Title:
Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis

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Abstract (words 250)

Objectives
Two thirds of individuals identified as ultra-high risk for psychosis do not develop psychotic disorder over the medium-term. This paper examines their outcome, including persistent attenuated psychotic symptoms, and incident and persistent non-psychotic disorders.

Method
Participants were help-seeking individuals identified as being at ultra-high risk for psychosis between two and 14 years previously (median=5.7). The current sample consists of 226 participants (125 females; 101 males) who completed follow-up assessment and had not developed psychosis. Mean age at follow-up was 25.5 years (SD=4.8).

Results
Significant psychopathology was found. 28% reported attenuated psychotic symptoms at follow-up; 68% of participants experienced non-psychotic disorder over the follow-up period; 48% experienced mood disorder, 34% anxiety disorder and 29% a substance use disorder. For the majority, non-psychotic disorder was present at baseline (90%), and was persistent for 57% of them. Over the follow-up period, 26% of the cohort remitted from a disorder, but 37% developed a new disorder. Only 7% did not experience any disorder over the follow up period.

The incidence of non-psychotic disorder was associated with higher negative symptoms at baseline. Females experienced higher rates of persistent/recurrent disorder. Meeting the brief limited intermittent psychotic symptoms group at intake was associated with lower risk for persistent/recurrent disorder.

Conclusions
Non-transitioned ultra-high risk cases are at significant risk for continued attenuated psychotic symptoms, and persistent/recurrent and incident disorders. The ultra-high risk phenotype, while relatively specific to incident psychosis, also captures patients with a range of emerging or chronic psychopathology. Findings have implications for on-going clinical care.
Introduction

The period preceding the onset of psychotic disorder has received growing attention since the introduction of criteria for identifying youth at ultra-high risk for psychosis (1). These combine state and trait risk factors to identify young people potentially in the prodrome of psychotic illness. The average transition rate to psychotic disorder is estimated at 36% after three years (2). Although this reflects a much higher rate of psychosis than in the general population or other clinical samples, two thirds of those identified as at-risk do not develop psychotic disorder in the medium-term.

One possible explanation is that the majority of individuals referred to at-risk services present with transient psychotic experiences. While they fulfil at-risk criteria, these experiences may not be indicative of impending psychotic illness (3). Psychotic experiences often occur in the general population, but persist in only a small proportion of those who report them (4), and an even smaller proportion develop psychotic disorder (5). Rather, psychotic experiences may be related to other psychopathology, such as depression and anxiety (6, 7), which are common in at-risk samples (8-12).

Given the common occurrence of non-psychotic disorders in this population (8-12) and the declining rate of transition to psychotic disorder in recent cohorts (13, 14), it is important to examine the outcomes of those individuals who do not develop psychosis. Results from small samples show high rates of mood disorder at six (15) and 12-month follow-up (16-18). Anxiety disorders are also common (16, 17). In a large at-risk sample, Addington and colleagues (19) showed that, in the group who did not develop psychosis, 29% had mood disorder and 38% had anxiety disorder after one year. These rates dropped to 15% and 32% respectively by two year follow-up (19). Substance use disorders were also prevalent, but reduced after two years. These statistics suggest that young people meeting at-risk criteria who do not develop psychosis continue to experience significant mental health problems.

It is also possible that non-transitioned cases continue to experience attenuated psychotic symptoms and meet at-risk criteria. Rates of attenuated psychotic symptoms at one year follow-up vary from 23% to 42% (16, 18, 19). At two years, attenuated symptoms are evident in 35% (20) and 40% (19) of at-risk samples, and 25% (21) and 50% (22) at 3 years. Continued attenuated symptoms could represent an extended prodrome with transition to psychosis yet to occur. Alternatively, young people with attenuated symptoms may not be prodromal, but their ongoing symptoms may be distressing and disabling in their own right.
and may be comorbid with threshold or subthreshold mood or anxiety disorder. Although there are now substantial data on persistent attenuated psychotic symptoms, definitions and rates are inconsistent, making it difficult to ascertain true remission rates.

