Psychosis prediction: 12-month follow up of a high-risk (‘‘prodromal’’) group

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Abstract

Intervention in the prodromal phase of schizophrenia and related psychoses may result in attenuation, delay or even prevention of the onset of psychosis in some individuals. However, a “prodrome” is difficult to recognise prospectively because of its nonspecific symptoms. This study set out to recruit and follow up subjects at high risk of transition to psychosis with the aim of examining the predictive power for psychosis onset of certain mental state and illness variables. Symptomatic individuals with either a family history of psychotic disorder, schizotypal personality disorder, subthreshold psychotic symptoms or brief transient psychotic symptoms were assessed and followed up monthly for 12 months or until psychosis onset. Twenty of 49 subjects (40.8%) developed a psychotic disorder within 12 months. Some highly significant predictors of psychosis were found: long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression and disorganization. Combining some predictive variables yielded a strategy for psychosis prediction with good sensitivity (86%), specificity (91%) positive predictive value (80%) and negative predictive value (94%) within 6 months. This study illustrates that it is possible to recruit and follow up individuals at ultra high risk of developing psychosis within a relatively brief follow-up period. Despite low numbers some highly significant predictors of psychosis were found. The findings support the development of more specific preventive strategies targeting the prodromal phase for some individuals at ultra high risk of schizophrenia.

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Keywords: Psychosis; Schizophrenia; Prevention; Prediction; High risk; Prodrome

1. Introduction

Schizophrenia and other psychotic disorders are usually characterized by a prepsychotic or “prodromal” phase of illness in which a change from premorbid functioning occurs. This period is characterized by various mental state features, including nonspecific symptoms such as depressed mood and anxiety as well as subthreshold or attenuated psychotic symptoms.
Subtle subjectively experienced cognitive, vegetative and perceptual disturbances, called “basic symptoms”, have also been described (Gross, 1989, 1997). The prodrome extends from a stable or premorbid phase until the time of onset of frank psychotic features (Keith and Matthews, 1991; Loebel et al., 1992; Beiser et al., 1993). It may be lengthy, lasting on average between 1 and 5 years (Loebel et al., 1992; Beiser et al., 1993; Häfner et al., 1993), and is often associated with substantial levels of psychosocial impairment and disability (Jones et al., 1993; Yung et al., 1996). The mechanism by which this prodromal state evolves into psychosis is not really understood (Hodges et al., 1999).

One important aspect of the prodrome is that it is a period in which early intervention could occur if it could be recognized prospectively. The possibility of preventing, delaying or ameliorating the onset of diagnosable psychotic disorder then arises (McGorry, 1998). Such intervention in a subthreshold syndrome, aiming to prevent the full-blown disorder from developing, is known as ‘indicated prevention’ (Mrazek and Haggarty, 1994).

So far, however, the diverse range of symptoms and signs manifest in a psychotic prodrome has only limited predictive power in relation to subsequent psychosis, (McGorry, 1998). This cluster of symptoms may well be followed by psychosis (a true positive), or may not (a false positive). The retrospective term “prodrome” therefore cannot appropriately be applied to prospective investigations. The term “at risk mental state” (ARMS) has been suggested instead, implying that a subthreshold syndrome can be regarded as a risk factor for subsequent psychosis, but that psychosis is not inevitable (McGorry and Singh, 1995). Indicated prevention will need to be based upon the delineation of ARMS features with increased sensitivity and specificity for subsequent psychosis. Researchers in Germany have made some inroads into this search. They assessed a cohort of patients presenting with personality and neurotic disorders for presence of “basic symptoms” and then followed them up several years later. After an average follow-up period of 8 years, over 50% of the cohort had developed schizophrenia. Presence of certain ‘basic symptoms’ (subjective disturbances of attention, thinking, perception, speech and motor action) was found to be highly predictive of psychosis (Klosterkötter et al., 1997, 2001).

