Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis

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Objective: Two-thirds of individuals identified as at ultra-high risk for psychosis do not develop psychotic disorder over the medium term. The authors examined outcomes in a group of such patients.

Method: Participants were help-seeking individuals identified as being at ultra-high risk for psychosis 2–14 years previously. The 226 participants (125 female, 101 male) completed a follow-up assessment and had not developed psychosis. Their mean age at follow-up was 25.5 years (SD=4.8).

Results: At follow-up, 28% of the participants reported attenuated psychotic symptoms. Over the follow-up period, 68% experienced nonpsychotic disorders: mood disorder in 49%, anxiety disorder in 35%, and substance use disorder in 29%. For the majority (90%), nonpsychotic disorder was present at baseline, and it persisted for 52% of them. During follow-up, 26% of the cohort had remission of a disorder, but 38% developed a new disorder. Only 7% did not experience any disorder at baseline or during follow up. The incidence of nonpsychotic disorder was associated with more negative symptoms at baseline. Female participants experienced higher rates of persistent or recurrent disorder. Meeting criteria for brief limited intermittent psychotic symptoms at intake was associated with lower risk for persistent or recurrent disorder.

Conclusions: Individuals at ultra-high risk for psychosis who do not transition to psychosis are at significant risk for continued attenuated psychotic symptoms, persistent or recurrent disorders, and incident disorders. Findings have implications for ongoing clinical care.

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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 rate of transition to psychotic disorder is estimated at 36% after 3 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 services for at-risk individuals are experiencing transient psychotic experiences. While they fulfill at-risk criteria, these experiences may not indicate impending psychotic illness (3). Psychotic experiences often occur in the general population, but they persist in only a small proportion of the people 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 nonpsychotic 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 the individuals who do not develop psychosis. Results from small samples show high rates of mood disorder at 6-month (15) and 12-month (16–18) follow-up. Anxiety disorders are also common (16, 17). In a large at-risk sample, Addington and colleagues (19) showed that, of the individuals who did not develop psychosis, 29% had mood disorder and 38% had anxiety disorder after 1 year. These rates dropped to 15% and 32%, respectively, by 2-year follow-up (19). Substance use disorders were also prevalent, but their number was reduced after 2 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 at-risk individuals who have not transitioned to psychosis continue to experience attenuated psychotic symptoms and meet at-risk criteria. Rates of attenuated psychotic symptoms at 1-year follow-up vary from 23% to 42% (16, 18, 19). At 2 years, attenuated symptoms have been evident in 35% (20) and 40% (19) of at-risk samples and in 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 nonpsychotic DSM-IV diagnoses, and predictors of nonpsychotic outcomes in those who did not transition to psychotic disorder from a cohort identified as ultra-high risk between 2 and 14 years previously at the Personal Assessment and Crisis Evaluation (PACE) clinic; the group is known as the PACE 400 sample (14). On the basis of the previous studies (15–19), we expected high rates of nonpsychotic 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 (14). The current sample consisted of 226 participants (125 female, 101 male) who completed a follow-up assessment but had not transitioned to psychosis. Figure 1 shows the composition of the current sample.

At baseline, the participants were ages 15 to 30 years and met criteria for being at ultra-high risk for psychotic disorder. 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 reference 14 for a 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, and past antipsychotic exposure equivalent to a haloperidol dosage of more than 15 mg/day.

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

Follow-up assessment. Axis I diagnoses at follow-up were assessed by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (24). Face-to-face interviews were completed for 194 participants (85.8%), telephone interviews for 29 (12.8%), and written assessments for three (1.3%). The Comprehensive Assessment of At-Risk Mental States (CAARMS) (25) was used to assesses the presence of attenuated psychotic symptoms.