There is also a lack of data on the course of psychopathology for at-risk youth who do not develop psychosis. In the current study we investigated the presence of attenuated psychotic symptoms, the prevalence and course of non-psychotic DSM-IV diagnoses, and predictors of non-psychotic outcomes in those who did not transition to psychotic disorder from a cohort identified as ultra-high risk between two and 14 years previously [the PACE 400 sample (14)]. Based on the previous studies (15-19), we expected high rates of non-psychotic psychopathology in this group.
Method

Participants and procedure

PACE is a specialist clinic for young people at ultra-high risk for psychosis, in Melbourne, Australia. The current data are from a study aiming to reassess all research participants at PACE between 1993 and 2006 (N=416). Follow-up interviews were completed by 311 participants (74.8%), 85 of whom had developed psychotic disorder [see (14)]. The current sample consists of 226 participants (125 females; 101 males) who completed follow-up assessment but had not transitioned to psychosis. Figure 1 shows the composition of the current sample.

At baseline, participants were aged 15 to 30 years and met ultra-high risk criteria. These are: 1) attenuated psychotic symptoms, 2) brief limited intermittent psychotic symptoms, and/or 3) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning [see (14) for full description of determination of ultra-high risk status of this cohort]. Exclusion criteria for entry to PACE are a previous psychotic episode, organic cause for presentation or past anti-psychotic exposure equivalent to a haloperidol dose of >15 mg.

A previously developed tracking system (23) was used to relocate participants. If participants did not consent to face-to-face assessment, they were asked for a telephone interview or written assessment. This study was approved by the local Research and Ethics Committee. All participants provided written informed consent.

Measures

Current assessment (follow-up): Axis I diagnoses at two to 14 year follow-up were assessed using the Structured Clinical Interview for DSM-IV [SCID-I; (24)]. Face-to-face interview was completed for 194 (85.5%), a telephone interview for 29 (12.8%) and in writing for three (1.3%). The Comprehensive Assessment of At-Risk Mental States [CAARMS; (25)] was used to assess the presence of attenuated psychotic symptoms.

Previous assessment at initial presentation to PACE (baseline): Baseline psychopathology was measured using the Brief Psychiatric Rating Scale [BPRS; (26)], Scale of Assessment for Negative Symptoms [SANS; (27)], and CAARMS (25). We used the BPRS psychotic subscale (items: unusual thought content, hallucinations, suspiciousness, conceptual disorganisation) and affective subscale (items: anxiety, depression, guilt, somatic concerns, tension). CAARMS positive subscales were disorders of thought content, perceptual
abnormalities and conceptual disorganisation. Functioning was assessed with the Global Assessment of Functioning (GAF). Diagnoses were assessed using the SCID-I.

Current IQ was measured using the Wechsler Adult Intelligence Scale-Revised [WAIS-R; (28)] or the Wechsler Abbreviate Scale of Intelligence [WASI; (29)]. Eight of the younger participants were assessed using the Wechsler Intelligence Scale for Children [WISC-III; (30)]. IQ was estimated using 1) Ward’s (31) 7-subtest estimate of verbal, performance and full-scale IQ (n=52); 2) Kaufman’s 4-subtest (32) estimate of full-scale IQ (n=9); or 3) WASI estimate of verbal, performance and full-scale IQ (n=123).

Statistical analyses

Data were examined for the frequency of current attenuated psychotic symptoms, non-psychotic DSM-IV disorders during the follow-up period (current or since baseline) and the course of disorders. Three disorder groups were examined: mood, anxiety and substance use disorders, as well as the frequency and course of any disorder. Somatoform and eating disorders occurred rarely and were not included.

The course of disorders was examined for participants who had diagnostic assessment at baseline and follow-up (n=203 for mood/anxiety; n=192 for substance use). Participants were classed as ‘never’ if the disorder was not present at baseline or during follow-up; ‘persistent/recurrent’ if disorder was present at baseline and during follow-up; ‘remission’ if disorder was present at baseline but absent during follow-up; ‘incident’ if disorder was absent at baseline but present during follow-up (see Figure 2).

