at 6- and 12-month follow-up, where the association was consistent across several dimensions of outcome, including positive symptoms, negative symptoms, all symptoms, and social functioning. Patients with long *versus* short DUP were also less likely to achieve remission. At 24-month follow-up, the quantity of data in the meta-analysis was limited, and DUP no longer predicted negative symptoms. Only two studies included in the meta-analysis of Marshall *et al*. (2005) looked at the association between DUP and negative symptoms after controlling for pre-morbid adjustment. In another review and meta-analysis, Perkins *et al*. (2005) found that prolonged DUP was associated with more severe negative symptoms at initiation of treatment and poorer outcome and treatment response regarding global psychopathology, psychotic symptoms, negative symptoms and functional outcome.

Recent studies show conflicting results regarding DUP as a predictor of course of symptoms. One study (Schimmelmann *et al*. 2008) of a very large ($n=636$) first-episode psychosis (FEP) cohort found that longer DUP was associated with a lower rate of remission of positive symptoms, and after controlling for relevant confounders, DUP explained approximately 5% of variance of remission of positive symptoms in the total sample. Another study (Malla *et al*. 2008) of predictors of relapse following treatment of FEP found no association between DUP and length of time to relapse.

Clarke *et al*. (2006) studied the association between DUP and 4-year outcome, and found, when looking at the schizophrenia and schizophreniform group, that poorer outcome of negative symptoms was associated with shorter DUP (the direction opposite to the expected) and with longer duration of the prodrome.

Results from the TIPS (Early Treatment and Identification of Psychosis) study have shown that the DUP can be reduced through an early detection (ED) programme. A reduction in DUP was associated with lower levels of positive and negative symptoms at first presentation (Melle *et al*. 2004). At 1-year follow-up (Larsen *et al*. 2006), the ED cohort 'caught up' with the no-ED cohort in terms of levels of symptoms and functioning, except for negative symptoms. Better outcome of negative symptoms was independently predicted by being in the ED cohort and having better pre-morbid social functioning, but not by DUP.

The heterogeneity of findings regarding the association between DUP and outcome of negative symptoms in FEP patients was explored by use of latent class regression modelling, Schmitz *et al*. (2007) finding no association between DUP and negative symptoms in half of patients and the expected association between long DUP and poor negative symptom outcome in only one-third of patients.

The aim of the current study was to examine the independent contributions of DUP and pre-morbid adjustment to clinical and social outcomes at initiation of treatment and after 1-year and 2-year follow-up. We hypothesized that longer DUP was independently associated with poorer outcome of psychotic symptoms and that poorer pre-morbid adjustment was independently associated with poorer outcome of negative symptoms and social functioning.

Method

Study sample

The sample was drawn from a randomized controlled trial (RCT) of integrated *versus* standard treatment of first-episode schizophrenia spectrum disorders, and constitutes a representative cohort of first-episode schizophrenia and schizophrenia-like psychoses, aged 18–45 years and living within a defined catchment area. The details of the study design and sampling are described elsewhere (Petersen *et al*. 2005).

Patients were included consecutively from all in-patient and out-patient mental health services in Copenhagen (Copenhagen Hospital Corporation) and Aarhus County. From January 1998 until December 2000, 547 patients fulfilling the following criteria were included in the RCT: (1) age 18–45 years and legal residence in the catchment areas; (2) F2 diagnosis: schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorder, schizo-affective disorder, induced delusional disorder, or unspecified non-organic psychosis according to ICD-10 research criteria (WHO, 1993), based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.0, since 1999 version 2.1 (WHO, 1998); (3) no exposure to antipsychotic medication exceeding 12 weeks of continuous medication; (4) absence of mental retardation,