This paper describes an alternative method of investigating the predictive power of some prodromal features. It builds on previous interim reports from the same sample (Yung et al., 1998a,b).

1.1. Aim

The aim of the project was to recruit and follow up putatively prodromal or ultra-high-risk (UHR) subjects, to determine the number of subjects who became psychotic within a year of study entry and to assess the predictive power of certain variables, including markers of psychopathology and disability.

1.2. Hypothesis

It was hypothesized that the rate of transition to psychosis over 12 months would be 20–30% of cases. This estimate was based on our experience during a pilot study in a similar high-risk group in which the 12-month transition rate was 21.2% (7 of 33 cases: Yung et al., 1996). The pilot study inclusion criteria were modified for the current project in an attempt to increase the proportion of cases developing a psychosis, for example by including only first-degree relatives of psychotic patients (the pilot study also allowed the recruitment of second degree relatives). Such criteria already define a sample with massively increased risk of incidence when compared with the general population (greater than 10,000 times the risk: Jablensky, 2000).

It was also hypothesized that subjects who became psychotic would display higher levels of certain dimensions of psychopathology and other clinical features than those who did not develop psychosis. These features could then be utilised in enhancing the predictive power within the already enriched sample.

2. Method

2.1. Setting: the PACE Clinic

The “Personal Assessment and Crisis Evaluation (PACE) Clinic” was the deliberately generic name given to the outpatient clinical service specifically developed to assess, manage and follow up putatively high-risk subjects. PACE is located at a community...
adolescent service for general medical as well as psychological problems. Its location was intended to promote access and avoid stigma. The rationale, development and the clinical infrastructure of this service have been described previously (Yung et al., 1995, 1996). Subjects received supportive counselling and case management in addition to treatment of target symptoms such as depression. Participants in this project may have received antidepressant or anxiolytic medication but no neuroleptic medication was used.

2.2. Sample

The lack of specificity of many ARMS symptoms means that additional risk factors need to be identified in order to enhance the predictive power. Such an approach is called a “close in” strategy (Bell et al., 1982), and for example could involve adding presence of a family history of psychosis (a known risk factor: Gottesman and Shields, 1982) to presence of an ARMS to improve predictive capacity. Alternatively, symptoms that seem to have some specificity for subsequent psychosis could be added to the non-specific symptoms. These include subthreshold or attenuated forms of frank psychotic features (Cameron, 1938; Chapman, 1966; Strauss, 1969; Chapman and Chapman, 1980; Allen et al., 1987; van Os et al., 2000) and brief, transient episodes of psychotic symptoms, which spontaneously resolve (Faegerman, 1963; Allen et al., 1987; Jauch and Carpenter, 1988). We used these strategies to operationally define three groups thought to be at very high risk of developing a psychotic disorder in the near future (“prodromal”) or ultra high risk (UHR).

Group 1: “Attenuated Psychotic Symptoms” defines a group of people who have symptoms that deviate from normal phenomena but which are not yet frankly psychotic. For example, overvalued ideas that people are laughing at or are hostile towards the subject, but the subject realises that it is not really true and that he or she is “just being a bit paranoid”. A strange feeling that something has changed in the world or with one’s self in the absence of any crystallised delusion is another example. Also included in this group were people who had perceptual disturbances of below psychotic intensity such as visual or auditory distortions. Thus, the difference between these phenomena and frank psychotic symptoms is in the degree or intensity of the symptom. These types of phenomena, which can be seen as subthreshold psychotic symptoms, have been described in retrospective studies of emerging first episode psychosis or psychotic relapse (Yung and McGorry, 1996a,b; Yung et al., 1996; Møller and Husby, 2000).

Group 2: “Brief Limited Intermittent Psychotic Symptoms (BLIPS)” defines a group who have symptoms of psychotic intensity but which are very infrequent, or which have a total duration of less than 7 days before resolving spontaneously. For example, a person with auditory hallucinations that occur twice a month for 6 months (psychotic phenomena infrequent but have been occurring for a long time), or auditory hallucinations that have been occurring every second day for 6 days before resolving spontaneously (psychotic phenomena frequent but present for only a short duration) would meet this intake criterion.

