Eur Arch Psychiatry Clin Neurosci (2014) 264 (Suppl 1):S9–S16
DOI 10.1007/s00406-014-0541-5

REVIEW

Prediction and prevention of psychosis: current progress and future tasks

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Received: 1 September 2014 / Accepted: 6 September 2014 / Published online: 26 September 2014

Abstract Prevention of psychoses has been intensively investigated within the past two decades, and particularly, prediction has been much advanced. Depending on the applied risk indicators, current criteria are associated with average, yet significantly heterogeneous transition rates of ≥30 % within 3 years, further increasing with longer follow-up periods. Risk stratification offers a promising approach to advance current prediction as it can help to reduce heterogeneity of transition rates and to identify subgroups with specific needs and response patterns, enabling a targeted intervention. It may also be suitable to improve risk enrichment. Current results suggest the future implementation of multi-step risk algorithms combining sensitive risk detection by cognitive basic symptoms (COGDIS) and ultra-high-risk (UHR) criteria with additional individual risk estimation by a prognostic index that relies on further predictors such as additional clinical indicators, functional impairment, neurocognitive deficits, and EEG and structural MRI abnormalities, but also considers resilience factors. Simply combining COGDIS and UHR criteria in a second step of risk stratification produced already a 4-year hazard rate of 0.66. With regard to prevention, two recent meta-analyses demonstrated that preventive measures enable a reduction in 12-month transition rates by 54–56 % with most favorable numbers needed to treat of 9–10. Unfortunately, psychosocial functioning, another important target of preventive efforts, did not improve. However, these results are based on a relatively small number of trials; and more methodologically sound studies and a stronger consideration of individual profiles of clinical needs by modular intervention programs are required.

Keywords Psychosis · Clinical high risk · Prediction · Prevention · Prodrome · Basic symptoms · Ultra-high risk · COGDIS

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Introduction

Mental disorders often develop early in life, last for long periods and hence adversely affect psychosocial functioning [69]. In Europe, the five most expensive brain disorders in 2010 were neuropsychiatric diagnoses [24]. Indirect costs accounted for almost half of the costs of mental disorders [24]. Regarding psychoses, theses costs rose to roughly 70 % [24]. A main cause is chronic unemployment beginning early during life time [15, 69, 100]. This reflects a still considerable proportion of unfavorable courses, despite advances in treatments [31]. Preventing the outbreak of psychoses is therefore considered a key strategy for reducing their burden [27, 99]. Particularly, non-affective psychoses are frequently preceded by a prodrome, an essential requirement for an early detection [25, 39, 79, 88]. However, as the clinical characteristics of this period were considered to be too unspecific for an early diagnosis for almost a century [39], research on this topic started only in the 1990s [21]. Two developments facilitated this rising scientific interest: the adaptation of "indicated prevention" to psychiatry in 1994 [56] and the explicit formulation of a risk enrichment and "close-in" approach for prospective studies, which led to the development of criteria aiming to

predict conversion to psychosis within a time feasible for studies (e.g., within the next 12–24 months) [8, 48].

Indicated prevention targets high-risk individuals, who exhibit clinically "minimal but detectable signs or symptoms foreshadowing mental disorders, or biological markers indicating predisposition for mental disorder" ([56], p. 25), but do not meet the diagnostic criteria of a classification system such as ICD-10 or DSM-V. Like the older concept of primary prevention, an indicated prevention aims at lowering incidence rates [56], thereby considering the complex and probabilistic relationship between potential pathogenic factors and the manifestation of an illness [56]. In light of this, early clinical signs and symptoms represent primarily risk indicators rather than risk factors or early expressions of the disorder [23]. Hence, different to the definition of a prodrome that will inevitably lead to illness manifestation, a "risk state" can remit—temporarily or persistently, or become chronic [73].

Prediction of psychosis

Some error probability is inherent to any risk estimation, and as any intervention may place some burden on individuals, indicated prevention of psychoses calls for a most scrutinized benefit-cost analysis. Thereby, a most important variable is the accuracy of prediction (see [37, 71] for a detailed discussion of ethical and methodological aspects). While different approaches have been studied [17, 45, 67, 72, 75, 84], two concepts in particular have received broad attention: the ultra-high-risk (UHR) and the basic symptom (BS) criteria.