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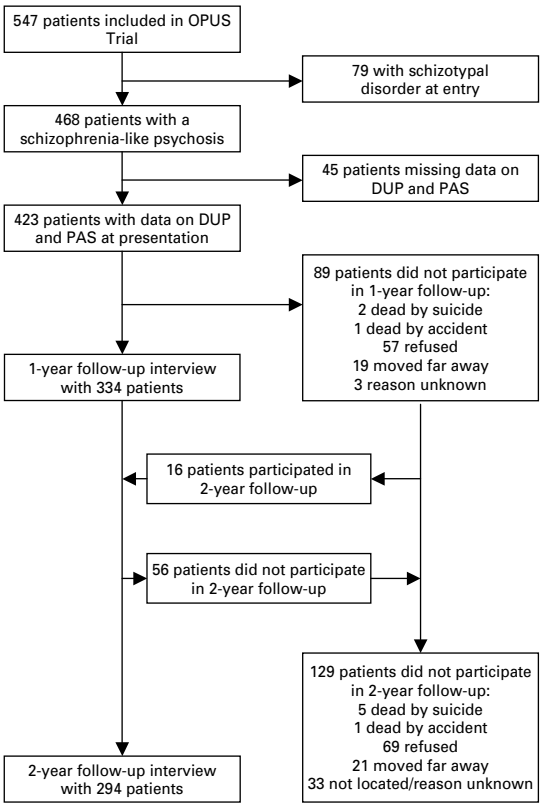

Fig. 1. Profile diagram.

organic mental disorder, and psychotic condition due only to acute intoxication or a withdrawal state; (5) after complete description of the study to the subjects, written informed consent was obtained. Out of 547 patients included in the RCT, 79 patients with schizotypal disorder were excluded from the present study of DUP (see Fig. 1).

Assessments

DUP

The DUP was defined as the time period with at least one psychotic symptom definitely present until initiation of treatment. The onset and temporal course of psychotic symptoms was determined with a modified version of the IRAOS, an instrument for the assessment of onset and early course of schizophrenia (Hafner *et al*. 1992). The IRAOS includes items on psychotic symptoms originally drawn from the PSE (Present State Examination, now part of SCAN) but reduced in number for practical reasons in terms of time and patients' memory. We assessed the onset, course and end of each psychotic symptom included in IRAOS. The data were collected through the IRAOS interview performed as a continuation of the SCAN interview. To improve the accuracy of the patient's recall, the assessor and the patient marked the onset and end of each psychotic symptom on a time-line, with major events of the patient's life as anchor points (Maurer & Hafner, 1995). The duration of each symptom was counted in intervals of weeks and months, and the criteria for rating a symptom present was a retrospective rating of at least 1 on the SCAN, rating scale II (symptom definitely occurring during the period). The onset of adequate treatment was operationalized as the date of inclusion in the study and random allocation to integrated or standard treatment. For both treatment groups the date of inclusion marked the onset of structured treatment with antipsychotic medication, hospitalization or out-patient treatment aimed at treating the psychosis. We did not use date of onset of adequate antipsychotic medication as the end-point of DUP so as not to confound the DUP with periods of non-compliance with medication after initiation of treatment. In cases of acute state of severe psychosis, the interview on the duration of each of the psychotic symptoms was postponed until the patient was able to cooperate. When possible, data from other sources (such as case-notes including information from parents) were used in the interview with the patient to help complete the time-line and check the validity of the information.

Pre-morbid adjustment

Pre-morbid functioning was assessed retrospectively by the Pre-morbid Adjustment Scale (PAS; Cannon-Spoor *et al*. 1982) based on interview with the patient. The PAS conceptualizes good pre-morbid adjustment as the achievement of certain age-appropriate developmental goals, viewed as milestones for healthy functioning.

