Prediction of conversion to psychosis in individuals with an at-risk mental state: a brief update on recent developments

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Purpose of review
So far, only little more than one-third of individuals classified as being at-risk for psychosis have been shown to actually convert to frank psychosis during follow-up. There have therefore been enormous efforts to improve the accuracy of predicting this transition. We reviewed the most recent studies in the field with the aim to clarify whether accuracy of prediction has been improved by the different research endeavors and what could be done to further improve it, and/or what alternative goals research should pursue.

Recent findings
A total of 56 studies published between May 2015 and December 2016 were included, of which eight were meta-analyses. New meta-analytical evidence confirms that established instruments for checking clinical risk criteria have an excellent clinical utility in individuals referred to high-risk services. Within a such identified group of ultra-high-risk (UHR) individuals, especially Brief Limited Intermittent Psychotic Symptoms and Attenuated Psychotic Symptoms seem to predict transition. Further assessments should be performed within the UHR individuals, as risk of transition seems particularly high in those with an even higher severity of certain symptoms such as suspiciousness or anhedonia, in those with lower global or social functioning, poor neurocognitive performance or cannabis abuse. Also, electroencephalography, neuroimaging and blood biomarkers might contribute to improving individual prediction. The most promising approach certainly is a staged multidomain assessment. Risk calculators to integrate all data for an individualized prediction are being developed.

Summary
Prediction of psychosis is already possible with an excellent prognostic performance based on clinical assessments. Recent studies show that this accuracy can be further improved by using multidomain approaches and modern statistics for individualized prediction. The challenge now is the translation into the clinic with a broad clinical implementation.

Keywords
conversion, prediction, psychosis, schizophrenia, transition

INTRODUCTION

Early detection of emerging psychosis has been a major goal of psychiatric research in the last two decades. In an earlier retrospective study [1], we had shown that about 70% of schizophrenic psychoses do not start with frank psychotic symptoms but emerge slowly over an average period of 4–5 years, first with quite unspecific so-called prodromal symptoms and then with more specific subthreshold, so-called 'attenuated' psychotic symptoms or even very short self-limiting psychotic symptoms. The construct of a clinical high risk (CHR) or at-risk mental state (ARMS) for psychosis was suggested to capture this early phase of disease [2]. Increasing recognition of this concept has led to the introduction of the 'Attenuated Psychosis Syndrome' into the Diagnostic and Statistical Manual-5 appendix as a 'condition for further study' [3].

Research has so far focused on detecting individuals in this early stage of disease to predict transition to frank psychosis and at the same time to offer a therapy for those seeking help.

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KEY POINTS

- Identification of individuals at risk and prediction of transition to psychosis is possible with an excellent accuracy comparable with other preventive approaches in medicine.
- Recent studies show that this accuracy might be further improved by using stepwise multidomain approaches and modern statistical methods.
- For further improvement of prediction, we need multicenter studies with larger samples, inclusion of a broader age range of at-risk individuals and longer follow-ups.
- Methodology has to be further improved by better standardization of assessment methods and better control of intercenter effects. Studies on risk prediction models should more strictly adhere to current checklists and guidelines on clinical prediction modeling.
- For translation into the clinic, easy-to-use, stepwise risk assessment tools and guidelines as well as individualized prediction calculators should be developed. More effort has to be put into a broad clinical implementation.

As regards the prediction of transition, two recent meta-analyses [4,5▪] have shown that about 37% of those fulfilling current risk criteria develop psychosis, mainly schizophrenia spectrum disorders, within 3 years.

This review summarizes more recent studies and meta-analyses regarding the prediction of conversion to frank psychosis in patients meeting clinically defined at-risk criteria, excluding studies on individuals with a purely genetic risk. We first look into studies on predictors from single domains and then into those with a multidomain approach and modeling. We aimed at clarifying whether accuracy of prediction has been improved by the different research endeavors and what could be done to further improve it, and/or which alternative goals research should pursue.

