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## Statistical approaches to explore clinical heterogeneity in psychosis

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## **CHAPTER 7**

### **Factors contributing to the duration of untreated psychosis**

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**Abstract**

**Background:** Shortening the duration of untreated psychosis (DUP) - with the aim of improving the prognosis of psychotic disorders - requires an understanding of the causes of treatment delay. Current findings concerning several candidate risk factors of a longer DUP are inconsistent. Our aim was to identify factors contributing to DUP in a large sample that represents the treated prevalence of non-affective psychotic disorders.

**Method:** Patients with a non-affective psychotic disorder were recruited from mental health care institutes from 2004 to 2008. Of the 1120 patients enrolled, 852 could be included in the present analysis. Examined candidate factors were gender, educational level, migration status, premorbid adjustment and age at onset of the psychotic disorder. DUP was divided into five ordinal categories: less than one month, one month to three months, three months to six months, six months to twelve months and twelve months and over. An ordinal logistic regression analysis was used to identify the risk factors of a longer DUP.

**Results:** Median DUP was less than one month (IQR 2). The factors migration status ( $p = 0.028$ ), age at onset of the psychotic disorder ( $p = 0.003$ ) and gender ( $p = 0.034$ ) were significantly associated with DUP in our analysis.

**Conclusion:** First generation immigrant patients, patients with an early onset of their psychotic disorder and male patients seem at risk of a longer DUP. These findings can assist in designing specific interventions to shorten treatment delay.

**Keywords:** duration of untreated psychosis; DUP; migration status; age at onset; gender

## 1. Introduction

The duration of untreated psychosis (DUP) is defined as the time from the emergence of the first psychotic episode to the initiation of adequate treatment. DUP can last days, months or even years (Marshall et al., 2005). A longer DUP is associated with worse short-term (Marshall et al., 2005; Perkins et al., 2005) and long-term outcomes (Bottlender et al., 2003; Crumlish et al., 2009; Boonstra et al., 2012a). The potential of DUP being modifiable raises the possibility of improving outcome by shortening DUP. In designing interventions to shorten DUP, it is important to identify factors contributing to DUP.

Factors previously associated with a longer DUP include stigma-related concerns (Corrigan, 2004; Tanskanen et al., 2011), an insidious mode of onset (Morgan et al., 2006; Compton et al., 2008) and a diagnosis of non-affective psychosis compared with affective psychosis (Morgan et al., 2006; Bechard-Evans et al., 2007; Schimmelmann et al., 2008).

Inconsistent results have been reported for the association between DUP and several other factors. Concerning gender, even though studies continue to show that men have (a tendency for) a longer DUP compared with women (Chang et al., 2011; Fridgen et al., 2012), a review could not confirm the association (Cascio et al., 2012). Also inconsistent are the findings with respect to the association between DUP and educational level: longer DUP was found to be associated with a higher level (Chong et al., 2005), a lower level (Verdoux et al., 1998) and not with educational level at all (Morgan et al., 2006; Bechard-Evans et al., 2007; Compton et al., 2008, 2011). Most studies did not find an association between DUP and ethnicity (Anderson et al., 2013). Interestingly however, three recent studies reported an association between DUP and migration status (Sterk et al., 2010; Boonstra et al., 2012b; Nerhus et al., 2013). Furthermore, inconsistent results have been reported with respect to the association between DUP and overall premorbid adjustment (Chen et al., 2005; versus Harrigan et al., 2003; Schimmelmann et al., 2008) and the association between DUP and age at onset of the psychotic disorder (Bechard-Evans et al., 2007; Schimmelmann et al., 2008; versus Drake et al., 2000; Morgan et al., 2006). Notably, many previous studies examining DUP had relatively small sample sizes, a mixed sample of patients with affective and non-affective psychotic disorders and a substantial variation in definition of DUP.

Given the importance of knowledge concerning the factors associated with DUP, the inconsistency of previous findings and the limitations of previous research, the association between DUP and candidate risk factors needs further elucidation. The aim of this study was to identify risk factors of a longer DUP in a large sample that represents the treated prevalence of non-affective psychotic disorders. Specifically, we aimed to test the hypothesis that being an immigrant, having a poor premorbid adjustment and having an earlier age at onset of the psychotic disorder is associated with a longer DUP. Furthermore, we hypothesized that gender and educational level were not associated with DUP.

