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ORIGINAL PAPER

Course of clinical high-risk states for psychosis beyond conversion

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Abstract
Background The main focus of research on clinical high-risk states for psychosis (CHR) has been the development of algorithms to predict psychosis. Consequently, other outcomes have been neglected, and little is known about the long-term diagnostic and functional outcome among those not converting to psychosis.
Methods In a naturalistic study, incidence, persistence, and remission rates of CHR states according to symptomatic ultra-high risk or cognitive disturbances criteria were investigated in 160 of 246 outpatients of an early detection of psychoses service (21.1% CHR negative and 78.9% CHR positive at baseline) who had not converted to psychosis within follow-up (median 53.7 months, range 13.9–123.7 months).
Results Remission rate of CHR status was 43.3% of all 194 CHR-positive cases, including converters, or 72.4% if only the 116 non-converters were considered, persistence rate was 27.6%, and new occurrence rate in initially CHR-negative patients was 9.1%. At follow-up, 54.5% of the non-converters met criteria of at least one Axis-I diagnosis, mainly affective and anxiety disorders, and had functional problems. The severity of risk at baseline was not associated with a higher presence of Axis-I diagnosis at follow-up.
Conclusions During follow-up, CHR symptoms remitted in one-third of initially CHR-positive patients, while almost 10% met CHR criteria newly in CHR-negative adults presenting at early detection services. The presence of CHR criteria seems to maintain the risk for lower functioning and mental disorders, particularly for affective disorders. Thus, therapeutic efforts targeting CHR patients should also focus on the current mental disorders as well as social and role functions to improve the long-term outcome.

Keywords Clinical high risk · Non-conversion · Persistence · Remission · Axis-I diagnosis

Introduction

Early detection of and intervention in psychotic disorders currently employ two complementary clinical high-risk (CHR) approaches [1]: the ultra-high risk (UHR) criteria to predict an imminent transition to psychosis within 12 months [2–4] and/or the basic symptom (BS) criteria for the earliest possible clinical detection of the developing disorder [5]. However, after promising results in the first early detection studies [6, 7], recent UHR studies reported rates above 30% only if follow-up periods exceeded 4 years [1]. However, higher conversion rates were reported for BS samples [1]. The dependency of conversion rates on inclusion criteria was substantiated by studies demonstrating higher conversion rates when both UHR and BS criteria were fulfilled [8, 9]. However, across all studies, a substantial number

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of subjects classified as being at CHR by the current criteria did not develop psychosis within the respective observation periods. Although non-conversion over a certain, in particular short-term, follow-up period, does not equal remission of CHR symptoms per se, or exclude individuals from the risk for future psychosis or mental health problems [10], this non-conversion rate is an important challenge for any preventive strategy [1, 11].

The number of reports detailing the outcome of non-converters is still low. Despite the known 6-year average duration of the prodrome [12], few studies have investigated non-conversion rates beyond 2 years of follow-up [13–19].

Reports on functional (and symptomatic) outcomes according to the Global Assessment of Functioning (GAF) scale [20, 21] have been inconsistent. While in one 6-year study, non-converters hardly improved [18], significant improvement was found in two shorter studies for both the GAF and symptom dimensions assessed by the Structured Interview for Prodromal Syndromes (SIPS) [13, 15, 22]. Two further studies observed good role and social functioning outcomes [16] and improved by at least ten GAF points [15].

More than 50% of non-converters met DSM-IV diagnostic criteria for a specific disorder at 1–6-year follow-ups; these were mainly represented by anxiety, mood, and/or personality disorders [13, 17, 23, 24].

The course of CHR criteria and symptoms has mainly been reported for follow-ups of 2 years or less. Remission from UHR status [25–29] or significantly decreased positive symptoms [13, 14, 24, 30] were mainly demonstrated in at least 50% of the non-converters, with six studies reporting lower rates between 19.2 and 40.9% [6, 13, 17, 23, 31, 32].

Because only a few studies have examined the long-term diagnostic outcomes, and little data exist on the course of BS beyond conversion, the goal of this study was to examine the outcome of UHR and BS criteria and symptoms in non-converting patients of an early detection service. Thereby, we investigated the clinical course of CHR-positive patients and initially CHR-negative patients, i.e., patients referred for CHR assessment for the clinical impression of potentially developing psychosis, but not meeting CHR criteria at baseline, from the same help-seeking sample. The aims were to determine (1) the remission and persistence rates of CHR criteria in CHR-positive patients and (2) the incidence rates of CHR criteria at follow-up in patients that were CHR-negative at baseline. In addition, we analyzed the potential associations of different CHR states at follow-up with the functional and diagnostic states.

