Specificity of Incident Diagnostic Outcomes in Patients at Clinical High Risk for Psychosis

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It is not well established whether the incident outcomes of the clinical high-risk (CHR) syndrome for psychosis are diagnostically specific for psychosis or whether CHR patients also are at elevated risk for a variety of nonpsychotic disorders. We collected 2 samples (NAPLS-1, PREDICT) that contained CHR patients and a control group who responded to CHR recruitment efforts but did not meet CHR criteria on interview (help-seeking comparison patients [HSC]). Incident diagnostic outcomes were defined as the occurrence of a SIPS-defined psychosis or a structured interview diagnosis from 1 of 3 nonpsychotic Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) groups (anxiety, bipolar, or nonbipolar mood disorder), when no diagnosis in that group was present at baseline. Logistic regression revealed that the CHR vs HSC effect did not vary significantly across study for any emergent diagnostic outcome; data from the 2 studies were therefore combined. CHR ($n = 271$) vs HSC ($n = 171$) emergent outcomes were: psychosis 19.6% vs 1.8%, bipolar disorders 1.1% vs 1.2%, nonbipolar mood disorders 4.4% vs 5.3%, and anxiety disorders 5.2% vs 5.3%. The main effect of CHR vs HSC was statistically significant (OR = 13.8, 95% CI 4.2–45.0, $df = 1$, $P < .001$) for emergent psychosis but not for any emergent nonpsychotic disorder. Sensitivity analyses confirmed these findings. Within the CHR group emergent psychosis was significantly more likely than each nonpsychotic DSM-IV emergent disorder, and within the HSC group emergent psychosis was significantly less likely than most emergent nonpsychotic disorders. The CHR syndrome is specific as a marker for research on predictors and mechanisms of developing psychosis.

Key words: validity/bipolar disorder/nonbipolar mood disorder/anxiety disorder

Introduction

For the past 30 years efforts have been made to identify signs of psychosis as early as possible,[1–6] with the ideal goal of identifying individuals at risk for psychosis before symptoms fully manifest. The hope is that early identification may lead to faster clinical engagement that delays or prevents transition to full-blown cases of this possibly devastating disease. There is evidence that early intervention in patients with established psychosis leads to improved outcomes,[7–9] and preliminary evidence that intervening before the onset of frank psychosis may reduce subsequent disease burden.[10–12]

Centers specializing in early psychosis detection typically use structured diagnostic instruments such as the SIPS[13] or Comprehensive Assessment of At-Risk Mental States.[14] These instruments are administered by specially trained personnel and examine symptom severity in multiple domains of psychotic behavior and general mental health functioning in order to classify those likely to be at clinical high risk (CHR) for eventual conversion to psychosis. Use of the SIPS carried a low rate of endorsement for the most common CHR syndrome in an epidemiologic sample,[15] and use of these instruments carries a positive predictive value of 32% for conversion to psychosis at 3 years in clinical samples of help-seeking CHR subjects assessed by high-risk services.[16]

While structured rating instruments provide a useful risk assessment for conversion to psychosis, there has been concern about whether clinical outcomes in CHR patients are specific to psychosis, or whether patients so identified are generally at increased risk for many psychiatric disorders.[17–19] This concern arises in part because most CHR subjects do not go on to develop full psychosis,[16] and in part because two-thirds or more of CHR subjects have other comorbid Axis I diagnoses at ascertainment,[20–25] primarily affective and anxiety disorders, that contribute to the functional deficits[21] and psychopathologic symptoms[21] seen in CHR samples.

Whether CHR points specifically to risk for future psychosis vs to nonspecific deterioration in mental health has clear research and policy implications. If the CHR designation offers no specific prognosis with regard to psychosis, then making a CHR assessment may be of little additional help beyond general mental health screening, because it would not differentiate a need for specialty treatment programs aimed at psychosis. Moreover, research studies of CHR would not be investigating risk factors or biomarkers that are specific for psychosis but rather general risk factors for a mixture of mental disorders. In fact, a recent study found that affective/anxiety comorbidity in CHR patients was associated with lower gray matter volumes in anterior cingulate than in CHR patients without comorbidity.[26]

Understanding whether a CHR designation specifically delineates risk for developing psychosis necessarily relies on comparing incident rates of psychosis vs incident rates of other classes of psychiatric disorders. Unfortunately, however, while baseline comorbidity of psychiatric disorders in CHR patients is already well described, only 1 study has examined incident nonpsychotic diagnostic outcomes in CHR patients,[27] and we are aware of none that have directly compared such outcomes in CHR with those from psychiatric patients who did not meet CHR criteria. We therefore conducted the present analyses using data from 2 large naturalistic samples.

