Original Investigation

Long-term Follow-up of a Group at Ultra High Risk ("Prodromal") for Psychosis
The PACE 400 Study

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IMPORTANCE The ultra high-risk (UHR) criteria were introduced to prospectively identify patients at high risk of psychotic disorder. Although the short-term outcome of UHR patients has been well researched, the long-term outcome is not known.

OBJECTIVE To assess the rate and baseline predictors of transition to psychotic disorder in UHR patients up to 15 years after study entry.

DESIGN Follow-up study of a cohort of UHR patients recruited to participate in research studies between 1993 and 2006.

SETTING The Personal Assessment and Crisis Evaluation (PACE) clinic, a specialized service for UHR patients in Melbourne, Australia.

PARTICIPANTS Four hundred sixteen UHR patients previously seen at the PACE clinic.

MAIN OUTCOMES AND MEASURES Transition to psychotic disorder, as measured using the Comprehensive Assessment of At-Risk Mental States, Brief Psychiatric Rating Scale/Comprehensive Assessment of Symptoms and History, or state public mental health records.

RESULTS During the time to follow-up (2.4-14.9 years after presentation), 114 of the 416 participants were known to have developed a psychotic disorder. The highest risk for transition was within the first 2 years of entry into the service, but individuals continued to be at risk up to 10 years after initial referral. The overall rate of transition was estimated to be 34.9% over a 10-year period (95% CI, 28.7%-40.6%). Factors associated with transition included year of entry into the clinic, duration of symptoms before clinic entry, baseline functioning, negative symptoms, and disorders of thought content.

CONCLUSIONS AND RELEVANCE The UHR patients are at long-term risk for psychotic disorder, with the highest risk in the first 2 years. Services should aim to follow up patients for at least this period, with the possibility to return for care after this time. Individuals with a long duration of symptoms and poor functioning at the time of referral may need closer monitoring. Interventions to improve functioning and detect help-seeking UHR patients earlier also may be indicated.
treatment of the prodromal phase of schizophrenia and other psychotic disorders could lead to prevention of these disorders and enables examination of risk factors and biomarkers for these disorders. The challenge is to identify the prodrome prospectively. In the mid-1990s the ultra high-risk (UHR) criteria were developed to identify people putatively in the prodromal phase. Three UHR groups were defined: (1) attenuated psychotic symptoms (APS) (subthreshold, attenuated positive psychotic symptoms), (2) brief limited intermittent psychotic symptoms group (BLIPS) (short episodes of frank psychotic symptoms that have resolved without treatment), and (3) trait and state risk factor (Trait) (has a presumed genetic vulnerability (due to having a schizotypal personality disorder, or a first-degree relative with a psychotic disorder) in addition to chronic low or a significant decrease in functioning. Age between 15 and 30 years was an additional criterion because this is the age range of highest risk for psychosis.

The UHR criteria have been used widely, with rates of psychosis onset (transition) found to range between 8% and 54% within 1 to 2.5 years. Short-term predictors of onset of psychosis in UHR samples include long duration of symptoms before treatment,2 basic and negative symptoms,6,12-15 depression,2,15 schizotypal disorder,10 sleep disturbances,10 and substance abuse.4 Of particular note are subthreshold positive symptoms,2,6,10,14 poor functioning,2,6,10,16 and having genetic risk with functional decline,4 which were all found to be significant predictors in the large North American Prodrome Longitudinal Study17 and were validated in an independent sample.17

However, there is evidence of a decline in transition rates in more recent UHR cohorts with rates as low as 8% to 28% in 1 year. Consistent with this, a recent meta-analysis revealed a significant effect toward transition rates reducing over time. In one study, brief duration of symptoms before first contact with the clinic was associated with decreased transition rate, prompting speculation that a lead-time bias may be operating; that is, because of earlier detection, more recent UHR cohorts will take longer to develop psychosis compared with previous UHR cohorts. Medium-term (3-5.4 years) follow-up studies found that the risk of transition to psychotic disorder extended beyond the first year after presentation, consistent with a lead-time bias. However, longer-term follow-up studies are needed to investigate this further.