Baseline assessment. Baseline psychopathology was measured by using the Brief Psychiatric Rating Scale (BPRS) (26), Scale for Assessment of Negative Symptoms (SANS) (27), and CAARMS (25). We used the BPRS subscales for psychotic symptoms (unusual thought content, hallucinations, suspiciousness, conceptual disorganization) and affective symptoms (anxiety, depression, guilt, somatic concerns, tension). Positive symptoms measured by CAARMS subscales were disorders of thought content, perceptual abnormalities, and conceptual disorganization. Functioning was assessed with the Global Assessment of Functioning (GAF). Diagnoses were assessed with the SCID-I.

Current IQ was assessed with the Wechsler Adult Intelligence Scale–Revised [WAIS-R) (28) or the Wechsler Abbreviated Scale of Intelligence (WASI) (29). Eight of the younger participants were assessed by means of the Wechsler Intelligence Scale for Children (WISC-III) (30). IQ was estimated by using 1) Ward's seven-subtest (31) estimate of verbal, performance, and full-scale IQ (N=52), 2) Kaufman's four-subtest (32) estimate of full-scale IQ (N=9), or 3) the WASI estimate of verbal, performance, and full-scale IQ (N=123).

Statistical Analyses

Data were examined for the frequency of current attenuated psychotic symptoms, nonpsychotic 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 assessments at baseline and follow-up (N=203 for mood/anxiety, N=192 for substance use). For each disorder, the participant's status was classed as "never" if the disorder was not present at baseline or during follow-up, "persistent/recurrent" if the disorder was present both at baseline and during follow-up, "remission" if the disorder was present at baseline but absent during follow-up, or "incident" if the 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 with participants who never had the disorder. Participants with persistent or recurrent disorder were compared with those with remitted disorder. Candidate predictors were intake group; GAF score; BPRS scores for psychotic and affective symptoms; SANS total score; CAARMS scores for disorders of thought content, perceptual abnormalities, and conceptual disorganization; and verbal, performance, and full-scale IQ. For primary analyses, predictors with a univariate association at $p<0.1$ were entered together into a 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 or recurrence of any disorder from 67% to 45% associated with removal of a common risk factor (e.g., gender) with 50% prevalence, and we had 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.

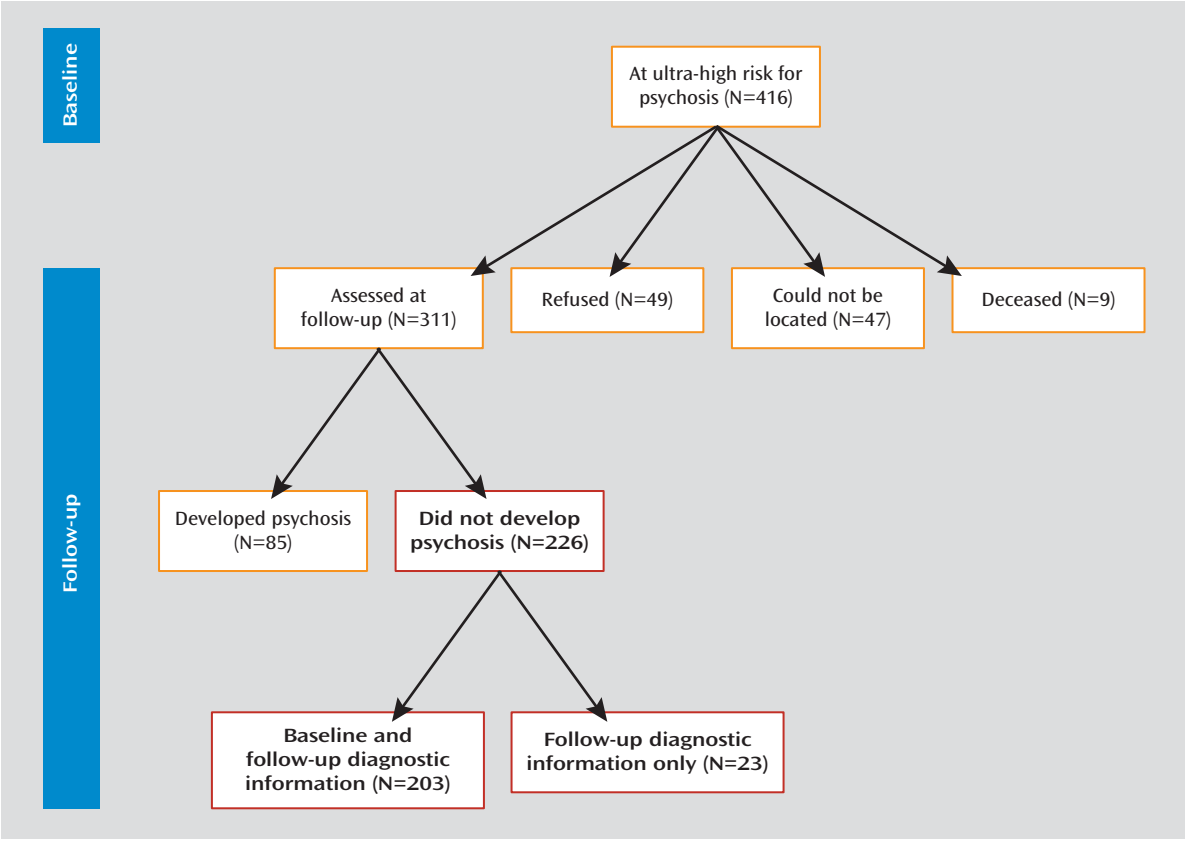
Given the large variability in follow-up period, the cohort was divided into three subsamples on the basis of when they were identified as at risk: long follow-up period (1993–2000, N=82), medium follow-up (2001–2003, N=77), and short follow-up (2004–2006, N=67). Frequencies are presented for the entire 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 female than male participants completed follow-up (55.3% female; $\chi^2=5.12$, df=1, p=0.02). There were