Method

We report data from 2 cohorts of CHR syndrome patients that each also included a comparison group of patients who did not meet criteria for CHR syndrome or psychosis. The comparison patients are termed "help-seeking comparison subjects" (HSCs). Both CHR and HSC patients responded to CHR recruitment efforts, passed a phone screen designed to eliminate those who had no target symptoms or were obviously psychotic, and were invited to and underwent SIPS evaluation. CHR patients met SIPS criteria at evaluation, and HSC patients did not. These patient groups have been shown to differ on rate of conversion to psychosis, positive and negative symptoms, current functioning, mood disorder comorbidity, and family history.[25] A recent meta-analysis of 11 studies confirms the higher risk of psychosis in the CHR patients vis-a-vis HSC, with an OR estimate of 20.2.[28]

The present 2 cohorts were the first sample of the North American Prodromal Longitudinal Study (NAPLS-1) and the PREDICT study. Our newer NAPLS-2 sample[29] did not follow HSCs or collect detailed baseline data on them. Methods for NAPLS-1[30] and PREDICT[31] have been reported previously.

Subjects

NAPLS-1 merged data collected at 8 sites on 303 CHR syndrome and 135 HSC patients enrolled between early 1998 and early 2005 and for whom data were available for at least 1 follow-up timepoint (supplementary figure 1).[25] The dataset includes interim data from the first 44 CHR and 24 HSC qualifying patients enrolled in the PREDICT study. For the present analyses these subjects are included in the PREDICT sample rather than in the NAPLS-1 sample, because when the NAPLS-1 dataset was closed, PREDICT follow-up was still ongoing. Of the remaining 259 CHR and 111 HSC NAPLS-1 patients, 160 (62%) and 100 (90%), respectively, underwent structured diagnostic interviews for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I diagnoses at baseline and also at 1 or more follow-up evaluations. Among the HSC patients, 69 (69.0%) had no positive symptoms in the SIPS CHR severity range at baseline, and 31 (31.0%) had symptoms that met severity criteria but not worsening or frequency criteria.

PREDICT was conducted at 3 of the NAPLS-1 sites (University of North Carolina, University of Toronto, and Yale University), and enrolled 151 CHR syndrome and 86 HSC patients between late 2003 and early 2008 who contributed follow-up data (supplementary figure 1). Of these, 111 CHR (74%) and 71 HSC (83%) also underwent structured diagnostic interviews for DSM-IV Axis I diagnoses at baseline and at 1 or more follow-up evaluations. Among the HSC patients, 34 (47.9%) had no positive symptoms in the CHR severity range at baseline, and 37 (52.1%) had symptoms that met severity criteria but not worsening or frequency criteria.

Data on the recruitment sources in these 2 studies were not collected systematically, but recruitment methods were broadly similar to those reported in the later NAPLS-2 sample, where approximately 15% of both CHRs and HSCs were referred by the school/community sector, roughly 40% of CHRs and 35% of HSCs were referred by the health/mental health sector, and about 45% of CHRs and 50% of HSCs were referred by self, family/friends, or other.[29] Inclusion and exclusion criteria were also similar in the 2 studies. One exception is that CHR and HSC patients in PREDICT could not enroll if they had received antipsychotic medication in the past week and there was a clinical need for the antipsychotic to continue.

Assessments

Each site in both studies utilized the Structured Interview for Psychosis-risk Syndromes (SIPS) to determine whether psychosis and CHR syndrome criteria were met.[13] Reliability of the SIPS has been reported previously[32–35] and was established in these studies for all sites.[30] Structured assessment of DSM-IV Axis-I diagnoses in NAPLS-1 varied somewhat within and across sites,[25] with most subjects receiving versions of the Structured Clinical Interview for DSM-IV (SCID)[36] or the Schedule for Affective Disorder and Schizophrenia for School-Aged Children (K-SADS).[37] The Comprehensive Assessment of Symptoms and History[38] was used for some subjects. PREDICT employed the SCID-NP[39] for subjects 16 and older and the K-SADS[37] for those 15 and under. Follow-up assessments were available at 6-month intervals in both studies, out to 30 months in NAPLS-1 and to 48 months in PREDICT. Only follow-up timepoints with DSM-IV diagnostic interviews were permitted to contribute to data analysis.