To investigate candidate predictors of the course of disorders, participants with incident disorder were compared to participants who never had the disorder. Participants with persistent/recurrent disorder were compared to those with remitted disorder. Candidate predictors were intake group, GAF, BPRS psychotic score, BPRS affective score, SANS total, CAARMS disorders of thought content, CAARMS perceptual abnormalities, CAARMS conceptual disorganization, verbal IQ, performance IQ and full-scale IQ. For primary analyses, predictors with a univariate association at p<0.1 were entered together into binary logistic regression to identify the strongest predictors. Age at baseline, gender and length of the follow-up period were always included as predictors. Analyses were conducted for mood, anxiety and substance use disorders separately, and then for any disorder. Our study numbers gave us 80% power to detect (at significance level p<0.05) a reduction in persistence/recurrence of any disorder from 67% to 45% associated with removal of a
common risk factor (e.g. gender) with 50% prevalence and similar power to detect a reduction from 67% to 41% associated with removal of a rarer risk factor with 25% prevalence. For incidence of any disorder, we were similarly powered to detect a reduction from 84% to 57% associated with a common risk factor and 84% to 54% with a rarer risk factor.

Given the large variability in follow-up period, the cohort was divided into three subsamples based on when they were identified as at-risk: long- (1993-2000, \(N=82\)), medium- (2001-2003, \(N=77\)) and short-term follow-up periods (2004-2006, \(N=67\)). Frequencies are presented for the entire cohort and each subsample. Given the volume of data, some analyses (including exploratory analyses of neurocognitive predictors) are presented in online supplementary data only.
Results

Sample characteristics

More females completed follow-up than males (55.3% female; $\chi^2=5.12$, $p=0.02$). There were no other significant differences between participants who were followed-up and those that were not. The mean age of participants at baseline was 18.6 years ($SD=3.3$) and 25.5 years ($SD=4.8$) at follow-up. Follow-up was conducted between 2.4 and 14.1 years after baseline ($M=6.9$; $SD=3.1$; median=5.72). Eighty-two (36.3%) participants received trial treatment at PACE [cognitive-behaviour therapy ($n=25$); cognitive-behaviour therapy and low-dose antipsychotics ($n=38$); low-dose lithium ($n=19$), all $\leq 12$ months]. There were no significant differences between participants who received trial treatment and those who did not on rates of disorders during follow-up. Further characteristics for each subsample are presented in Supplementary Table 1.

The use of antipsychotic and ‘any psychiatric medication’ in the two years prior to follow-up were documented for 184 participants (81% of the sample). Of these participants, 5 (2.7%) reported using antipsychotic medication and 70 (38%) used any psychiatric medication ‘some or all of the time’ in the past two years.

Frequency and comorbidity of non-psychotic disorders at follow-up

Diagnostic outcomes at follow-up are presented in Table 1. Of the entire cohort, 68.1% met criteria for at least one disorder during the follow-up period. Mood disorder was present during follow-up for 48.7%, anxiety disorder for 34.5% and substance use disorder for 29.2%. Proportions were not notably different between subsamples.

For the entire cohort, both mood and anxiety disorders were present in 24.3%, mood and substance use disorders in 17.7%, anxiety and substance use disorders in 13.7% and all three disorders in 10.2%. Patterns of comorbidity were similar in the 1993-2000 and 2003-2006 subsamples, but lower in the 2001-2003 group (see Table 1).

Attenuated psychotic symptoms

The proportion of participants reporting attenuated psychotic symptoms at follow-up that were at or above the threshold for ultra-high risk was 28.3% for the entire cohort, 24.4% for the 1993-2000 subsample, 23.4% for the 2001-2003 subsample, and 41.9% for the 2004-2006 subsample (data missing for 30 of the participants with telephone/written assessment at follow-up).
The co-occurrence of attenuated symptoms and disorders at follow-up is presented in Table 2. For the entire cohort, the presence of attenuated psychotic symptoms was significantly associated with mood disorder ($\chi^2=7.81$, $p=0.005$) and with any non-psychotic disorder over the follow-up period ($\chi^2=5.91$, $p=0.02$), but not with anxiety and substance use disorders. Results were similar for the 2004-2006 subsample (mood disorders, $\chi^2=9.14$, $p=0.003$; any disorder, $\chi^2=8.19$, $p=0.004$).