Group 3: “Trait and State Risk Factors” defines a group who have nonspecific symptoms such as lowered mood or anxiety symptoms plus some trait-risk factors for psychotic disorder, either a schizotypal personality disorder or a family history of a psychotic disorder in a first-degree relative. The nonspecific symptoms must have a duration of at least 1 month and be associated with marked disability or decrease in functioning. This severity criterion is necessary to exclude otherwise normal relatives of patients with psychotic illnesses who have a brief period of mild symptoms.

The operationalised criteria for each of these groups are described in Table 1.

Additionally, all subjects were required to be aged between 14 and 30 (the period of maximum risk of becoming psychotic; Häfner et al., 1993).

Exclusion criteria were: intellectual disability, lack of fluency in English, presence of known organic brain disorder and history of previous psychotic disorder for longer than 1 week (treated or untreated).

2.3. Instruments

At intake, the Psychotic Disorders section of the Structured Clinical Interview for DSM IV (SCID: First et al., 1996) was administered to all cases to establish that none was psychotic at study entry. The Family Interview for Genetic Studies (FIGS: Max-
Table 1  
Inclusion and acute psychosis criteria

**Group 1: Attenuated Psychotic Symptoms**  
Presence of at least one of the following symptoms—ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behaviour and appearance (2–3 on Unusual Thought Content scale; 1–2 on Hallucinations scale; 2–3 on Suspiciousness scale or 1–3 on Conceptual Disorganisation scale of BPRS: McGorry et al., 1988).  
Held with a reasonable degree of conviction, as defined by a score of 2 on the Comprehensive Assessment of Symptoms and History (CASH) rating scale for delusions (Andreasen et al., 1992).  
Frequency of symptoms—at least several times per week.  
Change in mental state present for at least 1 week and not longer than 5 years.

**Group 2: “Brief Limited Intermittent Psychotic Symptoms” (“BLIPS”)**  
Transient psychotic symptoms—Presence of at least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech [4+ on Unusual Thought Content scale; 3+ on Hallucinations scale; 4+ on Suspiciousness scale (or it is held strong conviction, as defined by a score of 3 or more on the CASH rating scale for delusions) or 4+ on Conceptual Disorganisation scale of BPRS].  
Duration of episode of less than 1 week.  
Symptoms resolve spontaneously.  
The BLIP must have occurred within the past year.

**Group 3: Trait and State Risk Factors**  
First degree relative with a DSM-IV psychotic disorder or schizotypal personality disorder (as defined by DSM-IV).  
Significant decrease in mental state or functioning—maintained for at least a month and not longer than 5 years (reduction in GAF Scale of 30 points from premorbid level).  
The decrease in functioning occurred within the past year.

**Acute psychosis threshold**  
Presence of at least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech [4+ on Unusual Thought Content scale; 3+ on Hallucinations scale; 4+ on Suspiciousness scale (or it is held strong conviction, as defined by a score of 3 or more on the CASH rating scale for delusions) or 4+ on Conceptual Disorganisation scale of BPRS].  
Frequency of symptoms is at least several times a week.  
Duration of mental state change is longer than 1 week.

SPSS for Windows (SPSS, 1998) and S-PLUS for Windows (MathSoft, 1997) were used to perform the analysis. For categorical variables, such as gender, the chi-square or Fisher’s exact test were used to assess if different categories of a variable differ in terms of the proportion of subjects becoming psychotic within 1 year. For numerical variables, such as GAF, the t-test was used to compare mean scores of those who became psychotic within 1 year and those who did not. The Cox proportional hazards regression model was also applied to each variable to test for the association between a particular variable and the risk of psychosis. The Cox model is widely used for ‘survival’ data. It takes into account the time to psychosis and can accommodate time-dependent variables such as BPRS for which repeated measures were collected over time. The calculation of measures such as sensitivity and specificity are an attempt to provide a practically oriented interpretation of the results.
3. Results