## 2. Methods

### 2.1. Study design and population

Data were extracted from the baseline assessments of a longitudinal, multi-site, naturalistic cohort study: the Genetic Risk and Outcome of Psychosis (GROUP) study (data release 3.02). Patients were

recruited from mental health care institutes in selected representative geographical areas in the Netherlands and Belgium. They were identified through clinicians, whose caseloads were screened for inclusion criteria. Subsequently, patients presenting consecutively at these services either as outpatients or inpatients were recruited. Inclusion criteria for patients were: 1) age range of 16 to 50 years; 2) diagnosis of a non-affective psychotic disorder, according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria; and 3) good command of the Dutch language. The GROUP study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht, and subsequently by local review boards of each participating institute. Informed consent was obtained from all participants after complete description of the study and before the start of the first assessment. Detailed information about the GROUP study is published elsewhere (Korver et al., 2012).

The GROUP sample consisted of 1120 patients, of which 852 could be included in the present study. Reasons for and numbers of exclusion were the following: 1) 19 patients were excluded because of a final diagnosis other than a non-affective psychotic disorder; 2) 226 patients were excluded because DUP could not be calculated, as data were incomplete; and 3) 23 patients were excluded because their calculated DUP was longer than the recorded duration of the first psychotic episode, meaning data were incorrect.

## **2.2. Definitions and measures**

To establish the DSM-IV diagnosis of a non-affective psychotic disorder two structured diagnostic instruments were used, in accordance with the standard practice in the study sites: the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) and the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1) (Wing et al., 1990). All raters had completed training in the instruments and diagnostic consensus was achieved in the presence of an independent psychiatrist.

Information regarding DUP was assessed with the Life Chart Schedule (LCS) (Sartorius et al., 1996) by clinical trained interviewers. DUP was defined as the number of months from the onset of the first psychotic episode to the initiation of appropriate treatment for this episode. The first psychotic episode was defined as the first period in which hallucinations, delusions and/or clear disorganized speech or thinking were present for at least one week, according to criteria by the CASH or SCAN. Appropriate treatment, the end-point for DUP, was defined as the use of antipsychotic medication and/or regular treatment contact with a mental health professional for psychosis. The starting month and year of receiving medication or initiation of treatment contact was noted – whichever started first. When treatment was started before the onset of the first psychotic episode, this resulted in a negative DUP. This can happen in case treatment is started during the prodromal phase. These negative values were truncated to zero values.

The following variables were considered as candidate factors contributing to DUP: gender, educational level, migration status, premorbid adjustment and age at onset of the psychotic disorder. Educational level was based on a subdivision by Verhage (Verhage, 1964) and ranged from zero (no education) to eight (university degree). Together the subdivisions of lower, higher and pre-university

secondary education bear resemblance with internationally well-known secondary education. The three types of vocational education should be regarded as “universities of professional education”.

Migration status was defined as follows: when a patient and at least one of the parents were born abroad, the patient was classified as a first generation immigrant. When a patient was born in the Netherlands or Belgium and at least one of the parents was born abroad, the patient was classified as a second generation immigrant. All other patients were considered as natives.

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) was used to determine premorbid adjustment. PAS is designed to evaluate the levels of functioning at several periods of a subject’s life, before the onset of the psychotic disorder. It covers sociability and withdrawal, peer relationships, scholastic performance, adaption to school and capacity to establish socio-sexual relationships. For analyses a PAS overall score was used, calculated by averaging the period scores - before onset of the psychotic disorder - per patient. Age at onset of the psychotic disorder was, like information regarding DUP, assessed by using the LCS.