The PAS was designed to evaluate the level of functioning in four life periods: childhood, up to 11 years; early adolescence, 12–15 years; late adolescence, 16–18 years; and adulthood, 19 years and beyond. The 'pre-morbid' period by definition ends 6 months before first psychiatric contact or evidence of florid psychotic symptomatology. For each life period (subscale), there are items covering 'sociability and withdrawal', 'peer relations', 'scholastic performance', 'adaptation to school' (the last two items are not relevant in adulthood) and 'socio-sexual aspects' (the latter not relevant in childhood). In accordance with recommendations, we did not use the general scale (van Mastrigt & Addington, 2002). Adulthood scores are not reported because many patients had onset of psychosis prior to age 19. The PAS scores are expressed as the sum of scores divided by the highest (worst) possible score obtainable for that subscale, thus creating an index, range 0–1.

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Several reports of factor analyses confirm that the PAS covers two discrete areas of functioning: academic ('scholastic performance', 'adaptation to school') and social ('sociability and withdrawal', 'peer relations' and 'socio-sexual aspects') (Larsen *et al*. 2004).

An overall score (range 0–1, higher score indicates lower functioning) for each of the two dimensions of PAS was calculated by averaging the indexes for the relevant subscales completed up to 6 months prior to onset of psychosis. The two indexes, called 'pre-morbid school adaptation' and 'pre-morbid social adaptation', serve as primary measures of pre-morbid functioning. For both dimensions we also defined a poor starting level as childhood mean score $\geqslant 3$ (Larsen *et al*. 2004), and a pattern of deterioration from childhood over early and late adolescence as change score $\geqslant 1.50$, equivalent to a 2-point change over four pre-morbid stages (Haas & Sweeney, 1992).

Outcome measures

Clinical outcome was measured by the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). The scales are summed in three dimensions: psychotic, negative and disorganized (scored 0–5) (Andreasen *et al*. 1995). The social outcome regarding vocational status (working or in education) was extracted from case records and/or interviews. The Social Network Schedule (Dunn *et al*. 1990) is a structured interview that collects detailed information on all social contacts in the previous month in order to count the number of family members and friends in contact with the patient. Diagnosis at entry was based on SCAN version 2.0/2.1 (WHO, 1998).

Inter-rater reliability

All investigators had 1 week of education in SCAN and continued training in the use of the study instruments (SCAN, IRAOS, PAS, SAPS and SANS) through live interviews at bimonthly meetings throughout the study period. Measures of reliability of DUP are problematic, because a patient's answer regarding first onset of a given psychotic symptom can vary with the rigour of the interview, but once the patient has answered, they tend to stick to the same answer. Some study groups have used vignettes and found very high degrees of reliability (Melle *et al*. 2004). Unfortunately, we did not measure the reliability of DUP and PAS interviews and ratings. Reliability for SAPS and SANS dimensions was measured with an interclass correlation coefficient: 0.54 for the negative dimension (moderate agreement) and 0.88 for the psychotic dimension.

Data analyses

Analyses were performed with the statistical package SPSS/PC version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). All tests were two-tailed at the 5% level of significance. To avoid undue influence from the right skewness in distribution of DUP, the natural logarithm transformation was applied. For the convenience of interpretation, we divided ln(DUP) by ln 2. Then, the regression coefficient is an estimate of the change in the dependent variable, when DUP is changed by a factor 2. The DUP was also categorized into short DUP and long DUP groups split at 52 weeks (close to the median, but more comparable with other studies) to estimate the relative risk (RR) of not being in remission of psychosis (defined as all global SAPS items <2) at 1-year and at 2-year follow-up in the short *versus* long DUP group.

The univariate relationships between the historical variables DUP, pre-morbid school adaptation, pre-morbid social adaptation and age of onset of psychosis, and between these and the dependent variables, were analysed by the non-parametric Spearman correlation coefficient.

The outcomes of psychotic and negative symptoms at entry, 1-year and 2-year follow-up were modelled with multiple linear regression models to evaluate the independent contributions of DUP, pre-morbid school adaptation and pre-morbid social adaptation after the effects of other important predictors had been accounted for. The model was planned to control for possible confounding effects from gender, age of onset of psychosis, centre (Copenhagen or Aarhus) and treatment allocation (only at 1 and 2 years), and all of these factors were kept in the model regardless of their statistical significance. We did not control for diagnosis within the schizophrenia spectrum because diagnosis partly depends on duration of psychosis. In addition, we did not control for co-morbid alcohol or drug abuse because co-morbid abuse was regarded to be a consequence of psychosis and not a cause.