3.1. Referrals

Between March 1995 to October 1996, 162 referrals were made to PACE. Telephone screening assessment of these referrals excluded 23 (14.2%), the remaining 139 (85.8%) were offered a screening interview at the PACE Clinic. Forty-four of these never attended the appointment. The reasons for this are unknown. The other 95 (58.6% of the 162 referred) were seen in the clinic by either the PACE consultant psychiatrist (ARY) or a research psychologist (CAM, LJP, and MH) or both. Of these, 60 met the intake criteria and 35 did not and forty-five of those meeting intake criteria consented to involvement in the research project. Reasons for not being recruited included refusal to participate (n=13), and being subsequently treated with neuroleptic medication by another clinician (despite not being psychotic: n=2). Additionally, four subjects who had been seen at PACE in the months prior to March 1995 were recruited into the study. They had been included in the pilot project but still met PACE inclusion criteria at the commencement of this project. Thus, the total number in the research sample was 49.

All subjects included in the study were assessed by at least two experienced clinicians prior to study entry. In all cases, a psychiatrist was either directly involved in the assessment or the case was discussed in detail with a psychiatrist prior to being formally accepted into the clinic. Subjects were frequently reviewed at a consensus meeting by all clinicians. On one occasion, a person originally included in the study revealed more symptoms to his clinician some time after being first involved in the research. This led the team to suspect that he had actually been psychotic at the time of entry into the study. He was subsequently completely withdrawn from the study and appropriate treatment was commenced. We are confident that no other subject was psychotic at the time of entry into the study. However, eight individuals defined by our criteria as having “BLIPS” met DSM IV criteria for a past “Brief Psychotic Disorder” (four subjects) or “Substance Induced Psychosis” (four subjects). These diagnoses can be made with a duration of psychotic symptoms as brief as 1 day. In all cases, duration of frank psychosis was less than 1 week, and resolution of symptoms was spontaneous. As indicated below, the threshold for onset of a psychotic episode was aligned with the consensus between PACE psychiatrists of when neuroleptic treatment would usually be commenced.

A separate study (n=21) was conducted to assess the inter-rater reliability of clinicians and research staff in relation to assessing whether potential subjects met intake or exit criteria for the study. Written case summaries including detailed description of symptomatology, frequency, duration and recency of symptoms were presented to five staff members who then rated whether potential subjects met intake or exit criteria. The pairwise kappa values for entry criteria (0.81–1.0) and exit criteria (0.77–1.0) were excellent, indicating that all raters were consistent when evaluating intake and exit criteria.

3.2. Intake criteria

Most subjects met the “attenuated” intake criterion (n=35: 71.4%). Twelve cases (24.5%) met the “BLIP” criterion and 18 cases (36.7%) met the “trait marker” criterion. There was a considerable degree of overlap between the groups. Six cases (12.2%) fulfilled both the “trait” criterion and the “attenuated” criterion, four (8.1%) subjects met both “attenuated” and “BLIP” criteria and two (4.1%) met both “trait” and “BLIP” criteria.

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criteria. Two subjects (4.1%) fulfilled all three criteria. Fig. 1 illustrates this.

3.3. Intake characteristics

Mean age at first assessment was 19.1 years (median 19, SD=3.8, range 14–28). Twenty-five of the subjects were male (51.0%) and 24 were female (49.0%). The 15 who met criteria but did not consent to involvement in the study did not differ significantly from the research sample in terms of age (mean 18.5 years, median 18, SD=2.6, range 14–24; $p=0.48$) or gender [seven (46.7%) male, eight (53.3%) female; $p=1.00$].

The time between symptom onset and first contact with psychiatric services in the pathway to the PACE Clinic varied widely between subjects, with a range of 0 to 4015 days (11 years), median 183 days. Time to being seen at the PACE Clinic was similarly variable (range 3 to 7286 days, median 495 days) (see Table 2).