Materials and methods

Sample and procedure

The initial sample consisted of patients who (1) had consulted the FETZ, an early detection of psychosis service, from 01-1998 to 12-2003, (2) had not been diagnosed with past or present psychosis at baseline (for detailed descriptions of the FETZ sample and recruitment/referral procedure, see [33]), and (3) had been re-contacted between 2004 and 2009. The study was approved by the local ethics committee, and participation was voluntary and followed written informed consent. For detailed clinical and sociodemographic baseline characteristics of the 482 eligible patients, see Schultze-Lutter et al. [9]. Of these, 246 participated in the study, 194 (78.9%) with a symptomatic CHR status (UHR criteria and/or the basic symptom criterion Cognitive Disturbances, COGDIS) at baseline [9]. Symptomatic UHR criteria comprised either attenuated (APS; in 96% of UHR cases) or transient psychotic symptoms (BLIPS; in 13% of UHR cases); BLIPS without APS occurred in only four UHR cases. A 'trait state' UHR criterion [34] would have been met by only two patients; however, because of a change in definition throughout the baseline [33], "trait state" was not used as a CHR criterion in the present study [9]. During follow-up, 86 (35%) of the 246 patients presented with a first-episode psychosis within a mean observation period of 15.33 months (SD = 14.62, Mdn = 9.49). The observation period in the 160 non-converters varied between 13.90 and 123.73 months (mean = 54.34; SD = 20.35; Mdn = 53.65). Clinical and sociodemographic characteristics are presented in Table 1.

In line with Ruhrmann et al. [8] and Schultze-Lutter et al. [9], we distinguished the following four baseline groups: 'CHR-negative' ($n = 44$; 27.5%), 'Only COGDIS' ($n = 24$; 15.0%), 'Only UHR' ($n = 28$; 17.5%), and 'UHR + COGDIS' ($n = 64$; 40.0%).

Assessments

COGDIS was assessed with the Bonn Scale for the Assessment of Basic Symptoms [35] until 2000 and with the Schizophrenia Proneness Instrument, Adult version [36] thereafter. Until 2000, UHR criteria were assessed with the SIPS, version 2.1 [37] and replaced by SIPS 3.0 [22] thereafter. We note that the definitions of CHR symptoms, i.e., the five positive symptom items of the SIPS, and related CHR criteria, remained unchanged during the study [9]. Thus, it is unlikely that our results are influenced by the change in instruments. Both BSABS/SPI-A and SIPS require CHR symptoms only be rated when they are not a direct effect of a drug. Thus, CHR criteria were only confirmed when CHR symptoms were

Table 1 Comparison of clinical and sociodemographic baseline characteristics of converters and non-converters ($N=246$)

	Non-converters ($n=160$; 65%)	Converters ($n=86$; 35%)	Statistical values
Age in years (mean ± SD, median, range)	25.76 ± 6.00, 24.96, 14.71–39.69	24.46 ± 5.88, 23.24, 16.56–39.35	$U=5946.00$; $p=0.079$[a]
Sex (% male)	59.4%	69.8%	$\chi^2=2.592$, $df=1$; $p=0.107$
'CHR-negative' group	27.5%	9.3%	$\chi^2=11.112$, $df=1$; $p=0.001$
'Only COGDIS' group	15.0%	7.0%	$\chi^2=3.363$, $df=1$; $p=0.067$
'Only UHR' group	17.5%	10.5%	$\chi^2=2.166$, $df=1$; $p=0.141$
'UHR + COGDIS'	40.0%	73.3%	$\chi^2=24.771$, $df=1$; $p<0.001$
Positive family history of psychosis (%)	9.4%	18.2%	$\chi^2=1.571$, $df=1$; $p=0.2010$
Nationality (% German)			$\chi^2=1.279$, $df=1$; $p=0.258$
Marital status			
Single	89.3%	95.3%	$\chi^2=2.606$, $df=2$; $p=0.272$
Married	5.7%	2.3%	
Separated, divorced, etc	5.0%	2.3%	
Highest school graduation[b]			
ISCED level ≤2	37.7%	50.0%	$\chi^2=3.342$, $df=1$; $p=0.068$[c]
ISCED level 3A	62.3%	50.0%	
Current occupation			
None or unemployed	18.7%	30.6%	$\chi^2=7.620$, $df=3$; $p=0.055$[d]
Sheltered working place	1.3%	0.0%	
Irregular or temporary	3.2%	0.0%	
Regular or in training/school	76.8%	69.4%	
Baseline SOFAS (mean ± SD, median, range)	54.52 ± 14.85, 54.00, 30–90	44.99 ± 15.62, 44.00, 25–90	$U=3941.50$; $p<0.001$[a,e]
Clinical Axis-I diagnosis[f]			
Any (% present)	51.3%	52.9%	$\chi^2=0.062$, $df=1$; $p=0.803$
Depressive disorder (% present)	18.8%	12.9%	$\chi^2=1.344$, $df=1$; $p=0.246$
Current psychotropic substance use (%)	13.1%	8.1%	$\chi^2=1.378$, $df=1$; $p=0.240$
Medication at baseline			
Neuroleptics (% prescribed)	10.6%	19.8%	$\chi^2=3.925$, $df=1$; $p=0.048$[g]
Antidepressants (% prescribed)	15.0%	9.3%	$\chi^2=1.605$, $df=1$; $p=0.205$
Mood stabilizers (% prescribed)[h]	0.6%	1.2%	$\chi^2=0.201$, $df=1$; $p=0.654$