METHODS

Articles published from 1 May 2015 until 14 December 2016 were systematically searched via the *PubMed* database. The following search terms were applied: 'psychosis and ('ultra-high risk' or UHR or 'clinical high risk' or CHR or prodrom* or 'psychosis risk' or 'risk of psychosis' or 'clinically at high risk' or 'at-risk mental state' or ARMS or 'at-risk patients') and (conversion or convert* or transit* or predict*) and ['2015/05/01'(EDat): '2016/12/14'(EDat)]. Furthermore, a hand-search of relevant journals and reference lists of included articles was performed. Only peer-reviewed original articles and meta-analyses were included according to the criteria shown in Table 1 [2].

Table 1. Inclusion and exclusion criteria of studies

Inclusion criteria
1. Only prospective studies with mean follow-up period ≥12 months or meta-analyses relevant to prediction of transition
2. Study participants at baseline had to fulfil clearly defined clinical high risk (HR) criteria for psychosis (see Table 2)
3. Transition to psychosis had to be clearly defined (usually according to Yung *et al.* [2]).
4. Transition of ≥10 participants
Exclusion criteria
1. Therapy studies

RESULTS

From the mentioned period, 56 studies were included (Fig. 1). Of these, eight were meta-analyses [6–7,8▪,9,10,11▪–13▪]. Detailed lists of the included original studies and meta-analyses are provided in Supplementary Tables S1 and S2, http://links.lww.com/YCO/A37, respectively. Figure 2 shows the predictor domains investigated; 21 studies developed prediction models from multiple domains. It is important to note that most predictors were only studied within the group of individuals clinically classified as being at risk.

Clinical predictors

Clinical characteristics assessed at baseline had a very high predictive power. This is especially true for the fulfillment of predefined clinical risk criteria in individuals referred to early detection clinics.

Risk criteria

Help-seeking individuals were generally classified as being at CHR for psychosis

- if they met at least one of three UHR inclusion criteria [brief limited intermittent psychotic symptoms (BLIPS) and/or subthreshold so-called attenuated psychotic symptoms (APS) and/or genetic risk and deterioration syndrome (GRD)],
- or if they met basic symptom criteria (i.e. subjective disturbances of cognitive processes and perception) [5▪].

See also Table 2 [4].

We have recently compared the risk of transition to psychosis between the different risk groups in a

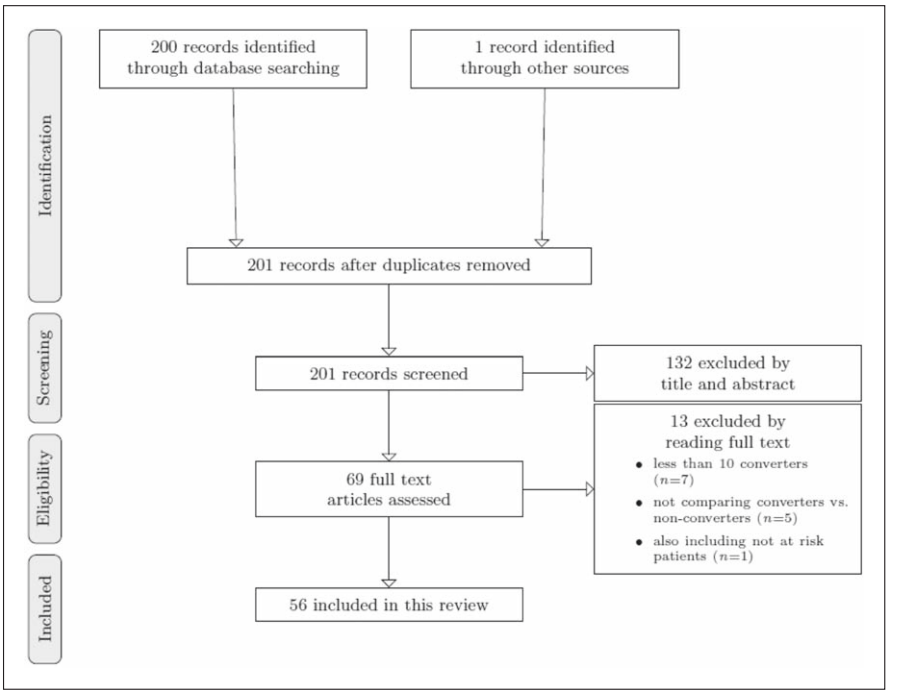

FIGURE 1. Flow chart of literature search.

