TECHNICAL COMMENTARY

NeuRA
Discover. Conquer. Cure.
SCHIZOPHRENIA LIBRARY

Early detection

Introduction

The need for comprehensive evaluation of clinical assessment instruments and criteria for the early detection of schizophrenia is motivated by clinical and policy making considerations. The importance of early detection and intervention of schizophrenia has arisen from observations that the longer the period of untreated psychosis, the worse the outcomes. Therefore investment of resources in the early stages prior to the onset of psychotic symptoms might substantially reduce the frequency and severity of chronic disablement.

Early detection in this context may be defined as the identification of people thought to be at "ultra-high risk" of developing psychosis - those displaying "at-risk mental states", traditionally referred to as "prodromal symptoms." A number of new assessment instruments have been constructed aimed at detecting at-risk mental states. Two main approaches have been adopted. One focuses on a triad of at risk mental states in individuals defined as: (1) a Family History (FH) of psychosis plus non-specific symptoms and recent decline in functioning, (2) recent onset Attenuated Psychotic Symptoms (APS) with decline in functioning and (3) Brief Limited Intermittent Psychotic Symptoms (BLIPS) with decline in functioning. The other is based on Huber's Basic Symptoms (BS) that focuses on a detailed way of describing phenomenological (subjective) disturbances.

Three scales of measurement in the former approach are; the Comprehensive Assessment of At-Risk Mental States (CAARMS), the Structured Interview of Prodromal Syndromes (SIPS), and the Basel Screening Instrument for Psychosis (BSIP). There are also differences in the cut-off criteria; for example, some subjects that were classified in the Brief Limited Intermittent Psychotic Symptoms (BLIPS) subgroup by CAARMS would be classified as psychotic by SIPS, and some subjects classified in the APS subgroup by CAARMS would be regarded as BLIPS by SIPS. SIPS dictates a lower threshold for a psychosis classification. The symptoms highlighted by various instruments also differ, for example, CAARMS emphasizes more stable and persistent symptoms pertaining to the FH subgroup, whereas SIPS emphasises more recent symptoms, reflecting any deterioration. Two Basic Symptoms scales were examined, the Bonn Scale for the Assessment of Basic Symptoms (BSABS), and the Schizophrenia Prediction Instrument (SPI-A [adult] and SPI-CY [child and youth]). The BSABS was designed to detect early subtle symptoms in the domains of perception, cognition, language, motor function, will, initiative and level of energy, and stress tolerance. The SPI-A was designed to be used as a supplement to SIPS and CAARMS. Ratings are linked to cognitive deficits that may be present prior to a prodromal state. Symptoms rated as severe on SPI-A should correspond to symptoms of moderate severity on SIPS, symptoms rated as severe on SIPS should correspond to moderate ratings on PANSS. It is important to determine which scales are most sensitive to detecting these symptoms.

Screening instruments have also been developed for research recruitment purposes, and for clinical screening. PRODscreen is intended to detect persons with elevated risk of psychosis, who will subsequently be assessed with SIPS. PRODscreen is suitable for telephone interview and self-rating and may be useful in screening first-degree relatives, mixed populations and supposedly also the general public, but is not very useful in highly symptomatic, help-seeking individuals. Another screening instrument, the Prodromal Questionnaire (PQ), has items based on SIPS and the Schizotypal Personality Questionnaire (SPQ). This instrument is not sensitive to the threshold between prodromal and psychotic state. The Structured Interview of Prodromal Syndromes Screen (SIPS screen) instrument

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

consists of 12 items covering positive symptoms only, the Youth Psychosis At Risk Questionnaire (Y-PARQ) is a self-report screening instrument based on the CAARMS for adolescents, and the Community Assessment of Psychic Experiences (CAPE) measures lifetime frequency of positive, negative and depressive symptoms and the level of distress associated with these symptoms.

The quality of assessment tools can be measured in various ways. 'Reliability' refers to the reproducibility of an instrument's results across different assessors, settings and times. 'Construct validity' is the extent to which an instrument measures the theoretical construct it was designed to measure. This involves 'convergent validity', which is the degree of correlation between different scales measuring the same construct, confirming they are measuring the same thing; and 'divergent validity', which is the lack of correlation between scales measuring different constructs, confirming that they are measuring different things. Similarly, 'known groups' validity' is the extent to which an instrument can demonstrate different scores for groups known to vary on the variables being measured. 'Content validity' is the extent to which each individual item on a scale represents the construct being measured, and 'internal consistency' is the degree of correlation between individual items within a scale.