Depressive and anxiety comorbidities are the most common in CHR patients,[21] and we felt it important to distinguish between bipolar and nonbipolar disorders. Accordingly, for both studies nonpsychotic DSM-IV Axis-I diagnoses were classified into 3 groups: bipolar disorders (DSM-IV nonpsychotic bipolar I disorder, bipolar disorder NOS, bipolar II disorder, and cyclothymic disorder), nonbipolar mood disorders (DSM-IV nonpsychotic major depressive disorder, dysthymic disorder, depressive disorder not otherwise specified [NOS], and mood disorder NOS), and anxiety disorders (panic disorder with or without agoraphobia, generalized anxiety disorder, agoraphobia without panic disorder, social phobia, specific phobia, obsessive compulsive disorder, post-traumatic stress disorder, separation anxiety disorder, and anxiety disorder NOS).

Emergence of psychosis, or "incident psychosis," was defined by SIPS criteria as previously described.[25] Emergent nonpsychotic disorders was defined among subjects who did not convert to psychosis as the emergence at any time during follow-up of a DSM-IV diagnosis from 1 of the 3 nonpsychotic groups, when no diagnosis in that DSM-IV group was present at baseline.

Data on psychotropic medication use at baseline were collected in both studies and were reported previously for NAPLS-1.[40–42] Duration of CHR syndrome data was collected from fields in the SIPS. When more than 1 CHR syndrome was present, the longer duration was used. Current functioning at baseline was assessed in both studies with the Global Assessment of Functioning[43] included in the SIPS.

Statistical Methods

Analyses were conducted using SPSS version 19. *P* values < .05 were considered statistically significant. Baseline characteristics were compared using Student's *t* tests and χ². In 1 case, 2 incident nonpsychotic disorders emerged at the same timepoint (nonbipolar mood disorder and anxiety disorder in a PREDICT CHR subject). In order to permit initial omnibus multinomial regression and 2×5 χ² analyses of incident outcome, the nonbipolar mood disorder was treated as trumping the anxiety disorder. In the remaining analyses this "trumping" rule was not applied. The multinomial regression incorporated terms for baseline diagnosis (CHR vs HSC) and study (NAPLS-1 vs PREDICT).

Logistic regression was used to compare disorder-specific incident outcome rates, incorporating the same terms as for the multinomial regression, with post hoc 2×2 χ² analyses. Product terms were added to the logistic models to test interaction effects between study and baseline CHR vs HSC diagnosis; when models either would not converge or did not reach a level of statistical significance, interaction terms were omitted. When baseline characteristics differed significantly across CHR and HSC groups in either study, effects of inclusion of terms for these characteristics were evaluated in models showing significant independent CHR vs HSC effects. Effects of baseline characteristics were examined similarly in models showing significant effects of study. The primary analyses expressed rates of incident disorder as number of emergent cases divided by number of all cases. Because rates of baseline disorders varied across CHR vs HSC (table 1), sensitivity analyses were conducted excluding patients with baseline disorder and expressing rates of incident disorder as number of emergent cases divided by number of cases not excluded.

Because rates of baseline disorder varied across diagnosis, within group comparisons of emergent disorder across diagnostic outcome were restricted to pairwise analyses vs emergent psychosis and to analyses excluding baseline cases of comparator disorder. These comparisons employed Cochran's *Q*.

Results

Baseline Characteristics

Table 1 compares CHR and HSC samples on baseline characteristics. CHR patients had higher Scale of Psychosis-risk Symptoms (SOPS) total, positive, and general symptom scores and higher use rates of any psychotropic than HSC in both studies. In NAPLS-1, CHR patients were also older and had lower functioning scores and higher SOPS negative and disorganization scores, higher rates of antipsychotic and antidepressant use, and higher rates of any mood/anxiety disorder and nonbipolar mood disorder comorbidity than HSC. CHR samples differed across study at baseline on age (1.5 years younger in NAPLS-1), functioning (lower in NAPLS-1), SOPS scores (total, negative, and disorganized all higher in NAPLS-1), and antipsychotic and mood stabilizer use (both higher in NAPLS-1). CHR syndrome duration