meta-analysis of 33 independent studies comprising 4227 individuals [11▪]. Most individuals (85%) had been included because of APS, 10% because of BLIPS and 5% solely because of GRD. The risk of transition was higher in BLIPS than in APS individuals (e.g. 39 versus 19% at 24 months). The group with GRD had no higher risk of transition than those without supposed risk. In an earlier meta-analysis, we had found a conversion rate comparable with UHR samples at 2 years and an even higher rate after 4 years in the basic symptom group with cognitive disturbances [5▪]. Most transitions occur within 2 years and half of these within the first 8 months [14], but there are also later transitions [15–17].

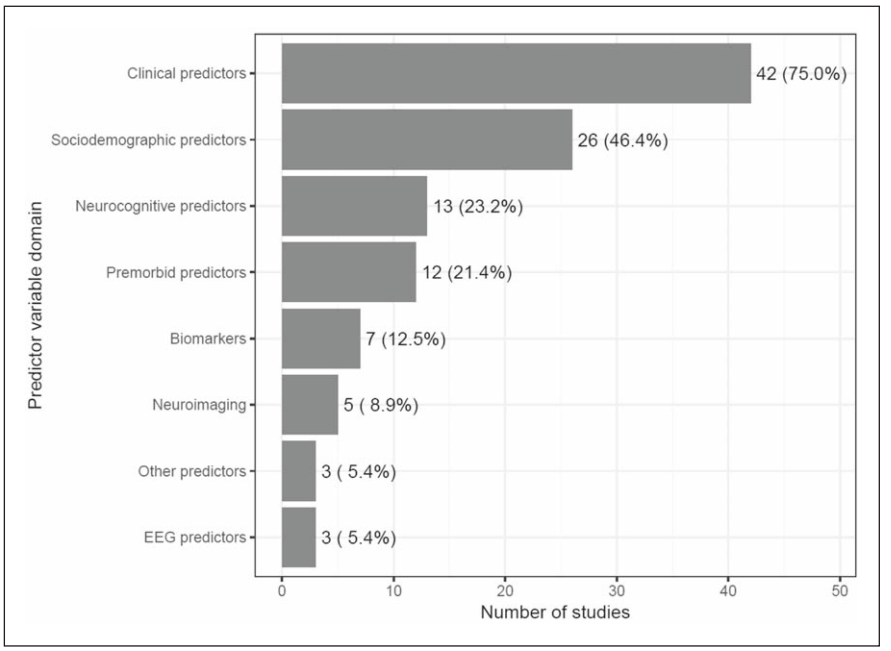

FIGURE 2. Predictor variable domains of included studies. Note: Prediction was always performed within Cinical High Risk (CHR) individuals previously identified by clinical criteria. Multiple domains were tested in many studies.

Table 2. Clinical high risk criteria for psychosis and assessment instruments[*,a]