'Predictive validity' refers to sensitivity, which is the proportion of correctly identified positives, and specificity, which is the proportion of correctly identified negatives. Sensitivity and specificity are measured by comparing an instrument's results with known 'gold standard' results. 'Responsiveness' is the extent to which an instrument can detect clinically significant or practically important changes over time, and 'area under the curve' (AUC) is a global measure of test performance.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. As part of a wider search for all topics included in the library, reviews on early detection for schizophrenia were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. The decision to include or exclude reviews was conducted in duplicate by two reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two independent reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been

checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 13 systematic reviews that met our inclusion criteria[3-15].

- Moderate to high quality evidence indicates the mean rate of transition to full psychotic episode in clinical high-risk groups is around 16% by 2 years and 29% by 3 years following assessment of initial risk.
- Studies with older samples reported higher transition rates than studies with younger samples, and more recent publications reported lower transition rates than older publications. Studies using the basic symptoms approach reported higher transition rates than studies using the ultra-high-risk approach. Studies of people receiving psychosocial treatments (e.g. cognitive behavioral therapy) reported lower transition rates than studies of people receiving standard care (e.g. case management). Studies of people on antipsychotics reported lower transition rates than studies of people not on antipsychotics.
- Moderate quality evidence suggests an increased rate of a diagnosis of schizophrenia compared to affective psychosis at ~2.5 year follow-up in people who were previously assessed as being at high risk for psychosis. This risk is highest for older people and those assessed for risk using the basic symptoms criteria.
- Moderate quality evidence suggests conversion to psychosis in children and adolescents assessed as being at clinical high risk was between 17% and 20% by 1 year follow-up and between 7% and 21% at 2 year follow-up. 36% recovered from their clinical high-risk status by 6-year follow-up, and 40% continued to meet clinical high risk criteria. Children presented with mostly perceptual abnormalities and suspiciousness, and frequently also had depressive and anxiety disorders. Compared to healthy controls, they presented with lower general intelligence and no structural brain changes.
- Moderate to high quality evidence suggests instruments based on ultra-high-risk criteria have good sensitivity and moderate specificity. Moderate to low quality evidence also suggests the BSABS, based on basic symptoms approach, has good sensitivity and moderate specificity.
- For specific tools, moderate quality evidences shows the SIPS had better sensitivity than the CAARMS, although both were found to be ‘excellent’. Both showed moderate specificity. The PQ was found to have good overall predictive value. The CAPE has good internal reliability with three

distinct factors representing positive, negative and depression symptoms.

- Moderate quality evidence suggests the pretest risk for psychosis in help-seeking people is around 15%, with highest pretest risk in studies recruiting primarily from mental health services.
- Moderate quality evidence suggests the model with the highest PPV (86%) was a clinical model including odd beliefs, marked impairment in role functioning, blunted affect, auditory hallucinations, and anhedonia/asociality. A biological model using grey matter volume, and a neurocognitive model using IQ, verbal memory, executive functioning, attention, processing speed, and speech perception, both had a PPV of 83%. An environmental predictive model with a PPV of 63% involved urbanicity, social-sexual aspects, and social/personal adjustment. The best combination model had a PPV of 82% involved disorganised communication, suspiciousness, verbal memory deficit, and decline in social functioning.
- Moderate to high quality evidence suggests rates of transition to non-psychotic disorders are three times higher than rates of transition to psychotic disorders in people at clinical high risk for non-psychotic disorders (13.1% vs. 3.9% 3-year incidence). Obsessive-compulsive risk syndrome is associated with higher risk of transition to psychosis than bipolar risk syndrome, with depression risk syndrome showing the lowest risk.