Of the 5 participants using antipsychotics in the two years before follow-up, three had persistent attenuated psychotic symptoms, and two had no attenuated symptoms. Participants who reported any psychiatric medication use were more likely to report current attenuated psychotic symptoms than those who did not (45.7% vs. 26.3%; $\chi^2=6.46$, $p=.01$).

**Course of non-psychotic disorders**

Table 3 shows the frequencies of baseline disorder, remission, incidence, persistence/recurrence and absence of non-psychotic disorders. Below we report results for the entire cohort. Of the participants who had a mood disorder at baseline (64.2%), 53.8% had persistent/recurrent disorder. In those without mood disorder at baseline, 32.8% developed one. Of those with anxiety disorder at baseline (35.8%), 40.7% experienced persistent/recurrent anxiety. Of those without anxiety disorder at baseline, 29.5% developed one. Substance use disorders were present at baseline for 21.9% individuals (of 192 with available baseline substance use diagnoses). Of them, over half (52.4%) showed persistent/recurrent substance use disorder over follow-up. Of those without substance use disorder at baseline, 22.3% developed a substance use disorder.

In terms of any disorder, 90.1% of the cohort had any non-psychotic disorder at baseline. Over the follow-up period, 26.0% of the entire cohort remitted from a disorder, but 37.5% developed a new disorder. 57.2% of the cohort had a persistent/recurrent non-psychotic disorder. Only 7.3% never experienced any disorder.

For the most part, the course of disorders were not notably different between subsamples, with the exception of the 2004-2006 subsample presenting with lower rates of substance use disorders at baseline. However, the rate of incident substance use disorder in this subsample was comparable to the other groups.
Predictors of the incident disorder and remission

Baseline symptomatology, GAF, IQ and age were poor predictors of the course of disorder. Gender emerged as a significant predictor of specific disorders, although the overall models were not statistically significant. Being female was associated with persistent/recurrent mood disorder, compared to remitted mood disorder (odds ratio = 2.07, 95% CI for odds ratio = 1.02-4.23, \(p=0.05\)), and with incident anxiety disorder compared to never having an anxiety disorder (odds ratio = 2.66, 95% CI for odds ratio = 1.11-6.39, \(p=0.03\)).

The incidence of any disorder was associated with higher baseline scores on the SANS (odds ratio = 1.14, 95% CI for odds ratio = 1.01-1.29, \(p=0.03\)) compared to never having a disorder. The persistence/recurrence of any disorder, as opposed to remission from any disorder, was associated with being female (odds ratio = 2.40, 95% CI for odds ratio = 1.12-5.15, \(p=0.02\)). Meeting the criteria for brief limited intermittent psychotic symptoms at intake to PACE was associated with a decreased chance of persistent/recurrent disorder (odds ratio = 0.19, 95% CI for odds ratio = 0.05-0.72, \(p=0.01\)). Despite its variability, the length of follow-up did not predict the course of disorder in the entire cohort.

Predictors of the course of disorders for each subsample and exploratory analyses of neurocognitive performance are presented in online supplementary data.
Discussion

In this study, we examined the clinical outcome for individuals who did not transition to psychotic illness in a cohort identified as ultra-high risk for psychosis between two and 14 years earlier. The frequency and course of mood, anxiety and substance use disorders were examined. Approximately a quarter of cases experienced attenuated psychotic symptoms at follow-up assessment. Non-psychotic disorders were often present at baseline, and tended to persist over the follow-up period. Incident non-psychotic disorder was also common, occurring in over one third of the sample. Baseline and demographic variables were not strong predictors of the course of non-psychotic disorders.