Instrument	Basic symptoms[b]	Genetic risk and deterioration syndrome	Brief limited intermittent psychotic episode	Attenuated psychotic symptoms
CAARMS	NA	Family history of psychosis OR an individual with schizotypal personality disorder AND drop in functioning OR sustained low functioning[c]	Transient psychotic symptoms: symptoms in the subscales of unusual thought content, nonbizarre ideas, perceptual abnormalities, disorganized speech; duration of the episode <1 week; spontaneous remission; symptoms occurred within the past 12 months; AND decline in functioning OR sustained low functioning[c,d]	Subthreshold attenuated positive symptoms: e.g. ideas of reference, 'magical' thinking, perceptual disturbance, paranoid ideation, odd thinking and speech; held with either subthreshold frequency or subthreshold intensity; present for >1 week in the past 12 months AND decline in functioning OR sustained low functioning[c]
SIPS/SOPS	NA	First-degree relative with a psychotic disorder OR an individual with schizotypal personality disorder AND a significant decrease in functioning in the past month compared with 1 year ago[e]	Transient psychotic symptoms in the realm of delusions, hallucinations and disorganization; intermittently for at least several minutes per day at least once per month, but <1 h/day, <4 d/week over 1 month. Onset in the past 3 months. Symptoms are not seriously disorganizing or dangerous[f]	Subthreshold attenuated positive symptoms: e.g. unusual ideas, paranoia/suspiciousness, grandiosity, perceptual disturbance and conceptual disorganization; without psychotic-level conviction; onset or worsening in the past year; frequency: ≥1/week in the past month
SPI-A/SPI-CY	Cognitive-perceptive basic symptoms (COPER): ≥1 of 10 basic symptoms with a score of ≥3 in the past 3 months and first occurrence ≥1 year ago irrespective of earlier frequency or persistence AND/OR cognitive disturbances (COGDIS): ≥2 of 9 basic symptoms with a score of ≥3 in the past 3 months	NA	NA	NA
BSIP	NA	Genetic risk AND further risk factors according to screening instrument (e.g. social decline and unspecific prodromes) OR unspecified category: combination and minimal amount of certain unspecific risk factors/prodromes	Transient psychotic symptoms above transition cutoff each time <1 week with spontaneous remission[g]	Subthreshold attenuated positive symptoms at least several times per week, in total persisting for >1 week

BS, basic symptom; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of the At-Risk Mental State; NA, not assessed; SIPS, Structured Interview for Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms; SPI-A, Schizophrenia Proneness Instrument, adult version; SPI-CY, Schizophrenia Proneness Instrument, child and youth version.

[a]Reproduced with permission from Cannon TD, et al. *Schizophr Bull* 2007; 33:661–664. Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia inclusion criteria are not shown.

[b]Basic symptoms include COPER (cognitive-perceptive symptoms) and COGDIS (cognitive disturbances).

[c]A significant decline in functioning is defined as a Social and Occupational Functioning Assessment Scale (SOFAS) score at least 30% below the previous level of functioning, occurring within the last year and sustained for at least 1 month; a sustained low functioning is defined as a SOFAS score of 50 or less for the past 12 months or longer.

[d]CAARMS: a first-episode psychosis is diagnosed when psychotic symptoms extend for more than 1 week.

[e]A significant decrease is defined as a 30% decrease in Global Assessment of Functioning Scale score from premorbid baseline.

[f]SIPS: a first-episode psychosis is diagnosed when psychotic symptoms extend more than 1 h/day for more than 4 days/weeks during 1 month OR when they are seriously disorganizing and dangerous.

[g]BSIP: a first-episode psychosis is diagnosed above the transition cutoff (Brief Psychiatric Rating Scales scores of hallucination ≥4, delusions ≥5, unusual thought content ≥5 and suspiciousness ≥5 and symptoms persist for >1 week).

Instruments for assessing risk criteria

As the instruments used to check risk criteria might also influence the accuracy of prediction, we conducted a prognostic accuracy meta-analysis of the different psychometric interviews used in the field [13▪] (see also Table 2 [4]). All instruments showed an excellent prognostic performance (AUC = 0.89) with no significant differences between them. However, although sensitivity was outstanding, specificity was poor and showed some heterogeneity between instruments.

Current psychopathology

Several studies have additionally examined if a more detailed assessment of symptomatology within the group of patients already identified as CHR can increase the accuracy of prediction. In fact, more severe positive symptoms [18,19], severity of unusual thought content, suspiciousness, reduced ideational richness and difficulty with focus/concentration [20], physical anhedonia [21] and perceptual disturbance [22] might further increase the risk of transition, whereas negative symptoms in general [23] or initial anxiety [24] did not further contribute to prediction. Disorganized communication seems to be predictive in children [25] and adolescents [26].

