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# Prediction of a single psychotic episode: A 7.5-year, prospective study in first-episode psychosis

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ABSTRACT

*Background:* Around 20% of patients who suffer from psychosis will experience a single psychotic episode (SPE), but relatively little is known about the characteristics and predictors for this group of patients. This study sought to: 1) characterise the subgroup of first-episode psychosis (FEP) patients who experienced a SPE over a 7.5-year follow-up; and 2) to identify significant predictors for this subgroup independent of potential confounders.
*Methods:* A representative sample of 413 FEP patients treated at a specialist early psychosis service were assessed at baseline and followed-up for 7.5 years. Binary logistic regression models were employed to investigate univariate and adjusted associations between baseline predictors and experiencing a SPE. Results were adjusted for the influence of known prognostic factors for psychosis.
*Results:* Follow-up data was available for 274 participants. Forty-six (16.5%) achieved clinical remission and experienced no recurrence over the follow-up period. Duration of untreated psychosis (DUP) shorter than 60 days (OR = 3.89, $p = 0.007$), more rapid response to antipsychotic treatment (OR = 0.33, $p = 0.019$) and no parental loss (OR = 5.25, $p = 0.045$) significantly predicted a SPE. The association remained significant after controlling for potential confounders.
*Conclusions:* Early treatment (within two months of onset of psychotic symptoms) and social support significantly reduce vulnerability to subsequent psychotic episodes. Future studies need to investigate the interplay between biological factors (i.e. sensitized dopaminergic system), environmental variables (i.e. exposure to trauma, stigma and discrimination), and psychological attributes (i.e. cognitive schemata) in order to elucidate the processes underlying the vulnerability to recurrent psychotic episodes.



## 1. Introduction

Despite previous longitudinal studies showing that around 20% of patients who suffer from psychotic disorders will only experience one psychotic episode (Linszen et al., 2001; Shepherd et al., 1989; Wiersma et al., 1998), little research has been dedicated to identifying this subgroup of patients. There are many potential benefits to both research and clinical practice in establishing the factors associated with only experiencing a single psychotic episode (SPE). Firstly, the identification of a separate group of patients who achieve clinical remission with a non-relapsing course of illness may enable more benign treatment approaches tailored to this subgroup's particular needs, minimizing side effects associated with prolonged

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exposure to antipsychotic medication (Alvarez-Jimenez et al., 2008, 2009a,b; an der Heiden and Hafner, 2000; Bola and Mosher, 2002; Carpenter and Heinrichs, 1981). Secondly, establishing treatment and environmental factors that have an effect on the long-term course of the illness would shed light on modifiable prognostic characteristics. This would, in turn, inform public health policies and the development of novel therapies targeting these factors (van Os and Kapur, 2009).

A study that aims to discriminate factors associated with experiencing a SPE from potential confounders needs to meet strict methodological criteria. Firstly, a prospective first-episode psychosis (FEP) study is necessary in which participants are recruited and assessed at first treatment contact, free from the confounding effects of previous treatment interventions or secondary morbidity (Ram et al., 1992). Secondly, such a study should include recruitment of an incident, multi-diagnostic FEP cohort, as opposed to convenience samples of limited diagnostic range which are likely to create selection biases that impede generalizability of the findings to 'real world' settings (Henry et al., 2007). Thirdly, the study should be properly powered to investigate the influence of relevant predictors independent of potential confounders. Finally, the duration of follow-up should extend beyond the critical period (i.e. the first 5 years after the onset of psychosis) after which the level of disability sustained, or recovery achieved, is thought to endure into the long-term (Birchwood et al., 1998; Crumlish et al., 2009).

