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Further examination of the reducing transition rate in ultra high risk for psychosis samples: The possible role of earlier intervention

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ABSTRACT

Background: The rate of transition to psychotic disorder in ultra high risk (UHR) patients has declined in recent cohorts. The reasons for this are unclear, but may include a lead-time bias, earlier intervention, a change in clinical characteristics of cohorts, and treatment changes.
Aims: In this paper we examined the two possibilities related to reduction in duration of symptoms prior to clinic entry, i.e., lead-time bias and earlier intervention.
Method: The sample consisted of all UHR research participants seen at the PACE clinic, Melbourne between 1993 and 2006 ($N = 416$), followed for a mean of 7.5 years (the 'PACE 400' cohort). Duration of symptoms was analysed by four baseline year time periods. Analysis of transition rate by duration of symptoms was restricted to more homogenous sub-samples (pre-1998 and pre-2001) in order to minimize confounding effects of change in patient characteristics or treatments. These cohorts were divided into those with a short and long duration of symptoms using a cut-point approach.
Results: Duration of symptoms prior to entry did not reduce significantly between 1993 and 2006 ($p = 0.10$). The group with a short duration of symptoms showed lower transition rates and did not catch up in transition rate compared to the long duration of symptoms group.
Discussion: These data suggest that, while earlier intervention or lead-time bias do not fully account for the declining transition rate in UHR cohorts, it appears that earlier intervention may have exerted a stronger influence on this decline than length of follow-up period (lead-time bias).

1. Introduction

The development of criteria for identifying help-seeking young people at risk of schizophrenia and other psychotic disorders has introduced a potent paradigm for researching risk factors, illness biomarkers and pathogenetic mechanisms, as well as conducting preventive intervention trials (Fusar-Poli et al. 2013; Yung et al. 2012a). These "ultra high risk" (UHR) criteria, also referred to as "clinical high risk" or "prodromal" criteria, are based around attenuated positive psychotic symptoms, brief psychotic symptoms and trait vulnerability due to schizotypal personality disorder or family history of psychotic disorder (Yung et al. 1996; Yung et al. 2003; Yung et al. 2004), in addition to being help-seeking and in the adolescent to young adult age range (the highest period of risk for psychosis).

The UHR criteria have been widely used (Cannon et al. 2008; McGlashan et al. 2007) with rates of psychosis onset ("transition" or "conversion") found to range between 8 and 54% within 1–2.5 years (Cannon et al. 2008; Cornblatt et al. 2003; Mason et al. 2004; Miller et al. 2002; Morrison et al. 2012; Ruhrmann et al. 2003; Ruhrmann et al. 2010; Yung et al. 2003). However, there is evidence of a decline in transition rates in more recent UHR cohorts with rates as low as 8–28% in one year (Amminger et al. 2010; Demjaha et al. 2012; Morrison et al. 2012; Simon and Umbricht; Velthorst et al. 2009; Yung et al. 2007). Consistent with this, a recent meta-analysis indicated a significant relationship between transition rates and year of journal article publication, with more recent publications reporting lower transition rates (Fusar-Poli et al. 2012). In our medium to long-term follow-up study of 416 UHR cases ("PACE 400"; Nelson et al. 2013) recruited over a 13 year period (1993–2006) we found a strong effect of more recent cohorts having a lower transition rate than older cohorts, consistent with an earlier publication from our group (Yung et al. 2007). We argued that there may be multiple (possibly overlapping) reasons for

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this. The first two of these reasons relate to reduction in duration of symptoms prior to clinic entry.

1. Lead-time bias. This refers to patients in more recent cohorts possibly being referred to treatment earlier in the course of their symptoms and therefore requiring a longer observation or follow-up period to register transitioned cases. The shorter "window of observation" would give the false impression of more recent cohorts having lower transition rates. This implies that extending this window of observation by following patients from recent cohorts for a longer period of time may reveal comparable transition rates to earlier cohorts.
2. Earlier intervention. A shorter duration of symptoms prior to entry in more recent cohorts may have allowed intervention to be *more effective* in delaying or preventing transition to psychosis, consistent with the clinical staging model in psychiatry (McGorry et al. 2006).
3. Change in sample characteristics. More recent cohorts may inherently be at lower risk of psychosis due to differences in clinical characteristics of UHR cohorts over the years (e.g., symptom dimensions, neurocognitive functioning, etc.). This may be related in part to sampling patterns associated with referral pathways and identification approaches (Fusar-Poli et al. 2015; Wiltink et al. 2015).
4. Treatment changes. It is possible that standard treatment for UHR patients has become more effective over the years in delaying or preventing transition to psychosis.

There has been considerable discussion in the literature about the issue of the declining transition rate in high risk samples with regards to implications for the validity of the UHR criteria (van Os and Linscott 2012), for effectively researching pathogenetic mechanisms driving psychosis onset (Nelson et al. 2014a, 2014b), the proposal to include Attenuated Psychosis Syndrome in the DSM-5 (Yung et al. 2012b), and for the identification of sufficiently enriched samples for preventive intervention trials (McGorry et al. 2009). A central limitation noted in several recent UHR intervention trials has been the reasonably low transition rates in the treatment groups being compared (McGorry et al. 2013b; Morrison et al. 2012). It is important to understand the reasons for the reducing transition rate as this will assist in introducing measures to enrich UHR samples.