### 2.3. Statistical analysis

Patient’s characteristics were summarized by using descriptive statistics. Differences between the included and excluded patients were tested using Mann-Whitney tests, chi-squared tests and Fisher’s exact tests as appropriate. Due to the very high positive skewed distribution of DUP, it was necessary to convert DUP into categories prior to statistical analysis. Because there are no agreed-on cutoff points (Marshall et al., 2005), categorization was based on a combination of cutoff points selected in two previous studies (Harrigan et al., 2003; Chang et al., 2012). DUP was converted into a set of five ordinal categories: less than one month; one month to three months; three months to six months; six months to twelve months; and twelve months and over. An ordinal logistic regression analysis was used to analyze the data.

The full model included all five preselected candidate risk factors, based on literature. We then applied a backward selection procedure to come up to our final model, by eliminating candidate risk factors one by one when p-values for all levels from Type 3 tests were larger than or equal to 0.05. The proportional odds assumption was checked for the final model.

Analyses were conducted using Statistical Analysis System (SAS Institute Inc., Cary, NC). The level of significance was set at 0.05.

## 3. Results

### 3.1. Sample characteristics

Socio-demographic and clinical characteristics of the included and excluded patients are presented in Table 1. The excluded patients differed significantly from the included patients concerning diagnostic categories ( $p < 0.001$ ), age at onset ( $p = 0.012$ ) and illness duration ( $p < 0.001$ ). The median DUP of the included patients was less than one month (range  $< 1 - 226$ ; interquartile range 2). DUP had a heavily skewed distribution, with a majority of patients (63.1%) having a DUP of less than one month. Figure 1 illustrates the distribution of DUP.

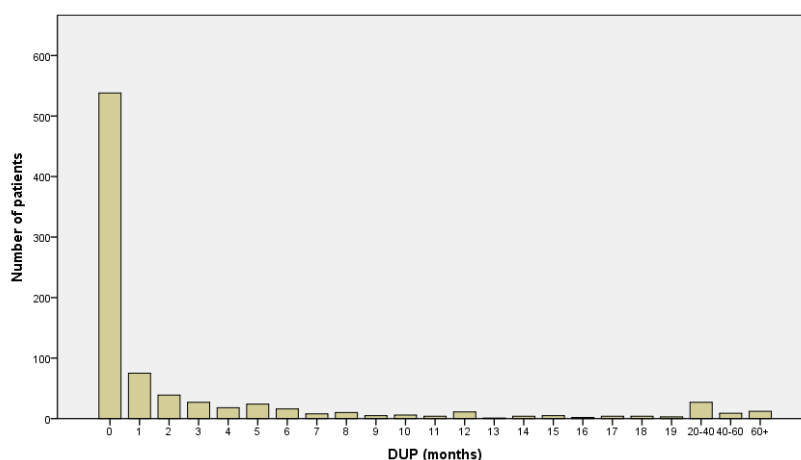


Figure 1: Distribution of the duration of untreated psychosis (N = 852).

Table 1: Socio-demographic and clinical characteristics of the included and excluded patients.

