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Declining transition rates to psychotic disorder in "ultra-high risk" clients: Investigation of a dilution effect

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ABSTRACT

During recent years, a decrease has been noted in the rate of transition of ultra-high risk (UHR) clients to a psychotic disorder. Although important to the concept of the at-risk mental state, the reasons for this decline remain largely unknown. We investigated the possibility of a 'dilution effect' in contributing to the decline, i.e. if later UHR cohorts present with less severe clinical intake characteristics than earlier cohorts.

Firstly, clinical intake characteristics of a large UHR sample (n = 397) were compared across baseline year epochs (1995–2006). Characteristics showing significant differences were included in a Cox-regression to examine if they could explain the decline in transition rates. Secondly, because later cohorts show lower transition rates, 'more stringent' UHR-criteria were retrospectively applied to these cohorts (post-2000, n = 219), investigating if this resulted in a higher transition rate.

Results indicated that earlier cohorts presented with (1) a larger array of attenuated psychotic symptoms, (2) higher ratings on conceptual disorganization (formal thought disorder) and (3) a higher proportion of individuals with trait risk factor (all $P < .001$). However, these factors could not fully account for the decline in transition rates. Applying more stringent UHR-criteria to the post-2000-subsample did not substantially change the rate of transition.

Our study suggests that later UHR cohorts presented with different clinical intake characteristics than earlier cohorts. While this may have contributed to the observed decrease in transition rates to psychosis, it does not appear to fully account for this decline, suggesting other factors have also impacted on transition rates over time.

1. Introduction

During the mid-1990s, substantial research attention was directed towards the development of criteria enabling the reliable identification of young individuals at 'ultra-high risk' (UHR) for a psychotic disorder (Miller et al., 2002; Yung et al., 1996; Yung et al., 2003). The resulting criteria, applying to help-seeking young individuals, require the presence of at least one of the following clinical presentations: attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS, i.e., full-blown psychotic symptoms that resolve within a week without treatment), or a trait risk factor (schizotypal personality disorder or having a first-degree relative with a psychotic disorder), in addition to a marked decrease in functioning or chronic low functioning. These criteria are assessed using semi-structured interviews specifically developed for this purpose, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al., 2005) and the Structural Interview of Prodromal Symptoms (SIPS, Miller et al., 2003).

In the initial years of applying these criteria, approximately 40% of those identified as UHR subsequently developed a first-episode psychosis (FEP; referred to as "transition" or "conversion") within 12 to 30 months (Cannon et al., 2008; Mason et al., 2004; Miller et al., 2002; Yung et al., 2003). However, a steady decrease in transition rates of UHR clients has been observed across continents and institutions, declining to a 12-month rate of approximately 15% (Nelson et al., 2013; Simon and Umbricht, 2010; Simon et al., 2014; Yung et al., 2006; Yung et al., 2007; Ziermans et al., 2011). This decrease has also been empirically verified in a meta-analysis (Fusar-Poli et al., 2012).

Labelling and treating individuals as being at 'high risk' for psychosis (Keith and Matthews, 1991; McGlashan et al., 2007; Miller et al., 2002), when in fact they may never be at increased risk of developing a psychotic disorder, is a contentious issue (Carpenter, 2009; Ruhrmann et al., 2010; Woods et al., 2009; Yung et al., 2010a; Yung et al., 2010b).

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Although these young individuals are distressed and help-seeking, calling for early intervention and preventive treatment, they may not be at risk for psychosis specifically (Lin et al., 2015). Therefore, it is crucial to identify the factors underlying the apparent decline in transition rates.

It has been argued that the decline could be explained by (i) a treatment effect (an improvement in clinical care provided to the UHR population reducing the transition rate) (Fusar-Poli et al., 2012; Nelson et al., 2013; Simon et al., 2014; Wiltink et al., 2015; Yung et al., 2007); (ii) a length time bias (an individual briefly meets the UHR criteria, but symptoms resolve quickly: he/she never would have met the criteria if assessed at a later point) (Yung et al., 2007); (iii) a lead time bias (increased community awareness of the concept of an at-risk state driving referrals to specialized services *earlier* in the illness course) (Nelson et al., 2013; Yung et al., 2007); and/or (iv) a combination of the latter two (improved care at an earlier stage of illness). Evidence for these hypotheses stems from studies showing that duration of symptoms prior to first contact with a clinical service has decreased over the years (Yung et al., 2007) and transition rates appear to be lower in individuals engaging in specific focused interventions (i.e., psychological therapy or antipsychotic medication) (Fusar-Poli et al., 2012). While these factors certainly contribute to the decline in transition rates to psychosis, they do not appear to fully account for it (Nelson et al., 2013).