Measures of functioning and symptomatology at intake are shown in Table 2. A mean GAF score of 58.1 indicates moderate difficulty in social and role functioning or moderate psychiatric symptoms. The mean QLS score of 77.1 is also consistent with moderate disability. The intake BPRS and SANS scores indicate moderate to high levels of symptomatology.

3.4. Transition to psychosis

The main outcome measure in this study was the development of psychosis. This onset point needed to be arbitrarily defined using the BPRS to determine a cut-off point at which psychosis is said to have begun (see Table 1). As is the case with any operational definition, there is inherent error in this approach. However, as we have discussed previously, there are difficulties in defining onset of a frank psychosis prospectively (Yung and McGorry, 1996a,b).

This threshold, which excludes cases of ‘brief psychosis’ (according to the DSM-IV), is essentially the threshold at which neuroleptic medication would be commenced in common clinical practice and was developed via local consensus of PACE and Early Psychosis Prevention and Intervention Centre (EPPIC, Melbourne, Australia: McGorry et al., 1996) psychiatrists.

Over the 12-month follow-up period, 20 subjects became psychotic according to the above definition. Therefore, the 12-month transition rate was 40.8% (20 of 49). Additionally, we have become aware of two further cases who developed psychosis after 12 months, at 15 and 25 months. However, the whole sample has not yet been followed up over a longer period and there may be further cases still with psychosis onset after the 12-month point. Fig. 2 shows a survival curve indicating the timing of onset of psychosis.

Table 2

<table>
<thead>
<tr>
<th>Intake data</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.1</td>
<td>3.8</td>
<td>19</td>
<td>14–28</td>
</tr>
<tr>
<td>GAF</td>
<td>58.1</td>
<td>14.4</td>
<td>60</td>
<td>30–90</td>
</tr>
<tr>
<td>QLS</td>
<td>77.1</td>
<td>22.2</td>
<td>76.0</td>
<td>34–26</td>
</tr>
<tr>
<td>BPRS</td>
<td>20.5</td>
<td>8.7</td>
<td>20.0</td>
<td>1–43</td>
</tr>
<tr>
<td>SANS</td>
<td>20.34</td>
<td>13.9</td>
<td>18.0</td>
<td>0–63</td>
</tr>
<tr>
<td>Duration of sys (days)</td>
<td>565</td>
<td>816</td>
<td>183</td>
<td>0–4015</td>
</tr>
<tr>
<td>Duration to PACE (days)</td>
<td>833</td>
<td>1232</td>
<td>495</td>
<td>3–7286</td>
</tr>
</tbody>
</table>

GAF=Global Assessment of Functioning; QLS=Quality of Life Scale; BPRS=Brief Psychiatric Rating Scale; SANS=Schedule for Assessment of Negative Symptoms; Duration of sys=time between onset of symptoms and first contact with psychiatric services in the pathway to the PACE Clinic; Duration to PACE=time between onset of symptoms and first contact with the PACE Clinic.
psychotic within 1 year, the mean number of days to psychosis was 123 days (SD=107), with median of 103 days, range 8–351 days.

Table 3 shows the 12-month SCID diagnoses (current diagnosis only). Thirteen subjects had an onset of schizophrenia, three cases had affective psychoses (one bipolar disorder, two major depression with psychotic features). One case developed schizoaffective disorder (depressed type) and one had a brief psychosis with duration greater than 1 week. There were two cases of psychotic disorder not otherwise specified (NOS). Of the remaining 29 nonpsychotic subjects, 12 had no current diagnosis at 12 months and 15 had other nonpsychotic diagnoses (mainly mood and anxiety disorders). Final diagnosis was missing for two subjects.