Variables	Included (N = 852)	Excluded (N = 258)	P-value
Age (years), mean (SD)	27.0 (7.2)	27.6 (7.6)	0.370 <sup>a</sup>
Gender			0.172 <sup>b</sup>
Male, N (%)	664 (77.9)	183 (73.8)	
Female, N (%)	188 (22.1)	65 (26.2)	
Educational level			0.388 <sup>c</sup>
No education, N (%)	6 (0.7)	1 (0.4)	
Primary education, N (%)	106 (12.5)	37 (16.2)	
Lower vocational education, N (%)	95 (11.2)	31 (13.5)	
Lower general secondary education, N (%)	167 (19.7)	44 (19.2)	
Higher general secondary education, N (%)	114 (13.5)	18 (7.9)	
Pre-university secondary education, N (%)	107 (12.6)	30 (13.1)	
Intermediate vocational education, N (%)	142 (16.8)	38 (16.6)	
Higher vocational education, N (%)	74 (8.7)	23 (10.0)	
University, N (%)	36 (4.3)	7 (3.1)	
Migration status			0.286 <sup>b</sup>
Native, N (%)	516 (76.0)	137 (70.3)	
Immigrant: first generation, N (%)	63 (9.3)	22 (11.3)	
Immigrant: second generation, N (%)	100 (14.7)	36 (18.5)	
Premorbid adjustment, mean (SD)	1.94 (0.90)	1.81 (0.87)	0.162 <sup>a</sup>
Diagnostic categories			<0.001 <sup>c*</sup>
Schizophrenia, N (%)	570 (67.1)	152 (63.1)	
Schizophreniform disorder, N (%)	50 (5.9)	12 (5.0)	
Schizoaffective disorder, N (%)	99 (11.6)	20 (8.3)	
Delusional disorder, N (%)	18 (2.1)	3 (1.2)	
Brief psychotic disorder, N (%)	19 (2.2)	10 (4.1)	
Substances induced psychosis, N (%)	4 (0.5)	1 (0.4)	
Psychosis NOS, N (%)	90 (10.6)	24 (10.0)	
Other, N (%)	0 (0.0)	19 (7.9)	
Age at onset (years), mean (SD)	22.7 (6.6)	21.3 (6.8)	0.012 <sup>a*</sup>
Illness duration (years), mean (SD)	3.8 (3.4)	6.3 (5.1)	<0.001 <sup>a*</sup>
DUP (months), median (range, IQR)	< 1 (< 1 – 226, 2)	...	...
Subdivision of DUP		...	...
Less than one month, N (%)	538 (63.1)	...	...
One to three months, N (%)	141 (16.5)	...	...
Three to six months, N (%)	58 (6.8)	...	...
Six to twelve months, N (%)	44 (5.2)	...	...
Twelve months and over, N (%)	71 (8.3)	...	...

N = number; SD = standard deviation; NOS = not otherwise specified; IQR = interquartile range; DUP = duration of untreated psychosis; <sup>a</sup> = Mann Whitney test; <sup>b</sup> = Chi-square test; <sup>c</sup> = Fisher's exact test; \*p < 0.05.

### 3.2. Factors contributing to DUP

The final logistic model produced by backward elimination included the variables gender, migration status and age at onset of the psychotic disorder. The score test for the proportional odds assumption of the final model was not significant ( $p = 0.112$ ), meaning that the assumption was not violated.

As shown in Table 2, gender was significantly associated with DUP ( $p = 0.034$ ). Since male was the reference category and the odds ratio was less than one, being male was associated with a longer DUP (odds ratio 0.65; 95% C.I. 0.44-0.97). Furthermore, being a first generation immigrant patient - compared to being a native patient - was associated with a longer DUP ( $p = 0.028$ ; odds ratio 1.74; 95% C.I. 1.06-2.87). Being a second generation immigrant patient was not significantly associated with DUP ( $p = 0.868$ ). Age at onset of the psychotic disorder was also significantly associated with DUP ( $p = 0.003$ ). This represents that being younger at onset was associated with a longer DUP (odds ratio 0.96; C.I. 0.94-0.99).

Table 2: Factors within the final logistic model and their association with the duration of untreated psychosis.

Parameter	Estimate	S.E.	Wald $\chi^2$	P-value	Odds Ratio	95% C.I.
Intercept (DUP > 12)	-1.57	0.32	24.75	<0.001	...	...
Intercept (DUP 6 to 12)	-1.01	0.30	11.00	<0.001	...	...
Intercept (DUP 3 to 6)	-0.46	0.30	2.39	0.122	...	...
Intercept (DUP 1 to 3)	0.35	0.30	1.41	0.235	...	...
Gender						
(Female vs. male)	-0.43	0.20	4.49	0.034*	0.65	0.44 - 0.97
Migration status 1	0.56	0.25	4.81	0.028*	1.74	1.06 - 2.87
(First generation vs. native)						
Migration status 2	-0.04	0.22	0.03	0.868	0.96	0.62 - 1.49
(Second generation vs. native)						
Age at onset	-0.04	0.01	8.92	0.003*	0.96	0.94 - 0.99

S.E. = standard error; C.I. = confidence interval; DUP = duration of untreated psychosis; Migration status 1 = immigrant: first generation; Migration status 2 = immigrant: second generation; \* $p < 0.05$ .

## 4. Discussion

### 4.1. Main findings

DUP was longer for male patients, first generation immigrant patients and patients being younger at onset of the psychotic disorder. Educational level, premorbid adjustment and being a second generation immigrant were not significantly associated with DUP in our sample.