FIGURE 1. Composition of a Cohort of Young People at Ultra-High Risk for Psychotic Disorder Who Did or Did Not Transition to Psychosis[a]



[a] 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 information at baseline.

no other significant differences between participants who were followed up and those who were not. Their mean age was 18.6 years (SD=3.3) at baseline and 25.5 years (SD=4.8) at follow-up. Follow-up was conducted between 2.4 and 14.1 years after baseline (mean=6.9, SD=3.1, median=5.72). Eighty-two (36.3%) of the participants received trial treatment at PACE—cognitive-behavioral therapy, N=25; cognitive-behavioral therapy and low-dose antipsychotics, N=38; or low-dose lithium, N=19)—all for 12 months or less. There were no significant differences in disorder rates during follow-up between participants who received trial treatment and those who did not. Further characteristics for each subsample are presented in Table S1 in the data supplement accompanying the online version of this article.

The use of antipsychotics or any psychiatric medication in the 2 years prior to follow-up was documented for 184 participants (81.4% of the sample). Of these participants, five (2.7%) reported using antipsychotic medication and 70 (38.0%) had used any psychiatric medication "some or all of the time" in the past 2 years.

Frequency and Comorbidity of Nonpsychotic Disorders at Follow-Up

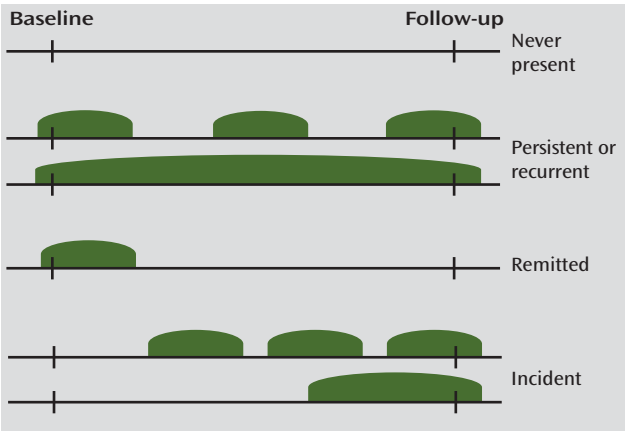
Diagnostic outcomes at follow-up are presented in Table 1. Of the entire cohort, 68.1% met criteria for at least one disorder during the follow-up period. Mood disorder was present during follow-up for 48.7%, anxiety disorder for 34.5%, and substance use disorder for 29.2%. Proportions were not notably 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 2004–2006 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 were missing for 30 of the participants with telephone or written assessment at follow-up).