Longer-term outcomes of UHR patients also have clinical implications regarding how long patients should be considered at risk and the length of treatment. It is important to consider predictors that take longer-term outcome into account; limiting analysis to predictors of short-term (1-2 years) outcome may present a distorted picture of true risk factors for psychosis. The issue of longer-term outcome is salient given the decision to include an attenuated psychosis syndrome based on the UHR criteria in Section III (conditions requiring further research) of DSM-5.24-26

The current study is the first long-term follow-up of a UHR cohort. We followed up all UHR participants involved in research studies at the Personal Assessment and Crisis Evaluation (PACE) clinic, Orygen Youth Health, between 1993 and 2006. The aims of the study were to assess (1) the rate of transition to a psychotic disorder up to 15 years after entry to a specialist clinic and (2) the baseline clinical predictors of transition to psychotic disorder.

### Methods

#### Setting and Sample

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 during the baseline studies was 15 to 30 years. Young people are accepted into PACE if they meet criteria for at least 1 of 3 UHR groups: APS, BLIPS, and Trait (Table 1). There were minor changes to the UHR criteria from 1993 to 1995, when group 3 (trait plus state risk factors) omitted the second-degree relative criterion and operationalized the required decline in functioning. The measures used to determine UHR status have also changed slightly during the baseline recruitment period (see the Measures subsection). Exclusion criteria for PACE are the 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 more than 15 mg (this may modify risk of transition).

The sample consisted of all UHR patients who participated in studies at the PACE clinic between 1993 and 2006 (N = 416). Seven studies (3 intervention, 4 cohort) were conducted during this period.

#### Measures

##### UHR Status

From 1993 to 1999, UHR status at baseline was assessed using the Brief Psychiatric Rating Scale (BPRS)/Comprehensive Assessment of Symptoms and History (CASH)/Global Assessment of Functioning (GAF) method and the Comprehensive Assessment of At-Risk Mental States (CAARMS)/GAF.
Follow-up of Prodromal Psychosis

Method

The concurrent validity of the CAARMS was established. From 1999, the CAARMS replaced the BPRS/CASH as the means of establishing UHR status.

Outcome Measures

The main outcome of interest was transition to psychotic disorder. This was defined as at least 1 fully positive psychotic symptom several times a week for more than 1 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 the 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. If CAARMS data were not available (e.g., because of not being able to locate the individual(s), the state public mental health records were accessed.

Candidate Baseline Predictors

Duration of symptoms before treatment at PACE was assessed with the CAARMS. Negative symptoms were assessed using the Schedule for the Assessment of Negative Symptoms. General psychiatric symptoms were assessed with the BPRS. Psychosocial functioning was measured using the GAF and the Quality of Life Scale.

Baseline year (i.e., year of entry into PACE) also was examined because factors that may influence the outcome variable may have changed over time (e.g., patient characteristics, referral patterns, and treatment characteristics). Baseline year was divided into 4 epochs: 1993 to 1997, 1998 to 2000, 2001 to 2003, and 2004 to 2006. The aim was to have periods equally spaced but with a reasonable number of patients in each epoch. All but the first epoch pertain to 3 years. This is because a small number of participants were recruited in 1993 to 1994, and so these 2 years were combined with 1995 to 1997.

Procedure

A previously developed tracking system was used to locate and recontact participants. The steps followed were accessing (1) the National Death Index to determine whether any participant had died since last contact, (2) research files, (3) public mental health service record systems, (4) the National Electoral Roll (it is compulsory in Australia to enroll to vote), (5) the telephone directory, (6) previous contacts, and (7) Internet-based searching. If individuals did not consent to face-to-face assessment, they were asked if they would consent to a brief telephone or written assessment, enabling collection of a minimum dataset.

Statistical Analysis

Transition to psychotic disorder was analyzed using survival analysis. The Kaplan-Meier method was used to estimate transition rates and Cox regression was used to examine the significance of candidate predictors. Stepwise Cox regression was used to determine possible predictors of transition out of the large number of candidates. The α threshold was set at .05. Some patients were randomized to intervention trials during previous research at PACE and therefore received nonstandard (trial) treatments. To account for this, the analysis was conducted twice: once for the treatment-as-usual participants (i.e., excluding 244 who had received trial treatments) and once for the entire cohort, providing a type of sensitivity analysis. Results were essentially the same for both groups, including the prediction analysis, so only the results for the entire cohort are presented (eTables 1-3 in Supplement report the treatment-as-usual data).