The purpose of the current report is to use the PACE 400 data set to examine the plausibility of the first two reasons listed above (lead time bias and earlier intervention) and to examine which of these two possibilities might be more likely to be influencing the transition rate. The analytic approach is exploratory rather than hypothesis driven. We have used the same data set to examine the third reason (change in clinical characteristics of the samples) in another report (Hartmann et al. 2016). This analysis indicated that although there was some change in clinical characteristics over the years (greater array of attenuated psychotic symptoms and higher thought disorder in earlier cohorts) this was not substantial enough to fully account for the declining transition rate. Also, a previous report from our group indicated that a reduction in duration of symptoms prior to clinic entry may play a role in the reducing transition rate (Yung et al. 2007). We therefore decided to examine the first two possibilities listed above, both of which are related to a possible reduction in duration of symptoms prior to clinic entry, in greater detail. This paper extends on the previous report from our group (Yung et al. 2007) by using a larger sample with a substantially longer follow-up time. Reason four (change in treatment) will be the subject of future work.

2. Method

2.1. Setting and sample

Full details of the PACE 400 study are provided in Nelson et al. (2013). The PACE clinic is a specialist clinic for UHR patients. The catchment area of the service includes northwestern metropolitan Melbourne, Australia. The age range accepted to PACE over the time period of the baseline studies was 15–30 years. Young people are accepted to PACE if they meet criteria for at least one of three UHR groups: Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS) and Trait groups (see Nelson et al. 2013). Exclusion criteria for PACE are presence of a current or past psychotic disorder, known organic cause for presentation, and past neuroleptic exposure equivalent to a total continuous haloperidol dose of >15 mg.

The sample consisted of all UHR patients who participated in studies at the PACE clinic between 1993 and 2006 ($N = 416$). Seven studies - three intervention (Berger et al. 2012; McGorry et al. 2002; Yung et al. 2011) and four cohort (Phillips et al. 2009; Thompson et al. 2007; Yung et al. 1996; Yung et al. 2003) studies - were conducted over this period.

2.2. Measures

2.2.1. UHR status

From 1993 to 1999 UHR status at baseline was assessed using both the Brief Psychiatric Rating Scale (BPRS)/Comprehensive Assessment of Symptoms and History (CASH)/Global Assessment of Functioning (GAF) method (Yung et al. 1996; Yung et al. 2003) and the Comprehensive Assessment of At Risk Mental States (CAARMS)/GAF method (Yung et al. 2005) while the concurrent validity of the CAARMS was being established. From 1999 the CAARMS replaced the BPRS/CASH as the means of establishing UHR status.

2.2.2. Outcome measures

Psychosis status: The main outcome of interest was transition to psychotic disorder. This was defined as at least one fully positive psychotic symptom several times a week for over one week. From 1993 to 1999 psychosis threshold was determined using both the BPRS/CASH and the CAARMS while the concurrent validity of the CAARMS was being established. From 1999 the CAARMS replaced the BPRS/CASH for determination of psychosis status. The CAARMS allows intensity, conviction, frequency, recency and duration of symptoms to be assessed using one instrument and has well-defined anchor points. The CAARMS has good to excellent reliability (Yung et al. 2005). If CAARMS data were not available for determination of psychosis status (e.g., due to not being able to locate the participant), then the State public mental health records were accessed.

2.2.3. Baseline variables

A range of clinical, neurocognitive and neurobiological assessments were conducted in this cohort (see (Nelson et al. 2013) for full details). "Duration of symptoms prior to treatment" refers to the duration between the first noted change from premorbid state, retrospectively determined using all available information (self report and informant report), and date of acceptance into the PACE clinic, as per our previous research (Nelson et al. 2013; Yung et al. 2007). Accordingly, the variable is more inclusive than attenuated psychotic symptoms – it refers to the onset of any psychiatric symptoms that eventually led to referral to the PACE clinic, in line with the fact that the early stage of the psychosis prodrome tends to be characterized by non-specific symptomatology, including mood disturbance, anxiety and basic symptoms. The CAARMS (Yung et al. 2005) was used to operationalise this variable, as per our previous research. If accounts of first onset of any psychiatric symptom varied between patient and informant (generally, family members), then the patient estimation was used, given that patients themselves can more accurately provide the date of first subjective change and that insight is not generally impaired in this cohort (Yung et al. 2007). Psychosocial functioning was measured using the Global Assessment of Functioning (GAF; APA, 1994) and the Quality of Life Scale (QLS; Heinrichs et al. 1984). Baseline year was divided into four time periods, as per previous analyses: 1993–1997, 1998–2000, 2001–2003 and 2004–2006. The aim was to have time periods equally spaced but with

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