SOFAS Social and Occupational Functioning Assessment Scale of DSM-IV

[a]Non-normal distribution in the sample (Kolmogorov–Smirnov test; $p<0.05$)

[b]According to the International Standard Classification of Education (ISCED)

[c]Cramer's $V=0.118$ (less than small effect of group)

[d]Cramer's $V=0.178$ (less than small effect of group)

[e]Rosenthal's $r=0.332$ (medium effect of group)

[f]Based on the clinical interview and following supervision by senior clinicians at the FETZ to achieve a best estimate diagnosis; no structured assessment, e.g., with the SCID

[g]Cramer's $V=0.126$ (less than small effect of group)

[h]Only including anticonvulsants, no prescription of lithium

reported to have occurred in any drug-free period of at least 4 weeks to rule out an exclusive effect of drug intoxication. Furthermore, good interrater reliabilities [5, 22] were reported for the assessment of CHR criteria according to SIPS and BASABS/SPI-A. These instruments possess good test–retest reliability across short periods of time as well as between face-to-face and telephone assessment [38]. At follow-up, conversion to psychosis and other non-psychotic Axis-I disorders were assessed with the Structured Clinical Interview for DSM-IV (SCID-I) [39]. All interviews were conducted by well-trained staff of the FETZ and supervised by F.S.-L. For a detailed description of the assessments, see Schultze-Lutter et al. [9].

Analyses

Using SPSS 23.0 throughout, groups were compared using the $k \times l$ χ^2 tests, Mann–Whitney U test, or the Kruskal–Wallis test. If $k \times l$ χ^2 tests of $df > 1$ revealed a p value of ≤ 0.10, post-hoc 2×2 χ^2 tests were conducted and Fisher's correction was used to interpret significance if any cell of the table contained less than five observations. To determine if a CHR state at baseline was predictive for a non-psychotic Axis-I diagnosis or CHR state at follow-up, Cox regression analyses were employed. The assumption of proportionality of the hazard function over time was tested prior to each Cox regression analysis and maintained for all potential predictors.

Remission rates were calculated twice, with regard to the total CHR-positive baseline sample, i.e., including those subjects who converted to psychosis during the follow-up period, and with regard to the non-converters only.

Results

Comparison of general characteristics at follow-up between baseline groups

The four groups did not significantly differ in age or sex. At follow-up, no differences in time to follow-up, educational or occupational level, marital status, family history of psychosis, or medication were detected (Table 2).

Remission, persistence, alteration, and new occurrence of CHR criteria

Of all 160 non-converters, 36 (22.5%) reported any CHR criterion at follow-up: 32 (88.9%) had reported a CHR criterion at baseline, with four (11.1%) patients newly meeting CHR criteria (Fig. 1).

The remission rate of CHR status was 43.3% of all 194 CHR-positive cases, including converters, or 72.4% ($n = 84$) if only the 116 non-converters were considered. The persistence rate of CHR status in those 116 non-converters with a CHR status at baseline was 27.5% ($n = 32$). The rate of new CHR-positive cases in the 44 non-converters that were CHR-negative at baseline was 9.1% (Fig. 1). These four cases did not include the two patients meeting the UHR state-trait criterion exclusively at baseline.

With regard to the course of COGDIS irrespective of the presence of UHR, 23 non-converters (14.3%) reported COGDIS at follow-up, including three patients who newly met this criterion. Sixteen patients had reported COGDIS at baseline, resulting in a COGDIS persistence rate of 18.2% in the 88 non-converters. The remission rates for COGDIS were 69.3% in the non-converters and 38.9% in all patients with COGDIS at baseline (Fig. 1).

The rate of new occurrences of COGDIS in the 44 CHR-negative patients at baseline was 6.8% (Fig. 1).

