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# Predictive validity of clinical variables in the "at risk" for psychosis population: International comparison with results from the North American Prodrome Longitudinal Study

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ABSTRACT

*Background:* There has been recent optimism with regard to improving the predictive validity of those individuals who develop a psychotic disorder from the "Ultra High Risk" (UHR) or putatively prodromal population using combinations of clinical variables. We aimed to test the recent results from a large collaborative consortium in an independent cohort from the PACE (Personal Assistance and Clinical Evaluation) clinic in Australia.
*Method:* The North American Prodrome Longitudinal Study (NAPLS) consortium study reported 5 important clinical predictive variables within their US sample of UHR patients: genetic risk with functional decline; high unusual thought content score; high suspicion/paranoia score; low social functioning and history of substance abuse. We examined the predictive validity of these variables using data from a cohort of 104 UHR patients from the PACE clinic in Melbourne, Australia. Cox regression was used to explore the relationship between these variables at baseline and transition to psychosis by 28 months.
*Results:* Three of the five variables were found to be associated with transition in our sample: high unusual thought content scores; low functioning; and having genetic risk with functional decline. A combination of two out of three of these features produced a reasonable predictive validity (positive predictive value (PPV) 65.4%, sensitivity 37.3%, and specificity 87.2%) but with overall lower PPVs than that reported by the NAPLS consortium.
*Conclusions:* Three out of five of the identified clinical predictors for transition to psychosis from the NAPLS study were replicated in an independent sample. Using a combination of clinical variables the predictive validity of determining whether a UHR individual develops a psychotic disorder was improved above UHR criteria alone. Although psychosis prediction is improved using this model, the probability of a person not developing psychotic disorder is still quite high at 35%.



## 1. Introduction

In the mid 1990s our research group in Melbourne defined criteria that identified a group at imminent high risk of developing a psychotic disorder, such as schizophrenia, using a combination of genetic and clinical risk factors (Yung and McGorry, 1996; Yung et al., 1998, 2003) and based on a "close in" to the onset of psychosis strategy (Bell, 1992). These "Ultra High Risk" (UHR) criteria have been described in detail previously (Yung et al., 2004a) but in brief consist of three groups: (1) Attenuated Psychotic Symptoms (APS). Presence of attenuated (subthreshold for a diagnosis of a psychotic disorder) psychotic symptoms within the previous 12 months. (2) Brief Limited Intermittent Psychotic Symptoms (BLIPS): history of brief self limited psychotic symptoms which

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spontaneously resolve (within 7 days) in the previous 12 months. (3) Trait group (FH): genetic vulnerability to psychotic disorder (either schizotypal personality disorder or family history of psychotic disorder in a first degree relative) and a drop in functioning or persistent low functioning for at least one month within the previous 12 months. The initial proof of concept study in this group found a rate of first onset psychosis of 41% within a 12 month period (Yung et al., 2003). Other groups have subsequently adapted the UHR criteria (Miller et al., 2003). A review of studies using these types of criteria found that 36.7% of these individuals made a "transition" to a frank psychotic disorder within 12 months if they did not receive antipsychotic medication (Ruhrmann et al., 2003).

Despite the relative consensus in identifying and classifying the population, there appears to be some variability between research groups internationally in terms of rates of transition to psychosis (ranging from 9% to 76% across varying time periods (Ruhrmann et al., 2003, 2005)). In addition to this, our group in Melbourne (the Personal Assistance and Clinical Evaluation (PACE) clinic) has experienced a drop since 2000 in the rate of patients who have made the transition to a frank psychotic disorder, with the rates now as low as 12% over 12 months (Yung et al., 2007). The decreased transition rate was partly explained by a reduction in the duration of symptoms prior to presentation at the clinic (Yung et al., 2007). Other proposed reasons for the reduced transition rates were: treatments may be more effective at an early stage (a "time effect"); or that and more false positives were being detected who were not indeed at risk of developing psychosis (a "dilution effect"). This reduced transition rate increases the importance of "enriching" the UHR population and attempting to minimise the "false positives" by further closing in on the highest "at risk" UHR patients.

