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Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: A systematic review

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ABSTRACT

Background: Research on patients at clinical high risk (CHR) for psychosis has so far mainly focused on those with transition to frank psychosis (CHR-T patients). However, the majority of CHR patients do not transition (CHR-NT patients) and relatively little information is available on their clinical and functional outcome.
Methods: We conducted a systematic review on clinical and functional long-term outcome of CHR-NT patients. Studies were included if they had an average follow-up period of at least 24 months and reported on long-term outcome of CHR-NT patients in one or more of the following domains: (non-)remission from CHR, prevalence of clinical symptoms and/or clinical diagnoses (axis I and II), and psychosocial functioning.
Results: Ten publications from seven different single or multicenter studies with average follow-up durations of 2–7.5 years could be included. At the last follow-up assessment 28–71% of CHR-NT patients were not remitted from their CHR and 22–82% still had at least one clinical diagnosis. Approximately half of CHR-NT patients presented with poor psychosocial outcome at 2-year and 6-year follow-up.
Conclusions: The results suggest that, in the long-term, the majority of CHR-NT patients are not in full clinical remission and seem to suffer from one or more clinical disorders and psychosocial impairments. Since relatively few studies could be identified, further research is required to better understand the trajectories and clinical needs of CHR-NT patients.

1. Introduction

Early detection and intervention have become a central topic of schizophrenia research in the past two decades (Riecher-Rössler and McGorry, 2016). Recently, the "Attenuated Psychosis Syndrome" was included in the research section of the DSM-5 (American Psychiatric Association, 2013), highlighting the relevance of this topic (Fusar-Poli et al., 2014a). To identify patients at high risk for psychosis, several research groups have specified clinical high risk (CHR) for psychosis criteria that are now internationally established (Fusar-Poli et al., 2013). There are two main CHR concepts, namely ultra-high risk (UHR) and basic symptom criteria. UHR criteria include the presence of attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), and a combination of trait vulnerability (e.g., genetic predisposition or schizotypal personality disorder) and reduced psychosocial functioning. Basic symptoms comprise self-experienced unspecific changes in the processes of thought or perception. In the following, we use the term "CHR" when referring to one or both concepts and "CHR patients" for patients with a CHR for psychosis, accordingly. In addition to fulfilling CHR criteria, CHR patients frequently present with non-psychotic clinical symptoms and disorders such as anxiety and depression at baseline (Fusar-Poli et al., 2014a, b). Psychosocial impairments are also common (Fusar-Poli et al., 2015) and seem to persist, even in patients without transition (Carrión et al., 2013; Lin et al., 2013a).

Research has so far mainly focused on investigating the characteristics and trajectories of CHR patients who transition to frank psychosis (CHR-T patients) with the long-term goal of identifying more specific risk factors and preventing or at least delaying the onset of a psychotic disorder (Riecher-Rössler and McGorry, 2016; Riecher-Rössler and Studerus, 2016; Yung, 2017). However, the majority (≈65%) of CHR patients do not transition (CHR-NT patients) (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015) and furthermore, transition rates are declining (Fusar-Poli et al., 2012; Nelson et al., 2013; Riecher-Rössler and Studerus, 2017).

So far, only one systematic review (Simon et al., 2011) and one meta-analysis (Simon et al., 2013) have been conducted on follow-up outcomes of CHR-NT patients and both only reported on the rates of

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remission from CHR. Six studies with follow-up durations of 6 months to 3 years presenting rates of remission from CHR which ranged from 15.4% to 54.3% were included in the systematic review (Simon et al., 2011). The meta-analysis included 8 studies with an average follow-up duration of 2 years and found that 46% of CHR-NT patients had fully remitted from attenuated psychotic symptoms at follow-up. Both analyses were based on relatively few studies with mostly short follow-up durations of only 2 years or less and were conducted already several years ago (the more recent meta-analysis included studies published until 01/2012). To the best of our knowledge, so far there is no review or meta-analysis reporting on the long-term course of CHR-NT patients including other important clinical and functional outcomes, such as non-psychotic clinical symptoms and diagnoses or psychosocial functioning. This is unfortunate because a considerable proportion of CHR-NT patients might still require clinical attention over the long-term course and further insight on their long-term outcomes could greatly improve clinical care in these patients.

Therefore, the aim of this study was to systematically review the current state of research on the long-term outcome of CHR patients without transition to frank psychosis. Specifically, we aimed to describe the rates of remission from CHR, the prevalence of clinical symptoms and diagnoses (axis I and II) as well as psychosocial functioning. Since the great majority of CHR patients who develop psychosis, transition during the first and second year after their initial identification (Fusar-Poli et al., 2013), we only included studies with an average follow-up duration of at least 24 months.

2. Methods

2.1. Search

A systematic search strategy was applied to retrieve relevant studies. Studies were identified by a literature search in the electronic databases Pubmed, Web of Science and Embase.

The following search terms were applied: ((ARMS OR "at-risk mental state" OR UHR OR "ultra-high risk" OR CHR OR "clinical high risk" OR "psychosis risk syndrome" OR prodromal OR prodrome OR emerging OR beginning) AND (psychosis OR psychotic OR schizophrenia) AND (transition OR remission OR "non-converters" OR "non-conversion" OR nonconverters OR nonconversion OR "non converters" OR "non conversion")).

Additionally, we performed a manual search of the reference lists of the included studies.

