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Why transition risk to psychosis is not declining at the OASIS ultra high risk service: The hidden role of stable pretest risk enrichment

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ABSTRACT

Background: The reason for declining risk to psychosis across individuals assessed and meeting Ultra High Risk (UHR) criteria is still unclear. No studies have investigated the potential substantial role of the underlying risk enrichment across all the individuals undergoing an UHR assessment.
Methods: Cohort study including all non-psychotic subjects who were assessed on suspicion of psychosis risk by the OASIS UHR service in the period 2001 to 2015. Posttest (after UHR assessment) and pretest risk (before UHR assessment) of psychosis were stratified and compared across three time periods (2001–2005, 2006–2010, 2011–2015) with Cox analysis and modulating factors were investigated.
Results: The posttest risk of psychosis at the OASIS service has increased from the initial pilot years of the service (2001–2005) and then stabilised and not declined over the following decade (2006–2010 and 2011–2015). This was paralleled by a similar course of pretest risk for psychosis. Stability of pretest risk for psychosis over the past decade was associated with a lack of change in ethnicity and to counterweighting changes in the type of referral sources over different time periods.
Conclusions: The time course of transition risk to psychosis in UHR services is strictly associated with the time course of pretest risk enrichment. If the latter remains stable over time, as for the OASIS service, no declining transition risk is observed over the most recent years. Pretest risk enrichment is determined by recruitment and sampling strategies. This study confirms the need to control these factors in the UHR field.

1. Introduction

The prevention of psychosis has become clinically feasible due to the introduction of the Ultra High Risk (UHR hereafter) construct (Fusar-Poli et al., 2015a) to reliably identify young individuals who are at heightened risk for the development of psychotic disorders (Fusar-Poli and Schultze-Lutter, 2016) - mostly schizophrenia spectrum disorders (Fusar-Poli et al., 2013a) - over the following few years (Kempton et al., 2015). Conversely, there is no evidence that individuals meeting UHR criteria are at increased risk of developing new and incidental non-psychotic disorders compared to individuals assessed for an UHR state but not meeting criteria (Fusar-Poli et al., 2016c; Webb et al., 2015). The meta-analytical prognostic accuracy of the UHR designation is considered good (AUC at 38 months = 0.9) (Fusar-Poli et al., 2015a) and comparable to other preventative approaches in medicine (Fusar Poli et al., 2014). However, declining transition risks from an UHR state to psychosis over recent years has put the field into question. The two-year risk of transition to psychosis from an initial UHR state has shifted from an early 30% (Fusar-Poli et al., 2012) to the current 20% (see Table 4 in Fusar-Poli et al. (2016a)). Declining transition risk is concerning because it can undermine the clinical significance of preventative detection (Fusar-Poli, 2017c) and treatment, yielding negative findings (Fusar-Poli, 2017b). Understanding the reason for declining transition risk is of paramount relevance to overcome these limitations. Earlier studies had suggested that declining transition risk in UHR samples may be due to the fact that treatments were more effective (treatment effect). However, with the largest randomized controlled trials in UHR individuals yielding negative findings (Fusar-Poli, 2017b), there is no strong evidence indicating that the recommended preventative treatments are effective in preventing psychosis (Morrison et al., 2012). In fact, recent studies concluded that treatment effect (Nelson et al., 2016) cannot fully account for the observed decline in transition risks. Another line of research has suggested that the declining transition risk may be due to a dilution effect (Hartmann et al., 2016) i.e. finding more false positives despite individuals meeting the initial UHR criteria (dilution effect) (Yung et al., 2007). The dilution effect was only partially explained by different clinical characteristics of the UHR samples at

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intake over time periods (Hartmann et al., 2016). While these studies have been entirely focused on transition risk in individuals who meet the UHR criteria (posttest risk), no studies have investigated whether the dilution effect is secondary to a change in the level of risk enrichment of the entire pool of individuals undergoing an UHR assessment (pretest risk, for explanatory details see Fusar-Poli and Schultze-Lutter (2016)). The strong association between pretest risk enrichment and observed transition risk in UHR samples is an established finding and has been confirmed in all UHR samples worldwide (Fusar-Poli et al., 2016d; Fusar-Poli et al., 2016f). Since the prognostic accuracy of the UHR criteria depends on the pretest risk of the sample to which they are being applied (Fusar-Poli, 2017a), it is possible that changes of transition risk over time may parallel changes in the underlying pretest risk of the samples undergoing UHR assessment. Furthermore, the changes in pretest risk enrichment of individuals undergoing an UHR assessment are in turn modulated by outreach campaigns of clinical services, recruitment strategies (Fusar-Poli et al., 2016f) and referral pathways (Fusar-Poli et al., 2016d).

In this study, we first hypothesized that the changes in posttest transition risk over time would be determined by changes in pretest risk over time. To test this hypothesis, we stratified the course of posttest and pretest transition risk over the same fifteen-year referral period in the entire pool of individuals who were undergoing an UHR assessment at the Outreach and Support in South London (OASIS) UHR service (Fusar-Poli et al., 2013b), and addressed the relationship between pretest and posttest risk of psychosis. Our second aim was to investigate potential sociodemographic and referral pathway factors (Fusar-Poli et al., 2016d) that may account for any changes in pretest psychosis risk enrichment over different time periods.