Functioning

In 2016, a meta-analysis of 10 studies found that converters have moderately lower baseline functioning than nonconverters [6]. More recent studies confirmed that functioning at baseline is quite a robust predictor for later transition to psychosis, be it global [19,27] or social [28] functioning. Although most studies on functioning have focused on real-world achievements, one recent study [29] used a laboratory-based measure. Poor performance on this measure also significantly predicted conversion, even after adjusting for important confounders.

Substance abuse

Cannabis use has shown to be associated with an increased risk of psychotic outcomes [30]. Within the group of UHR individuals, meeting criteria for current cannabis abuse or dependence was predictive of transition to psychosis, as shown by a meta-analysis based on five prospective studies [8▪]. A more recent study [31] found a history of cannabis abuse in 58% of UHR individuals, of whom 26% reported cannabis-induced APS. These individuals were 4.9 times more likely to convert to psychosis.

Duration of untreated illness

Recent studies imply that at-risk individuals with a longer duration of untreated prodromal symptoms have a higher conversion rate [19], whereas the duration of negative or positive symptoms seems not predictive [18].

Recruitment strategies

Recruitment strategies play an important role for the risk enrichment. In a recent meta-analysis, we could show the best overall risk enrichment in centers directing their outreach campaigns to mental health professionals, whereas intensive campaigns predominantly targeting the general population resulted in a higher proportion of self-referrals with lower risk for psychosis [12▪]. To overcome this problem, several authors have suggested a stepwise enrichment strategy, using different instruments consecutively [32–34].

Sociodemographic predictors

Sex was not found to be predictive of conversion to psychosis in any included study [19,35–42,43▪,44–50], which is in accordance with a recent systematic review [51].

As regards age, our meta-analysis had shown lower conversion rates in children and adolescents [5▪]. Most recent studies failed to find an association between baseline age and later transition to psychosis [18,21,29,35–42,43▪,44–50,52▪▪], whereas others found younger age [19,52▪▪] or older age [16,21,28,53] to be a risk factor.

Level of education was not found to be predictive [21,38,42,44,47,48,50] except for one study [40] reporting lower levels of education in converters. Another study [35] found parental education of converters to be higher.

Parental socioeconomic status seems not predictive [54]. As regards marital status, results were contradictory [19,50].

Premorbid risk factors

Poor 'premorbid' functioning during adolescence has been reported to increase the risk of transition in CHR individuals [55]. Early indicators of enhanced vulnerability and early stressors, which have been associated with schizophrenia, were more commonly found in CHR individuals than in healthy controls, but there were no significant differences between those who made the transition and those who did not [50].

Childhood trauma, abuse, stigma and discrimination

Although earlier studies had found sexual abuse in childhood to be a predictor of transition in UHR

individuals, recent studies could not confirm this. Neither was childhood trauma in general predictive [39,56].

Perceived discrimination during lifetime was reported to increase the risk of transition in CHR individuals [56]. The same was true for more perceived harm because of stigma at study intake, even after adjusting for age, sex, symptoms and functioning [36].

Genetic risk

As mentioned above, individuals qualifying for CHR because of a combination of genetic risk and decrease in functioning have a much lower risk of conversion than those with APS or BLIPS. Thus, genetic risk does not seem to predict if an individual converts within a short time.

In 2016, interesting results also came from epigenetics, which refers to the interplay between genes and environment in emerging psychoses. In a first longitudinal prospective study of genomic DNA methylation in help-seeking young individuals, it could be shown that conversion to psychosis was associated with specific methylation changes, which were significantly different between converters and nonconverters [43▪].

In another interesting approach, individuals with 22q11.2 deletion syndrome, which is characterized by high rates of psychosis, were examined [57]. At baseline, 25% of study participants met UHR criteria for psychosis. In this group, the transition rate to frank psychosis was 27% within a mean interval of 33 months. Interestingly, also in those not fulfilling risk criteria, the transition rate was almost 5%. An additional predictor was global functioning at baseline.