The independent contributions of DUP, pre-morbid school adaptation, and pre-morbid social adaptation to the social network size (split into two categories: <7 persons and $\geqslant 7$ persons) and to vocational status (working or in education: yes or no) were examined by binary logistic regression analysis with control for gender, age, centre and treatment allocation.

Results

Attrition

Figure 1 shows the profile diagram. From the group of 468 patients of interest, 423 individuals had complete DUP and PAS information and were included

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Table 1. *Demographic and clinical characteristics of 423 subjects with a first episode of schizophrenia-spectrum psychosis at initiation of treatment*

Age (years), mean (S.D.)	26.8 (6.4)
Male, *n* (%)	240 (56.7)
Married, *n* (%)	27 (6.4)
Foreign citizenship, *n* (%)	30 (7.1)
Completed high school (>11 years in school), *n* (%)	142 (33.6)
Vocational education (in training or completed), *n* (%)	178 (42.1)
Living independently (alone, with partner or with child), *n* (%)	330 (78.0)
In-patient at entry, *n* (%)	240 (57)
Diagnosis, *n* (%)	
Schizophrenia	325 (76.8)
Delusional disorder	21 (5.0)
Brief psychosis	43 (10.2)
Schizo-affective disorder	23 (5.4)
Unspecified non-organic psychosis	11 (2.6)
Co-morbid harm or dependence syndrome (drug or alcohol)	113 (26.7)
Psychopathology scores (range 0–5), mean (S.D.)	
Psychotic dimension	3.0 (1.3)
Negative dimension	2.2 (1.1)
Disorganized dimension	1.0 (0.9)
Social functioning	
GAF function (range 0–100), mean (S.D.)	40.4 (13.3)
Number of family and friends, median (IQR)	6 (4–10)
Historical variables	
Duration of untreated psychosis (weeks), median (IQR)	48 (13–146)
Age of onset of psychosis (years), mean (S.D.)	24.5 (6.5)
Pre-morbid social adaptation (0–1), mean (S.D.)	0.29 (0.21)
Pre-morbid school adaptation (0–1), mean (S.D.)	0.42 (0.20)
Pathway to care	
Detected by psychiatric hospital or community centre, *n* (%)	382 (90.4)
General practitioner, *n* (%)	30 (7.1)
Social welfare centre and others outside health care, *n* (%)	11 (2.5)

GAF, Global Assessment of Functioning; IQR, interquartile range; S.D., standard deviation.

in the analyses. Of these, 89 did not participate in the 1-year follow-up interview, and another 56 did not participate in the 2-year follow-up interview, whereas 16 of the 89 patients who missed the 1-year interview did participate in the 2-year follow-up. Thus, 334 (79%) were reinterviewed after 1 year and 294 patients (70%) were reinterviewed after 2 years. Those who were lost to follow-up at 1 year ($n=89$) scored worse on pre-morbid school adaptation ($p=0.007$) and negative symptoms at first presentation ($p=0.028$), compared to those ($n=334$) who completed the first-year assessment, and they were more likely to have less than 11 years of schooling ($p=0.006$) and to have foreign citizenship ($p=0.012$). Those who were lost to follow-up at 2 years had the same characteristics. There were no significant differences in age, gender, marital status, pre-morbid social adaptation, DUP, severity of psychotic symptoms or Global Assessment of Functioning (GAF) at first presentation between those who completed the assessments and those who were lost to follow-up at 1 year and/or 2 years.

Sample characteristics

The sociodemographic and clinical characteristics of the 423 subjects at initiation of treatment are shown in Table 1. The mean age of this FEP sample was 26.8 years, 56.7% were males, 76.8% were diagnosed with schizophrenia, and the majority were single (93.6%) and had Danish citizenship (92.9%).