Results

The Sample—Baseline and Follow-up

Descriptive statistics of the sample at baseline are presented in eTable 4 in Supplement. At follow-up, 311 of the 416 participants (74.8%) were available for interview (268 [64.4%] face-to-face, 40 [9.6%] telephone, and 3 [0.7%] written). Forty-nine people (11.8%) refused follow-up and 47 individuals (11.3%) could not be located. Those who were not interviewed were evenly spread across the baseline year cohorts. There were no significant baseline demographic or clinical differences between the interviewed and noninterviewed participants, apart from sex, with a slightly higher percentage of women in the interviewed group (56.7% vs 43.2%). Nine members of the cohort had died. The reasons for death were suicide, 4; prescription medication overdose (intentionality unknown), 2; and opiate overdose, 1; the cause of death for 2 cases was unknown.

Time to Follow-up

Time to follow-up ranged from 2.4 to 14.9 years after baseline (Table 2). The mean follow-up time was 7.5 years (SD, 3.2 years).

Rate of Onset of Psychotic Disorder

One hundred fourteen individuals developed a psychotic disorder (i.e., transitioned to psychosis). Thirty-one of these transitions were determined using the BPRS/CASH, 74 using the CAARMS, and 9 using state public mental health records. Table 3 reports the corresponding estimated transition rates.

The highest rate of transition was within the first 2 years (20.4%), with ongoing but reduced rates of transition after this point. The latest transition occurred 9.7 years after entry.

Table 2. Time to Follow-up

<table>
<thead>
<tr>
<th>Time to Follow-up, y</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2-4</td>
<td>52 (16.7)</td>
</tr>
<tr>
<td>&gt;4-6</td>
<td>83 (26.7)</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>44 (14.1)</td>
</tr>
<tr>
<td>&gt;8-10</td>
<td>35 (11.3)</td>
</tr>
<tr>
<td>&gt;10-12</td>
<td>71 (22.8)</td>
</tr>
<tr>
<td>&gt;12-15</td>
<td>26 (8.4)</td>
</tr>
<tr>
<td>Total</td>
<td>311 (100)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.5 (3.2)</td>
</tr>
<tr>
<td>Median (Q1-Q3)</td>
<td>6.7 (4.6-10.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Q1, 25th percentile; Q3, 75th percentile.

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Baseline Predictors of Transition

Cox regression was used to test the association between transition to psychosis and each potential predictor individually. The variables with significant P values are listed in Table 4. The variables that were significantly associated with transition were baseline year, low functioning (assessed with the GAF and the Quality of Life Scale), belonging to the BLIPS group, negative symptoms, conceptual disorganization and disorder of thought content, positive psychotic symptoms (BPRS psychotic subscale), motor disturbances, impaired motor functioning, impaired bodily sensation, and long duration of symptoms (time between symptom onset and first contact with PACE).

The next step was to examine the significance of the variables after adjusting for one another. In view of so many potential predictors, we used a stepwise Cox regression procedure in which the most significant variable considered individually was entered at step 1. Then, for subsequent steps, the variables were entered or removed according to their significance after adjusting for all variables in the model. The final model was obtained when no more variables could be entered or removed. This resulted in the following predictive variables: baseline year ($P = 10^{-3}$), global functioning ($P = 2 \times 10^{-6}$), and duration of symptoms ($P = .001$). When only treatment as usual participants were analyzed the same predictive variables emerged, with significant values for baseline year ($P = 10^{-7}$), global functioning, ($P = 4 \times 10^{-6}$), and duration of symptoms ($P = .02$).