3.5. Prediction of psychosis

3.5.1. Baseline measures

Comparison was made between the subjects who became psychotic and those who did not become psychotic over the 12-month follow-up period in order to assess predictive utility of some of the independent variables. Age and gender were not significantly related to the onset of psychosis. The time between the onset of symptoms and first contact with psychiatric services was significantly longer in the group that became psychotic (mean=915 days, SD=1134) compared with the group that did not (mean=324, SD=347: t-test, p=0.035). The association was even more significant using Cox regression (p=0.0051).

3.5.2. Repeated measures

As the pattern of symptoms experienced by putatively prodromal individuals are likely to vary over time, ratings of psychopathology were completed at monthly periods over a course of a year. These repeated measures were analysed using survival analysis and Cox regression to identify factors that make the development of psychosis more likely. If a subject were nonpsychotic at 2 months, the measures of psychopathology at 1 month were treated as those for someone who was not psychotic. If the same person then became psychotic at 10.5 months, then the psychopathological measures immediately preceding the transition (i.e. 10 months) were treated as for someone with psychosis (the measures at 1 month would still be analysed as if for someone without psychosis).

We needed to determine how long the psychopathological measures were assumed to be valid, given that they are likely to change over time (we called this time period the duration of validity). Ideally, this would have been 30 days in line with the monthly follow-up design. A number of subjects were missing one or more monthly assessments, or assessment occurred late, however, so a valid limit of only 30 days would have resulted in the loss of important information. If the subject described above had missed assessments at both 9 and 10 months, then the length of time between last assessment and psychosis onset is about 75 days. Hence, if a duration of validity of 60 days were used, then we would not be able to include this subject in the analysis (as the length of time between last assessment and psychosis onset is over 60 days). However, this subject would be included using a duration of validity of 130 days.

In order to assess the effects of different values for the duration of validity, Cox regression was applied with duration of validity ranging from 60 to 390 days. The p-values associated with total BPRS score, BPRS psychotic subscales (unusual thought content, suspiciousness, hallucinations, conceptual disorganization), total SANS score, SANS subscales, HRSD, HRSA and MRS scores using Cox regression are shown in

### Table 3

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13</td>
<td>26.5</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Bipolar disorder with psychotic features</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Major depression with psychotic features</td>
<td>2</td>
<td>4.1</td>
</tr>
<tr>
<td>Brief psychotic disorder</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>2</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Nonpsychotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diagnosis</td>
<td>12</td>
<td>24.5</td>
</tr>
<tr>
<td>Other nonpsychotic diagnosis</td>
<td>15</td>
<td>30.6</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Table 4. For the sake of simplicity, only the p-values and hazard ratios for duration of validity of 60 and 130 days are shown. Scores on BPRS total, BPRS psychotic subscales, SANS attention and HRSD were consistently highly significant predictors, even with different durations of validity.

3.5.3. Measures of predictive ability

Using only the consistently highly significant predictors (p<0.01 based on Cox regression across all durations of validity tested): time between the onset of symptoms and first contact with psychiatric services (‘duration’), GAF score, BPRS total, BPRS psychotic subscale score, SANS attention and HRSD scores, we then examined how well these variables together predict onset of psychosis. For each variable, a cutoff point was used to define a “positive result”. This was achieved by establishing which point gave the lowest p-value using Cox regression. Using this method, the following cut off points were found: duration of symptoms greater than 900 days, GAF score less than 51, BPRS total greater than 15, BPRS psychotic subscale greater than 2, SANS attention score greater than 1 and HRSD greater than 18. These features were then considered as “potential predictors of psychosis”. Next, an examination was made of how many of these features were needed to most accurately distinguish between those likely to develop psychosis and those likely to remain nonpsychotic.

The risk of developing psychosis associated with having 2 or more, 3 or more, 4 or more and 5 or more "potential predictors of psychosis" was examined using Cox regression. The smallest p-value (1.3×10^{-10}) corresponded to having 4 or more "potential predictors" (and a duration of validity of 130 days for the repeated measures). In order to gain an idea of the predictive ability of this ‘4 or more’ prediction rule, each subject was classified as positive or negative according to whether or not his/her baseline measurements of the “potential predictors” satisfied this rule. This classification was then compared with the actual outcome within 90, 180, 270 and 360 days from entry. Results are shown in Tables 5 and 6. Note that conceptually, the prediction rule could also be applied to measurements at the follow-up time points. However, this was not done because of the reduction in sample size at these time points due to subjects missing assessments or becoming psychotic.