Only 41 (9.6%) of the patients were referred directly from general practitioners, social welfare agencies or others outside the psychiatric health-care system. A total of 382 (90.4%) were referred from psychiatric hospitals, community centres or specialists, and these patients had been hospitalized, offered medication

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Table 2. *The univariate relationships between historical and outcome variables in patients with first-episode schizophrenia-spectrum psychosis at entry, 1-year and 2-year follow-up*

	Time	Psychotic symptoms (SAPS)	Negative symptoms (SANS)	Work or study (yes/no)	Social network (no. of family and friends in contact last month)
DUP	Entry	0.160***	0.080		−0.208***
	1-year	0.281***	0.107*	−0.141*	−0.189**
	2-year	0.224***	0.074	−0.114	−0.186**
Pre-morbid social adaptation	Entry	0.026	0.261***		−0.372***
	1-year	0.099	0.248***	−0.108*	−0.273**
	2-year	0.092	0.153**	−0.029	−0.228**
Pre-morbid school adaptation	Entry	0.035	0.182***		−0.180**
	1-year	0.130*	0.201***	−0.164**	−0.123*
	2-year	0.061	0.100	−0.155**	−0.146*

SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; DUP, duration of untreated psychosis.

Data are expressed as Spearman's correlation coefficients.

* $p<0.05$, ** $p\leqslant0.01$, *** $p\leqslant0.001$.

or other treatments within 1 or 2 weeks prior to inclusion.

DUP was right-skewed, with a median value of 48 weeks, mean 117 weeks, interquartile range (IQR) 13–146 weeks and the longest DUP 970 weeks. A mean (S.D.) value of 0.29 (0.21) was obtained for the pre-morbid social adaptation index and 0.42 (0.20) for the pre-morbid school adaptation index.

The historical variables of interest were statistically significantly correlated in univariate analysis using Spearman's rank correlation coefficient: longer DUP correlated with earlier age of onset of psychosis ($r=-0.03$, $p<0.001$), poorer pre-morbid social adaptation ($r=0.19$, $p<0.001$) and poorer pre-morbid school adaptation ($r=0.10$, $p=0.05$). Lower pre-morbid social adaptation correlated with lower pre-morbid school adaptation ($r=0.42$, $p<0.001$), and both of these correlated with earlier age of onset of psychosis ($r=-0.11$, $p=0.03$, and $r=-0.15$, $p=0.002$).

Poor level of social adaptation in childhood (61/368, 16.6%) correlated with DUP ($r=0.14$, $p=0.008$) and poor level of school adaptation in childhood (121/368, 32.9%) correlated with DUP ($r=0.11$, $p=0.044$). Deteriorating pre-morbid course of social adaptation (39/364, 10.7%) and deteriorating pre-morbid course of school adaptation (45/349, 12.9%) did not correlate with DUP. Patients with a diagnosis of schizophrenia had significantly longer DUP, earlier onset of psychosis and worse pre-morbid social and school adaptation compared to patients with other schizophrenia-spectrum psychoses.

Results of univariate analyses

Longer DUP was significantly associated with higher levels of psychotic symptoms at entry, 1-year and 2-year follow-up in the univariate correlations (Table 2). The relative risk (RR) of not being in remission of psychosis for the short DUP *versus* the long DUP group was 0.68 [95% confidence interval (CI) 0.57–0.81, $p<0.001$] at 1-year follow-up and 0.66 at 2-year follow-up (95% CI 0.54–0.81, $p<0.001$).

There was a weak positive association between longer DUP and higher levels of negative symptoms at 1-year follow-up. Poorer pre-morbid social adaptation and poorer pre-morbid school adaptation were both significantly associated with higher levels of negative symptoms at entry and at 1-year follow-up. Even at 2-year follow-up, poorer pre-morbid social adaptation was associated with more negative symptoms in the univariate correlations (Table 2).