FIGURE 2. Definitions Used for the Course of Nonpsychotic Disorders



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 (χ^2=7.81, df=1, p=0.005) and with any nonpsychotic disorder over the follow-up period (χ^2=5.91, df=1, p=0.02), but not with anxiety and substance use disorders. Results were similar for the 2004–2006 subsample (mood disorders: χ^2=9.14, df=1, p=0.003; any disorder: χ^2=8.19, df=1, p=0.004).

Of the five participants using antipsychotics in the 2 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% versus 26.3%; χ^2=6.46, df=1, p=0.01).

Course of Nonpsychotic Disorders

Table 3 shows the frequencies of baseline disorder and of remission, incidence, persistence/recurrence, and absence of nonpsychotic disorders. In the following, we report results for the entire cohort. Of the participants who had a mood disorder at baseline (71.4%), 53.8% had persistent or recurrent disorder. In those without mood disorder at baseline, 32.8% developed one. Of those with anxiety disorder at baseline (39.9%), 40.7% experienced persistent or recurrent anxiety. Of those without anxiety disorder at baseline, 29.5% developed one. Substance use disorders were present at baseline for 21.9% (of the 192 with available baseline substance use diagnoses). Of them, over half (52.4%) showed persistent or recurrent substance use disorder over follow-up. Of those without substance use disorder at baseline, 22.0% developed a substance use disorder.

In terms of any disorder, 90.1% of the cohort had any nonpsychotic disorder at baseline. Over the follow-up period, 26.0% of the entire cohort had remission of a nonpsychotic disorder, 37.5% developed a new disorder, and 51.6% had a persistent or recurrent disorder. Only 7.3% never experienced any disorder.

For the most part, the courses of disorders did not notably differ between subsamples. An exception was seen for the 2004–2006 subsample, who had a lower rate of substance use disorders at baseline. However, the rate of incident substance use disorder in this subsample was comparable to the rates for the other groups.

Predictors of Incident Disorder and Remission

Baseline symptoms, GAF score, 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 or recurrent mood disorder compared with remitted mood disorder (odds ratio=2.07, 95% confidence interval [CI] for odds ratio=1.02–4.23, p=0.05) and with incident anxiety disorder compared with 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 a higher baseline score on the SANS (odds ratio=1.14, 95% CI for odds ratio=1.01–1.29, p=0.03) compared with never having a disorder. The persistence or 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 was associated with a lower chance of persistent or 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 the 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 having ultra-high risk for psychosis between 2 and 14 years earlier. The frequency and course of mood, anxiety, and substance use disorders were examined. Approximately a quarter of the participants experienced attenuated psychotic symptoms at follow-up assessment. Nonpsychotic disorders were often present at baseline, and they tended to persist over the follow-up period. Incident nonpsychotic disorder was also common, occurring in over one-third of the sample. Baseline and demographic variables were not strong predictors of the course of nonpsychotic disorders.

Persistent Attenuated Psychotic Symptoms

Attenuated psychotic symptoms were reported by 28.3% of the current sample at follow-up assessment. Considered together with the individuals in the cohort who developed psychosis (14), half of those who met the criteria for

TABLE 1. Rates of Axis I Diagnoses During Follow-Up in Young People at Ultra-High Risk for Psychosis at Baseline