Persistent attenuated psychotic symptoms

Twenty-eight per cent of the current sample reported attenuated psychotic symptoms at follow-up assessment. Considered together with the cases in the cohort that developed psychosis (14), half of those who met ultra-high risk criteria at PACE showed continued or recurrent positive psychotic symptoms (threshold or subthreshold). The presence of attenuated psychotic symptoms may reflect that some individuals are still at risk for psychosis. This is possible since transitions occurred up to ten years after identification of risk in this sample (14). Alternatively, attenuated symptoms may occur in the context of non-psychotic disorders, which resolve with resolution of that disorder (3, 6, 7). This would be consistent with the idea of “incidental” psychotic symptoms (33). The fact that participants with the shortest follow-up period showed the highest rates of attenuated symptoms, and that their attenuated symptoms were associated with non-psychotic disorders, could support either of these possibilities.

Non-psychotic disorders

Mood disorders were the most common diagnosis during follow-up, specifically major depressive disorder. This was followed by high rates of anxiety disorders, cannabis dependence and alcohol abuse. These rates are higher than would be expected in the general population. A detailed comparison of our cohort with Australian general population data (34) is presented in online Supplementary Table 3. Briefly, the rates of non-psychotic disorders in this cohort were higher than the 12-month prevalence of these disorders for a similar age group in the general population, as well as higher than lifetime prevalence of adults of all ages. Notably, the prevalence of mood disorder over follow-up in our cohort was increased by
a factor of five compared to 12-month prevalence and a factor of three compared to lifetime prevalence in the general population.

This would be expected of a selected help-seeking sample. Indeed, many non-psychotic disorders were already present at baseline. Importantly, disorders persisted for approximately half of these young people who did not develop psychosis. In addition, for those without a non-psychotic disorder at baseline, the incidence of new disorders was common. In fact, over a third of the sample developed an incident disorder over the follow-up period. Thus the ultra-high risk criteria might also represent a useful system for identifying young people at risk for chronic and emerging non-psychotic disorder, especially since they are already linked with youth mental health services. This highlights the need for further investigation to develop a better understanding of the risk factors associated with non-psychotic disorder in this population.

We explored positive and negative psychotic symptoms, affective symptoms, functioning, IQ, gender and age as predictors of course of disorder. Being female was associated with higher risk of disorder than being male, consistent with general population data (34). However, no other baseline variables were associated with the course of a specific disorder. Interestingly, higher SANS scores at baseline and not meeting brief limited intermittent psychotic symptoms criteria were associated with the incidence and persistence/recurrence of any disorder, respectively. This could demonstrate the specificity of brief limited intermittent psychotic symptoms to psychotic disorder and, on the other hand, the non-specificity of symptoms measured on the SANS. It may be that depressive symptoms were interpreted as negative symptoms and rated on the SANS. Alternatively, those with high negative symptoms and depressive disorder may continue to be in the prodrome of a psychotic disorder, as both are known to occur during this phase in schizophrenia (35, 36).

Although highly variable, the length of the follow-up period was not strongly associated with the course of disorders. Notably, in the subsample with the shortest follow-up period, persistence/recurrence of any disorder was associated with a shorter follow-up period, consistent with the decrease in the rate of non-psychotic disorders that was noted by Addington and colleagues (19). Together with the finding of considerably higher attenuated psychotic symptoms in this subsample, our data suggest that the time for which participants are monitored may be important over the short-term (first two to four years), but becomes less important over the longer-term. This has implications for many studies, which typically track at-risk participants for one to three years.
The lack of strong predictors of non-psychotic disorder is distinctly different from the prediction of psychotic illness in at-risk samples, where a number of baseline symptoms are consistently shown to predict onset of psychosis. This does not imply that the course of non-psychotic illness cannot be predicted. Rather, it suggests that clinical variables that predict non-psychotic disorder may be different from those that predict psychotic illness, highlighting the need to design studies with a focus on multiple outcomes at inception (37).

The strength of this study is the large sample size recruited from a single site, the long follow-up period and high follow-up rates. The greatest limitation is the variable length of the follow-up period. Although we have presented data for the entire cohort as well as for subsamples of short-, medium- and long-term follow-up, subsamples do differ in some respects and analyses are complicated by this. Moreover, the epochs used are arbitrary.

Another limitation is that we did not comprehensively document treatment over the entire follow-up period, limiting it as a potential predictor of the course of disorders. Additionally, follow-up diagnosis of 32 participants was made via telephone or written interview. Finally, females were over-represented at follow-up, which may bias towards higher levels of mood and anxiety disorder.