Seventeen non-converters (10.6%) reported meeting any UHR criterion (irrespective of COGDIS) at follow-up: 11 had already reported any UHR at baseline, and two newly met any symptomatic UHR criterion. The persistence rate of any UHR criterion was thus 12.0% in the 92 non-converters with any UHR at baseline. The corresponding remission rates for UHR were 76.1% in the non-converters and 42.7% in all patients with UHR at baseline (Fig. 1).

The new-occurrence rate of any UHR in the 44 CHR-negative patients at baseline was 4.5% (Fig. 1).

Twenty-three of the 194 CHR-positive patients (11.8, 19.8% of the 116 non-converters) met a different CHR criteria at follow-up (Fig. 1).

Comparing the remission, persistence, and alteration rates between CHR-positive groups (Fig. 1), a significant difference was found in persistence rates with more patients persisting in the 'Only COGDIS' (20.0, 25.0% of non-converters) group compared with the 'Only UHR' (2.7, 3.6% of non-converters) and 'UHR + COGDIS' (1.6, 3.1% of non-converters) groups ($\chi_{(2)}{}^2 = 26.299$, $p < 0.001$; in non-converters: $\chi_{(2)}{}^2 = 29.584$, $p < 0.001$). Furthermore, fewer patients with 'UHR + COGDIS' (37.0, 73.4% in non-converters) and with 'Only COGDIS' (46.7, 58.3% in non-converters) than with 'Only UHR' (62.2, 82.1% in non-converters) remitted ($\chi_{(2)}{}^2 = 9.719$, $p < 0.007$; in non-converters: $\chi_{(2)}{}^2 = 4.067$, $p = 0.1309$).

None of the four baseline conditions predicted CHR status at follow-up (Cox regression, binary outcome variable: any CHR criterion present/absent; Supplementary Table 1).

Diagnoses and functioning at follow-up

At follow-up, 87 of the 160 non-converters (54.5%) met criteria of at least one Axis-I diagnosis, mostly of an affective or anxiety disorder (Table 3). The presence of an Axis-I disorder at follow-up was not significantly related to a positive CHR status at baseline ($\chi_{(1)}{}^2 = 0.612$, $p = 0.434$), but was related to a positive CHR status at follow-up ($\chi_{(1)}{}^2 = 4.045$, $p = 0.044$).

Remission of CHR status was not significantly related to the absence of any Axis-I disorder at follow-up ($\chi_{(1)}{}^2 = 3.467$, $p = 0.063$). However, with regard to the diagnostic groups, non-remission of CHR criteria was related to a higher frequency of both an affective disorder (non-remission: 41.9%, remission: 22.9%; $\chi_{(1)}{}^2 = 4.054$, $p = 0.044$) and, at a trend level, cannabis use disorder (non-remission: 9.7%, remission: 1.2%; $\chi_{(1)}{}^2 = 4.785$, $p = 0.029$, after Fisher's correction: $p = 0.061$).

Table 2 Comparison of general characteristics of non-converters at follow-up ($N = 160$)

	'CHR-negative' group ($n = 44$; 27.5%)	'Only COGDIS' group ($n = 24$; 15%)	'Only UHR' group ($n = 28$; 17.5%)	UHR + COGDIS' group ($n = 64$; 40%)	Statistical values
Duration of follow-up (FU; in months) (mean ± SD, median, range)	50.09 ± 17.15, 50.35, 17.38–81.25	57.96 ± 22.58, 56.20, 13.90–101.65	59.02 ± 27.81, 54.26, 21.29–123.73	53.86 ± 17.31, 54.06, 20.90–93.40	$\chi^2 = 2.014$, $df = 3$ $p = 0.570$[a]
Age at FU (in years) (mean ± SD, median, range)	30.43 ± 6.59, 30.23, 20.03–43.03	29.34 ± 5.60, 28.89, 19.49–38.64	31.93 ± 6.22, 32.47, 18.02–43.48	29.84 ± 6.22, 28.78, 18.20–46.66	$\chi^2 = 3.076$, $df = 3$; $p = 0.380$[a]
Sex (% male)	54.5%	66.7%	57.1%	60.9%	$\chi^2 = 1.077$, $df = 3$; $p = 0.783$
Nationality (% German)	97.7%	87.5%	85.7%	92.2%	$\chi^2 = 4.066$, $df = 3$; $p = 0.254$
Highest school graduation[b] at FU					
ISCED level ≤ 2	24.4%	10.0%	18.5%	20.3%	$\chi^2 = 1.797$, $df = 3$; $p = 0.616$
ISCED level 3A	75.6%	90.0%	81.5%	79.7%	
Current occupation at FU					
None or unemployed	27.3%	13.6%	25.0%	23.3%	$\chi^2 = 12.268$, $df = 3$; $p = 0.424$
Sheltered working place	2.3%	0.0%	0.0%	0.0%	
Irregular or temporary	4.5%	4.5%	7.1%	11.7%	
Regular or in training/school	63.6%	81.8%	60.7%	65.0%	
Marital status					
Single	84.1%	91.3%	78.6%	80.0%	$\chi^2 = 11.610$, $df = 3$; $p = 0.478$
Married	9.1%	4.3%	17.9%	16.7%	
Separated, divorced, etc	6.8%	4.3%	3.6%	3.3%	
Family history of psychosis (% with positive history)	2.4%	13.6%	14.3%	10.2%	$\chi^2 = 3.645$, $df = 3$; $p = 0.302$
Prescriptions at FU					
Neuroleptics (%)	4.5%	4.3%	0.0%	6.7%	$\chi^2 = 1.969$, $df = 3$; $p = 0.579$
Antidepressants (%)	25.0%	13.0%	25.0%	18.3%	$\chi^2 = 1.840$, $df = 3$; $p = 0.606$
Mood stabilizers (%)	9.1%	0.0%	0.0%	3.3%	$\chi^2 = 5.322$, $df = 3$; $p = 0.150$