Table 1. Baseline Characteristics of NAPLS-1 and PREDICT Samples

Measure	NAPLS-1		PREDICT	
	CHR (n = 160)[a]	HSC (n = 100)[b]	CHR (n = 111)[c]	HSC (n = 71)[d]
Age	18.1 ± 4.4[g,j]	15.7 ± 2.9[i,j]	19.6 ± 4.7[g]	19.3 ± 4.2[j]
No. male	92 (57.5%)	64 (64.0%)	60 (54.1%)	37 (52.1%)
No. Caucasian	123 (76.9%)	68 (68.0%)	82 (73.9%)	53 (74.6%)
Parental education	5.58 ± 1.69	5.89 ± 1.95	6.00 ± 2.48	5.56 ± 2.37
Global functioning	48.7 ± 11.6[i,j]	54.9 ± 11.9[i]	54.9 ± 12.5[j]	56.2 ± 11.8
CHR duration, days[e]	722 ± 1056[i]	NA	261 ± 298[i]	NA
SOPS total	36.6 ± 14.0[i,j]	22.5 ± 12.5[i]	30.2 ± 11.3[h,j]	25.2 ± 13.4[h]
SOPS positive	11.2 ± 4.2[i]	4.0 ± 3.4[i,k]	10.9 ± 3.1[j]	6.9 ± 4.3[j,k]
SOPS negative	11.6 ± 6.7[f,i]	9.9 ± 6.5[f]	8.4 ± 5.7[i]	8.7 ± 6.0
SOPS disorganized	6.3 ± 3.7[i,j]	3.4 ± 3.1[h]	4.0 ± 2.6[j]	3.9 ± 3.0
SOPS general	7.9 ± 4.3[i]	5.4 ± 4.3[i]	7.0 ± 4.0[f]	5.7 ± 4.2[f]
Any mood/anx disorder	122 (76.3%)[i]	52 (52.0%)[i]	77 (69.4%)	43 (60.6%)
DSM-IV bipolar	4 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DSM-IV nonbipolar mood	92 (57.5%)[i]	37 (37.0%)[i]	54 (48.6%)	27 (38.0%)
DSM-IV anxiety	69 (43.1%)	33 (33.0%)	50 (45.0%)	23 (32.4%)
Any psychotropic	77 (50.0%)[g]	32 (32.0%)[g]	48 (43.2%)[f]	20 (28.2%)[f]
Antipsychotic	33 (21.4%)[g,i]	8 (8.0%)[g,f]	1 (0.9%)[i]	0 (0.0%)[f]
Antidepressant	55 (35.7%)[f]	23 (23.0%)[f]	39 (35.1%)	17 (23.9%)
Mood stabilizer	9 (5.8%)[f]	1 (1.0%)	1 (0.9%)[f]	0 (0.0%)
Stimulant	8 (5.2%)	10 (10.0%)[f]	5 (4.5%)	1 (1.4%)[f]
Benzodiazepine	9 (5.8%)	2 (2.0%)	10 (9.0%)	4 (5.6%)

Notes: CHR, clinical high risk; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SOPS, Scale of Psychosis-risk Symptoms; NA, not applicable.
[a]varied from 137–160 across measure other than CHR duration.
[b]varied from 78–100 across measure.
[c]n = 111 except for CHR duration.
[d]varied from 70–71 across measure.
[e]n = 55 for NAPLS-1 and 105 for PREDICT.
[f]groups with these letters differ P < .05.
[g/h]groups with these letters differ P < .01.
[i/j/k]groups with these letters differ P < .001.

was not recorded systematically in NAPLS-1 but when recorded was nearly 3 times as long as in PREDICT. HSC samples differed at baseline on age (lower in NAPLS-1, table 1), SOPS positive symptoms (higher in PREDICT), and stimulant use (higher in NAPLS-1).

Incident Diagnoses

The multinomial regression for emergent disorder produced a highly significant model (χ^2 = 67.4, df = 8, P < .001), with highly significant main effects of baseline CHR vs HSC diagnosis (χ^2 = 38.1, df = 4, P < .001). Multinomial models including baseline CHR vs HSC diagnosis × study product terms or restricted to either study would not converge due to zero cells. Main effects of study (NAPLS-1 vs PREDICT) were also highly significant (χ^2 = 29.3, df = 4, P < .001). Follow-up logistic models containing product terms testing interactions between CHR vs HSC and study would either also not converge (anxiety and bipolar) or did not reach a level of statistical significance (nonbipolar mood disorder); thus further analyses focused on the merged samples (supplementary figure 1).

Logistic regression revealed that the significant effect of CHR vs HSC diagnosis on emergent disorder was accounted for by effects on emergent psychosis (19.6% vs 1.8%, P < .001, figure 1 and supplementary table 1). No significant effects of CHR vs HSC diagnosis were observed for other emergent disorders (figure 1, supplementary table 2). Logistic regression further revealed that CHR vs HSC rates for any emergent nonpsychotic disorder (ie, any of bipolar, nonbipolar mood, or anxiety) also did not significantly differ, in the merged (supplementary table 2) or NAPLS-1 (OR = 1.07, 95% CI 0.41 to 2.85) or PREDICT (OR = 0.75, 95% CI 0.34 to 1.68) samples. Significant main effects of study were seen for emergent psychosis (NAPLS-1 higher) and for emergent anxiety disorders (PREDICT higher.