2. Methods

2.1. Sample

We included all non-psychotic individuals who were assessed on suspicion of psychosis risk by the OASIS UHR service (Fusar-Poli et al., 2013b). All subjects referred to the OASIS in the period 2001 to 2015 were initially considered eligible. We then excluded those who were referred but never assessed by the team, and those who were already psychotic at baseline. The remaining sample was therefore composed of all non-psychotic subjects undergoing a Comprehensive Assessment of At Risk Mental States (CAARMS)-based UHR assessment (Yung et al., 2005) at the OASIS. Details of the clinical care received at the OASIS service have been described elsewhere (Fusar-Poli et al., 2015b).

2.2. Procedure

This was a clinical register-based cohort study. Measures of interest were automatically extracted with the use of the Clinical Record Interactive Search (CRIS) tool (Stewart et al., 2009). CRIS is a case register system that provides anonymized information from electronic clinical records, which are documented by professionals involved in each patient's clinical care relating to mental health care services across South London and the Maudsley (SLaM). SLaM is a National Health Service (NHS) mental health trust that provides secondary mental health care to a population of roughly 1.3 million residents of four London boroughs, namely, Lambeth, Southwark, Lewisham and Croydon. The OASIS team is part of SLaM, which has a near-monopoly in terms of secondary mental health care provision to its local catchment area. Also, it is a legal requirement for SLaM healthcare professionals to keep these records up to date (Stewart et al., 2009). Because the CRIS model draws directly from these electronic health records, it provides valuable 'real-world' and 'real-time' information on routine mental health care (Perera et al., 2016). Ethical approval for the study was granted by the Oxfordshire Research Ethics Committee C (reference 08/H0606/71 + 5) (Stewart et al., 2009).

2.3. Study measures

The primary measure of interest for the current study was the pretest and posttest risk of developing psychosis, stratified across referral periods. Pretest risk of psychosis was measured across the entire pool of individuals who were undergoing UHR assessment at the OASIS (for explanatory details see Fusar-Poli and Schultze-Lutter (2016)). Posttest risk of psychosis was measured within those individuals who met the UHR criteria post-assessment (for explanatory details see Fusar-Poli and Schultze-Lutter (2016)). Psychosis onset was defined by the presence of ICD-10 (WHO, 1990) diagnosis of psychotic disorders in the CRIS electronic clinical records. Time to diagnosis of a psychotic disorder was measured from the date of first referral to OASIS, censored at February 1, 2016, and was truncated at a maximum of 5-year follow-up to mitigate the potential differences in follow-up time across the referral periods. The referral period was categorized into three 5-year groups (2001–2005, 2006–2010, 2011–2015). The first group, 2001–2005, corresponded to the early setup period of the OASIS (for details see Fusar-Poli et al. (2013b)). In addition, secondary measures included ethnicity and source of referral as previously defined (Fusar-Poli et al., 2016d).

2.4. Statistical analysis

Sociodemographic characteristics of the sample were described with means and standard deviations for continuous variables and absolute and relative frequencies for categorical variables. The impact of referral period on posttest risk of psychosis and pretest risk of psychosis (first aim) was investigated using Cox proportional hazards models, which evaluated the effects of referral period on psychosis onset and time to transition, after checking for proportional hazards assumption (Grambsch and Therneau, 1994). The relationship between pretest and posttest risk of psychosis onset (first aim) was formally investigated with a regression of the individualized 5-year posttest risk estimates, on the 5-year pretest risk estimates. The association of ethnicity and source of referral with the referral period (second aim) was investigated and contingency tables reported the standardized adjusted residuals with an alpha corrected at 0.001 to account for multiple comparisons (which corresponded to a value of ± 2.58 for the adjusted standardized residuals). All analyses were conducted in STATA 13 (STATA Corp., TX, USA).

3. Results

3.1. Sociodemographic and clinical characteristics of the sample

From 2001 to 2015, a total of 1115 subjects were referred to the OASIS clinic for UHR assessment. Among them, 125 subjects did not undergo the UHR assessment and had no contact with the OASIS service. An additional 280 subjects were already psychotic at baseline (the clinical fate of these subjects is described elsewhere (Fusar-Poli et al., 2016b)). Therefore, a final sample of 710 non-psychotic subjects who underwent UHR assessment was used in the current study (Table 1).

The mean follow-up was 1472 days (median 1181, range 8–5015). The average age of the sample was 23 years and 56% were male. Half of the sample was of white ethnicity. The vast majority were single. Approximately one-third of referrals (34%) came from general practitioners. The Index of Multiple Deprivation (IMD) score was 32% (for details on the IMD see the Supplementary material).

3.2. Pretest and posttest risk of psychosis over referral period

There was a significant effect of referral period on the posttest risk for developing psychosis in individuals who met the UHR criteria ($X^2 = 6.19$, $P = 0.0453$) (Fig. 1 and Table 2). This was due to an increase of posttest risk of psychosis in the 2011–2015 period as compared to the 2001–2005 period. In fact, the study analysis revealed that there were

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