2.2. Eligibility criteria

Studies evaluating patients with a clinical high risk (CHR) for psychosis as defined as follows were assessed for eligibility: CHR was defined as the presence of ultra-high risk (UHR) and/or basic symptom criteria. An UHR status was indicated by at least one of the following criteria: 1) Attenuated psychotic symptoms (APS), 2) Brief limited intermittent psychotic symptoms (BLIPS) or 3) Genetic risk for psychosis or Schizotypal Personality Disorder and deterioration in or chronically low functioning (GRD) (Yung et al., 2004). A CHR based on basic symptom criteria was operationalized as either the presence of the cognitive-perceptive basic symptoms (COPER) or the cognitive disturbances (COGDIS) criterion (Schultze-Lutter et al., 2012b).

UHR and basic symptom criteria were required to be assessed by an established psychometric instrument with adequate reliability and validity. For UHR criteria these include standardized measures such as the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2010), the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005), the Basel Screening Instrument for Psychosis (BSIP; Riecher-Rössler et al., 2008) or the Early Recognition Inventory (ERIraos; Maurer et al., 2006). For basic symptom criteria these include the Schizophrenia Proneness Instrument, Adult (SPI-A; Schultze-Lutter et al., 2007) or Child & Youth version (SPI-CY; Schultze-Lutter et al., 2012a), the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross et al., 1987) or the ERIraos.

No restrictions concerning age or gender of participants were applied. No publication date restrictions and no language restrictions were imposed. The last search was conducted on 06/27/17.

Studies were excluded if they met one or more of the following exclusion criteria: (1) No primary study, (2) $n < 11$, (3) conference poster or abstract, (4) no CHR patients, (5) no follow-up assessments/no longitudinal data, (6) minimum follow-up duration shorter than 12 months or mean follow-up duration shorter than 24 months, (7) no results concerning clinical or functional outcome of CHR-NT patients at the time of the last long-term follow-up assessment reported, and (8) the psychometric instrument for the assessment of a CHR for psychosis used at baseline was not also applied at follow-up.

2.3. Study selection

At the first stage, titles and abstracts were screened by one reviewer and records were excluded, if it was clear that at least one exclusion criterion was fulfilled. In a next step two reviewers independently evaluated the full texts of the remaining studies. Disagreements were resolved through discussion with a third reviewer. If several eligible studies had overlapping samples, for every relevant outcome parameter the most recent study was selected.

2.4. Outcome parameters

For all parameters, long-term outcome was defined as the respective outcome at the time of the last follow-up evaluation.

Remission from CHR was defined as the absence of (attenuated) psychotic symptoms or the absence of UHR or basic symptom criteria at the last follow-up assessment.

The outcome parameter "clinical symptoms" comprises psychopathological symptoms such as (attenuated) positive, negative, depressive and anxiety symptoms.

All clinical diagnoses according to any version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or Chapter V of the International Classification of Diseases (ICD), respectively were considered.

In regard to psychosocial functioning, results from psychometric rater-based and self-rating measures were included.

2.5. Data extraction and analysis

Information was extracted for each included publication – if reported - regarding: 1) (name of) the superordinate single or multicenter study, 2) sample size at baseline and follow-up as well as the number of CHR-NT patients at the last follow-up assessment, 3) duration of follow-up (mean and range), 4) type of CHR criteria applied and instrument (s) used to assess the presence of a CHR as well as (non-)transition and – if applicable – remission from CHR, 5) proportion of CHR patients who had transitioned to frank psychosis, 6) percentage of CHR-NT patients who had remitted from their CHR at the last follow-up assessment, 7) prevalence of clinical symptoms, 8) prevalence of clinical diagnoses, and 9) psychosocial functioning at the last follow-up assessment.

Data collection and reporting was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.6. Risk of bias evaluation

Risk of bias was evaluated with The Cochrane Collaboration's tool for assessing risk of bias (Higgins and Altman, 2008). We only rated risk of bias in regard to parameters applicable to our systematic review, i.e., attrition bias (incomplete outcome data) and reporting bias

(selective outcome reporting). Two authors independently performed the rating for each outcome parameter of the included publications.

3. Results

Ten studies from seven different single or multicenter studies, assessing long-term outcomes of CHR patients over a mean follow-up duration of ca. 2 to 7.5 years, could be included in this systematic review. Further information on the selection process can be found in Fig. 1. Due to the small number of eligible studies and their heterogeneity regarding, e.g., reported outcome parameters, measures and follow-up durations, we refrained from performing a meta-analysis of the results.

The study characteristics and summary of main findings are displayed in Tables 1 to 4. Risk of bias rating of the outcome parameters of the included studies is presented in Supplementary Table 1.

3.1. Remission from clinical high risk at long-term follow-up

Six of the included publications reported rates of remission from CHR in CHR-NT patients at the last follow-up assessment.

In most studies, the majority of CHR-NT patients, i.e., about 50–70%, had remitted from their CHR (CHR remitters). Studies with longer average follow-up durations ranging from 6 to 7.5 years (Cropley et al., 2016; De Wit et al., 2014; Rutigliano et al., 2016) tended to reveal higher remission rates than the studies with shorter follow-up periods with average follow-up durations ranging from 2 to 3 years (Buchy et al., 2015; Lemos-Giráldez et al., 2009; Schlosser et al., 2012; Schneider et al., 2016).