Longer DUP, poorer pre-morbid social adaptation and poorer pre-morbid school adaptation were associated with poor vocational outcome (no employment and not undergoing education) at the 1-year follow-up in the univariate analyses, and the association between poorer pre-morbid school adaptation and poor vocational outcome was maintained at the 2-year follow-up (Table 2).

Longer DUP and poorer pre-morbid social adaptation and poorer pre-morbid school adaptation were associated with a small social network at entry, 1-year and 2-year follow-up in the univariate analyses (Table 2).

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Table 3. *Multiple linear regression analyses of the independent effects of duration of untreated psychosis (DUP), pre-morbid social adaptation and pre-morbid school adaptation on the level of psychotic symptoms at entry, 1-year and 2-year follow-up*

	Historical variables	β (95% CI)	S.E.	p value
At entry	DUP	0.12 (0.07–0.17)	0.03	<0.001
	Pre-morbid social adaptation	−0.48 (–1.14 to 0.17)	0.33	0.15
	Pre-morbid school adaptation	0.19 (–0.48 to 0.86)	0.34	0.57
At 1-year follow-up	DUP	0.15 (0.08–0.21)	0.03	<0.001
	Pre-morbid social adaptation	−0.16 (–0.96 to 0.64)	0.41	0.69
	Pre-morbid school adaptation	0.78 (–0.04 to 1.60)	0.42	0.06
At 2-year follow-up	DUP	0.11 (0.04–0.18)	0.03	0.001
	Pre-morbid social adaptation	0.05 (–0.81 to 0.92)	0.44	0.90
	Pre-morbid school adaptation	0.12 (–0.78 to 1.02)	0.46	0.78

CI, Confidence interval; S.E., standard error.

The DUP was transformed by the natural logarithm and divided by ln 2. The regression coefficient, β, is an estimate of the change in the dependent variable, when DUP is changed by a factor of 2. Adjusted variables: gender, age of onset of psychosis, centre and treatment allocation (the latter only at 1-year and 2-year follow-up).

Results of the multivariate analyses

The independent effect of DUP on psychotic symptoms in the multiple linear regression analyses (Table 3) was estimated by the regression coefficient β. At entry, $\beta = 0.12$ (95% CI 0.07–0.17, $p < 0.001$), meaning that the mean score of psychotic symptoms increased by 0.12 of one scale point when DUP increased by a factor of two. The independent effect of DUP on psychotic symptoms remained at the same magnitude at the 1-year follow-up ($\beta = 0.15$, 95% CI 0.08–0.21) and at the 2-year follow-up ($\beta = 0.11$, 95% CI 0.04–0.18). The effect of DUP accounted for 10% of the variance in psychotic symptoms at the 1-year follow-up and 5% of the variance of psychotic symptoms at the 2-year follow-up.

The multiple linear regression analyses were conducted again: (1) including change scores of pre-morbid social adaptation and of pre-morbid school adaptation as covariables, and (2) including the dichotomized ratings of deterioration of pre-morbid social adaptation and of pre-morbid school adaptation as covariables. Both models yielded the same results as the primary analyses: there were no independent effects of any of the included covariables measuring pre-morbid functioning, and the estimated independent effects of DUP on outcome of psychosis remained at the same magnitude at all times.

Because of the high level of intercorrelation between the two PAS scores, only pre-morbid social adaptation was associated with negative symptoms in the multiple linear regression analyses, when controlling for the other possible confounders (Table 4). The independent effect of pre-morbid social adaptation on negative symptoms at entry was estimated to be $\beta = 1.27$ (95% CI 0.68–1.86, $p < 0.001$). The independent effect of pre-morbid social adaptation on negative symptoms at 1 year was estimated to be $\beta = 1.18$ (95% CI 0.53–1.82, $p < 0.001$), meaning that the mean score of negative symptoms increased by 1.27 respectively 1.18 scale points when pre-morbid social adaptation changed from the best possible score (index = 0) to the worst possible score (index = 1). There was no significant effect of pre-morbid social adaptation on negative symptoms at the 2-year follow-up in the multivariate analysis.

