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Association between the duration of untreated psychosis and short- and long-term outcome in schizophrenia within the Northern Finland 1966 Birth Cohort

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ABSTRACT

Background: Long duration of untreated psychosis (DUP) may relate to poor outcome in schizophrenia. However, the associations between DUP and outcomes, particularly in later course of illness, remain unclear. Our aim was to explore the associations between DUP and short- and long-term outcomes in schizophrenia.
Methods: Data was collected for subjects with schizophrenia (n = 89) in the population-based Northern Finland 1966 Birth Cohort. DUP was obtained from medical records, and its associations with short- (under 2 years) and long-term clinical and social outcomes were assessed extending to 20 years after the onset of the illness.
Results: Longer DUP predicted longer length of first hospitalisation and increased the risk of rehospitalisation during the first two years. Longer DUP associated with decreased probability of disability pension, smaller amount of time spent in hospital, and higher proportion of time at work during the first 10 years of the follow-up.
Conclusions: Regarding early outcome, long DUP may be a modest marker and proxy measure of a more severe clinical phenotype. The divergent results of earlier studies and the association between long DUP and better long-term outcome in our study, indicate that the length of DUP does not necessarily predict poor outcome in long-term follow-up. This may also be due to methodical difficulties, e.g. insufficient power and residual confounding linked to long follow-up studies.

1. Introduction

Factors relating to first-episode psychosis might have a significant effect on outcome in schizophrenia. For instance, good recovery from first-episode psychosis correlates with better outcome later on (Emsley et al., 2006, 2007). Since the 1980s there has been growing interest in the effects of the untreated phase of the first episode and possibilities for early intervention (Johnstone et al., 1986; Rabiner et al., 1986; Bosanac et al., 2010). Some studies (Norman and Malla, 2001; Marshall et al., 2005; Perkins et al., 2005) state that longer DUP is associated with poorer outcome, especially in the short term (i.e. the first 2-3 years). However, results have been somewhat inconsistent, especially concerning the association between the DUP and negative (Schmitz et al., 2007) and positive symptoms (Perkins et al., 2005) and longer-term outcomes. Studies with 4–8 years of follow-up have found some association between longer DUP and poorer outcome (Whitty et al., 2008; Crumlish et al., 2009), but studies with more than 10 years of follow-up have shown inconclusive results (Waddington et al., 1995; Huber, 1997; Scully et al., 1997; Wiersma et al., 1998; Bottlender et al., 2003; Röpcke and Eggers, 2005; White et al., 2009). The earlier studies are described in more detail in Table 1.

Our aim was to analyse associations between the length of DUP and short- and long-term clinical and functional outcomes in the Northern Finland 1966 Birth Cohort. Our hypothesis was that longer DUP predicts poorer outcome, especially in the short-term follow-up.

2. Methods

2.1. Sample

The Northern Finland 1966 Birth Cohort (NFBC 1966) is an unselected, general population birth cohort initiated during mid-pregnancy. It includes 12,231 women who lived in the area of Oulu and Lapland and their 12,058 children. The expected births occurred during 1966, representing 96% of all births in the area (Rantakallio, 1969). The present study is based on 11,017 individuals living in Finland at the age of 16 years. Of these, 83 refused the use of their data, resulting in

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Table 1
Previous studies of the association between DUP and outcome with at least 10 years follow-up.

Authors, year	Length of follow-up	Sample size	Mean DUP	Cross-sectional outcome variables and their correlation with DUP	Longitudinal outcome variables and their correlation with DUP
Scully et al. (1997)	12 years	n = 48	13.9 years	Positive symptoms (PANSS) and executive function did not associate with DUP Increased negative symptoms (PANSS) ($p = 0.005$) and decreased general cognition (MMSE) ($p = 0.03$) correlated with long DUP	
Wiersma et al. (1998)	15 years	n = 240	Not given	Psychosis, negative symptoms, anxiety/depression did not associate with delayed treatment Full remission associated with delayed treatment ($p = 0.03$, $\beta = 0.19$)	Hospital care and any mental health care during follow-up did not associate with delayed treatment
Bottlender et al. (2003)	15 years	n = 58	Not given	Lower GAS ($p = 0.025$) and increased SANS ($p = 0.027$), positive ($p = 0.033$) and general symptoms ($p = 0.007$) in PANSS associated with long DUP Negative symptoms (PANSS) did not associate with DUP	
Röpcke and Eggers (2005)	15.4 years	n = 39	286 days	CGI, PANSS (negative, positive and sum) and GAS did not associate with DUP	
White et al. (2009)	10.5 years	n = 69	29 weeks	High outcome symptom burden[a] correlated with long DUP (0.28, $p = 0.03$)	Functional outcome and service dependency did not correlate with DUP
Shrivastava et al. (2010)	10 years	n = 101	12.7 months	DUP did not associate with PANSS, HDRS, aggression, living, social functionality, suicidality or recovery.	No association was found between DUP and hospitalizations or working.
Kinoshita et al. (2005)[b]	10 and 15 years	n = 52	9.9 months	Long DUP associated with poor outcome in 10 year follow-up ($p = 0.036$) but not in 15-years ($p = 0.828$)	
Ichinose et al. (2010)[b]	28 years	n = 34	9 months	Long DUP correlated with decreased GAS ($p = 0.001$), DAS ($p = 0.003$) and CGI ($p = 0.002$).	