As can be seen from the tables, the PPV suggests that the majority (13 of 15 subjects or 80%) of those with 4 or more “potential predictors of psychosis” at baseline will become psychotic within 6 months. The hazard ratio of having 4 or more of these features is estimated to be 30 [95% CI (8110), using Cox regression]. Although the estimate lacks precision, both the

Table 5
Number of subjects becoming psychotic within limited time periods using a score of 4 or more potential predictors of psychosis as a “positive test”

<table>
<thead>
<tr>
<th>Outcome</th>
<th>At 90 days</th>
<th>At 180 days</th>
<th>At 270 days</th>
<th>At 360 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of predictors</td>
<td>≤3</td>
<td>32</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>4 or more</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>NP=not psychotic; P=psychotic.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6
Sensitivity, specificity, PPV and NPV of having 4 or more potential predictors of psychosis at baseline

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>90</td>
<td>84</td>
<td>60</td>
<td>97</td>
</tr>
<tr>
<td>180 days</td>
<td>86</td>
<td>91</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>270 days</td>
<td>72</td>
<td>93</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>360 days</td>
<td>65</td>
<td>92</td>
<td>87</td>
<td>77</td>
</tr>
</tbody>
</table>

PPV=positive predictive value; NPV=negative predictive value.
value 30 itself and the confidence interval are way above 1, suggesting that those with 4 or more “potential predictors of psychosis” are at higher risk of becoming psychotic than those with fewer than four predictors. Subjects with 4 or more “potential predictors of psychosis” can be considered to have been truly in the prodromal phase of illness when recruited.

The above analysis assumed that all factors contribute equally to the risk of psychosis, which may not be the case. To address this problem, the risks associated with different combinations of the potential predictors were estimated using Cox regression. These estimated risks were then utilised in the prediction of psychosis. The results were not changed significantly.

4. Discussion

The search for predictors of psychosis is an important area of investigation with implications for early intervention in a subsample of the population at ultra high risk (UHR) of psychosis. This design of this study is unique in that it prospectively investigates symptomatic high-risk individuals in the peak age range of psychosis onset. This was a two-stage process. Subjects who met specific intake criteria were selected (the ‘UHR’ cohort). Enhanced prediction of psychosis within this enriched sample was then investigated. Monthly assessment allowed close monitoring of change in psychopathology and functioning and accurate determination of timing and pattern of onset of psychosis.

The high rate of transition to psychosis in our study group suggests that we are identifying many young people who are in the prodromal phase preceding a first episode of psychosis. The 12-month risk of 40.8% (a vastly increased risk for 12-month incidence in contrast to young people in the general population) may in fact have been higher if the subjects had not attended PACE where they received some treatment. Hence, there may be some “false false positives” where the genuine risk was averted or postponed at least (Yung and McGorry, 1996a,b), as well as cases who were never at risk of psychosis (“true false positives”).

Moderate levels of disability and psychopathology were found in the sample at intake. This is to be expected, as the subjects tended to be help-seekers who were referred to the PACE service by other professionals. Nonetheless, as is the case with first episode psychosis (Johnstone et al., 1986; Vaglum, 1996), there were still long delays in some subjects seeking and/or receiving help (Phillips et al., 1999). This may be because of diagnostic confusion, uncertainty about what help is needed and where to seek it and/or a lack of appropriate services. Unfortunately, for many individuals, this delay in receiving help may result in social decline and increasing levels of disability, and indeed the PACE attendees invariably were distressed and experiencing a significant decline in functioning.