The UHR criteria aim to predict an imminent transition to psychosis and commonly include three non-exclusive criteria [35, 45, 72, 75, 101]: (1) attenuated positive symptoms (APS), (2) brief limited intermittent psychotic symptoms (BLIPS) and (3) a combination of a biological risk factor (primarily a family history of psychosis) and a recent functional deterioration (GRFD). However, details of operationalization of UHR criteria and transition differ—sometimes considerably—between studies with regard to requirements on onset, frequency and functional impairment, and consideration of axis-I diagnoses and substance use [89]. The impact of these differences on the results of prediction and prevention studies has still to be examined in head-to-head studies, and particularly, the arbitrary character of the definitions of transition should be considered in research on the biological underpinnings of psychosis [102]. Irrespective of these differences, however, a recent meta-analysis reported a pooled transition rate (TR) of 30.0 % (9 studies) within a 3-year follow-up, increasing to about 38 % (3 studies), if 4 years were exceeded [87]; these results were in line with another meta-analysis including also some studies using BS risk criteria [20].

BS are conceptualized as the earliest primarily self-experienced psychopathological correlates of the physiological disturbances of information processing underlying the development of psychosis that develops on basis of and partly in reaction to them [83]. In line with the early character of these symptoms, BS based criteria are not thought to define an imminent risk of psychosis but to enable a truly early detection, which does not only precede the onset of psychosis, but also any significant decline in social and role functioning that has frequently taken place already at the time UHR criteria are met [13, 16, 57, 59, 73].

In a first prospective study with an average follow-up period of 9.6 (±7.6 SD) years, 70 % of those reporting 1 of 66 basic symptoms at baseline developed a psychotic disorder [36]. Particularly, cognitive and perceptive basic symptoms were predictive for a later psychosis, leading to the evaluation of two partly overlapping criteria, "COPER" (any 1 of 10 BS) and "COGDIS" (any 2 of 9 BS) [84]. In a study using COPER as inclusion criterion, 80.1 % showed also APS, which might demonstrate that the decision to seek help is often made only when proximal signs of an imminent psychosis have already developed [85]. The overall TR was 34.9 % (mean follow-up 20.6 ± 16.1 months), the TR in those showing also APS 37.6 %. However, if only APS would have been used for inclusion, 15.4 % of the transitions would have remained undetected.

To increase sensitivity, the European Prediction of Psychosis Study (EPOS) used COGDIS and UHR criteria as alternative inclusion criteria [75]. The 18-month hazard rate (*hr*) for COGDIS irrespective of UHR was 0.19, the *hr* for UHR irrespective of COGDIS 0.21, yet decreased to 0.18, when COGDIS cases were excluded; a combined presence of both criteria achieved a *hr* of 0.22.

This approach was further investigated in a recent analysis of a help-seeking sample of the Cologne Early Detection and Intervention Center for Mental Crises (FETZ Cologne), followed up for 48 months [86]. The general *hr* was 0.42, with 0.50 in the clinical high-risk (CHR) group and 0.14 in that without UHR or COGDIS at baseline. Interestingly, *hr* rose to 0.66 in those reporting both UHR and COGDIS, whereas those reporting only COGDIS but no UHR only had a *hr* of 0.23 and those with UHR but no COGDIS only of 0.28. The high predictive performance of the co-occurrence of COGDIS and UHR, in nearly all cases APS, is well in line with the role of impaired cognition in frank psychosis, one of the eight dimensions of psychotic symptom severity in DSM-5 [5]. A detailed analysis of the course of TRs showed that (1) in the group reporting only UHR, TRs were highest already after 12 months; (2) a marked separation between the UHR group (irrespective of COGDIS) and the "UHR and

COGDIS" group only after 24 months, which fits to the EPOS results, and (3) a slower rise of TRs in the "only COGDIS" group, which is in line with the assumed earlier occurrence of BS during the prodromal phase. This assumption had also led to the first development of a two-stage approach within the German Research Network on Schizophrenia (GNRS) [38, 72], with COPER and GRFD defining an early and APS and BLIPS a late at-risk of psychosis state. Meanwhile, the assumed sequence from unspecific symptoms to BS to APS and finally to BLIPS/positive symptoms was further supported in a retrospective study on first-episode psychosis patients [88].

A recent meta-analysis on the diagnostic outcome revealed that 73 % of those developing a first psychotic episode developed an ICD/DSM schizophrenia spectrum disorder (SSD) and only 11 % an affective psychosis [risk ratio (RR) 5.43] [19]. If BS criteria were part of the inclusion criteria, the RR for SSD increased to 17.1.