Further Examination of Significant Predictors

Examination of hazard ratios of baseline year epochs (after adjusting for GAF and duration of symptoms) using the 1993 to 1997 cohort as the comparison group indicated that the 1998 to 2000 epoch had 95% the risk (95% CI, 37%-95%, $P = .03$), the 2001 to 2003 epoch had 22% the risk (95% CI, 13%-40%, $P < .001$), and the 2004 to 2006 epoch had 14% the risk (95% CI, 7%-31%, $P < .001$) of the 1993 to 1997 epoch (Table 5). The 1998 to 2000 epoch had a significantly higher risk than the 2 later epochs ($P = .002$ and .005, respectively). The 2 later epochs were not significantly different ($P = .31$).

Poor functioning (low GAF score) at clinic entry was a highly significant predictor of psychosis. For 2 patients with a 10-point difference in baseline GAF, the one with the higher functioning would have 61% the risk of the other, after adjusting for baseline year and duration of symptoms (Table 5).

For every extra year’s duration of symptoms prior to clinic entry the likelihood of transition increased by 12% after adjusting for baseline year and GAF score (Table 5).

Secondary Analyses

Prediction Rule Analysis

We were interested in investigating whether a prediction rule could be developed using the identified predictors. The significant predictors of GAF and duration of symptoms were included in the analysis. Baseline year was excluded because it cannot be regarded as a risk factor owing to its fixed nature. The analysis consisted of identifying a cut point for each sig-

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**Table 3. Kaplan-Meier Estimated Transition Rates at Various Time Points**

<table>
<thead>
<tr>
<th>Time From Baseline, y</th>
<th>Estimated Transition Rate % (95% CI)</th>
<th>Cumulative No. of Transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.5 (12.7-20.1)</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>20.4 (16.3-24.4)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>24.9 (20.4-29.2)</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>27.6 (22.8-32.1)</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>30.1 (25.0-34.8)</td>
<td>108</td>
</tr>
<tr>
<td>10</td>
<td>34.9 (28.7-40.6)</td>
<td>114</td>
</tr>
<tr>
<td>&gt;10</td>
<td>34.9 (28.7-40.6)</td>
<td>114</td>
</tr>
</tbody>
</table>

**Table 4. Cox Regression P Values for Association Between Transition and Each Variable Individually**

<table>
<thead>
<tr>
<th>Sample Characteristics and Baseline Measures</th>
<th>P Value</th>
<th>$\beta$</th>
<th>SE, $\beta$</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline year</td>
<td>.0000002</td>
<td>-.231</td>
<td>.231</td>
<td>416</td>
</tr>
<tr>
<td>Intake group: BLIPS</td>
<td>.04</td>
<td>.515</td>
<td>.240</td>
<td>398</td>
</tr>
<tr>
<td>Time to PACEb</td>
<td>.0000007</td>
<td>.00047</td>
<td>.00008</td>
<td>383</td>
</tr>
<tr>
<td>Log, time to PACEc</td>
<td>.0005</td>
<td>.299</td>
<td>.088</td>
<td>383</td>
</tr>
<tr>
<td>GAF</td>
<td>.000003</td>
<td>-.043</td>
<td>.009</td>
<td>397</td>
</tr>
<tr>
<td>QLS total</td>
<td>.01</td>
<td>-.013</td>
<td>.004</td>
<td>407</td>
</tr>
<tr>
<td>BPRS psychotic subscale</td>
<td>.02</td>
<td>.073</td>
<td>.031</td>
<td>411</td>
</tr>
<tr>
<td>SANS total</td>
<td>.006</td>
<td>.019</td>
<td>.007</td>
<td>412</td>
</tr>
<tr>
<td>SANS affective flattening or blunting</td>
<td>.03</td>
<td>.037</td>
<td>.016</td>
<td>412</td>
</tr>
<tr>
<td>SANS avolition-apathy</td>
<td>.047</td>
<td>.062</td>
<td>.031</td>
<td>412</td>
</tr>
<tr>
<td>SANS anhedonia-asociality</td>
<td>.02</td>
<td>.044</td>
<td>.019</td>
<td>412</td>
</tr>
<tr>
<td>CAARMS scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders of thought content</td>
<td>.000009</td>
<td>.459</td>
<td>.106</td>
<td>397</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>.002</td>
<td>.304</td>
<td>.100</td>
<td>396</td>
</tr>
<tr>
<td>Motor disturbances</td>
<td>.04</td>
<td>.202</td>
<td>.094</td>
<td>394</td>
</tr>
<tr>
<td>Basic symptom-impairment motor functioning</td>
<td>.02</td>
<td>.228</td>
<td>.095</td>
<td>391</td>
</tr>
<tr>
<td>Basic symptom-impairment bodily sensation</td>
<td>.02</td>
<td>.195</td>
<td>.085</td>
<td>390</td>
</tr>
</tbody>
</table>