Sensitivity analyses showed that the CHR vs HSC difference for incident psychosis continued to hold whether analyses included or excluded subjects with each or any baseline disorder from the model (all p's ≤ **0.001**, Table S1). Similarly, the lack of CHR vs HSC differences for incident nonpsychotic disorders also continued to hold whether models included subjects with baseline

disorder (as noncases of emergent disorder) or excluded them (all p's ≥ **0.390**, Table S2).

Two-by-five and pairwise χ^2 analyses (table 2) revealed similar findings as the multinomial and logistic regression models. CHR and HSC groups significantly differed only on incident psychosis, and this difference was significant in each study.
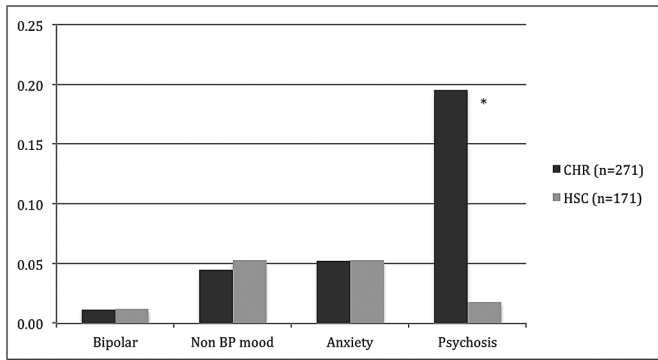

Fig. 1. Incident diagnostic outcomes in combined NAPLS-1 and PREDICT studies. CHR, clinical high risk ($n = 271$). HSC, help-seeking comparison patients ($n = 171$). Models also contain a term for study. Non-BP: nonbipolar. One subject with simultaneous emergent anxiety and nonbipolar mood disorders appears in both groups (see text). *CHR vs HSC comparison OR = 13.8, 95% CI 4.2–45.0, $df = 1$, $P < .001$, no asterisk - n.s., (supplementary table 1).

Within group comparisons of incident disorder in the merged CHR sample showed that emergent psychosis was significantly more likely than emergent nonpsychotic disorder for each of the 3 individual nonpsychotic classes (table 3). Incident psychosis was not significantly more likely, however, than any incident nonpsychotic disorder. In the NAPLS-1 sample alone, findings were similar or stronger than in the merged samples, and incident psychosis did occur significantly more frequently than any incident nonpsychotic disorder (supplementary table 3). In the PREDICT sample alone, however, emergent psychosis was significantly more likely than emergent nonpsychotic disorder only for bipolar disorder (supplementary table 3).

Within group comparisons of emergent disorder in the merged HSC sample showed that emergent psychosis was significantly *less* likely than emergent nonbipolar mood disorder, anxiety disorder, or any nonpsychotic disorder (table 3). In the NAPLS-1 sample alone, findings were similar to those in the merged samples, except that there were no cases of incident anxiety disorder (supplementary table 4). In the PREDICT sample alone, emergent psychosis was significantly less likely than emergent anxiety disorder and any nonpsychotic disorder (supplementary table 4).

Potential Confounders

Entry of terms for global functioning, SOPS total, positive, negative, or disorganized symptoms, nonbipolar

Table 2. Emergent Diagnostic Outcomes by Baseline CHR Diagnosis in Each Study

Study	Subjects (n)	Emergent Diagnostic Outcomes (%)			
		Bipolar Disorder	Nonbipolar Mood	Anxiety Disorder	Psychosis
NAPLS-1	CHR (160)	3 (1.9%)[a]	7 (4.4%)[b]	2 (1.3%)[c]	39 (24.3%)[d]
	HSC (100)	1 (1.0%)[e]	6 (6.0%)[f]	0 (0%)[g]	1 (1.0%)[h]
PREDICT	CHR (111)	0 (0%)[i]	5 (4.5%)[j]	12 (10.8%)[k]	14 (12.6%)[l]
	HSC (71)	1 (1.4%)[m]	3 (4.2%)[n]	9 (12.7%)[o]	2 (2.8%)[p]