However, TRs show significant heterogeneity over time and across studies [87], and several reasons for this can be considered:

- TRs were predominantly derived from help-seeking samples of early detection centers, implying risk enrichment by unsystematic epidemiological filters, which can substantially vary [98]. However, risk criteria are neither designed nor epidemiologically sufficient for use beyond samples seeking help for mental problems [70].
- TRs vary markedly depending on centers and years of inclusion [13, 47, 57, 74, 87]. A role of environmental differences is indicated by markedly different incidence rates of psychoses in the general population of different cities in the UK [34]. Other reasons may be an improved preventive support or an earlier referral caused by a raised awareness of early signs and symptoms and improved acceptance of the prevention approach. Earlier referral may lead to a higher proportion of less severe CHR cases, which may have a higher capability to re-stabilize their mental state spontaneously or with low-dose, supportive interventions—alike the clinical courses observable in mild depression—or may just require longer follow-up periods.
- Some samples included only adults, others included only adolescents and most were mixed. Thus, developmental aspects important for the pathogenesis of psychoses and their early detection might work in samples to different degrees, hence affecting TRs [77]. Recent meta-analyses indicated indeed that predictive as well as preventive figures differ with age, showing lower transition rates in UHR children and adolescents and a lower-risk reduction [82, 87].

The heterogeneous TRs introduce an unfavorable degree of additional uncertainty into clinical risk estimation, hampering benefit-cost estimations for clinicians and patients alike, and endangering the feasibility of prevention studies [70]. If earlier referrals are indeed crucial, observation periods should be prolonged. However, retrospective studies of first-episode psychosis samples reported an average (!) duration of the prodromal phase of approximately 6 years [25, 88], i.e., a time period generally not covered by prevention studies for reasons of feasibility.

Thus, prevention studies greatly depend on the accuracy of both prediction per se and the estimation of the imminence of this risk. Several approaches have been suggested to improve risk estimation:

1. Narrowing criteria [57, 73] to increase specificity works usually only at the cost of sensitivity, i.e., results in the potential exclusion of later psychotic persons from preventive interventions. An example is the addition of an obligatory functional decline criterion to all UHR criteria [101] that may not only decrease sensitivity unfavorably [57], but precludes the prevention of such a decline, which is an important aim of prevention in itself.
2. Employing additional predictors without compromising sensitivity could be another approach. Yet, most potential predictors have been examined for their predictive value in risk samples already identified by UHR and/or BS criteria, e.g., [10, 22, 28, 41, 50, 55, 58, 59, 63, 64, 68, 78, 90, 93, 96, 97], thus only qualifying them for further risk characterization in multi-step algorithms for risk estimation, but not for initial risk detection. Furthermore, most studies reported only mean group differences that might not translate into individual risk estimation in clinical practice [46]. Promising candidates for additional predictors are currently electroencephalographic paradigms, i.e., mismatch negativity [9, 62], P300 [58] and quantitative EEG [96, 103], abnormalities in structural MRI [41] and neurocognitive deficits [50, 68].
3. Introducing a risk stratification approach that considers risk not only at an "all-or-nothing" level but at inter-individually different levels with regard to severity and time to transition. To this aim, prognostic risk scores are calculated, which are stratified in different risk classes for clinical usability, resulting in a "prognostic index." This procedure that does not exclude any risk patient identified by UHR and/or BS criteria and thus does not result in a loss of sensitivity is already well established in somatic medicine, e.g., cardiology [4, 43]. For mental disorders, this approach was introduced by EPOS [75]: Four risk classes were identified with hazard rates between 0.04 and 0.85. As in somatic

medicine, the individualized information about magnitude of risk and time to transition should allow tailoring preventive measures to individual needs [43], with the opportunity to re-evaluate the course of risk and needs periodically. Stratification could also help solving the problem of risk enrichment by providing the required robust basis for calculation of sample size and follow-up period. Furthermore, it may help to identify subgroups in intervention trials with different patterns of response. Meanwhile, several further risk stratification approaches employing different additional predictors have been suggested [9, 41, 50, 58, 59, 96]; however, all available models still await validation in independent samples.

To further advance current prediction models, risk should be conceptualized as fluid [8]. Current risk criteria and prediction models, however, are based on predictor assessments made at initial examination, hence treating risk at baseline as stable over time and thus linearly related to a mental state in, e.g., 24 months. Yet, with regard to current developmental models of psychotic disorders [11, 12, 32, 60], this assumption could only be made, if risk was completely immune to any influences such as developmental changes during aging [80], changes in psychological conditions, resilience factors [33, 42, 81] or subject × environment interactions. However, since risk has to be conceptualized as complex and dynamic and thus presumably nonlinearly related to future outcome, the above sketched linear and static baseline-related approach will be rather insufficient.