**Abbreviations:** BLIPS, brief limited intermittent psychotic symptoms; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At-Risk Mental States; GAF, Global Assessment of Functioning Scale; PACE, Personal Assessment and Crisis Evaluation; QLS, Quality of Life Scale; SANS, Scale for the Assessment of Negative Symptoms.

* Baseline year is a factor of 4 levels (with 1993-1997 as the reference level); hence, 3 $\beta$ coefficients.
* Time between symptom onset and first contact with PACE (days).
* Log transformation was attempted because of the skewness of the variable.
significant predictor that provided the smallest $P$ value when the variable was tested using Cox regression. Using this method, the cut point found for GAF score was 44 ($P = .000005$) and for duration of symptoms was 738 days ($P = .0000001$). In other words, the greatest risk factors for transition were GAF score less than 44 and duration of symptoms longer than 738 days. Any given individual could have 0, 1, or 2 of these risk factors. The prediction measures of sensitivity, specificity, positive predictive value, and negative predictive value of having 1 or 2 of these risk factors is reported in Table 6. A UHR patient with either one or both of these factors had a 72% chance of developing psychosis within 5 years. A UHR individual with functioning above GAF 44 and/or duration of symptoms less than 738 days had a 69% chance of not developing psychosis within 5 years. These cut-off points provide an indication of which UHR patients might be at highest risk of transition over the medium term based on the modifiable risk factors found in the current data set. A positive count of more than 0 yielded stronger overall prediction measures than a positive count of 2 (positive on both risk factors).

### Analysis Without GAF

The analysis of predictors of transition was also performed without the GAF scale included because poor functioning may result from many different factors and may mask other significant predictors, including symptoms, since the GAF scale is scored on the basis of symptoms as well as functioning. That is, apparent poor social and role function may be associated with underlying symptoms, such as social withdrawal caused by suspiciousness (a disorder of thought content) or asociality (a negative symptom). Thus, a low GAF score may be due to prominent symptoms and not a true reflection of functioning. We therefore adjusted for baseline year and duration of symptoms, but not GAF score. In this exploratory analysis, baseline disorders of thought content (CAARMS scale) was found to be significantly associated with transition ($P = .00001$). Baseline negative symptoms were also significantly associated with transition when the GAF score was removed from the analysis, even after adjusting for a range of variables (Table 7).

### Discussion

To our knowledge, this was the first study to examine the longer-term outcome of a UHR cohort. Approximately 30% of the sample had a follow-up time of more than 10 years. There was an estimated transition rate of 34.9% of the sample during the follow-up period (2.4-14.9 years), with all transitions occurring within 10 years of entry to the clinic. The highest period of risk was within the first 2 years of entry, with more than two-thirds of the transitions occurring in this period. There was an ongoing but reduced rate of transition to psychosis after this point.

These data confirm that the UHR phenotype is a risk for future onset of psychotic disorder and indicate that the risk extends up to 10 years after initial identification. In this sense, the UHR phenotype is comparable to other conditions in general medicine. For example, most cases of multiple sclerosis (MS) are preceded by a clinically isolated syndrome, such as optic neuritis, transverse myelitis, and brainstem syndromes. The difficulty has been to identify which patients with a clinically isolated syndrome will go on to develop MS. During a 10-year period, a clinically isolated syndrome is associated with 11% to 22% risk for MS. This is analogous to the risk associated with initial presentation with UHR criteria. Notably, if a clinically isolated syndrome is accompanied by an abnormal magnetic resonance image of the brain, the 10-year risk of MS increases to between 56% and 83%. However, unlike in MS, we do not yet have robust biomarkers that enhance prediction of outcome in UHR, although they are the subject of ongoing research.