PANSS = Positive and Negative Syndrome Scale; MMSE = Mini-Mental State Examination; GAS = Global Assessment Scale; DAS = Disability Assessment Schedule; CGI = Clinical Global Impression; HDRS = Hamilton Depression Rating Scale.
[a] Positive and negative symptoms from the SAPS and SANS, GAF symptom scores, and life-chart: recent negative symptoms.
[b] Same sample analysed at different time points.

10,934 subjects. Permission to gather data was obtained from the Ministry of Social Affairs and Health, and the study design has been approved by, and is under review of, the Ethical Committee of the Northern Ostrobothnia Hospital District. Written informed consent was obtained from the participants (Haapea et al., 2007). Subjects (n = 10) who had deceased during the follow-up were included in the analyses when the required data was available.

Register-based information on outcome was used for all individuals who, at any time, fulfilled the DSM-III-R criteria for schizophrenia (codes: 2951, 2953, 2956 and 2959) (n = 111) according to detailed diagnostic validation (Moilanen et al., 2003; Haapea et al., 2007). 89 individuals with a diagnosis of schizophrenia were included in the current study. 22 subjects were excluded, as information regarding the onset of psychosis was not available in the medical records for 17 subjects, and DUP had ended after 1995 for 5 subjects (follow-up time less than 5 years). In addition to register data, data from assessments based on personal interviews were used for a subset of schizophrenia cases, diagnosed and interviewed in a field survey in 1999–2001 (n = 47) (Moilanen et al., 2003; Penttilä et al., 2010). The detection of subjects and validation of diagnoses are described in detail by Isohanni et al. (1997), Moilanen et al. (2003), and Haapea et al. (2007).

Participants in the field survey in 1999–2001 (n = 47) were rated according to PANSS (Positive and Negative Syndrome Scale) (Kay et al., 1987) and SOFAS (Social and Occupational Functioning Assessment Scale) (Spitzer et al., 2000) based on the SCID-I interview (Structural Clinical Interview for DSM-III-R) (Spitzer et al., 1989). Data concerning psychiatric hospitalisations was collected from the nationwide Finnish Hospital Discharge Register (FHDR), which covers all mental and general hospitals as well as beds in local health centres and private hospitals. Data collection is described in Fig. 1.

2.2. Information on DUP

Duration of untreated psychosis was defined retrospectively, based on information from medical records (Penttilä et al., 2010). Ratings were done independently to subjects' outcome. The information gathered included the onset of first psychotic symptoms, time of first psychiatric hospitalisation and first use of antipsychotic medication. Psychotic symptoms were defined as the onset of positive symptoms, considered to be at least moderate symptoms, corresponding to 4 points or more on PANSS but without a separate rating of PANSS at the onset of illness. DUP was defined as the period between the onset of first psychotic symptoms and the commencement of treatment (generally antipsychotic medication although for 3 subjects, who were not given medication during their first hospitalisation due to psychosis, the beginning of hospitalisation was used). The DUP assessments were made jointly by two clinician–researchers (MP and EJ) and, in problematic cases, in consensus with a senior clinician–researcher (HK). When assessing the DUP, we (MP, EJ, HK) independently performed inter-rater reliability rating for 15 cases. Reliability for continuous DUP was good (Intraclass Correlation Coefficient, ICC = 0.732). DUP could be defined for n = 89 individuals with a diagnosis of schizophrenia. These individuals formed the sample for this study.

2.3. Assessment of outcomes and course of illness

Outcome variables were divided into three categories: short- and long-term outcome and course of illness. Short-term outcome describes the outcome during the first two years of illness. Long-term outcome describes, on average, outcome after 11 (interview and register data) and 20 (register data) years of illness. Course of illness describes the longitudinal, continuous illness course since the onset.

2.4. Short-term outcome

Length of first psychiatric hospitalisation after the end of the DUP was used as dichotomised variable (1–14 days vs. 15 days or more). Data from the FHDR.

Rehospitalisation (yes vs. no) was defined as hospitalisation due to psychosis within two years of discharge from the first hospital treatment after the end of the DUP. Data from the FHDR.

Cumulative number of hospital treatment days due to psychosis within two years since the first hospital treatment day after the end of DUP was analysed as a continuous variable. Data from the FHDR.