Prevention of psychosis

Psychosis-preventive research is a young field, and only few intervention studies have been evaluated. So far, seven randomized controlled trials (RCTs) reported effects of psychological interventions on TR [2, 7, 47, 52–54, 94], four RCTs reported effects of either pharmacological [3, 46] or combined pharmacological and psychological interventions [47, 49]. Meanwhile, seven meta-analyses have been published [21, 29, 44, 65, 82, 91, 95], which support the preventive effect of psychological (CBT, integrated psychological intervention, family-focused intervention) and of pharmacological (i.e., olanzapine, risperidone and omega-3 fatty acids) interventions after 12 months. Van der Gaag et al. [95] reported a pooled risk ratio (RR) of 0.46 (95 % confidence interval (CI), 95 % CI 0.33, 0.64), equaling an average reduction in 12-month TRs by 54 %. The number needed to treat (NNT) was 9. For comparison, the NNT for standard stroke prophylaxis in atrial fibrillation with acetylsalicylic acid is 24–87 [43]. Accordingly, Schmidt et al. [82] reported a 12-month RR of 0.44 (95 %CI 0.31, 0.61) and a NNT of 10 (95 %CI 8, 17). Thereby, psychological or pharmacological interventions (including combined conditions) did not differ in reduction in TRs at 6- and 12-month follow-up [82, 95]. Thus, currently available interventions range from mild, well-tolerated approaches like psychotherapy to low-dose antipsychotics; the optimal intervention approach for each individual might be selected according to a patient's risk class by a risk stratification approach in the future.

However, more studies with sufficient sample sizes and follow-up periods are needed; fortunately, three large trials await completion [6], including two studies aiming at replication of the promising findings of the omega-3 fatty acid trial [3] (ACTRN12608000475347; NCT01429454). The first omega-3 fatty acid trial [3] already indicated that risk states of psychotic illness may respond to interventions, which fail to be (as) effective in later stages of the disease. Furthermore, similar to manifest psychoses and for their multifactorial development, it seems unlikely that one intervention will work for all risk patients, not even in equal risk classes. Moreover, long-term adherence is low in pharmacological as in psychological prevention studies, which might be a general problem of prophylactic measures [18]. Yet, it might also indicate that interventions so far did not already meet sufficiently the subjective or objective (long term) needs of a considerable proportion of risk patients, thus calling for a broader and modular "toolbox" of interventions.

Functioning

One of the reasons of the importance of prevention of mental disorders is the often associated impairment of psychosocial functioning. In line with retrospective findings in psychosis [26], many risk samples, in particular those with UHR, already show a declined psychosocial functioning [13, 16, 57, 59, 75]. In a considerable proportion of these samples, this impairment seems to be maintained, even if no conversion occurred [1, 76, 77]. Furthermore, impaired functioning was frequently identified as a predictor of transition [13, 16, 57, 59, 75, 92, 97] that might turn from a risk indicator into a risk-enhancing factor, when patients stressfully experience their impairments [61] or reality testing changes due to social withdrawal. Interestingly, reduced processing speed, which was already identified as a predictor of transition [50, 66], was also among the predictors of poor social outcome, whereas reduced verbal memory was associated with poor role functioning in a 3-year follow-up study [14].

Unfortunately, available preventive interventions were not effective with regard to functioning [82, 95]; however,

due to methodological concerns, current data are not conclusive [82]. As decreased functioning at baseline was another predictor of poor functional outcome [14, 77], not only interventions seem to be required, which target psychosocial functioning more specifically, e.g., by social–cognitive interventions, but also detection strategies, e.g., based on BS, that identify risk patients earlier, i.e., before functional deficits settle in. Furthermore, an appropriate assessment of the multifaceted character of functioning calls for the use of scales not reducing it to just one or two summary scores.

Future directions

The rationale for a prevention of psychosis is well established, and tremendous progress has been made during the last two decades of research [21]. Risk stratification models have demonstrated their potential to surpass the limitations of "one-risk-fits-all" approaches, providing a strategy to combine the high sensitivity of risk criteria (UHR and/or COGDIS) with an individual risk estimation (also of functional outcome) with potentially individually tailored interventions. In a next step, it has to be investigated whether additional parameters can improve the individualization of prediction of psychosis as well as of functional outcome. Furthermore, advanced models will have to consider the dynamic interplay between risk and resilience factors as well as their modulation over time. Risk stratification may produce more meaningful results and avoid inclusion of patients in prevention studies who do not (yet) require laborious and costly interventions. The range of interventions has to be broadened, e.g., by social cognitive or vocational approaches, and modularized to meet individual profiles of needs and resources. Convenience of usage has to be considered, e.g., by using computerized methods available at home, to improve adherence and thus tap the full potential of the offered interventions. Furthermore, as the success of preventive approaches also depends on reaching a sufficiently high rate of target persons, and, as retrospective studies suggest that only a minority of persons about to develop psychosis actively seek help for their mental problems [40], more research is needed to develop ethically justified means for a proactive identification of risk persons in primary care or even the general population such as well-validated and reliable screeners [30, 51].

Conflict of interest FSL, NK and SJS declare that they have no interest conflicting with the content of this manuscript. JK received investigator-initiated grant support from Bristol-Myers Squibb. SR received travel support and speaker fee from Servier, Roche and Janssen-Cilag.

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