[a]Non-normal distribution in the sample (Kolmogorov–Smirnov test; $p < 0.05$)

[b]According to the International Standard Classification of Education (ISCED)

Comparing the frequency of any Axis-I diagnosis at follow-up between the four baseline groups, only 'Only COGDIS' and 'UHR + COGDIS' significantly differed. The 'Only COGDIS' group generally reported more Axis-I diagnoses, particularly affective disorders, than the 'UHR + COGDIS' group (Table 3). Furthermore, 'UHR + COGDIS' received less affective diagnoses than 'CHR negative' and 'Only UHR'. There was no difference among the groups for any other Axis-I diagnosis, schizotypal personality disorder, or with regard to functioning (Table 3).

Mean and median GAF scores of all groups were still below 70 at follow-up, indicating at least some difficulty in social, occupational, or school functioning, and/or mild symptoms; no significant differences between baseline scores of CHR in the groups was observed (Table 3). However, regarding symptomatology at follow-up, the presence of CHR criteria (either newly developed or maintained) was associated with significantly lower functioning (non-remission: Mdn = 55, remission: Mdn = 68; $U = 609.00$, $p < 0.001$; and follow-up presence of CHR: Mdn = 55, absence of CHR: Mdn = 68; $U = 1163.50$, $p < 0.001$).