	Entire Cohort (N=226)		1993–2000 Subsample (N=82)		2001–2003 Subsample (N=77)		2004–2006 Subsample (N=67)	
Diagnosis	N	%	N	%	N	%	N	%
Any disorder	154	68.1	56	68.3	53	68.8	45	67.2
Mood disorder	110	48.7	41	50.0	34	44.2	35	52.2
Major depressive disorder	92	40.7	35	42.7	29	37.7	28	41.8
Dysthymic disorder	8	3.5	2	2.4	0	0.0	6	9.0
Bipolar I disorder[a]	6	2.7	2	2.4	3	3.9	1	1.5
Bipolar II disorder[a]	3	1.3	0	0.0	3	3.9	0	0.0
Other[b]	2	0.9	1	1.2	1	1.3	0	0.0
Anxiety disorder	78	34.5	30	36.6	23	29.9	25	37.3
Panic disorder with agoraphobia	11	4.9	2	2.4	3	3.9	6	9.0
Panic disorder without agoraphobia	16	7.1	6	7.3	4	5.2	6	9.0
Agoraphobia without panic	6	2.7	3	3.7	3	3.9	0	0.0
Social phobia	25	11.1	11	13.4	6	7.8	8	11.9
Specific phobia	8	3.5	2	2.4	3	3.9	3	4.5
Generalized anxiety disorder	14	6.2	6	7.3	2	2.6	6	9.0
Obsessive-compulsive disorder	7	3.1	3	3.7	2	2.6	2	3.0
Posttraumatic stress disorder	10	4.4	6	7.3	2	2.6	2	3.0
Other[c]	6	2.7	2	2.4	2	2.6	2	3.0
Substance use disorder	66	29.2	27	32.9	21	27.3	18	26.9
Alcohol abuse	23	10.5	10	12.2	8	10.4	5	7.5
Alcohol dependence	20	8.8	10	12.2	5	6.5	5	7.5
Cannabis abuse	7	3.1	2	2.4	3	3.9	2	3.0
Cannabis dependence	33	14.6	16	19.5	9	11.7	8	11.9
Amphetamine/stimulant abuse	15	6.6	6	7.3	5	6.5	4	6.0
Amphetamine/stimulant dependence	10	4.4	3	3.7	4	5.2	3	4.5
Other drug abuse[d]	14	6.2	4	4.9	6	7.8	4	6.0
Other drug dependence[d]	7	3.1	3	3.7	1	1.3	3	4.5
Somatoform disorder[e]	6	2.7	4	4.9	1	1.3	1	1.5
Eating disorder[f]	11	4.9	2	2.4	3	3.9	6	9.0
Mood and anxiety disorders	55	24.3	24	29.3	11	14.3	20	29.9
Mood and substance use disorders	40	17.7	17	20.7	10	13.0	13	19.4
Anxiety and substance use disorders	31	13.7	14	17.1	9	11.7	8	11.9
All three disorders	23	10.2	12	14.6	4	5.2	7	10.4

[a] Nonpsychotic cases only.
[b] Depressive disorder not otherwise specified, bipolar disorder not otherwise specified, and substance-induced mood disorder.
[c] Anxiety disorder not otherwise specified or substance-induced anxiety disorder.
[d] Sedatives, opioids, paint sniffing, or hallucinogens.
[e] Body dysmorphic disorder, hypochondriasis, undifferentiated somatoform disorder, pain disorder, or somatoform disorder not otherwise specified.
[f] Anorexia nervosa, bulimia nervosa, binge-eating disorder, or eating disorder not otherwise specified.

ultra-high risk showed continued or recurrent positive psychotic symptoms (threshold or subthreshold). The presence of attenuated psychotic symptoms may reflect continued risk for psychosis in some individuals. This is possible since transitions occurred up to 10 years after identification of risk in this sample (14). Alternatively, attenuated symptoms may occur in the context of nonpsychotic 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 periods showed the highest rates of attenuated symptoms and that their attenuated symptoms were associated with nonpsychotic disorders could support either of these possibilities.