Some highly significant predictors of psychosis were found. Long duration of prodromal symptoms before help seeking was one predictor. It may be that subjects with shorter duration of symptoms were earlier in the process of development of psychosis or psychotic disorder than those with longer durations, or perhaps the interventions provided were more effective at an earlier stage of disorder development. Alternatively, the high-risk period soon after study entry could indicate the presence of a referral bias with patients being referred to the PACE Clinic when there is a noticeable worsening of symptoms.

Poor functioning at intake was another significant predictor of psychosis transition within 12 months. It can be difficult to distinguish premorbid abnormalities, including developmental deviance, from the onset of prodrome, particularly in an adolescent population but conceptually it is very important to attempt this. Attempts were made to date the onset of prodrome by asking about change from normal self. However, since adolescence is a period of major psychological and social change as well as a time of brain maturation (Davies et al., 1998), the distinction between premorbid personality and prodromal symptoms may not be clear cut. Our sample with very long duration of prodrome may include some subjects with long-standing poor premorbid adjustment, a known risk factor for schizophrenia (Jones et al., 1993), and other psychotic disorders (Done et al., 1994). The finding that poor functioning at intake predicted onset of psychosis may also reflect this. It may also be that, since our criteria are weighted towards recruiting subjects with “positive” symptoms (attenuated psychotic symptoms and BLIPS), low functioning in combination with these positive symptoms increases risk of psychosis transition.
Level of psychopathology and particularly low level psychotic-like symptoms (attenuated positive symptoms) as measured by the psychotic subscales of the BPRS, depression, and disorganization (as assessed by the SANS attention variable) were all risk factors for development of psychosis within 60 and 130 days. Avolition/apathy and anxiety were also significantly associated with psychosis within 60 days. Thus, the hypothesis that impending psychosis can be detected prospectively and prediction further enhanced within the UHR group was supported.

Further data analysis yielded a strategy for psychosis prediction using a combination of risk factors. Having four or more of the following: duration greater than 900 days, GAF score less than 51, BPRS total greater than 15, BPRS psychotic subscale greater than 2, SANS attention score greater than 1 and HRSD greater than 18, predicted psychosis onset within 6 months with good sensitivity (86%), specificity (91%) PPV (80%) and PPV (94%). This compares favourably to the sensitivity and specificity data reported by Klosterkötter et al. (2001). They reported that the presence of ‘basic symptoms’ at intake predicted schizophrenia at follow up with a probability of 70%—specificity 0.59, false-positive predictions 20%. It should be noted, however, that the length of follow up from recruitment differs between this study and that of Klosterkötter with the current study being much shorter (12 months compared to 8 years).

It must be acknowledged that numbers are small and the findings cannot be generalised to the whole population of people in the prodromal phase of a first psychotic episode. Furthermore, these predictors only apply to young people at ultra high risk for psychosis as defined by our intake criteria. Values for sensitivity, specificity, PPV and NPV are affected by prevalence; hence, if our same test were applied to the general population, PPV would be lower and NPV higher due to the low prevalence of psychosis in the general community. However, services similar to the PACE Clinic are in development, and these findings have clinical implications for these and other like services. First, the period of highest risk of transition to psychosis was in the first 4.5 months after study entry. UHR patients should therefore be monitored most closely during this time.

Second, young people who meet PACE UHR criteria and four or more of the above markers should be monitored particularly closely for psychosis onset. Meeting the intake criteria alone is associated with a 40% risk of developing a psychotic episode. Refining the UHR sample further considerably increases the risk of psychosis. In the sample of 15 who not only met intake criteria but also four or more of the additional risk factors, 13 (87%) developed psychosis. These subjects were truly experiencing the prodromal phase of a first psychotic episode when initially recruited. Such a high rate of transition to psychosis in this subsample could justify assertive treatment in patients meeting these criteria. The result of this research therefore lays the groundwork for the development of targeted intervention or indicated prevention models (Mrazek and Haggarty, 1994), which aim to minimise the impact of, delay, or even prevent onset of psychotic disorder.

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