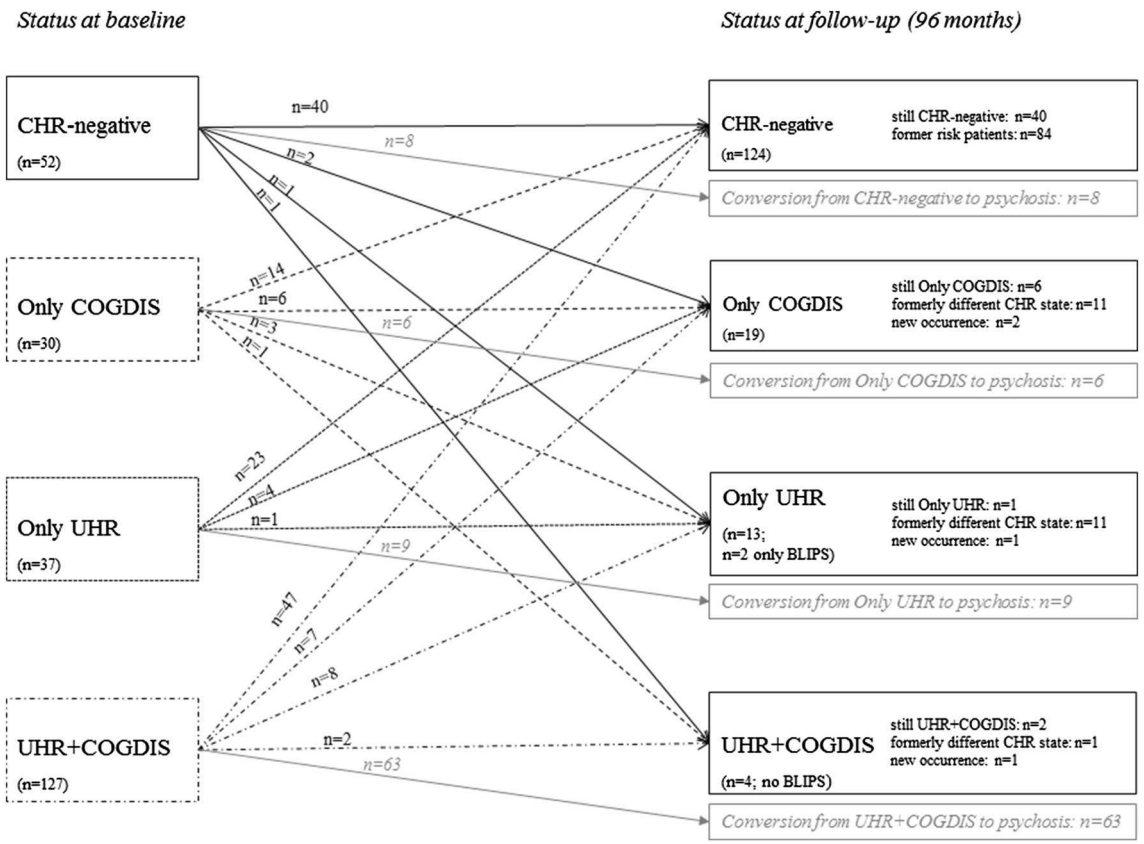

Fig. 1 Course of CHR criteria from baseline to follow-up according to the four at baseline defined groups

Discussion

The present study investigated remission and persistence rates of CHR status over a mean follow-up period of more than 4 years and the associations of different CHR states at baseline and follow-up with functional and diagnostic outcomes.

Course of CHR criteria

In our total sample of 246 patients, there was a conversion rate of 34.9% ($n=86$) and an overall remission rate from CHR status of 34.1% ($n=84$), while 16.3% ($n=40$) maintained their CHR-negative status and only 1.6% ($n=4$) newly developed CHR criteria. The persistence rate in non-converters ($n=160$) was 27.5% ($n=32$).

Our remission rate is consistent with Schlosser et al. [26] but lower than the rate of 48.3% observed by Ziermans et al. [25] over a 2-year follow-up. Considering only cases who met CHR criteria at baseline and did not convert during follow-up, our remission rate increased to 72.4%. The latter remission rates are in line with the previous results [27, 28, 41]. However, the variance in our remission rates demonstrates the general significance of the reference condition. For example, Addington et al. [24] found that 59.2% (45 of 76) of 2-year non-converters reported no APS at follow-up; however, this remission rate drops to 18.8% when the 89 converters of the total at-risk sample are also considered. Disregarding already converted cases and reporting only the rates for the non-converters [14, 24, 28, 41] may thus cause misleading conclusions about the predictive validity of CHR criteria.

Of the patients who had been CHR negative at baseline, 9.1% newly fulfilled the criteria of a CHR state at follow-up.

In a previous analysis of the total sample, patients meeting 'UHR + COGDIS' at baseline showed a higher risk of conversion to psychosis than those meeting 'Only UHR' or 'Only COGDIS' [9]. Consistent with this finding, 'UHR + COGDIS' demonstrated lower remission rates (37.0%) than the other two conditions ('Only COGDIS' 46.7%, 'Only UHR' 62.2%). Among the non-converters, 26.6% of the initial 'UHR + COGDIS' group were still at risk. Among these cases, 41.2% met 'Only COGDIS' and 47.1% 'Only UHR' at follow-up. The alteration in 'Only COGDIS' may indicate a (temporary) decrease of risk (according to the related conversion rates reported in Schultze-Lutter et al. [9]). However, the alteration to 'Only

Table 3 Comparison of clinical characteristics of non-converters at follow-up ($N = 160$)