The current findings demonstrate significant psychopathology in non-transitioned cases two to 14 years after identification of risk. Persistent or recurrent non-psychotic disorders were frequent even though these young people had previously been involved with youth mental health services, albeit in a time-limited manner. Clinically, the results suggest the need for at-risk clinics to include non-psychotic outcomes in their treatment and follow-up plans.

We have previously proposed a clinical staging model that posits that severe mental disorders (e.g. schizophrenia, bipolar disorder, severe unipolar depression) develop from initial non-specific symptoms, such as depressed mood, anxiety and distress (38). Acquisition of new symptoms, including psychotic symptoms and worsening of emotional dysregulation occurs in some people, who might then meet the psychosis at-risk criteria. From this clinical picture, a number of trajectories and outcomes are possible, including the major mental disorders noted above, remission, or persistence of subthreshold syndromes. The ultra-high risk criteria were developed to detect incident psychotic disorders and have proved valid to that end. It is not surprising therefore that they identify high rates of schizophrenia (39). Future studies need to investigate the risk factors for chronic and incident non-psychotic disorder by incorporating variables of interest to non-psychotic outcomes in their designs, for
example Axis II disorders, mood disturbance, cognitive biases or family history of non-psychotic disorders. Moreover, there is a need to investigate how functional outcome is associated with the presence of non-psychotic disorders. This knowledge will increase the understanding of the factors associated with the onset, course and outcome of disorders in this population, and how they can best be treated.
Text for Figures

Figure 1. Composition of the PACE ultra-high risk cohort and current sample

Note. The current sample (N=226) is indicated in bold. Of the 203 with diagnostic information at baseline and follow-up, 11 were missing substance use diagnoses at baseline.

Figure 2. Definitions used for the course of non-psychotic disorders in this study
Table 1. Rates of Axis I diagnoses during the follow-up period

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<td>4 4.9</td>
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<td>Any somatic disorder †</td>
<td>6 2.7</td>
<td>4 4.9</td>
<td>1 1.3</td>
<td>1 1.5</td>
</tr>
<tr>
<td>Any eating disorder †</td>
<td>11 4.9</td>
<td>2 2.4</td>
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<td>6 9.0</td>
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<tr>
<td>Mood + Anxiety</td>
<td>55 24.3</td>
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<td>Mood + Substance use</td>
<td>40 17.7</td>
<td>17 20.7</td>
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<tr>
<td>Anxiety + Substance use</td>
<td>31 13.7</td>
<td>14 17.1</td>
<td>9 11.7</td>
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<tr>
<td>All three disorders</td>
<td>23 10.2</td>
<td>12 14.6</td>
<td>4 5.2</td>
<td>7 10.4</td>
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Note: Bipolar disorder refers to non-psychotic cases only.

*Other mood disorders refers to depressive disorder not otherwise specified, bipolar disorder not otherwise specified and substance-induced mood disorders. Other anxiety disorder refers to anxiety disorder not otherwise specified or substance-induced anxiety disorder. Other drug abuse and dependence refers to sedatives, opioids, paint sniffing or hallucinogens.
Any somatoform disorder refers to body dysmorphic disorder, hypochondriasis, undifferentiated somatoform disorder, pain disorder or somatoform disorder not otherwise specified. Any eating disorder refers to anorexia nervosa, bulimia nervosa, binge eating disorder or eating disorder not otherwise specified.
Table 2. Co-occurrence of attenuated psychotic symptoms and non-psychotic disorders at follow-up assessment

<table>
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<tbody>
<tr>
<td></td>
<td>Attenuated psychotic symptoms (n=64)</td>
<td>No attenuated psychotic symptoms (n=132)</td>
<td>Attenuated psychotic symptoms (n=20)</td>
<td>No attenuated psychotic symptoms (n=50)</td>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
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<td>Mood disorder</td>
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<td>65.6</td>
<td>57</td>
<td>43.2</td>
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<td>Anxiety disorder</td>
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<td>48.4</td>
<td>46</td>
<td>34.8</td>
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<td>Substance use disorder</td>
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<td>42.2</td>
<td>39</td>
<td>29.5</td>
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<tr>
<td>Any non-psychotic disorder</td>
<td>54</td>
<td>84.4</td>
<td>88</td>
<td>66.6</td>
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Table 3. Course of non-psychotic disorders