Notes: HSC, help-seeking comparison subject patients; Bipolar Disorder: nonpsychotic, bipolar mood disorder; Nonbipolar Mood: nonpsychotic, nonbipolar mood disorder. The 1 subject with simultaneous emergent anxiety and nonbipolar mood disorders appears in both columns (see text).
Between-baseline CHR diagnosis comparisons ($P < .05$ underlined).
2 × 5 analysis of incident disorder— CHR vs HSC overall: $\chi^2 = 30.3$ $df = 4$ $P ≤ .001$; CHR vs HSC in NAPLS-1: $\chi^2 = 28.3$ $df = 4$ $P < .001$; CHR vs HSC in PREDICT: $\chi^2 = 6.7$ $df = 4$ $P = .153$.
Pairwise analyses of individual incident disorders— CHR vs HSC in NAPLS-1: a vs e $\chi^2 = 0.3$ $df = 1$ $P = .577$, b vs f $\chi^2 = 0.3$ $df = 1$ $P = .559$, c vs g $\chi^2 = 1.3$ $df = 1$ $P = .262$, d vs h $\chi^2 = 25.8$ $df = 1$ $P < .001$; CHR vs HSC in PREDICT: i vs m $\chi^2 = 1.6$ $df = 1$ $P = .210$, j vs n $\chi^2 = 0.0$ $df = 1$ $P = .929$, k vs o $\chi^2 = 0.1$ $df = 1$ $P = .701$, l vs p $\chi^2 = 5.2$ $df = 1$ $P = .023$.
Pairwise analysis of any incident nonpsychotic disorder— CHR vs HSC overall: 28/271 (10.3%) vs 20/171 (11.7%), $\chi^2 = 0.1$ $df = 1$ $P = .654$; CHR vs HSC in NAPLS-1: 12/160 (8.1%) vs 7/100 (7.0%), $\chi^2 = 0.0$ $df = 1$ $P = .880$; CHR vs HSC in PREDICT: 16/111 (14.4%) vs 13/71 (18.3%), $\chi^2 = 0.5$ $df = 1$ $P = .484$.
Between-study pairwise comparisons ($P < .05$ underlined).
2 × 5 analysis of incident disorder— NAPLS-1 vs PREDICT overall: $\chi^2 = 28.6$ $df = 4$ $P < .001$; NAPLS-1 vs PREDICT in CHR: $\chi^2 = 18.5$ $df = 4$ $P < .001$; NAPLS-1 vs PREDICT in HSC: $\chi^2 = 14.6$ $df = 4$ $P = .006$.
Pairwise analyses of individual incident disorders— NAPLS-1 vs PREDICT in CHR: a vs i $\chi^2 = 2.1$ $df = 1$ $P = .147$, b vs j $\chi^2 = 0.0$ $df = 1$ $P = .959$, c vs k $\chi^2 = 12.2$ $df = 1$ $P < .001$, d vs l $\chi^2 = 5.7$ $df = 1$ $P = .016$; NAPLS-1 vs PREDICT in HSC: e vs m $\chi^2 = 0.1$ $df = 1$ $P = .807$, f vs n $\chi^2 = 0.3$ $df = 1$ $P = .609$, g vs o $\chi^2 = 13.4$ $df = 1$ $P < .001$, h vs p $\chi^2 = 0.8$ $df = 1$ $P = .373$.
Pairwise analysis of any incident nonpsychotic disorder— NAPLS-1 vs PREDICT overall: 19/260 (7.3%) vs 29/182 (15.9%), $\chi^2 = 8.2$ $df = 1$ $P = .004$; NAPLS-1 vs PREDICT in CHR: 12/160 (7.5%) vs 16/111 (14.4%), $\chi^2 = 3.4$ $df = 1$ $P = .066$; NAPLS-1 vs PREDICT in HSC: 7/100 (7.0%) vs 13/71 (18.3%), $\chi^2 = 5.1$ $df = 1$ $P = .023$.

Table 3. Within Group Analyses Comparing Emergent Psychosis to Other Emergent Disorders

Merged CHR Sample	Emergent Disorder	Incidence Rates	Cochran's Q	df	P value
Baseline bipolar excluded	Psychosis	52/267 (19.5%)	43.7	1	<.001
	Bipolar	3/267 (1.1%)			
Baseline nonbipolar excluded	Psychosis	30/125 (24.0%)	7.7	1	.005
	Nonbipolar mood	12/125 (9.6%)			
Baseline anxiety excluded	Psychosis	34/152 (22.4%)	8.3	1	.004
	Anxiety	14/152 (9.2%)			
Any baseline mood/anxiety excluded	Psychosis	17/72 (23.6%)	0.9	1	.353
	Any mood/anxiety	12/72 (16.7%)[a]			