Neurocognition

In a recent review [58], we found that individuals with later transition to psychosis show a significantly worse cognitive performance than those without later transition in almost all cognitive domains.

In a more recent multicenter study [48], converters had significantly lower attention, working memory and declarative memory abilities. In a partially overlapping sample [37], later converters showed worse global neurocognitive performance and, more specifically, stronger impairments in IQ, verbal memory, processing speed, sustained attention and working memory. Similarly, IQ, processing speed, learning/memory, working memory and verbal fluency discriminated converters from nonconverters in another study [46].

Social cognition, in contrast, was not found to predict transition in the majority of studies after controlling for IQ, education and baseline symptoms; for a meta-analysis, see [7]. A more recent study [59] detected lower theory of mind abilities in those with later transition.

In a study on olfactory functioning [47], deficits in the identification of pleasant, but not unpleasant and neutral odors were a risk factor for conversion to psychosis.

Several recent studies have incorporated cognitive performance into multivariable risk prediction models [16,28,46,48,52▪▪,53]. Most of them confirm that cognitive variables contain nonredundant predictive information that can improve the prediction of psychosis although their predictive power is lower than that of psychopathological variables.

Neurophysiology (EEG)

A review and meta-analysis in 2015 [60] concluded that mismatch negativity so far is the most promising EEG parameter for predicting transition to psychosis in CHR patients. More recently, we [38] found that psychosis could be predicted with relatively high accuracy from the current source density but not the lagged phase synchronicity of γ and β oscillations at rest. The cortical areas most strongly contributing to the prediction were similar to those that have been found to be important for the generation of the P300 event-related potential component, which had been identified as a predictor of psychosis in an earlier study [61]. Other parameters could not be demonstrated to be significantly associated with later transition to psychosis [45].

Neuroimaging

Neuroimaging studies comparing baseline measurements of UHR individuals who later made the conversion to psychosis to those who did not reported differences in the volume of the medial temporal lobe, prefrontal and cingulate cortex, in the integrity of white matter pathways, and in glutamate levels in the caudate nuclei, as well as differences in activation in the prefrontal cortex, medial temporal lobe, midbrain and caudate (for a recent review, see [62]).

Recent studies have shown reduced functional connectivity in ARMS individuals, especially in those with later transition to psychosis [63,64]. Disconnectivity correlated with symptom severity [64].

Although in a first era of neuroimaging studies only average differences between groups were described, the clinical need to make predictions for individuals has recently been taken into account. Pattern recognition methods or machine-learning methods have been used, which allow for individual classification [62,65▪]. In one of the first of such

studies, we have been able to classify UHR transition outcomes across two centers with an accuracy of 80% [65▪].

Blood biomarkers, neuroinflammation, stress and stress hormones

As increasing evidence indicates an inflammatory contribution to some forms of psychosis, neuroinflammation biomarkers were also tested for their potential to predict transition. In fact, there is preliminary evidence that elevation of the baseline plasma levels of certain markers of inflammation, oxidative stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may be associated with transition [66], and there were first attempts to develop blood biomarker assays to increase the accuracy of prediction [67]. In the period under study, a 22-analyte molecular biomarker panel was developed in a multistage approach [68▪▪]. It achieved an excellent predictive performance for transition, which could be further improved by integrating a positive symptom score [68▪▪].

Stress is thought to play a role in the risk of developing psychosis. Well in line with this, more stressful life events at intake and more perceived stress in ARMS were predictive for later transition in a recent study [69].

As regards stress-related biomarkers, not only cortisol and the HPA axis were recently tested but also prolactin and the hypothalamic-pituitary-gonadal (HPG) axis. Baseline cortisol levels, although elevated in CHR as compared with controls, do not seem to predict conversion, as a recent meta-analysis showed [9]. Regarding the HPG axis, gonadal dysfunction with hypoestrogenism has been reported for a long time in women with schizophrenic psychoses, even when unmedicated [70]. There is now emerging evidence that this might be due to increased prolactin levels, which can suppress estrogen production and have recently been shown not only in antipsychotic-naive first-episode patients, but also in at-risk mental state patients [70]. In a study examining different stress-related biomarkers, among others cortisol and prolactin, only high prolactin levels seemed to predict transition [69]. This would be well in line with the potential of elevated prolactin to increase dopamine release in a feedback mechanism and thereby trigger the outbreak of psychosis, as suggested by Riecher-Rössler [70].