The multiple linear regression analyses were conducted again: (1) including change scores of pre-morbid social adaptation and of pre-morbid school adaptation, and (2) including the dichotomized ratings of deterioration of pre-morbid social adaptation and of pre-morbid school adaptation. Both models showed the same pattern of results as the primary analyses: there were no independent effects of DUP on outcome of negative symptoms at any time. The estimated independent effect of pre-morbid social adaptation was slightly increased and now significant at all times [$\beta = 1.49$ (95% CI 0.82–2.17), $p < 0.001$, at entry; $\beta = 1.57$ (95% CI 0.80–2.35), $p < 0.001$, at 1-year; and $\beta = 1.06$ (95% CI 0.15–1.97), $p = 0.023$, at 2-year follow-up], when ratings of deterioration of pre-morbid social adaptation and of pre-morbid school adaptation were included as covariables in the model.

All six multiple linear regression analyses of outcome of psychotic symptoms and of negative symptoms were conducted again including only patients diagnosed with schizophrenia. The results were also stable for this subsample of patients.

In the multiple binary logistic regression analyses (data not shown), poorer pre-morbid social adaptation

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Table 4. *Multiple linear regression analyses of the independent effects of duration of untreated psychosis (DUP), pre-morbid social adaptation and pre-morbid school adaptation on the level of negative symptoms at entry, 1-year and 2-year follow-up*

	Historical variables	β (95% CI)	S.E.	p value
At entry	DUP	0.02 (–0.03 to 0.06)	0.02	0.53
	Pre-morbid social adaptation	1.27 (0.68–1.86)	0.30	<0.001
	Pre-morbid school adaptation	0.29 (–0.31 to 0.89)	0.30	0.34
At 1-year follow-up	DUP	0.04 (–0.01 to 0.09)	0.03	0.15
	Pre-morbid social adaptation	1.18 (0.53–1.82)	0.33	<0.001
	Pre-morbid school adaptation	0.60 (–0.07 to 1.27)	0.34	0.08
At 2-year follow-up	DUP	0.04 (–0.02 to 0.09)	0.03	0.23
	Pre-morbid social adaptation	0.64 (–0.11 to 1.38)	0.38	0.09
	Pre-morbid school adaptation	0.15 (–0.62 to 0.93)	0.39	0.70

CI, Confidence interval; S.E., standard error.

The DUP was transformed by the natural logarithm and divided by ln 2. The regression coefficient, β, is an estimate of the change in the dependent variable, when DUP is changed by a factor 2. Adjusted variables: gender, age of onset of psychosis, centre and treatment allocation (the latter only at 1-year and 2-year follow-up).

predicted small social network at entry and 1-year follow-up, whereas DUP made no contribution to the model. Similarly, poorer pre-morbid school adaptation predicted poor vocational outcome at 1-year and 2-year follow-up, whereas DUP made no contribution to the model.

Discussion

Summary of findings

The major findings of this study are: (1) longer DUP was independently associated with more severe psychotic symptoms at first presentation for treatment and at 1-year and 2-year follow-up; (2) the association was consistent but of moderate size; (3) poorer pre-morbid social adaptation was independently associated with more severe negative symptoms and smaller social network at first presentation and at 1-year follow-up; and (4) poorer pre-morbid school adaptation was independently associated with poorer vocational outcome at 1-year and 2-year follow-up. These findings confirm our hypothesis that longer DUP is independently associated with poorer outcome of psychotic symptoms, whereas poorer pre-morbid adjustment is independently associated with poorer outcomes of negative symptoms and social functioning.