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<td><strong>PRESENT AT BASELINE</strong></td>
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<tr>
<td>Any disorder</td>
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<td>73 94.8</td>
<td>53 81.5</td>
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<tr>
<td>Any mood disorder</td>
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<td>33 54.1</td>
<td>61 79.2</td>
<td>51 78.5</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>81 39.9</td>
<td>21 34.4</td>
<td>34 44.2</td>
<td>26 40.0</td>
</tr>
<tr>
<td>Any substance use disorder</td>
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<td>17 34.0</td>
<td>21 27.3</td>
<td>4 6.1</td>
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<td>22 28.6</td>
<td>16 24.6</td>
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<tr>
<td>Any mood disorder</td>
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<td>31 40.3</td>
<td>23 35.4</td>
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<td>Any anxiety disorder</td>
<td>48 23.6</td>
<td>13 21.3</td>
<td>22 28.6</td>
<td>13 20.0</td>
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<tr>
<td>Any substance use disorder</td>
<td>20 10.4</td>
<td>7 14.0</td>
<td>12 15.6</td>
<td>1 1.5</td>
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<tr>
<td>Any mood disorder</td>
<td>19 9.3</td>
<td>9 14.8</td>
<td>4 5.2</td>
<td>6 9.2</td>
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<tr>
<td>Any anxiety disorder</td>
<td>36 17.7</td>
<td>13 21.3</td>
<td>11 14.3</td>
<td>12 18.5</td>
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<tr>
<td>Any substance use disorder</td>
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<td>7 14.0</td>
<td>12 15.6</td>
<td>14 21.5</td>
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<td><strong>PERSISTENCE/ RECURRANCE</strong></td>
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<td>Any disorder</td>
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<td>29 58.0</td>
<td>40 51.9</td>
<td>30 46.1</td>
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<td>Any mood disorder</td>
<td>78 38.4</td>
<td>20 32.8</td>
<td>30 39.0</td>
<td>28 43.1</td>
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<tr>
<td>Any anxiety disorder</td>
<td>33 16.2</td>
<td>8 13.1</td>
<td>12 15.6</td>
<td>13 20.0</td>
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<tr>
<td>Any substance use disorder</td>
<td>22 11.5</td>
<td>10 20.0</td>
<td>9 11.7</td>
<td>3 4.6</td>
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<tr>
<td><strong>NEVER</strong></td>
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<tr>
<td>Any disorder</td>
<td>14 7.3</td>
<td>5 10.0</td>
<td>3 3.9</td>
<td>6 9.2</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>39 19.2</td>
<td>19 31.1</td>
<td>12 15.6</td>
<td>8 12.3</td>
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<tr>
<td>Any anxiety disorder</td>
<td>86 42.3</td>
<td>27 44.3</td>
<td>32 41.6</td>
<td>27 41.5</td>
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<tr>
<td>Any substance use disorder</td>
<td>117 60.9</td>
<td>26 52.0</td>
<td>44 57.1</td>
<td>47 72.3</td>
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</tbody>
</table>

*11 participants in the 1993-2000 subsample had no available substance use disorder data at baseline. Hence, N for the entire cohort is 203 for mood and anxiety disorders, and 192 for substance use disorder or any disorder. N for 1993-2000 is 61 for mood and anxiety disorders, and 50 substance use disorder or any disorder.
Figure 1. Composition of the PACE ultra-high risk cohort and current sample

Note. The current sample (N=226) is indicated in bold. Of the 203 with diagnostic information at baseline and follow-up, 11 were missing substance use diagnoses at baseline.
Figure 2. Definitions used for the course of non-psychotic disorders in this study
References


Nathan (not his real name) was a 16-year old high school student who lived with his mother and 14-year old brother. He was referred to the PACE Clinic by his mother in 2004 as he had often been refusing to attend school in the last 3 months. On presentation, Nathan said that school made him nervous because he thought that everyone there was against him and hated him. He sometimes had difficulty even leaving the house as he felt that strangers may also be laughing at him and talking about him. He usually realised that he was “being a bit paranoid” because he knew it did not make sense for strangers to look at him, but at other times he wondered if there was something wrong with him. He would always wear a hoodie and sunglasses outside so that no-one would notice him.