Other predictors

Although we excluded therapy studies, some studies did allow antipsychotic treatment. In these studies, sensitivity of prediction decreased [13▪].

Finally, a small study reported a higher consumption of omega-6 fatty acids to be associated with an increased risk of transition [44].

Multidomain models for risk prediction

Cannon *et al.* [52▪▪] recently developed the first individualized psychosis risk calculator based on a big multicenter cohort. The calculator has been implemented as a web-based tool (http://riskcalc.org:3838/napls/) and assigns a 2-year probability of conversion to individuals based on their scoring on nine variables, which have to be assessed by skilled raters using specific instruments. In their own cohort, higher levels of unusual thought content and suspiciousness, greater decline in social functioning, lower verbal learning and memory performance, slower speed of processing and younger age at baseline each significantly increased the risk of conversion. This calculator was also found to provide a solid estimation of conversion outcome in a validation study [53].

In adolescents, Cornblatt *et al.* [16] showed disorganized communication, suspiciousness, verbal memory deficits and decline in social functioning during follow-up to predict transition. However, Addington *et al.* [28] found a poor discrimination of this model in an external validation with a slightly older sample. They developed a model finally containing unusual thought content, disorganized communication, baseline social functioning, verbal fluency, verbal memory, processing speed and age as predictors. In a study solely based on sociodemographic and clinical variables [42], transition was associated with observed blunted affect, subjective complaints of impaired motor function, beliefs about social marginalization, decline in social functioning and distress associated with suspiciousness. In a model based on clinical and neurocognitive variables, the combination of positive/negative symptom severity and IQ best predicted psychosis [46].

Several studies also applied multidomain models to test for independent associations of variables of interest with transition to psychosis. Significant associations were found for stigma stress [36], low functional capacity [29], physical anhedonia [21], deficits in olfactory identification [47], low neurocognitive performance [48], auditory and visual perceptual abnormalities [49] and history of cannabis-induced APS [31], but not for positive schizotypy [21], childhood trauma [39] or childhood adversity [71].

In a small study apart from clinical predictors, blood biomarkers and EEG measures were also integrated [45]. Although oxidative stress markers and EEG were not predictive, this was the case for a

combination of positive/negative symptoms, functioning, history of drug use and the biomarkers omega-3 and nervonic acid.

Finally, Schmidt *et al.* [10] performed statistical simulations based on published prediction models. They found the highest positive predictive value with a sequential three-stage testing strategy of CHR, using clinical and electroencephalography data first, then structural MRI and blood markers in a last step.

Declining transition rates

The rate of transition in UHR samples has declined in recent cohorts. This seems to have several causes such as different clinical intake characteristics, (i.e. a smaller array of attenuated psychosis symptoms, less conceptual disorganization and less trait risk factors) [72], different recruitment strategies [12▪,73] as well as earlier referral and intervention [74], possibly earlier antipsychotic treatment.

CONCLUSIONS

Recent studies confirmed that identification of individuals at risk and prediction of transition to psychosis is possible with an excellent overall prognostic performance, comparable with other preventive approaches in medicine [13▪,52▪▪]. The few clinical instruments used worldwide obviously have a very high sensitivity, accompanied by a moderate specificity [13▪], which is what is really wanted in a first clinical step in order to not exclude anybody at risk. In a stepwise approach, this most important basic clinical assessment can and should be followed by the assessment of other domains and a multilevel modeling of the risk.