Methodological strengths and limitations

This study has several strengths: a large sample, a prospective follow-up, an incidence cohort with good representativity, low attrition during follow-up, standardized assessment of DUP and pre-morbid adjustment and comprehensive follow-up data assessed by validated psychometric instruments. The present study is among the largest prospective follow-up studies of an incident cohort of patients with schizophrenia-spectrum psychosis that have investigated the independent effects of DUP and of pre-morbid adjustment on several dimensions of outcome of schizophrenia and schizophrenia-spectrum psychoses.

In our study, the median DUP was longer than in the non-early detection areas in the TIPS study. The data cannot determine whether the longer DUPs in our study reflect differences in method and/or in sampling.

The most important limitations of the study are shared by other studies in the field: data on DUP and PAS are assessed retrospectively and may be subject to recall bias; the correlational nature of the study does not offer conclusive evidence about causality of the associations between DUP, pre-morbid adjustment and outcome.

One weakness of the present study is that a reliability test of DUP was not performed. Some researchers have reported measures of inter-rater reliability on DUP based on ratings of vignettes, and have demonstrated very good inter-rater reliability (Melle *et al*. 2004). Other studies have validated ratings of DUP by including interviews with family members, hospital records and reviews of data after 1 year (Addington *et al*. 2004). Our ratings of DUP rest entirely on the patients' own reports and thus reflect the onset of the subjective experiences of psychosis. The key relatives were asked when they first noticed the changes in the behaviour of the ill relative. The median duration of illness in the view of the key relative was 2 years (Jeppesen *et al*. 2005). In our study,

the raw ratings on IRAOS and PAS were not blinded for the follow-up assessors, but DUP and PAS scores were calculated by complex computerized algorithms when the 2-year follow-up of the cohort had been completed. Results regarding the associations between pre-morbid functioning and outcome of negative symptoms should be interpreted with caution as the inter-rater reliability of ratings of negative symptoms was moderate, and the sample followed up at 1 and 2 years may be biased towards those with better pre-morbid school adaptation and lower levels of negative symptoms.

Mechanisms and clinical implications

The independent association between longer DUP and more severe psychotic symptoms throughout the first 2 years of treatment adds to the evidence of an association between longer DUP and poorer outcome of psychosis in schizophrenia-spectrum disorders, when pre-morbid functioning and other prognostic factors are controlled for. However, the association is of moderate size and of unknown mechanism. If the association is causal, substantial reductions in DUP are needed to attain clinically important improvements in the course of the illness. Improvement of psychosis involves cognitive, restructuring processes that may be attenuated after long periods of untreated psychosis. Another explanation of the mechanism of the association between DUP and outcome of psychosis may involve sensitization of the mesolimbic dopaminergic system (Glenthoj *et al*. 1999).

We found no independent effect of DUP on the course of negative symptoms, and from a theoretical point of view the duration of untreated negative symptoms might be suspected as a candidate for prediction of outcome of negative symptoms. The scores of pre-morbid social and school adaptation might be influenced by unrecognized early onset of negative symptoms (Hafner *et al*. 1992), thus confounding the association between poor pre-morbid social adaptation and poor outcome of negative symptoms. If not entirely an artefact, the independent effect of pre-morbid social adaptation on outcome of negative symptoms indicates a developmental continuity from pre-morbid cognitive and social impairments to negative symptoms (Hollis, 2003).

Lower levels of social and school adaptation in childhood were associated with longer DUP but, unlike the study by Larsen *et al*. (2004), we did not find an association between deteriorating courses of pre-morbid development and DUP, and deteriorating courses did not influence the effect of DUP on outcome of positive symptoms.

Our results support the idea that schizophrenia-spectrum disorders involve both neurodevelopmental processes and neurotoxic processes, the neurodevelopmental processes being reflected by impaired pre-morbid functioning already in childhood and the continuity between pre-morbid impairments and poor outcome of negative symptoms and social functioning, and the neurotoxic processes being reflected by the association between longer DUP and poorer outcome of psychosis even 2 years after initiation of treatment.

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Declaration of Interest

None.

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