Poor functioning, long duration of symptoms, and earlier cohorts were associated with higher risk of transition. When global functioning (the GAF scale) was excluded from analysis, baseline negative symptoms and disorders of thought content also predicted transition. These predictors are consistent with previous research findings in short- to medium-term follow-up studies.

The significant association between longer duration of symptoms and higher transition rate indicates the importance of detecting UHR patients and referring them to specialist services. Increased awareness and assessment of subthreshold psychotic symptoms in primary care, effective referral pathways, and access to appropriate clinics is important. Awareness campaigns of targeting general practitioners and other services that manage care for young people with mental health problems may be appropriate. This should be coupled
Table 7. Cox Regression P Values for Association Between Transition and Baseline Negative Symptoms

<table>
<thead>
<tr>
<th>Row</th>
<th>Adjusted for</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>.007</td>
</tr>
<tr>
<td>2</td>
<td>BPERS.PS</td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td>TC</td>
<td>.02</td>
</tr>
<tr>
<td>4</td>
<td>PA</td>
<td>.006</td>
</tr>
<tr>
<td>5</td>
<td>CD</td>
<td>.02</td>
</tr>
<tr>
<td>6</td>
<td>BPERS.PS + TC + PA + CD</td>
<td>.046</td>
</tr>
<tr>
<td>7</td>
<td>BLYEAR + None</td>
<td>.0008</td>
</tr>
<tr>
<td>8</td>
<td>BLYEAR + BPERS.PS</td>
<td>.003</td>
</tr>
<tr>
<td>9</td>
<td>BLYEAR + TC</td>
<td>.0004</td>
</tr>
<tr>
<td>10</td>
<td>BLYEAR + PA</td>
<td>.0001</td>
</tr>
<tr>
<td>11</td>
<td>BLYEAR + CD</td>
<td>.0002</td>
</tr>
<tr>
<td>12</td>
<td>BLYEAR + BPERS.PS + TC + PA + CD</td>
<td>.002</td>
</tr>
<tr>
<td>13</td>
<td>Time to PACE</td>
<td>.04</td>
</tr>
<tr>
<td>14</td>
<td>GAF</td>
<td>.32</td>
</tr>
<tr>
<td>15</td>
<td>BLYEAR + Time to PACE + GAF</td>
<td>.83</td>
</tr>
</tbody>
</table>

Abbreviations: BLYEAR, baseline year; BPERS.PS, psychotic subscale of the Brief Psychiatric Rating Scale; CD, conceptual disorganization; GAF, Global Assessment of Functioning; PA, perceptual abnormalities; PACE, Personal Assessment and Crisis Evaluation; TC, disorders of thought content.

* Row 1: no covariate is adjusted for. Rows 2-5: adjusted for each of the BPERS positive subscales, and Comprehensive Assessment of At-Risk Mental States disorders of thought content, perceptual abnormalities, conceptual disorganization, respectively. Row 6: adjusted for all of the above positive symptom measures together. Rows 7-12: repeat Rows 1-6 but with BLYEAR as an additional covariate. Rows 13-15: adjusted for significant predictors found previously.

with an enrichment strategy based on screening for attenuated psychotic symptoms in help-seeking young people. A recent study33,54 found that a screening method in a consecutive help-seeking population entering secondary mental health services for nonpsychotic problems resulted in higher transition rates than sampling from a population referred to an early psychosis clinic.