3.2. Prevalence of clinical symptoms at long-term follow-up

No study reported on prevalence, i.e., presence or absence of clinical symptoms other than (attenuated) positive symptoms (see Section 3.1) of CHR-NT patients at the last follow-up assessment. Some studies provided raw scores (means and standard deviations) of scales assessing negative, depressive and anxiety symptoms but these scores were not set in relation to a certain threshold, degree of severity or results of a non-psychiatric comparison group. As this information was not interpretable for the current review, we did not include it.

3.3. Prevalence of clinical diagnoses at long-term follow-up

Four publications evaluated prevalence of clinical diagnoses at the last follow-up assessment (Addington et al., 2011; De Wit et al., 2014; Lemos-Giráldez et al., 2009; Rutigliano et al., 2016).

In the majority of studies, more than half of CHR-NT patients had at least one axis I or axis II disorder (Addington et al., 2011; De Wit et al., 2014; Rutigliano et al., 2016). The study of De Wit et al. (2014) with the highest prevalence (82%) of clinical diagnoses evaluated a sample of adolescents and 16 (47% of the whole sample) had a pervasive developmental disorder. In the study of Rutigliano et al. (2016) the prevalence of presence of at least one clinical diagnosis was approximately equal in CHR remitters (63%) and CHR non-remitters (67%).

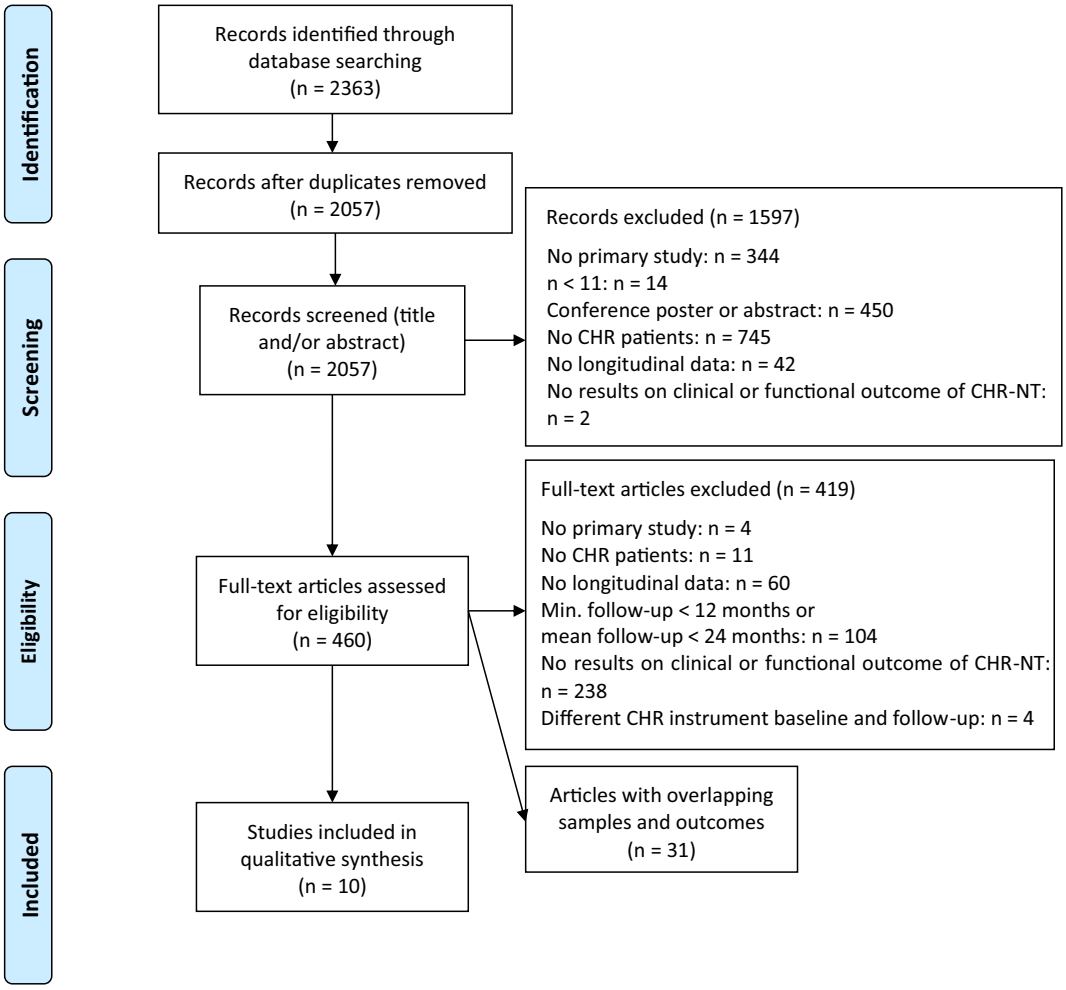

Fig. 1. PRISMA flow-diagram of the study selection process.

Table 1
Remission from CHR at long-term follow-up in patients without transition to psychosis (CHR-NT).