Merged HSC Sample	Emergent Disorder	Incidence Rates	Cohran's Q	df	P value
Baseline bipolar excluded	Psychosis	3/171 (1.8%)	0.2	1	.655
	Bipolar	2/171 (1.2%)			
Baseline nonbipolar excluded	Psychosis	3/107 (2.8%)	3.0	1	.083
	Nonbipolar mood	9/107 (8.4%)			
Baseline anxiety excluded	Psychosis	1/115 (0.9%)	6.4	1	.011
	Anxiety	9/115 (7.8%)			
Any baseline mood/anxiety excluded	Psychosis	1/76 (1.3%)	12.2	1	<.001
	Any mood/anxiety	15/76 (19.7%)[b]			

Notes: Nonbipolar, nonbipolar mood disorder; effect CHR vs HSC, - OR from logistic regression model including term for study.
[a]Emergent cases do not sum to 3 + 12 + 14 = 29 for 2 reasons: (1) in 1 PREDICT CHR patient 2 emergent nonpsychotic disorders appeared at the same time point (see text), and (2) unlike in the analyses above patients are considered emergent cases only if no disorder is present at baseline.
[b]Emergent cases do not sum to 2 + 9 + 9 = 20 for second reason above.

mood disorder, or baseline antipsychotic or antidepressant each significantly improved the logistic regression model for incident psychosis (supplementary table 5). Most reduced the significance of the CHR vs HSC effect, which nevertheless remained strong in all cases. Inclusion of terms for other variables differing between CHR and HSC samples in table 1 did not improve the model. With regard to the study effect on emergent psychosis, the NAPLS-1 vs PREDICT differences in table 1 each mediated the study effect. No baseline differences mediated the study effect on emergent anxiety (data available on request).

Discussion

The main finding of the present report is that incident diagnostic outcomes of the CHR syndrome were specific for psychosis, as compared with a comparison group of help-seeking patients who answered CHR recruitment efforts but did not meet CHR criteria. Psychosis was the only incident disorder that significantly differed between CHR and HSC patients in the merged sample or in either study; nonpsychotic disorders emerged in CHR patients at fairly low rates that were no higher than those in HSC patients. We also note, in the merged sample, that psychosis was significantly *more* likely than most incident nonpsychotic disorders among CHR patients and that it was significantly *less* likely than most incident nonpsychotic disorders among HSC patients.

Similar specificity of psychotic outcomes has also been observed in other studies of at-risk cohorts. A recent meta-analysis of 6 population-based studies of mostly adolescents and young adults showed that persons who reported subthreshold psychotic experiences developed psychotic clinical outcomes with a relative risk of 3.5, while nonpsychotic clinical outcomes developed with a relative risk of 1.4.[44] Our findings are also similar to those recently reported from a Melbourne CHR cohort,[27] where psychosis emerged in 27.3% of the total sample (compared with our merged sample 19.6%, figure 1), depression emerged in approximately 7.3% (compared with 4.4%), and anxiety disorder emerged in 13.9% (compared with 5.2%).

As noted, the similar rates of emergent nonpsychotic disorders across the CHR and HSC groups were fairly low (supplementary table 2). On an annualized basis, these low rates are, however, generally higher than incident rates of nonpsychotic disorders in population-based studies of adolescents and young adults,[45–54] consistent with CHR and HSC patients representing selected help-seeking clinical samples. By contrast, annualized rates of emergent depression or anxiety in the CHR group were lower than in population-based studies of adolescents or young adults at risk for depression because of subsyndromal depressive symptoms[52,55,56] (but see Jonsson U and colleagues[53]) or at risk for anxiety disorder because of subsyndromal anxiety.[54] Rates of emergent depression or anxiety in our CHR group were also lower than those in clinical samples randomized into selective or indicated prevention study control groups.[57–73]

Another important finding relates to study differences observed. Rates of emergent psychosis were lower

in PREDICT than in the NAPLS-1, and specificity of the emergent psychosis outcome was partially related to this difference. In PREDICT this rate within the CHR patient group did not differ significantly from that for most incident nonpsychotic disorder groups (supplementary table 3); however, psychosis remained the only emergent disorder that was significantly more likely in CHR patients than in HSC patients (table 2). Analyses indicated the study difference on emergent psychosis was partly accounted for by lower baseline severity of PREDICT CHR patients on several measures. The duration of the CHR syndrome, associated in previous samples with baseline functioning[74] and conversion,[75] may have shorter in PREDICT as well, although these data were not collected systematically in NAPLS-1. It is possible that the PREDICT exclusion antipsychotics led some severely ill or long duration CHR patients not to contact us. Alternatively, when a CHR clinic first opens more severely ill or longer duration patients may be preferentially sampled initially, removing them from subsequent sampling. Further work on prognostic variables in relation to a general lowering of conversion rates in CHR samples in recent years[75] is indicated.