As the concept of at-risk mental states has gained extensive community awareness over the years, the so-called dilution effect has been postulated (Yung et al., 2007). An increased attentiveness to at-risk mental states may have been associated with less selective referral patterns, leading in turn to a possible 'dilution' of the pool of young people who are screened using the UHR criteria (Nelson et al., 2013; Wiltink et al., 2015; Yung et al., 2007). Such a dilution increases the probability that individuals are included who will not develop psychosis, the 'false positives' (Fusar-Poli et al., 2012; Nelson et al., 2013; Yung et al., 2007). The present study builds on these ideas we first articulated in 2007 (Yung et al., 2007). It seeks to systematically investigate the influence of a possible dilution effect on the decline in transition rates by examining the clinical intake characteristics of UHR clients across earlier and later cohorts. Specifically, the present study aimed to answer the following questions:

(1) Do later UHR cohorts show less severe clinical characteristics at intake in terms of number and intensity of APS, level of general functioning, and presence of trait risk factor for psychotic illness compared to earlier cohorts? If so, do these contribute to explaining the drop of transition rates over the years?
(2) Would the transition rates of later cohorts be higher and comparable to earlier cohorts if more stringent criteria (requiring higher intensity and frequency ratings for APS in order to obtain UHR status) were applied retrospectively?

2. Materials and methods

2.1. Setting and sample

The sample comprised a cohort of young people referred to as the 'PACE 400' cohort and previously described in Nelson et al. (2013). This cohort consists of young individuals attending the UHR-specialized PACE Clinic (Melbourne, Australia) and participating in one of seven research studies (Berger et al., 2012; McGorry et al., 2002; Phillips et al., 2009; Thompson et al., 2007; Yung et al., 1996; Yung et al., 2011; Yung et al., 2003) conducted between 1995 and 2006 in this centre. All research studies were approved by the local ethics committee and written informed consent was obtained before study enrolment. Help-seeking young people were accepted into the clinic if they were aged between 15 and 30 years and met at least one of the three UHR groups (i.e. APS, BLIPS, Trait; see Table 1). Exclusion criteria for PACE are a past or current psychotic episode, past neuroleptic exposure corresponding to a total continuous dose of more than 15 mg of haloperidol, or a known organic cause for presentation. For a detailed description of the sample, see Nelson et al. (2013).

To investigate whether more stringent criteria applied retrospectively to later cohorts result in transition rates similar to those of earlier cohorts (Aim 2), only individuals allocated to PACE using the most recent version of the CAARMS, introduced in 2000, were selected ('post-2000 subsample').

2.2. Procedure

UHR status and clinical intake characteristics were assessed upon intake to the PACE clinic. UHR individuals were divided into four groups according to their year of entry to PACE: 1995–1997, 1998–2000, 2001–2003, and 2004–2006 (see Nelson et al., 2013). This grouping produced equally spaced periods with an adequate number of participants in each period and is herein referred to as baseline year epoch.

Transition status was ascertained as far as possible for all participants at follow-up (see Nelson et al. (2013) for full details of the procedure of transition ascertainment). Transition to psychosis was defined as the presence of one full positive psychotic symptom daily for at least one week, as assessed with the CAARMS; if no CAARMS data were available, state public mental health records were consulted.

2.3. Measures

2.3.1. UHR status

The Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), a semi-structured interview designed to assess UHR criteria, was used in conjunction with the Global Assessment of Functioning (GAF) (Jones et al., 1995) to establish UHR and transition status (see Table 1, third column, for an overview of the UHR criteria). The more stringent criteria were determined a priori by the researchers and applied retrospectively to post-2000 cohorts (Aim 2). They are shown in the fourth column of Table 1. These more stringent criteria required higher intensity and frequency ratings for APS in order to obtain UHR status (see Section 2.3.2.1).

2.3.2. Clinical characteristics at intake

2.3.2.1. Attenuated psychotic symptoms (APS). Attenuated psychotic symptoms were assessed using the CAARMS subscales 'disorders of thought content' (TC), 'perceptual abnormalities' (PA), and 'conceptual disorganization' (CD). The variable 'intensity of APS' ranged from 0 (not present) to 4 (severe) for TC, PA and CD. There was a change in CAARMS scoring when a new version was introduced in 2000. In order to make the two versions compatible for joint analyses for Aim 1, the post-2000 'intensity' score (0–6) was converted into the old CAARMS conviction scale (0–4).

The variable 'number of APS' ranged from 0 to 3, with 0 indicating the absence of any APS and 3 the presence of all three APS (TC, PA, and CD) in an individual participant. The absence of a symptom to a clinically significant degree on each of the three APS subscales was defined as low intensity rating (0–2) and presence as high intensity rating (3–4). The number of APS was computed using this definition.

2.3.2.2. General functioning. General functioning was assessed using the GAF (Jones et al., 1995) resulting in scores ranging from 0 to 100.

2.3.2.3. Trait risk factor. Family history (first degree) of psychosis was assessed using a shortened version of the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), while the presence of schizotypal personality disorder was defined according to DSM-IV (American Psychiatric Association, 2000). This variable was dichotomous (yes/no).