Authors	Study	Sample[a]	Age, years[b]	Time of long-term assessment[c]	CHR criteria (instrument)	Transition rate[d]	Attrition rate[e]	Outcome parameters (instrument)	Remission from CHR[e]
Schlosser et al. (2012)	CAPPS/UCLA	125/n.r./≈57	16.9 (3.5; n.r.)	24 months[f]	APS/BLIPS/GRD (SIPS/SOPS)	27 (30%)	41 (33%)	Sub-threshold positive symptoms (SIPS/SOPS)	32 (56.1%)
Buchy et al. (2015)	NAPLS-2	735/362/272	18.5 (4.2; n.r.)	24 months[f]	APS/BLIPS/GRD (SIPS/SOPS)	90 (12.2%)	n.r.	Sub-threshold positive symptoms (SIPS/SOPS)	109 (40.1%)
Schneider et al. (2016)		22/22/16	16.6 (4; 9–24)	32.6 (17.6; 12–85) months	APS/BLIPS/GRD (SIPS/SOPS)	6 (27.3%)	0	UHR criteria (SIPS/SOPS)	10 (62.5%)
Lemos-Giráldez et al. (2009)	Prevention program for psychosis (P3)	61/45/31	21.7 (3.8; 15–31)	36 months (n.r.; n.r.)	APS/BLIPS/GRD (SIPS/SOPS)	14 (23%)	16 (26.2%)	Sub-threshold positive symptoms (SIPS/SOPS)	9 (29%)
Rutigliano et al. (2016)	OASIS	154/74/53	23.2 (4.9; n.r.) and 23.6 (4.4; n.r.)[g]	6.19 (1.87; 4–10) years	APS/BLIPS/GRD (CAARMS)	21 (28.4%)	80 (51.9%)	APS (CAARMS)	38 (71.7%)
De Wit et al. (2014)	Dutch prediction of psychosis study	70/44/34	14.2 (1.8; n.r.) and 15.7 (2.3; n.r.)[h]	71.9 (11.3; 41–95) months	APS/BLIPS/GRD/COGDIS (SIPS/SOPS; BSAPS-P)	10 (14.3%)	26 (37.1%)	Sub-threshold positive symptoms (SIPS/SOPS)	18 (52.9%)
Cropley et al. (2016)	PACE-400	114/109/109	19.8 (3.5; n.r.) and 19.9 (3.4; n.r.)[h]	7.5 (2−12) years	APS/BLIPS/GRD (CAARMS)	n.a.[i]	n.r.	Sub-threshold positive symptoms (CAARMS)	79 (72.5%)

Note: Remission from CHR symptoms = absence of (attenuated) psychotic symptoms at the last follow-up assessment; Remission from CHR criteria = absence of CHR criteria at the last follow-up assessment; APS = Attenuated psychotic symptoms; BLIPS = Brief limited intermittent psychotic symptoms; GRD = Genetic risk for psychosis/Schizotypal Personality Disorder and deterioration in or chronically low functioning; COGDIS = cognitive disturbances; SIPS/SOPS: Structured Interview for Prodromal Syndromes/Scale of Prodromal Syndromes; CAARMS = Comprehensive Assessment of At-Risk Mental States; BSAPS-P = Bonn Scale for the Assessment of Basic Symptoms-Prediction List; n.r. = not reported.

[a] Baseline/Follow-up/CHR-NT at follow-up.
[b] Age of the whole sample at baseline. Mean (standard deviation; range).
[c] Mean (standard deviation; range) months/years after baseline.
[d] N (%), percentage refers to baseline sample.
[e] N (%), percentage refers to CHR-NT follow-up-sample.
[f] Clinical outcome at the time of 24 months after baseline is reported.
[g] CHR patients who participated in follow-up assessments and CHR patients who dropped out after the baseline assessment.
[h] Remitters and non-remitters.
[i] Sample consists of CHR-NT patients.

3.4. Psychosocial functioning at long-term follow-up

Seven studies reported on psychosocial functioning of CHR-NT patients at the last follow-up assessment (Addington et al., 2011; Brandizzi et al., 2015; Cropley et al., 2016; De Wit et al., 2014; Lemos-Giráldez et al., 2009; Lin et al., 2013b; Schlosser et al., 2012). Overall, these studies found that many CHR-NT patients continue to experience psychosocial difficulties and impairments.

Around half of CHR-NT patients showed good psychosocial outcome after 2 and 6 years of follow-up, respectively, in the studies of Schlosser et al. (2012) and Brandizzi et al. (2015).

Two studies reported the mean of CHR-NT patients' scores on measures of psychosocial functioning (Global Assessment of Functioning; GAF, Social and Occupational Functioning Assessment Scale; SOFAS) (Lemos-Giráldez et al., 2009; Lin et al., 2013b) which were all within the range defined as overall good psychosocial outcome in studies on functional outcome (Brandizzi et al., 2015; Lee et al., 2014; Rutigliano et al., 2016) as well as in the psychometric description of the instruments (American Psychiatric Association, 2000). However, the distribution of patients with good and poor psychosocial outcome remains unclear.

CHR-NT patients and even CHR remitters (De Wit et al., 2014) showed poorer functioning than non-psychiatric and healthy controls (Addington et al., 2011; De Wit et al., 2014), further indicating persistent functional impairments in these patients. However, there was evidence that remission from CHR is associated with better psychosocial outcome. CHR remitters presented with a higher level of psychosocial functioning than CHR non-remitters (Cropley et al., 2016). The study of De Wit et al. (2014) yielded the same result when comparing CHR remitters with the group of non-remitters and those who had transitioned (CHR-T patients) in regard to global daily functioning but not social functioning. They also reported that 75% of CHR remitters presented with good global daily functioning.