Researchers have attempted to further define risk factors in these UHR/prodromal populations in order to improve our predictive abilities and to inform treatment strategies/approaches. A study of 104 UHR individuals reported by our group investigated whether particular clinical or demographic factors in addition to the UHR criteria could be used to improve the prediction of which UHR individuals would develop a psychotic disorder (Yung et al., 2004b). Four baseline clinical predictors of transition to psychosis were identified: a combination of attenuated psychotic symptoms and genetic risk; a long duration of prodromal symptoms; poor social functioning as measured by the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994); and poor attention as measured by the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983). A model requiring the presence of at least one of these four potential predictors gave a good predictive validity with a positive predictive value (PPV) of 80.8% and a sensitivity and specificity of 60.0% and 92.6% respectively.

Other research groups have investigated the predictive validity of additional clinical variables in other UHR samples. Mason et al. (2004) reported high sensitivity and specificity of predicting transition to psychosis at 1 year in 74 individuals fulfilling UHR criteria and the addition of meeting the criteria for schizotypal disorder. They also reported that the variables of unusual thought content, magical ideation, poor role functioning, auditory hallucinations and anhedonia/asociality were the most useful additional predictors (Mason et al., 2004). However, they did not report PPVs for these additional variables. They also failed to replicate an association between the variables identified by our group at the PACE clinic in an independent sample. Lencz et al. (2004) reported high PPVs in those UHR individuals who scored particularly highly on the Scale of Prodromal Symptoms (SOPS) positive syndrome scale or on particular individual item scores in those fulfilling the Structured Interview for Prodromal Symptoms (SIPS) criteria (Lencz et al., 2004). Some authors have also proposed that "basic symptoms" or subtle, subjective clinical disturbances in several mental domains (Klosterkotter et al., 2001) might be used to supplement the UHR criteria and increase the predictive validity (Simon et al., 2006). However, there appears to be a lack of consistency in these findings and the majority of these studies were comprised of reasonably small samples.

Recently, the North American Prodrome Longitudinal Study (NAPLS) consortium (Addington et al., 2007) investigated the predictive power of a large number of variables using their pooled sample of 291 cases (Cannon et al., 2008). The NAPLS study was a multisite naturalistic study of UHR patients that enabled the investigators to examine a number of important questions regarding outcome prediction (Lencz et al., 2004). This was a particularly important study given that one of the methodological difficulties in UHR research to date has been that of small sample sizes. They found that five variables were strong predictors of transition to psychosis and that when these variables were combined the PPV was as high as 81%, without a substantial compromise in sensitivity or specificity. These predictors had substantial, but not complete, overlap with the predictors found from the earlier PACE study described earlier. A recent study from the EPOS group, again using multisite data, investigated predictors in a European sample. They reported a high positive predictive value (83.3%) for a 6 variable model that included higher positive symptoms, bizarre thinking, sleep disturbances, schizotypal personality disorder, GAF score and years of education. They also reported a different and innovative method of assessing "risk" in terms of using a prognostic index, which enables the risk of individual patients to be calculated. However, their inclusion criteria included both those who met UHR criteria as well as those who presented with cognitive "basic symptoms" (COGDIS) (Ruhrmann et al., 2010) so it is more difficult to compare this data with those meeting UHR criteria alone. Both of these studies used predictors generated from their own data set, and therefore it was expected that they would be predictive within those data sets.

Given the promising results of the NAPLS consortium and the current focus on the validity of prediction strategies outlined above, we decided to investigate the NAPLS predictive variables in our UHR sample from Melbourne. We aimed to see if the NAPLS combination of predictor variables would have similar predictive power in an independent sample and thus if they conferred an increased risk in an independent sample from which the potential predictors were generated.

## 2. Methods

### 2.1. Subjects

The study used baseline data from the cohort previously recruited to the PACE (Personal Assessment and Clinical