### 4.2. Comparison with previous studies

The median DUP of less than one month found in this study is short compared with the average median DUP of 26 weeks reported in most international studies (Marshall et al., 2005), but is in line with recently published Dutch studies (Wunderink et al., 2006; Boonstra et al., 2012b). There are several possible explanations for this difference with international studies. First this may partly be the merit of the Dutch and Belgium health care system, which is characterized by an easy service access. Health insurance is compulsory and there is an extensive system of hospital and community based mental health services, including in- and outpatient clinics, outreaching teams and psychiatric



emergency services. Second, DUP estimation varies greatly according to commonly used definitions (Polari et al., 2011). The most restrictive criteria for the start-point for DUP and the least restrictive criteria for the end-point for DUP, will lead to the shortest DUP estimation. In this study the start-point for DUP was defined by the onset of the first psychotic episode. The other common start-point used is the onset of the first psychotic symptoms. Since it is not uncommon that the first episode arises months to even years after the onset of the first psychotic symptoms, one can imagine that by choosing our definition the start-point moves towards the end-point, and DUP estimations will shorten. The end-point for DUP was defined as the initiation of antipsychotic medication and/or regular treatment contact with a mental health professional for psychosis. This definition is less restricted than many other definitions for the end-point for DUP, like for example “initiation of antipsychotic medication with good compliance”. By choosing our definition the end-point for DUP moves towards its start-point, and DUP estimations will shorten. Furthermore, noting DUP in months instead of weeks or days, restricts its distribution even more. It would be more detailed to do otherwise, but we were restricted by the available data. Because there are no agreed-on cutoff points for DUP being (too) long (Marshall et al., 2005), it is unclear to what duration DUP must be reduced at least, in order not to increase the risk of a worse prognosis. In our next study we will analyze whether there is an association between this relatively short DUP and various outcome variables.

The finding that gender was associated with DUP was not expected given the findings of a review article describing the literature up to 2010 (Cascio et al., 2012), but is in line with more recent studies showing men to have (a tendency for) a longer DUP compared with women (Chang et al., 2011; Fridgen et al., 2012), and with other studies showing delayed help seeking in men (Galdas et al., 2004). It is conceivable that in men a lower level of awareness and insight to illness might contribute to their treatment delay (Cotton et al., 2006).

The finding that first generation immigrant patients had a longer DUP than native-born patients is in line with findings of three smaller studies (Sterk et al., 2010; Boonstra et al., 2012b; Nerhus et al., 2013). There are several explanations for this association. First generation immigrants may be less familiar with the concept of mental illness and the mental health services (Wolff et al., 1996a), may be less likely to perceive themselves as having a psychiatric problem or to be in need for treatment (Commander et al., 1999) and may experience more pronounced negative emotions towards mental illnesses and visiting a psychiatrist (Wolff et al., 1996b; Sadeghieh Ahari et al., 2013). Language barrier may also cause delay. Although all patients spoke sufficient Dutch to enter this study, bilingual individuals are often less able to express themselves in their second language when they are acutely psychotic (Paradis, 2008), which may impede diagnostics and treatment. One may argue that these factors diminish in following generations (Boonstra et al., 2012b), which may explain why second generation immigrant patients did not have a longer DUP compared with native-born patients. A recent meta-analysis showed little evidence to support an association between ethnicity and DUP (Anderson et al., 2013). The difference between the present study and this meta-analysis is that we focused on migration status, not on ethnic origin. Differences in DUP might therefore be related to the effects of migration, and not to ethnic background.

The association between age at onset of the psychotic disorder and DUP was expected, and is in line with previous findings (Bechard-Evans et al., 2007; Schimmelmann et al., 2008). However, it is important to note that the odds ratio was nearly one, and therefore age at onset may not be a clinically relevant risk factor of DUP.

The finding that educational level was not associated with DUP was expected, and is in line with most observations made by others (Morgan et al., 2006; Bechard-Evans et al., 2007; Compton et al., 2008; Compton et al., 2011).