3.5. Prevalence of any clinical or psychosocial impairment at long-term follow-up

Only a minority of CHR-NT patients was clinically and functionally recovered. At 24-months follow-up approximately 30% in the study of Schlosser et al. (2012) and after an average of 6 years of follow-up 21% in the study of Rutigliano et al. (2016) of CHR-NT patients were fully remitted and did not show any clinical or psychosocial impairment.

3.6. Risk of bias evaluation

For the great majority of studies risk of bias is assumed to be low.

Of all studies reporting on remission from CHR, two of the three studies with an unclear risk of bias reported the lowest remission rates (Buchy et al., 2015; Lemos-Giráldez et al., 2009). However, both are also characterized by short follow-up durations. One of the two studies with a high risk of bias in regard to clinical diagnoses seems to report only those of CHR remitters, resulting in a distinctly lower prevalence. The results on psychosocial outcome of the two studies with an unclear risk of bias resemble those of the studies with low risk of bias. The two studies evaluating full clinical and functional recovery received a low risk of bias rating.

4. Discussion

To the best of our knowledge, this is the first systematic review on CHR-NT patients' long-term outcome covering not only remission

Table 2
Prevalence of clinical diagnoses at long-term follow-up in patients without transition to psychosis (CHR-NT).

Authors	Study	Sample[a]	Age, years[b]	Time of long-term assessment[c]	CHR criteria	Transition rate[d]	Attrition rate[e]	Outcome parameters (instrument)	Prevalence of clinical diagnoses[e]
Addington et al. (2011)	NAPLS	303/76/76	n.r. (n.r.; 12–36)[f]	24 months[g]	APS/BLIPS/GRD (SIPS/SOPS)	89 (29.4%)[h]	138 (45.5%)	Axis I diagnoses (SCID)	24 (31.6%) anxiety disorder, 11 (14.5%) depression, 1 (1.3%) mania, 3 (3.9%) substance use disorder
Lemos-Giráldez et al. (2009)	Prevention program for psychosis (P3)	61/45/31	21.7 (3.8; 15–31)	36 months (n.r.; n.r.)	APS/BLIPS/GRD (SIPS/SOPS)	14 (23%)	16 (26.2%)	Axis I & II diagnoses (SCID-I & -II)	2 (6%) affective disorder, 1 (3%) obsessive-compulsive disorder, 4 (13%) personality disorder
Rutigliano et al. (2016)	OASIS	154/74/53	23.2 (4.9; n.r.) and 23.6 (4.4; n.r.)[i]	6.19 (1.87; 4–10) years	APS/BLIPS/GRD (CAARMS)	21 (28.4%)	80 (51.9%)	Axis I & II diagnoses (SCID-I & -II)	Any clinical diagnosis: CHR-NT: 34 (64%) CHR non-remitters: 10 (66.7%)
De Wit et al. (2014)	Dutch Prediction of psychosis study	70/44/34	14.2 (1.8; n.r.) and 15.7 (2.3; n.r.)[j]	71.9 (11.3; 41–95) months	APS/BLIPS/GRD/COGDIS (SIPS/SOPS; BSAPS-P)	10 (14.3%)	26 (37.1%)	Axis I & II diagnoses (K-SADS-PL; clinical interviews, medical records)	28 (82%) one or more axis I diagnoses 2 (6%) Borderline personality disorder, 1 (3%) schizotypal personality disorder CHR remitters: 12 (66%) in full or partial remission of their axis I disorder

Note: APS = Attenuated psychotic symptoms; BLIPS = Brief limited intermittent psychotic symptoms; GRD = Genetic risk for psychosis/Schizotypal Personality Disorder and deterioration in or chronically low functioning; COGDIS = cognitive disturbances; SIPS/SOPS: Structured Interview for Prodromal Syndromes/Scale of Prodromal Syndromes; CAARMS = Comprehensive Assessment of At-Risk Mental States; BSAPS-P = Bonn Scale for the Assessment of Basic Symptoms-Prediction List; SCID-I & -II = Structured Clinical Interview for DSM-IV Axis I and Axis II Disorders; K-SADS-PL = Semi-structured Kiddie-Sads-Present and Lifetime Version interview; n.r. = not reported.

[a] Baseline/Follow-up/CHR-NT at follow-up.
[b] Age of the whole sample at baseline. Mean (standard deviation; range).
[c] Mean (standard deviation; range) months/years after baseline.
[d] N (%), percentage refers to baseline sample.
[e] N (%), percentage refers to CHR-NT follow-up-sample.
[f] Information on mean and standard deviation is only reported for the group CHR-NT patients who participated in the 1-year follow-up (n = 111; 18 ± 4.9 years).
[g] Clinical outcome at the time of 24 months after baseline is reported.
[h] At the time of 2.5 years after baseline.
[i] CHR patients who participated in follow-up assessments and CHR patients who dropped out after the baseline assessment.
[j] Remitters and non-remitters.

from CHR but also prevalence of non-psychotic clinical symptoms and clinical diagnoses as well as psychosocial functioning. Furthermore, it is the first to report rates of remission from CHR after a minimum average follow-up period of 24 months.