However, any awareness campaign must be balanced against the potential problem that such campaigns will spread into the community (non-help-seeking) population. Psychotic-like symptoms are common in the general population,55 especially in adolescents,56-58 with a recent study59 finding that between 0.09% and 8% of a general population sample of adolescents met criteria for a risk syndrome, depending on varying disability criteria. Extending early detection to these populations, for instance, by screening for psychotic experiences in schools, may identify a large number of young people, many with transient psychotic experiences, most of whom are not distressed by or seeking help for their symptoms. Although such a screening strategy may detect some people genuinely at risk,59 particularly if the psychotic experiences are severe and persistent,60 these would be outnumbered by “false-positive” individuals, who are not at risk for psychiatric disorder. These falsely identified individuals would therefore be at risk of labeling, stigma, and unnecessary treatment.60-64 Increasing sensitivity, that is, detecting more people at risk, must be balanced against decreased specificity, that is, identifying people who are not at risk. Thus, it is important to refine risk factors for psychosis onset within the UHR group. The current results indicate that reduced functioning, long duration of symptoms, and possibly negative symptoms and disordered thought content are promising candidates for enhancing psychosis prediction and possibly could be incorporated into UHR criteria. However, these variables need to be validated in independent samples and included in the criteria only if found to be robust across different at-risk cohorts. This may result in more enriched samples (reflected in higher transition rates) than those found in some recent UHR studies, such as the Early Detection and Intervention Evaluation 2 trial.8

Our results indicate that the transition rate decreased during the 13-year period of 1993 to 2006. However, the duration of symptoms before presentation did not show a corresponding trend of reduction. This suggests that, although the mechanisms of lead-time bias and/or early intervention may still be plausible, they cannot fully explain the decreasing transition rates over the years. Two further possibilities (not mutually exclusive) for the declining transition rate unrelated to early detection are (1) a change in “treatment as usual” over the years toward a form of intervention that is more effective in reducing the onset of psychosis (eg, possibly increased rates of antidepressant medication prescription65,66) and (2) a dilution effect (ie, identifying more people with lower actual risk despite still meeting UHR criteria).19,53

There have been previous proposals56,67 that there are different types of attenuated psychotic symptoms associated with different levels of risk for psychotic disorder. Some attenuated psychotic symptoms may reflect the emergence of an underlying core psychotic process, some may be “clinical noise” associated with a nonpsychotic clinical condition, and some may be normal variations among the general population. Attenuated psychotic symptoms in the latter 2 groups would be associated with a lower risk of transition to schizophrenia. The finding that poor functioning, negative symptoms, and disorders of thought content (central features of schizophrenia)68 predict transition is consistent with this model. All of these clinical phenomena may indicate attenuated psychotic symptoms in the first category. Other attenuated psychotic symptoms, such as perceptual abnormalities, may not necessarily reflect the emergence of a core psychotic process. It is possible that over time more people with these lower risk symptoms have been referred to our clinic because of changes in service structure and referral networks, particularly in 2002 to 2003, with the service becoming a broader youth mental health service rather than exclusively an early psychosis service.52 However, it is difficult to ascertain exactly the reason for the apparent decline in transition rate from the current data.

The significant association between poor functioning and transition, which is consistent with previous research,2,6,10,16,69 indicates the importance of maintaining research and clinical attention on functioning levels in the UHR population and not focusing solely on symptoms.70 Poor functioning may be the result of a variety of reasons, including neurocognitive71-73 or social cognition deficits,74-77 social disadvantage,78-79 and psychological factors.79 Developing psychosocial interventions that target poor functioning should be a priority. Apart from being beneficial in its own right, it also may halt (over both the
short and long term) the evolution of positive psychotic symptoms to the point of full threshold disorder. However, it is also possible that poor functioning is an indicator or proxy of an underlying neurobiological process and may therefore be an early marker of poor prognosis, that is, it may indicate a deterioration process and that the onset of psychotic disorder has in fact already begun.\(^{69,73}\) There is a need for research that better characterizes reasons for poor functioning in the UHR group and the effect of this on, or how it might be an expression of, the clinical trajectory.

It also may be that transition to psychotic disorder is not the best indicator of poor outcome.\(^{86}\) Negative symptoms, neurocognition, social cognition, functioning, and persistent non-psychotic disorders also should be considered as significant outcomes. People who have poor social role function, neurocognitive decline, poor social cognition, and high levels of negative symptoms, all in the context of having met UHR criteria, may be on the schizophrenia spectrum without ever having developed full-threshold psychosis.\(^{80,81}\) Thus, these outcomes may be more relevant to an underlying schizophrenia construct than positive symptoms alone.