The period under review has shown that we should integrate even more domains to address the complex interactions between neurobiological and environmental factors into prediction models. A thorough clinical assessment, including not only symptomatology but also functioning, still seems to have the best predictive power. Additional promising domains are neurocognition, neuroimaging, neurophysiology and – quite recently – also the development of blood biomarkers. Interesting contributions might also come from epigenetics. The familial risk of an individual rather seems to be a long-term risk factor, not influencing transition rates in the studies conducted so far, which had relatively short follow-up durations.

There were also important methodological achievements in the period under study. Thus, large meta-analyses on crucial clinical questions were conducted and large multicenter studies such as EU-GEI [75], NAPLS [76], PRONIA (https://www.pronia.eu/) and PSYSCAN (http://www.psyscan.eu/) are pursued with standardization of assessment methodology within these large consortia.

Last but not least, new promising methods for data analyses such as machine learning were implemented, which in a first step allowed individualized risk prediction based on neuroimaging [65▪], neurocognitive [77] and clinical data [27]. This method could also be applied on multidomain data in the future. A very important achievement certainly also is the development and validation of an individualized risk prediction tool based on clinical and neurocognitive data [52▪▪,53].

There are also some limitations of studies and methodological flaws. Thus, as we have outlined in a recent systematic review [78▪], most studies that developed a risk prediction model for psychosis relied on very small effective sample sizes. This increases the risk of overfitting and overestimating the performance of the model, if it is developed and assessed in the same sample [79]. Furthermore, it can lead to highly unstable sets of identified predictor variables. Multicenter studies, which could be a solution for that, have to struggle hard to overcome bias from between-center differences and to standardize their assessments. To achieve the latter, important initiatives such as 'HARMONY' [62] have been started.

We also found that poor modeling strategies are widespread [78▪], for example proper internal validation was rarely conducted and external validation studies were completely absent. Fortunately, the latter has changed recently with the publication of the first two external validation studies [28,53]. To improve the reliability and clinical usefulness of newly developed models, future studies should be conducted in accordance with current checklists and guidelines on clinical prediction models, such as the recently published Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) [79,80] (for specific recommendations for prediction of psychosis research, see also [78▪]).

Furthermore, the approach of 'one model fits all' has to be questioned. 'Psychoses' are probably a basket of different illness entities with different causes and therefore probably also different predictors. Etiological subtyping, however, has so far generally been quite neglected in psychosis research [81].

A further limitation is the age cutoff. Most studies only investigate individuals in between 15 and 18 up to 35 years, although many patients have their onset only later [82,83]. Thus, 10% of men and 20% of women get first diagnosed after age 40 [84]. Another limitation is the fact that most studies have

follow-up periods of less than 3 years. First long-term studies have, however, shown that there is a substantial number of conversions after that period [15–17]. Furthermore, some transitions might be missed in studies when individuals classified as 'at risk' are not seen frequently enough during follow-ups.

Finally, two major research gaps should be mentioned. One is the focus on transition, while recent research shows that levels of functioning can be clinically more meaningful than whether an individual has actually made the transition to psychosis or not [85]. Another and probably the most important point is that translation of research knowledge into the clinic with broad clinical implementation is more than incomplete. Obstacles to such a translation should be examined and worked on. Otherwise, not many patients will benefit from our research endeavors.

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Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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This guidance article of the European Psychiatric Association aims at providing evidence-based recommendations on the early detection of a clinical high risk for psychosis. To this end, a meta-analysis on 42 samples with more than 4000 CHR regarding conversion rates was conducted. Conversion rates for UHR criteria at more than 4-year follow-up were 37%. Rates were lower in children and adolescents.

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This meta-analysis on seven prospective studies with 1171 UHR individuals showed a significant association between a current diagnosis of cannabis abuse or dependence and transition to psychosis.

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This meta-analysis based on 33 independent studies comprising 4227 individuals shows the heterogeneity of psychosis risk within the group of individuals with clinical high risk. Although only 10% of individuals were included because of brief limited intermittent psychotic symptoms, they had the highest risk of transition to psychosis. The majority, that is 85%, included because of attenuated psychotic symptoms, had a medium risk, and the very small group included because of genetic risk and deterioration had a very low risk of transition.

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