Nathan would often stay up until 3-4am and had frequently been sleeping in until early afternoon. He would then claim to be too tired to go to school and spend his days playing video games. On questioning, Nathan admitted to feeling down sometimes and frequently being irritable and angry. He sometimes lost his temper with his mother and his brother over minor incidents.

Nathan reported that he was bullied, both physically and verbally, at primary school and in his early high school years. On assessment, Nathan met the ultra-high risk criteria based on attenuated psychotic symptoms and DSM-IV criteria for Major Depression. Social and Occupational Functioning Assessment Scale (SOFAS) score was 55.

**Progress**

Nathan was managed with cognitive behavioural therapy (CBT) that helped him identify triggers for paranoid thoughts, and reduce safety behaviours. He was encouraged to improve his sleep hygiene. He was prescribed 20 mg of fluoxetine daily. Using CBT techniques, Nathan discovered that if he walked down the street slowly and without his hood up that no-one would look at him. This helped him to feel less paranoid. At his request he changed schools for the start of a new year so he could make a fresh start. He gradually felt less irritable and his mood improved. By the time of discharge from the PACE Clinic six months after beginning treatment, Nathan no longer met criteria for Major Depression or the ultra-high risk criteria, and was attending school most days.

**Outcome:**

When Nathan was seen for research in 2008, he reported that he had been feeling “mentally well” since being discharged from the PACE Clinic. He had completed high school, receiving “average grades” and had almost completed his training as an apprentice electrician. He was in a steady relationship. He reported no attenuated psychotic symptoms and did not meet any DSM-IV criteria. His SOFAS score was 85.
Brittany (not her real name) was an 18 year old unemployed woman who lived with her mother, step-father and 2 younger half-sisters. She was referred to the PACE Clinic in 2001 by her General Practitioner (GP) due to concerns about her anxiety. Brittany described a lifelong history of generalised anxiety. She had been shy and timid at school and had left school at 15 because she felt she could not cope with the pressure. She had not worked since leaving school. Over the year prior to referral she reported increased anxiety as she felt she could not handle the challenges of being an adult. She believed that she should be able to work and have a boyfriend and friends, but felt tense even thinking about achieving any of these. Her had trouble sleeping, which left her feeling irritable and tired most of the time.

In the 3 months prior to referral Brittany started hearing whispering and mumbling noises, especially when she was stressed. She heard her name being called every few weeks. In the one month prior to referral she heard more clear voices. This occurred infrequently but made her concerned that she was “going crazy”. She rarely left the house.

On assessment, Brittany met the ultra-high risk criteria based on her attenuated psychotic symptoms and DSM-IV criteria for Generalised Anxiety Disorder and Social Anxiety Disorder. Her SOFAS score was 45.

**Progress**

Brittany received case management and supportive therapy. She was offered CBT but after two sessions stated that she did not like it as it made her feel like she was a “failure at thinking”. She was referred to a group program for social anxiety and to an outdoor activities program but did not attend either as she felt too anxious. Her intermittent auditory hallucinations remained stable. She continued to feel anxious although reported that she felt slightly better as she enjoyed talking to her case manager. After 6 months Brittany’s tenure of care at the PACE Clinic was complete and she was referred back to her GP.

**Outcome**

When Brittany was seen for research in 2008, seven years after initial presentation, she reported that she had developed depression and had been prescribed anti-depressant medication for the last 5 years by her GP. She sometimes experienced hearing “a soft noise, like a whisper” when she felt very down, but this only occurred once every month or two. She remained anxious and was unable to work, but had recently started a relationship with a man whom she had met in the GP’s waiting room. She still met criteria for Generalized Anxiety Disorder, as well Major Depression. Her SOFAS score was 55.