	All non-converters ($N = 160$)	'CHR-negative' group ($n = 44$; 27.5%)	'Only COGDIS' group ($n = 24$; 15%)	'Only UHR' group ($n = 28$; 17.5%)	'UHR + COGDIS' group ($n = 64$; 40%)	Statistical values
Any Axis-I diagnosis at FU (% present)	55.4% ($n = 87$)	60.5% ($n = 26$)	72.7% ($n = 16$)	60.7% ($n = 17$)	43.8% ($n = 28$)	$\chi^2 = 6.956$, $df = 3$; $p = 0.073$[a]
Affective disorder (% present)[b]	29.9% ($n = 47$)	34.9% ($n = 15$)	45.5% ($n = 10$)	35.7% ($n = 10$)	18.8% ($n = 12$)	$\chi^2 = 7.292$, $df = 3$; $p = 0.063$[c]
Anxiety disorder (% present)	28.7% ($n = 45$)	30.2% ($n = 13$)	27.3% ($n = 6$)	28.6% ($n = 8$)	28.1% ($n = 18$)	$\chi^2 = 0.082$, $df = 3$; $p = 0.994$
Substance use disorder (% present)	10.8% ($n = 17$)	18.6% ($n = 8$)	9.1% ($n = 2$)	3.6% ($n = 1$)	9.4% ($n = 6$)	$\chi^2 = 4.429$, $df = 3$; $p = 0.219$
Alcohol	6.4% ($n = 10$)	14.0% ($n = 6$)	9.1% ($n = 2$)	0.0% ($n = 0$)	3.1% ($n = 2$)	$\chi^2 = 7.455$, $df = 3$; $p = 0.059$
Cannabis	5.1% ($n = 8$)	9.3% ($n = 4$)	4.5% ($n = 1$)	3.6% ($n = 1$)	3.1% ($n = 2$)	$\chi^2 = 2.236$, $df = 3$; $p = 0.525$
Other	1.9% ($n = 3$)	0.0% ($n = 0$)	0.0% ($n = 0$)	0.0% ($n = 0$)	4.7% ($n = 3$)	$\chi^2 = 4.444$, $df = 3$; $p = 0.217$
Eating disorder (% present)	3.8% ($n = 6$)	4.7% ($n = 2$)	4.5% ($n = 1$)	7.1% ($n = 2$)	1.6% ($n = 1$)	$\chi^2 = 1.841$, $df = 3$; $p = 0.606$
Somatoform disorder (% present)	3.2% ($n = 5$)	2.3% ($n = 1$)	0.0% ($n = 0$)	3.6% ($n = 1$)	4.7% ($n = 3$)	$\chi^2 = 1.309$, $df = 3$; $p = 0.727$
Schizotypal personality disorder (% present)	2.6% ($n = 4$)	0.0% ($n = 0$)	0.0% ($n = 0$)	3.6% ($n = 0$)	4.9% ($n = 3$)	$\chi^2 = 2.997$, $df = 3$; $p = 0.392$
Current GAF score at FU (mean ± SD, median, range)	62.69 ± 16.37, 60.00, 21–99	60.93 ± 15.66, 58.00, 21–90	65.15 ± 16.40, 59.50, 40–96	59.75 ± 17.04, 54.00,31–89	64.53 ± 16.61, 63.00, 21–99	$\chi^2 = 2.946$, $df = 3$; $p = 0.400$[d]
Current GAF score < 70 (% present)	68.4% ($n = 104$)	72.7% ($n = 32$)	65.0% ($n = 13$)	67.9% ($n = 19$)	66.7% ($n = 40$)	$\chi^2 = 0.576$, $df = 3$; $p = 0.902$
Current GAF score < 60 (% present)	53.9% ($n = 82$)	59.1% ($n = 26$)	60.0% ($n = 12$)	57.1% ($n = 16$)	46.7% ($n = 28$)	$\chi^2 = 2.159$, $df = 3$; $p = 0.540$

GAF Global Assessment of Functioning Scale

[a]Cramer's V = 0.210 (small effect of group); post-hoc analysis revealed a significant difference between groups 'Only COGDIS' versus 'UHR + COGDIS' ($\chi_{(1)}^2 = 7.169$, $p = 0.007$)

[b]Only one current affective disorder was a non-psychotic bipolar disorder (of organic origin); furthermore, seven non-psychotic bipolar disorders had been diagnosed as lifetime within the follow-up, but had remitted by the time of follow-up [40]

[c]Cramer's $V = 0.216$ (small effect of group); post-hoc analysis revealed a significant difference between groups 'Only COGDIS' versus 'UHR + COGDIS' ($\chi_{(1)}^2 = 6.133$, $p > 0.001$); 'CHR-negative' versus 'UHR + COGDIS' ($\chi_{(1)}^2 = 4.827$, $p = 0.028$); 'Only UHR' versus 'UHR + COGDIS' ($\chi_{(1)}^2 = 5.241$, $p = 0.022$)

[d]Non-normal distribution in the sample (Kolmogorov–Smirnov test; $p < 0.05$)

UHR' could also indicate a further increase in risk, as—different to an initial 'Only UHR' condition without COGDIS—the shift from the combined condition may be caused by a transition from basic symptoms to (attenuated) psychotic symptoms, e.g., unstable ideas of reference may have developed into ideas/delusions of reference.

Considering such a transition for the three non-converters moving from 'Only COGDIS' to 'UHR only', taken together with the case meeting 'UHR + COGDIS' at follow-up, risk for conversion may have increased in 16.7% of the initial 'Only COGDIS' cases. This, as well as the fact that the remission rate in 'Only COGDIS' (46.7%) was significantly lower than that in 'Only UHR' (62.2%), may support the notion that cognitive basic symptoms signal a long-term risk for conversion [1, 42]. In contrast, UHR criteria signal an imminent risk of conversion [2]. Yet, these assumptions could only be proven by a second follow-up.