Only a few longitudinal FEP studies have conducted prospective assessments beyond 5 years; however they have exclusively focused on patients with schizophrenia (an der Heiden and Hafner, 2000; Breier et al., 1991; Mason et al., 1995; Munk-Jorgensen and Mortensen, 1989; Wiersma et al., 1998), recruited convenience or small samples of newly admitted inpatients (Bottlender et al., 2003; Carpenter and Strauss, 1991; Linszen et al., 2001), or they have examined predictors of recovery without isolating the subset of patients who only experience one psychotic episode (Crumlish et al., 2009; Robinson et al., 2004) or controlling for potential confounders (Robinson et al., 2004). To date, no single study has reliably characterized the group of patients who only experience one psychotic episode or identified prognostic factors for this subgroup independent of potential confounders.

In the present study we recruited a large, epidemiologically representative cohort of FEP patients presenting at a specialized FEP service followed them up over a 7.5-year period. We sought to: 1) characterise the subgroup of FEP patients who experienced a SPE; 2) identify independent predictors of SPE after controlling for potential confounders; and 3) evaluate an hypothesised model of the relationships between relevant predictive factors and experiencing a SPE.

## 2. Methods

### 2.1. Design and setting

The study participants were recruited into the Early Psychosis Prevention and Intervention Centre (EPPIC) long-term follow-up study, a longitudinal 7.5-year follow-up study of consecutive FEP patients admitted into EPPIC. The EPPIC programme is a front-line, youth-orientated, specialist mental health programme which provides comprehensive, community-based treatment for FEP patients originating from a geographically defined catchment area in metropolitan Melbourne, Australia with a population of approximately 800,000 (McGorry et al., 1996). All other publicly funded mental health services in the area refer their FEP patients to EPPIC. There are very few private psychiatric services in the area, including no private psychiatric inpatients services. Full details of the EPPIC long-term follow-up study design, sampling strategy, attrition and follow-up are available elsewhere (Henry et al., 2007, 2010).

### 2.2. Sample and procedure

Patients from the EPPIC programme were recruited between April 1993 and July 1997. Inclusion criteria for entry to the study were: 1) aged between 15 and 30 years; 2) a DSM-III-R (APA, 1987) and from 1995, a DSM-IV (APA, 1994) diagnosis of a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar psychotic disorder, major depressive disorder with psychotic features, brief reactive psychosis/brief psychosis and psychosis not otherwise specified); 3) informed consent for research participation; 4) living in the geographical catchment of the EPPIC service; 5) adequate English-language comprehension; and 6) experienced the first treated episode of psychosis with less than 6 months of prior neuroleptic medication. Exclusion criteria were: 1) primary organic mental syndrome; 2) intellectual disability; 3) drug and/or alcohol induced psychosis; and 4) epilepsy. Assessments were conducted at multiple time points including: within the first few days following entry into treatment (index presentation; T1); at the time of symptom remission or stabilization (median 8.9 weeks after index presentation; T2); approximately 6 months after stabilization (T3); 12 months after stabilization (T3); and a median 7.5 years after index presentation (T4). All assessments were conducted by interviewers with graduate psychology qualifications, who received specific training in the administration of all instruments, and ongoing supervision to maintain reliability and consistency. Very good to excellent inter-rater reliability was found for baseline measures including DSM diagnosis of schizophrenia (kappa = 0.92) and the onset and duration of symptoms (mean kappa = 0.79). Inter-rater reliability for the primary outcome variables at T4 was assessed by calculating the percentage of discrepancies between raters, with only 2% of ratings found to be discrepant (Henry et al., 2007). Raters were blind to diagnostic information and clinical ratings from previous assessments. The study was approved by relevant institutional human research ethics committees.

### 2.3. Measures

#### 2.3.1. Number of psychotic episodes

The main outcome variable was dichotomized into 'experienced a SPE' vs. 'experienced continuous or recurrent psychosis'. A psychotic episode was defined as a discrete period of symptomatology characterized by psychotic signs and symptoms of hallucinations, delusions, cognitive disorganization, marked psychomotor disturbance, and/or grossly inappropriate behaviour. Patients were classified as 'experienced a SPE' if they: 1) experienced only one discrete psychotic episode with a duration not exceeding 12 months over the 7.5-year follow-up period (i.e. no recurrence); and 2) achieved complete remission