4.1. Summary of evidence

The findings of our review suggest that in the long-term, the great majority of CHR-NT patients are not in full clinical and functional recovery. At least one third of CHR-NT patients were not remitted from their CHR, even after long follow-up periods of up to 7.5 years. Overall, the majority of CHR-NT patients had at least one clinical diagnosis at long-term follow-up, with mood and anxiety disorders being the most frequent ones. The results on psychosocial functioning suggest that many CHR-NT patients also experience psychosocial impairments at long-term follow-up. Approximately half of CHR-NT patients showed poor psychosocial outcome, CHR-NT patients had lower levels of psychosocial functioning than healthy controls and CHR non-remitters showed poorer functioning than CHR remitters but evidence here is scarce.

So far, there had been only one systematic review (Simon et al., 2011) and one meta-analysis (Simon et al., 2013) on CHR-NT patients' outcome and both solely reported on rates of remission from CHR. Simon et al. (2011) had originally aimed to evaluate a broader range of clinical and social outcomes but could then only identify eligible studies reporting on transition and CHR remission rates. In line with this, the findings of our review reveal that research on the clinical and functional long-term outcome of CHR-NT patients is still scarce.

4.1.1. Remission from clinical high risk at long-term follow-up

Simon et al. (2013) reported an estimated remission rate of 46% after an average follow-up period of 2 years, which is within the range of remission rates found in our review. Additionally, the results of our review indicate that remission rates increase over the long-term course. If the presence of basic symptom criteria would be additionally considered, the proportion of non-remitted CHR-NT patients might be even higher (Michel et al., 2018).

In this context it should be kept in mind that some non-remitters might experience a late transition, i.e., develop frank psychosis > 3 years after initial identification as CHR patients (Amminger et al., 2015; Beck et al., 2017; Cornblatt et al., 2015; Nelson et al., 2013).

4.1.2. Prevalence of other clinical symptoms and diagnoses at long-term follow-up

CHR patients often present with "comorbid" clinical symptoms and diagnoses at initial identification (Fusar-Poli et al., 2014b). The results of our systematic review indicate that the majority of CHR-NT patients continue to suffer from clinical disorders even many years later. This is in line with the findings of other studies that could not be included due to the presence of at least one of our pre-defined exclusion criteria (Addington et al., 2017; Lin et al., 2015; Michel et al., 2018). Lin et al. (2015) evaluated prevalence of axis I diagnoses in CHR-NT patients over the course of an average of 7 years and showed that 52% of CHR-NT patients experienced at least one persistent or recurrent disorder and overall, 68% had at least one diagnosis during this time span.

(Attenuated) psychotic symptoms can also occur in the context of various other clinical disorders such as depression and anxiety disorders as a sign of increased severity (van Os and Guloksuz, 2017). In these patients, treatment of the clinical disorder could lead to symptomatic improvement and remission from the CHR (Rothschild, 2013; Wigman et al., 2012; Simon, 2016). It was also hypothesized that CHR criteria might not only be predictive for psychotic but also other psychiatric disorders, potentially explaining the high rates of

Table 3
Psychosocial functioning at long-term follow-up in patients without transition to psychosis (CHR-NT).

Authors	Study	Sample[a]	Age, years[b]	Time of long-term assessment[c]	CHR criteria	Transition rate[d]	Attrition rate[d]	Outcome parameters (instruments)	Psychosocial functioning[e]
Addington et al. (2011)	NAPLS	303/76/76	n.r. (n.r.; 12–36)[f]	24 months[g]	APS/BLIPS/GRD (SIPS/SOPS)	89 (29.4%)[h]	138 (45.5%)	Psychosocial functioning (GFS:S; GFS:R)[i, j]	CHR-NT < non-psychiatric controls
Schlosser et al. (2012)	CAPPS/UCLA	125/n.r./≈57	16.9 (3.5; n.r.)	24 months[g]	APS/BLIPS/GRD (SIPS/SOPS)	27 (30%)	41 (33%)	Functional recovery (GFS:S; GFS:R)[i, j]	Good psychosocial functioning: 32 (56.1%)
Brandizzi et al. (2015)	OASIS	154/92/56	23.4 (4.6; 15–35)	6.63 (2; 3–11) years	APS/BLIPS/GRD (CAARMS)	36 (39%)	n.r.	Good psychosocial functioning (GAF)[k]	Good psychosocial functioning: 57%
De Wit et al. (2014)	Dutch prediction of psychosis study	70/44/34	14.2 (1.8; n.r.) and 15.7 (2.3; n.r.)[l]	71.9 (11.3; 41–95) months	APS/BLIPS/GRD/COGDIS (SIPS/SOPS; BSAPS-P)	10 (14.3%)	26 (37.1%)	Global daily functioning (mGAF) Social functioning (Adaptive Functioning Scale "Friends" of the ASEBA Adult Self Report)	CHR-NT < healthy controls CHR remitters < healthy controls Global daily functioning: CHR remitters > non-remitters Social functioning: CHR remitters = non-remitters
Lin et al. (2013)	PACE-400	325/246/165	19.1 (3.3; n.r.)	7.2 (2.4–14.9) years	APS/BLIPS/GRD (CAARMS)	81 (24.9%)	79 (24.3%)	Psychosocial functioning (GAF; SOFAS)	GAF: 69 (13)[m] SOFAS: 72 (14)[n]
Cropley et al. (2016)	PACE-400	114/109/109	19.8 (3.5; n.r.) and 19.9 (3.4; n.r.)[l]	7.5 (2–12) years	APS/BLIPS/GRD (CAARMS)	n.a.[o]	n.r.	Psychosocial functioning (GAF)	CHR remitters > CHR non-remitters
Lemos-Giráldez et al. (2009)	Prevention Program for Psychosis (P3)	61/45/31	21.7 (3.8; 15–31)	36 months[p]	APS/BLIPS/GRD (SIPS/SOPS)	14 (23%)	16 (26.2%)	Psychosocial functioning (GAF)	GAF: 81 (11)[q]