Axis-I disorders and functioning at follow-up

Despite the high remission rate of CHR status within the non-converter group, 54.5% of non-converters received an Axis-I diagnosis at follow-up; the rate of affective disorders was clearly highest at follow-up, followed by anxiety disorders. This is consistent with earlier studies, often with shorter follow-ups, reporting that a majority of non-converters still had some Axis-I morbidity, with affective and anxiety disorders being most frequently seen [13, 17, 23, 24, 41]. The two disorder types were also the most frequently seen in CHR samples at the initial examination [43–45], suggesting some stability in this group of patients. However, a study of UHR criteria and symptoms in the community reported that help seeking in persons with UHR symptoms was mainly for depressiveness and anxiousness [46]. Thus, a selection bias towards these two disorders might explain their prominence in clinical CHR samples. Other than the presence of anxiety disorders, the presence of affective disorders at follow-up was significantly related to both the presence and persistence of CHR criteria, suggesting a liability of CHR patients to develop depressive symptoms, possibly regardless of the future development of psychosis.

Functioning in non-converters was generally low irrespective of CHR status at follow-up; however, it was even lower in those who had maintained and/or newly developed CHR criteria. Our findings support the notion that CHR states relate to functional disability in non-converters [20, 24].

Strength and limitations

The sample size and inclusion of CHR negatives that permits an estimation of new rates of CHR status in individuals who initially had some clinical indication of psychosis proneness and, consequently, had been referred to an early detection service, are a strength of our study. However, the restriction to two observation points, also common in other studies [15, 16, 18, 23, 30, 41], is certainly a weakness as it precludes the detection of fluctuations in CHR criteria and mental states [41]. Another limitation of the naturalistic design of our follow-up study is the large variance in follow-up periods, with the shortest and longest observation periods being roughly 9 years apart. However, large variance in the duration to follow-up was also reported by another observational study, which reported follow-up periods of greater than 10 years in some individuals [47]. As we did not try to reconstruct the course of CHR symptoms throughout the follow-up but assessed CHR status at follow-up, transient remissions as well as intermittent new occurrences of CHR criteria were not assessed, yet might have been object to memory bias anyway, in particular in patients with longer follow-up. Thus, we could also not truncate the available observation periods for homogenizing the duration, as neither carrying-forward of baseline status nor carrying-backward of follow-up status could be assumed to reliably reflect CHR status at the set time. Consequently, we accounted for the different durations by employing appropriate statistical measures. Another strength of our study is the inclusion of all relevant symptomatic CHR criteria, both UHR and basic symptom criteria [1]. All but two earlier studies [25, 27] considered only the course of UHR symptoms. However, these two studies did not differentially examine the course of the various CHR criteria and had shorter follow-ups.

Conclusion

Our study indicates that CHR criteria, in particular UHR criteria, remit in about one-third over the course of several years and rarely newly develop in CHR-negative adults presenting at early detection services. As reported for baseline CHR samples [1], the presence of CHR criteria maintains the risk for lower functioning and mental disorders, in particular affective disorders. Thus, therapeutic efforts targeting CHR patients should also focus on the current mental disorders, as well as social and role functioning, to improve the long-term outcomes.

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Compliance with ethical standards

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Conflict of interest Drs Michel and Schultze-Lutter declare that there are no conflicts of interest in relation to the subject of this study. Professor Ruhrmann received speaker's honoraria from AstraZeneca, Bristol-Myers Squibb, Essex, and Janssen-Cilag; travel support from Servier; and consultancy honoraria from Roche. Professor Klosterkötter received speaker's honoraria from AstraZeneca, Bristol-Myers Squibb, and Janssen-Cilag; a research grant from Bristol-Myers Squibb; and is a former member of the expert advisory board of Janssen-Cilag Germany. Professor Schimmelmann has been a consultant and/or advisor to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, and Shire.

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Supplementary Material to:
Course of Clinical High Risk States for Psychosis Beyond Conversion

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Supplementary Table 1. Results of the four separate Cox regression analyses of effect of the four CHR baseline states on outcome at follow-up

	β	SE	Wald (df=1)	p	Exp(β)	95% CI
Prevalence of CHR state at follow-up: binary outcome (any CHR criterion present/absent)						
CHR-negative	-0.389	0.324	1.445	0.229	0.677	0.359-1.278
Only COGDIS	-0.186	0.328	0.323	0.570	0.830	0.437-1.577
Only UHR	1.053	0.484	4.737	0.301	2.866	1.110-7.399
UHR+COGDIS	-0.118	0.273	0.187	0.665	0.889	0.520-1.517

Note: Each baseline CHR state entered the respective analysis as a single variable coded 1=present, 0=absent of the respective CHR state.