The lack of association between premorbid adjustment and DUP was unexpected, but is in line with previous studies with (mainly) non-affective psychotic diagnoses samples (Chen et al., 2005; Harris et al., 2005)

### 4.3. Additional statistical analyses

An ordinal logistic regression analysis was applied to investigate factors contributing to DUP, but also several alternative analyses were applied.

DUP can be viewed as a time-to-event outcome, and it can therefore be analyzed with a Cox proportional hazards model. This analysis confirmed that first generation migration status and age at onset of the psychotic disorder are significantly associated with DUP, but did not confirm the association between gender and DUP. However, these results may be biased. Our DUP has a very high number of ties, which may affect the parameter estimates. Although the Efron's approximation method we used is considered the best possible approach for handling substantial numbers of ties (Hertz-Picciotto and Rockhill, 1997), this method may still result in serious biases (Scheike and Sun, 2007; Allison, 2010). It is therefore more difficult to interpret the results of this analysis compared to the results of ordinal logistic regression.

An alternative method is to treat DUP as a numerical outcome. Due to the high number of DUP values of less than one month, a zero-inflated regression model is suitable. Therefore a zero-inflated negative binomial model was applied. This analysis is more complex compared to ordinal logistic regression, but it supported its findings: the factors gender, migration status and age at onset of the psychotic disorder, were significantly associated with DUP.

Choosing the appropriate statistical analysis for DUP is not straightforward, since all analyses have their advantages and disadvantages. The ordinal logistic regression analysis was chosen because it has the easiest interpretation.

Several sensitivity analyses were conducted to determine the robustness of our conclusions. One sensitivity analysis investigated the effect of an additional category of "negative DUP". This analysis confirmed that first generation migration status and age at onset of the psychotic disorder are significantly associated with DUP, but did not confirm the association between gender and DUP. However, the assumption of proportionality was violated. This makes it difficult to value the results of this analysis. Another sensitivity analysis included patients with a calculated DUP exceeding the duration of the first psychotic episode. This analysis did not alter our conclusions.

#### **4.4. Strengths and limitations**

A major strength of this study is the large sample size and its representativeness for the treated prevalence of non-affective psychotic disorders. Concerning generalizability however, it is important to keep in mind that the included patients differed significantly from the excluded patients concerning age at onset and illness duration. Other strengths are the standardized instruments that were used and the use of a statistical model that takes into account the effect of other candidate factors. Using a categorical approach allowed inclusion of a number of patients with a very long DUP, which tend to get excluded in other studies. A limitation in all studies in which DUP is assessed, is that DUP is defined retrospectively and that data collection relies on self-reports. Also, we could not evaluate the contribution of “type of onset of the psychotic disorder” – a factor reported to be associated with DUP (Morgan et al., 2006; Compton et al., 2008). Furthermore, it would be of interest to explore whether ethnicity plays part in the association between DUP and migration status. This exploration could not be done within this study, because small numbers of the different ethnic groups precluded separate analyses.

#### **4.5 Implications**

Identifying factors contributing to a delayed identification of patients and a delayed start of treatment may be important, because it can give direction to early detection and early intervention initiatives. Although research into early detection programs is still sparse, the TIPS (Early Treatment and Intervention in First Episode Psychosis) researchers from Norway have demonstrated that reducing DUP is possible and that this might produce favorable long term improvements (Melle et al., 2004; Hegelstad et al., 2012).

The findings presented in this paper suggest that the process involved in men’s help seeking behaviour deserves attention. Furthermore, the association we found between migration status and DUP may be of major importance in countries like the Netherlands, where immigrants constitute more than one fifth of the population (Centraal Bureau voor de Statistiek, 2013). Future research should aim to explore the explanations for this association and how to design interventions to shorten treatment delay.

#### **4.6. Conclusions**

In this study, it was shown that DUP was longer for patients being younger at onset of the psychotic disorder, for first generation immigrant patients and probably also for male patients. Further research is warranted to detect what explains these associations and what interventions are needed to shorten DUP and thereby possibly improve prognosis. In our large non-affective psychotic sample, educational level and premorbid adjustment were not significantly associated with DUP.

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