Note: APS = Attenuated psychotic symptoms; BLIPS = Brief limited intermittent psychotic symptoms; GRD = Genetic risk for psychosis/Schizotypal Personality Disorder and deterioration in or chronically low functioning; COGDIS = cognitive disturbances; SIPS/SOPS: Structured Interview for Prodromal Syndromes/Scale of Prodromal Syndromes; CAARMS = Comprehensive Assessment of At-Risk Mental States; BSAPS-P = Bonn Scale for the Assessment of Basic Symptoms-Prediction List; GFS:S = Global Functioning Scale: social; GFS:R = Global Functioning Scale: role; GAF = Global Assessment of Functioning; mGAF = modified Global Assessment of Functioning scale; SOFAS = Social and Occupational Functioning Assessment Scale; n.r. = not reported.

[a] Baseline/Follow-up/CHR-NT at follow-up.
[b] Age of the whole sample at baseline. Mean (standard deviation; range).
[c] Mean (standard deviation; range) months/years after baseline.
[d] N (%), percentage refers to baseline sample.
[e] N (%), percentage refers to CHR-NT follow-up-sample, ">" indicates better psychosocial functioning.
[f] Information on mean and standard deviation is only reported for the group CHR-NT patients who participated in the 1-year follow-up (n = 111; 18 ± 4.9 years).
[g] Psychosocial outcome at the time of 24 months after baseline is reported.
[h] At the time of 2.5 years after baseline.
[i] Auther et al. (2006); Niendam et al. (2006).
[j] Functional recovery was defined as a score of 7 or higher over a 1-month period on the GF: S and GF: R scale.
[k] GAF score ≤ 61 = poor, GAF score > 60 = good psychosocial functioning.
[l] Remitters and non-remitters.
[m] Mean (standard deviation), GAF anchor point 61–70: "Some mild symptoms (e.g., depressed mood and mild insomnia) or some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships."
[n] Mean (standard deviation), Social and Occupational Functioning Assessment Scale (SOFAS) anchor point 70: "Some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships".
[o] Sample consists of CHR-NT patients.
[p] Psychosocial outcome at the time of 36 months follow-up is reported.
[q] Mean (standard deviation), GAF anchor point 81–90: "Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members)."

non-psychotic disorders in CHR-NT patients (Fusar-Poli et al., 2014a). However, recent studies evaluating help-seeking patients with and without a CHR state, assessed within designated centers and research projects, did not support this (Fusar-Poli et al., 2017; Webb et al., 2015; Woods et al., 2018).

Another important aspect that needs to be considered in this regard is the fact that symptoms of depression and anxiety are also typical signs of and frequently occur during the prodromal phase. Therefore, in some patients their persistence could indicate a (prolonged) prodromal phase and risk of late transition.

4.1.3. Psychosocial functioning at long-term follow-up

Existing research from short-term follow-up studies indicates that psychosocial impairments tend to persist over the short-term course, independent of transition status and despite treatment (Lin et al., 2013a; Schmidt et al., 2015). The findings of the current review suggest that in a considerable number of CHR-NT patients impairments persist also in the longer term. This finding could be related to the fact that a considerable number of CHR-NT patients persistently or recurrently experience (attenuated) psychotic symptoms (Cropley et al., 2016; De Wit et al., 2014). Furthermore, clinical disorders, which are frequently

Table 4
Absence of CHR symptoms, non-psychotic clinical symptoms and diagnoses, and psychosocial impairment at long-term follow-up in patients without transition to psychosis (CHR-NT).

Authors	Study	Sample[a]	Age, years[b]	Time of long-term assessment[c]	CHR criteria	Transition rate[d]	Attrition rate[d]	Outcome parameters (instrument)	Absence of clinical and functional impairment[e]
Schlosser et al. (2012)	CAPPS/UCLA	125/n.r./≈57	16.9 (3.5; n.r.)	24 months[f]	APS/BLIPS/GRD (SIPS/SOPS)	27 (30%)	41 (33%)	Sub-threshold positive symptoms (SIPS/SOPS) Global functioning (GFS)	17 (29.8%)
Rutigliano et al. (2016)	OASIS	154/74/53	23.2 (4.9; n.r.) and 23.6 (4.4; n.r.)[g]	6.19 (1.87; 4–10) years	APS/BLIPS/GRD (CAARMS)	21 (28.4%)	80 (51.9%)	Sub-threshold positive symptoms (SIPS/SOPS) Axis I & II diagnoses (SCID-I & -II) Psychosocial functioning (GAF)	11 (20.8%)