Nonpsychotic Disorders

Mood disorders were the most common diagnosis during follow-up. Major depressive disorder was especially common. 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 the Australian general population (34) is presented in online Table S3. Briefly, the rates of nonpsychotic disorders in this cohort were higher than the 12-month prevalences of these disorders for a similar age group in the general population, as well as higher than lifetime prevalences of adults of all ages. Notably, the prevalence of mood disorder over follow-up in our cohort was higher by a factor of five than the 12-month prevalence and higher by a factor

TABLE 2. Co-Occurrence of Attenuated Psychotic Symptoms and Nonpsychotic Disorders at Follow-Up in Young People at Ultra-High Risk for Psychosis at Baseline

	Presence or Absence of Attenuated Psychotic Symptoms															
	Entire cohort				1993–2000				2001–2003				2004–2006			
	Present (N=64)		Absent (N=132)		Present (N=20)		Absent (N=50)		Present (N=18)		Absent (N=46)		Present (N=26)		Absent (N=36)	
Nonpsychotic Disorder	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mood disorder	42	65.6	57	43.2	13	65.0	24	48.0	8	44.4	19	41.3	21	80.8	14	38.9
Anxiety disorder	31	48.4	46	34.8	12	60.0	18	36.0	6	33.3	17	37.0	13	50.0	11	30.6
Substance use disorder	27	42.2	39	29.5	8	40.0	19	38.0	9	50.0	12	26.1	10	38.5	8	22.2
Any nonpsychotic disorder	54	84.4	88	66.6	16	80.0	36	72.0	14	77.7	32	69.6	24	92.3	20	55.5

TABLE 3. Course of Nonpsychotic Disorders in Young People at Ultra-High Risk for Psychosis at Baseline

	Entire Cohort (N=203)[a]		1993–2000 Subsample (N=61)[a]		2001–2003 Subsample (N=77)		2004–2006 Subsample (N=65)	
Status of Nonpsychotic Disorder	N	%	N	%	N	%	N	%
Present at baseline								
Any disorder	173	90.1	47	94.0	73	94.8	53	81.5
Any mood disorder	145	71.4	33	54.1	61	79.2	51	78.5
Any anxiety disorder	81	39.9	21	34.4	34	44.2	26	40.0
Any substance use disorder	42	21.9	17	34.0	21	27.3	4	6.1
Remitted								
Any disorder	50	26.0	12	24.0	22	28.6	16	24.6
Any mood disorder	67	33.0	13	21.3	31	40.3	23	35.4
Any anxiety disorder	48	23.6	13	21.3	22	28.6	13	20.0
Any substance use disorder	20	10.4	7	14.0	12	15.6	1	1.5
Incident								
Any disorder	72	37.5	24	48.0	24	31.2	24	36.9
Any mood disorder	19	9.3	9	14.8	4	5.2	6	9.2
Any anxiety disorder	36	17.7	13	21.3	11	14.3	12	18.5
Any substance use disorder	33	17.2	7	14.0	12	15.6	14	21.5
Persistent or recurrent								
Any disorder	99	51.6	29	58.0	40	51.9	30	46.1
Any mood disorder	78	38.4	20	32.8	30	39.0	28	43.1
Any anxiety disorder	33	16.2	8	13.1	12	15.6	13	20.0
Any substance use disorder	22	11.5	10	20.0	9	11.7	3	4.6
Never present								
Any disorder	14	7.3	5	10.0	3	3.9	6	9.2
Any mood disorder	39	19.2	19	31.1	12	15.6	8	12.3
Any anxiety disorder	86	42.3	27	44.3	32	41.6	27	41.5
Any substance use disorder	117	60.9	26	52.0	44	57.1	47	72.3

[a] No baseline diagnostic information was available for 23 of the 226 total participants in the study. In addition, 11 participants in the 1993–2000 subsample had no available data on substance use disorders at baseline. Hence, in the entire cohort, N=203 for mood and anxiety disorders and N=192 for substance use disorder or any disorder. In the 1993–2000 subsample, N=61 for mood and anxiety disorders and N=50 for substance use disorder or any disorder.

of three than the lifetime prevalence in the general population.