**Clinical Implications**

The finding that transitions can occur up to at least 10 years after presentation but that risk is highest in the first 2 years indicates that the period of clinical care for UHR patients should be at least 2 years, with the possibility of reentry to services after this point if required. This need for ongoing clinical care is underlined by the substantial death rate in the sample (2.2%), mainly due to suicide. The association between UHR state and suicidality has been noted.\(^{35,82}\) Hutton et al\(^{82}\) found that 59% of UHR individuals presented with at least mild suicidal ideation and 47% reported at least 1 suicide attempt before being accepted in an early intervention service. As indicated by the prediction analysis, patients with poor functioning and long duration of symptoms may need prolonged monitoring.

It may be that different types of intervention are appropriate for patients with different durations of symptoms (ie, in an early or late phase of high-risk status\(^{84,85}\)). More benign treatments, such as supportive therapy\(^{32}\) or \(\omega-3\) fatty acids\(^{19}\) could be attempted before other, more intensive, forms of treatment such as cognitive-behavior therapy.\(^{84,85}\) All of these treatments (supportive therapy, cognitive therapy and \(\omega-3\) fatty acids) address the UHR group’s clear need for care and are used for a range of mental health problems. Thus, they are low stigma and may be effective for several different conditions, including anxiety and depression. Antipsychotic medication is no more effective than more benign treatments\(^{84,32,86,87}\) and is currently not recommended for use in this population.\(^{88,89}\)

**Limitations**

A limitation inherent to long-term follow-up studies is recall bias. At the follow-up interview, participants were asked to recall events and symptoms that they might have experienced a long time ago. A second limitation relates to the determination of transition status using the public mental health service records for individuals who were not available for interview. The database contains information relating to assessments in public mental health services only in the state of Victoria. It is possible that people had contact with public services outside Victoria or private services, although the latter are scarce for people with psychotic disorders, especially those from relatively disadvantaged backgrounds, as was the case with our patients. It is also possible that some individuals who were unavailable for interview transitioned to psychosis but did not attend a public mental health service and therefore were not detected as transitioned cases. Previous research\(^{89}\) indicates that difficulty recontacting members of adolescent and young adult psychiatric cohorts is associated with increased presence of disorder at follow-up. Together, these factors suggest that the transition rate may have been underestimated in the results. The study used data from a single center. It is possible that local factors (changes in service structure and referral networks) may have had an effect on the results. Finally, there were minor modifications to the UHR criteria and instruments used to assess UHR criteria over the baseline recruitment period. Although we do not believe that this would have had a significant effect on whether participants met UHR criteria, which UHR group they met, or transition risk, this has not been formally assessed.

**Implications for DSM-5 Proposal**

Attenuated psychosis syndrome was recently relegated to the DSM-5 section for further research. This was because of concerns about reliability. Indeed, William Carpenter, chair of the Psychosis Working Group, stated, “Psychotic risk syndrome is valid.”\(^{91}\) Thus, further research on its ability to predict future psychosis is still required, especially given the apparent return to the “risk syndrome” terminology.\(^{91}\) Commentators have interpreted 20% to 40% transition rates in both a favorable and unfavorable light regarding this diagnosis. Some argue that these rates of transition justify diagnosis and treatment to prevent psychosis, while others argue that this level of risk is not sufficient to warrant a formal diagnosis given issues such as the potential for unnecessary treatment and stigma (see Nelson and Yung\(^{92}\) for review of this subject). The apparent declining transition rate is also relevant and needs to be better understood. More research is needed to enhance specificity and sensitivity of prediction by modifying existing UHR criteria, combining the UHR criteria with additional risk factors such as biomarkers, or using a 2-stage screening process.

**Conclusions**

Patients at UHR are at long-term risk of transition to psychotic disorder, particularly in the first 2 years after service entry. This is an important finding given the doubt expressed recently about the predictive value of the concept.\(^{8,93}\) Long duration of symptoms, low functioning, negative symptoms, and disorders of thought content predicted psychosis. Ongoing research is needed to identify additional robust predictors. Services should aim to follow up patients for at least 2 years. Individuals with a long duration of symptoms and poor functioning may need closer monitoring.
ARTICLE INFORMATION

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