Note: APS = Attenuated psychotic symptoms; BLIPS = Brief limited intermittent psychotic symptoms; GRD = Genetic risk for psychosis/Schizotypal Personality Disorder and deterioration in or chronically low functioning; SIPS/SOPS: Structured Interview for Prodromal Syndromes/Scale of Prodromal Syndromes; CAARMS = Comprehensive Assessment of At-Risk Mental States; GFS = Global Functioning Scale; GAF = Global Assessment of Functioning; n.r. = not reported.
[a] Baseline/Follow-up/CHR-NT at follow-up.
[b] Age of the whole sample at baseline. Mean (standard deviation; range).
[c] Mean (standard deviation; range) months/years after baseline.
[d] N (%), percentage refers to baseline sample.
[e] N (%), percentage refers to CHR-NT follow-up-sample.
[f] Outcome at the time of 24 months after baseline is reported.
[g] CHR patients who participated in follow-up assessments and CHR patients who dropped out after the baseline assessment.

present in CHR-NT patients over the long-term course, usually come along with psychosocial impairments. Rutigliano et al. (2016) were the first to evaluate this association in CHR patients at long-term follow-up and reported that patients with persistent or recurrent concomitant affective disorders were at higher risk of being functionally impaired at 6-year follow-up.

Future studies are necessary to facilitate further insight concerning potential underlying causes of persistent psychosocial impairments in CHR-NT patients.

4.1.4. Prevalence of any clinical or psychosocial impairment at long-term follow-up

In line with recent studies with shorter follow-up periods, the results of our systematic review indicate that the majority of CHR-NT patients is not fully clinically and functionally remitted.

4.2. Implications for treatment

So far, research on treatment in CHR patients focuses mainly on interventions aiming to decrease the risk of transition (Riecher-Rössler and Studerus, 2016; Yung, 2017), with some recent encouraging results (Schmidt et al., 2015). This certainly is an important outcome but at the same time, CHR patients with and without later transition are distressed by, and seeking help because of their current symptoms and psychosocial impairments (Falkenberg et al., 2015; Fusar-Poli et al., 2013, 2014a). Since these symptoms and impairments often seem to persist over the long-term course, they must not be neglected in the monitoring and treatment of CHR patients.

4.3. Outlook

In addition to the investigation of factors associated with adverse outcomes, predictors of a positive course, i.e., protective factors such as resilience and psychosocial support should be examined. Resilience has proven to be a protective factor in schizophrenia (Bozikas et al., 2016; Galderisi et al., 2016; Torgalsbøen, 2012) and can be targeted by therapeutic interventions; however, its impact in CHR patients has been barely evaluated (Kim et al., 2013; Marulanda and Addington, 2016). There are several potential pathways on which protective factors could not only decrease the risk of transition but also improve symptoms and functional outcome, which could be useful for the development of effective treatment strategies.

4.4. Limitations

Our findings should be interpreted with caution due to the small number of included studies as well as the heterogeneity of study samples, reported outcomes and follow-up durations. The clinical and functional long-term outcomes of CHR-NT patients evaluated in this review were usually not the main focus of the respective studies. Furthermore, it needs to be considered that study samples with extensive follow-up durations usually have a higher attrition rate and their samples might be biased. Patients who (almost) fully recovered from clinical and functional impairments as well as those with a very poor clinical and functional outcome might have a higher tendency to drop out of long-term follow-up studies. However, risk of bias due to inadequate handling of incomplete outcome data ("attrition bias") or selective outcome reporting ("reporting bias") is assumed to be small.

The studies included in our review identified CHR patients based on the SIPS/SOPS and CAARMS. Despite slight differences between their operationalizations of UHR criteria, both scales recently showed mostly large accordance in classifying patients as CHR patients and as having transitioned to frank psychosis or not (Fusar-Poli et al., 2016). When remission from CHR is rated based on (non-)fulfillment of UHR criteria, CHR-NT patients with stable attenuated symptoms are classified as remitted within the SIPS/SOPS but non-remitted in the CAARMS, which can lead to variability of results. However, the impact of this issue on the results of our systematic review is likely small as only two of the included studies operationalized remission from CHR solely based on UHR criteria (SIPS/SOPS and CAARMS). The difference in remission rates was only small and is likely mostly due to the difference in follow-up durations.

Of the studies we included, there is only one whose sample consisted partially of CHR patients who at baseline met basic symptom criteria. However, remission from CHR was assessed only by SIPS/SOPS and also no differentiation between the groups (basic symptom and UHR entry criteria) was made regarding clinical and functional outcome. Therefore, we are not able to provide further insight in this regard.

Subclinical psychotic experiences seem to be more common in adolescents (Simon, 2016). Compared to adults, remission from CHR might be either more or less likely in CHR patients identified during their adolescence, depending on age and follow-up duration. Across all outcomes, the results of our systematic review do not show any specific patterns in this regard.

4.5. Conclusions

The findings from our review suggest that the majority of CHR-NT patients is not in full clinical and functional remission and seem to suffer from one or more clinical disorders and psychosocial difficulties even several years after initial presentation. This underlines the relevance of further research evaluating the long-term clinical and functional outcome of CHR-NT patients as this has only been investigated to a very limited extent. CHR patients are a heterogeneous group and different trajectories are possible (Carpenter and Schiffman, 2015; Polari et al., 2018). Further knowledge on the long-term prevalence of symptoms and impairments is necessary to determine the need for routine diagnostic assessments and treatment over the long-term course in this population. In conclusion, insight into different trajectories and their predictors is fundamental for a better understanding of the CHR concept and for the development and implementation of targeted intervention strategies.

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