Limitations

The requirement for DSM-IV structured diagnostic interview completion in the present report led to selection of patient subsamples in both studies. The CHR rate of emergent psychosis in the current subsample (NAPLS-1 24.2%, PREDICT 12.6%, table 2) is somewhat lower than the raw conversion rates in the full sample (NAPLS-1 29.4%[25] PREDICT 19.3%). These differences are largely due to conversions recorded after the last DSM-IV diagnostic interview in both studies that were not counted as cases of incident psychosis in the present analyses. The structured interview completion requirement also selected for a CHR sample of somewhat lower clinical severity on several measures, especially in NAPLS-1 (see full sample[25]) but also in PREDICT, and also to higher rates of baseline antipsychotic in NAPLS-1 (see full sample[42]).

Another limitation is the different rates of incident anxiety disorder in PREDICT vs NAPLS-1. Baseline rates of anxiety disorder were similar in the 2 studies (table 1), and differences between studies on other measures did not account for the incident anxiety differences. Because NAPLS-1 data were collected in independent protocols,[30] structured interviews for DSM-IV disorders were not standardized across sites, and there are no fields in the database to identify which interviews were used in which patients. Thus, we cannot determine whether incident anxiety differences relate to interview differences.

A third limitation concerns sample size. Although our combined samples were relatively large, samples in the sensitivity analyses, and particularly in analyses excluding patients with any baseline affective or anxiety disorder,

were smaller (supplementary tables 1 and 2). In the analyses with the smallest sample sizes, statistical power was sufficient to detect the emergence of any nonpsychotic disorder as significantly different between groups if the effect size was medium (as large as 0.46[76]). The main findings still seem convincing, however, since the observed CHR vs HSC effect size for any nonpsychotic disorder was very small at 0.05 (supplementary table 2) and the large effect size for psychosis (1.02) led to sufficient power to detect the CHR vs HSC difference as statistically significant despite the analyses with smaller sample sizes (supplementary table 1).

A fourth limitation is that SIPS versions varied across site and over time in the NAPLS-1 sample and between NAPLS-1 and PREDICT. This variation is unlikely to have seriously influenced study conclusions, because the primary changes in the SIPS during this period involved adding explicit ratings of symptom qualifiers that had previously been included as free text fields, and thus the definitions of CHR were unchanged.[77]

A final area of limitation involves the HSC patients. While this group offers advantages as a comparison group in that their recruitment was identical to that CHR patients, the distinction between groups is that CHR patients did, and HSC patients did not, meet criteria for a *current* CHR syndrome. Unfortunately neither study permitted structured determination of whether HSC subjects had *ever* met CHR syndrome criteria.[78] Future studies should compare emergent outcomes between CHR cases and age-matched psychiatric patients who never met CHR criteria.

Conclusion

The clinical high-risk syndrome is unusual as a research diagnostic entity in that it specifies risk for a future disorder. Its utility as a research diagnostic entity thus depends in large part upon whether it can indeed predict increased likelihood of conversion to psychosis and whether it can do so with specificity relative to other incident disorders. In our 2 samples the differential risk for developing psychosis when compared with help-seeking comparison patients was substantial and contrasted sharply with no observed difference in risk for bipolar disorder, nonbipolar mood disorder, and anxiety disorder. Risk for emergent nonpsychotic disorders was fairly low and lower than that reported in previous studies selecting specifically for risk of affective or anxiety disorders. We interpret these findings to indicate that the CHR syndrome does not identify patients at a globally increased risk for psychopathology, but instead points towards a specific risk for psychosis, at least in these samples.

Although our data indicate that the CHR criteria identify patients at specific risk for psychosis, it should also be noted that nonpsychotic disorders did emerge in CHR patients, just as they did in non-CHR patients and at

comparable rates, and that these emergent nonpsychotic disorders represent important clinical prevention targets in both CHR and non-CHR patients.

Our findings suggest that the CHR syndrome does offer a specific marker for use in research on predictors and mechanisms of developing psychosis and, in addition, suggest a number of future directions. In the research arena, the CHR syndrome may represent a fairly late stage in the development of frank disorder,[18,79–81] and the specificity of diagnostic outcome for patients at an earlier stage of psychotic illness should be investigated. Additional population-based studies that examine markers of risk for multiple disorders and their relation to multiple diagnostic outcomes would be most welcome. In the clinical arena intervention studies should investigate whether existing treatments differentially prevent specific diagnostic outcomes, whether prevention specificity varies by illness stage, and whether new treatments that target specific outcomes can be developed.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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