This would be expected of a selected help-seeking sample. Indeed, many nonpsychotic disorders were already present at baseline. An important finding was that disorders persisted for approximately half of these young people who did not develop psychosis. In addition, for those without a nonpsychotic 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 nonpsychotic 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 nonpsychotic disorder in this population.

We explored positive and negative psychotic symptoms, affective symptoms, functioning, IQ, gender, and age as

Case 1

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 as he had often refused 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 might also be laughing at him and talking about him. He usually realized 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 3:00 or 4:00 a.m. and frequently slept 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. His score on the Social and Occupational Functioning Assessment Scale was 55.

Progress. Nathan was managed with cognitive-behavioral therapy (CBT), which helped him identify triggers for paranoid thoughts and reduce safety behaviors. 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 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 6 months after beginning treatment, Nathan no longer met the criteria for major depression or the ultra-high risk criteria, and he was attending school most days.

Outcome. When Nathan was seen for research 4 years after being referred to the PACE clinic, he reported that he had been feeling "mentally well" since being discharged from the 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 score on the Social and Occupational Functioning Assessment Scale was 85.

Case 2

Brittany (not her real name) was an 18-year-old unemployed woman who lived with her mother, step-father, and two younger half-sisters. She was referred to the PACE clinic by her general practitioner (GP) because of concerns about her anxiety. Brittany described a life-long history of generalized 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 she felt tense even thinking about achieving any of these. She 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 month before 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 on the basis of her attenuated psychotic symptoms and the DSM-IV criteria for generalized anxiety disorder and social anxiety disorder. Her score on the Social and Occupational Functioning Assessment Scale 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 but 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 7 years after initial presentation, she reported that she had developed depression and had been prescribed antidepressant 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 occurred only 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 the criteria for generalized anxiety disorder, as well major depression. Her score on the Social and Occupational Functioning Assessment Scale was 55.

predictors of course of disorder. Being female was associated with a higher risk of disorder than being male, a finding that is consistent with general population data (34). However, no other baseline variables were associated with the course of a specific disorder. It is interesting that higher SANS scores at baseline and not meeting the criteria for brief limited intermittent psychotic symptoms were associated with the incidence and the persistence or 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 nonspecificity of symptoms measured on the SANS. It may be that depressive symptoms were interpreted as negative symptoms and rated on the SANS. Alternatively, individuals with high negative symptom scores 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 or recurrence of any disorder was associated with a shorter follow-up period, consistent with the decrease in the rate of nonpsychotic disorders that was noted by Addington and colleagues (19). Together with the finding of considerably higher levels of 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 2 to 4 years) but becomes less important over the longer term. This has implications for many studies, which typically track at-risk participants for 1 to 3 years.

The lack of strong predictors of nonpsychotic 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 nonpsychotic illness cannot be predicted. Rather, it suggests that clinical variables that predict nonpsychotic 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 strengths of this study are the large number of participants 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, the subsamples did differ in some respects and the analyses were complicated by this. Moreover, the epochs used were 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 from telephone or written interviews. Finally, women were overrepresented at follow-up, which may bias toward higher levels of mood and anxiety disorders.

The current findings demonstrate significant psychopathology in nontransitioned cases 2 to 14 years after identification of risk. Persistent or recurrent nonpsychotic 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 nonpsychotic outcomes in their treatment and follow-up plans.

We previously proposed a clinical staging model positing that severe mental disorders (e.g., schizophrenia, bipolar disorder, severe unipolar depression) develop from initial nonspecific symptoms, such as depressed mood, anxiety, and distress (38). Acquisition of new symptoms, including psychotic symptoms, and worsening of emotional dysregulation occur 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 nonpsychotic disorder by incorporating variables of interest to nonpsychotic outcomes in their designs—for example, axis II disorders, mood disturbance, cognitive biases, or family history of nonpsychotic disorders. Moreover, there is a need to investigate how functional outcome is associated with the presence of nonpsychotic 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.

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