Chuma J, Mahadun P

Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria

The British Journal of Psychiatry 2011; 199: 361-366

View review abstract online

Comparison	**Sensitivity and specificity of instruments that assess high-risk mental states.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, direct, appears precise) suggests instruments based on ultra-high-risk criteria have good sensitivity and moderate specificity. Moderate to low quality evidence (small sample, direct, appears precise) also suggests the BSABS, based on basic symptoms approach has good sensitivity and moderate specificity.**
Ultra-high-risk criteria	
Authors conclude that the ultra-high-risk criteria has moderate sensitivity and specificity; 12 studies, N = 1918, mean follow-up period = 18.6 months Sensitivity = 0.66, 95%CI 0.61 to 0.70 Specificity = 0.73, 95%CI 0.71 to 0.75 *Excluding two studies (outliers) that did not systematically enrol participants increased sensitivity but not specificity;* 10 studies, N = 1444 Sensitivity = 0.81, 95%CI 0.76 to 0.85 Specificity = 0.67, 95%CI 0.64 to 0.70	
Basic symptoms criteria **Measured using the BSABS**	
Authors conclude that basic symptoms criteria has good sensitivity and moderate specificity; 1 study, N = 160, follow-up period = 9.6 years Sensitivity = 0.97, 95% CI 0.91 to 1.00 Specificity = 0.59, 95% CI 0.48 to 0.70	
Consistency in results‡	Authors report the ultra-high-risk approach studies' results were consistent.

Precision in results[§]	Appears precise
Directness of results[‖]	Direct

Fusar-Poli P, Schultze-Lutter F, Cappucciati M, Rutigliano G, Bonoldi I, Stahl D, Borgwardt S, Riecher-Rossler A, Addington J, Perkins DO, Woods SW, McGlashan T, Lee J, Klosterkotter J, Yung AR, McGuire P.

The Dark Side of the Moon: Meta-analytical Impact of Recruitment Strategies on Risk Enrichment in the Clinical High Risk State for Psychosis

Schizophrenia Bulletin. 2016; 42(3): 732-43

View review abstract online

Comparison	**Pretest risk of psychosis; the probability of developing psychosis before a test result is known which depends on the underlying risk in the population being tested.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, appears imprecise, direct) suggests the pretest risk for psychosis in help-seeking people is around 15% with highest risk in studies recruiting primarily from mental health services.**
Study recruitment techniques	
11 studies, N = 2519, mean follow-up period = 38 months *The pretest risk for psychosis in help-seeking patients was around one-sixth of the sample;* 15%, 95%CI 9% to 24%, I^2 = 96%, $p < 0.001$ Studies directing their outreach campaigns to mental health services had higher pretest risk of psychosis than those reaching out to the general public and those with a high proportion of self-referrals. Studies with intensive outreach campaigns showed reduced pretest risk of psychosis. Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Fusar-Poli P, Cappucciati M, Rutigliano G, Schultze-lutter F, Bonoldi I, Borgwardt S, Riecher-Rössler A, Addington J, Perkins D, Woods SW, McGlashan TH, Lee J, Klosterkötter J, Yung A, McGuire P

At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction

World Psychiatry 2015; 14(3): 322-32

View review abstract online

Comparison	**Predictive validity of psychometric tools that assess the risk of developing psychosis in help-seeking individuals referred to high-risk services. Mean follow-up was 38 months.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, appears precise, direct) suggests excellent sensitivity and poor specificity for psychometric tools that assess the risk of developing psychosis in help-seeking individuals referred to high-risk services.**

Predictive validity for transition to psychosis

High-risk assessment tools: CAARMS, SIPS, BSIP, BSABS, SPI-A, SPI-CY

Psychosis outcome assessment tools: ICD, DSM, BPRS or CAARMS

Excellent sensitivity and poor specificity was reported, although overall test performance (AUC) was very good;

Sensitivity: 11 studies, N = 2519, 0.96, 95%CI 0.92 to 0.98, I^2 55%, p = 0.02

Specificity: 11 studies, N = 2519, 0.47, 95%CI 0.38 to 0.57, I^2 95%, p = 0.001

AUC: 11 studies, N = 2519, AUC = 0.90, 95%CI 0.87 to 0.93

Testing positive for clinical high risk was associated with a 26% risk of developing psychosis within 38 months and testing negative for clinical high risk was associated with a 1.56% risk of developing psychosis.

Meta-regression analyses revealed a moderating effect for exposure to antipsychotics, such that there was significantly less sensitivity in the five studies where subjects were exposed to antipsychotics than in the six studies where subjects were not exposed to antipsychotics (0.94 vs. 0.98). No moderating effects were found for age, sex, follow-up time, sample size, study quality, or proportion of clinical high-risk individuals.

Authors report low positive predictive value in; the general population, unselected psychiatric adolescent samples, patients accessing public treatment or primary care services, patients admitted

to forensic units, post-partum women, ethnic minorities, military, refugees, patients with epilepsy, and prisoners.	
Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Fusar-Poli P, Bechdolf A, Taylor M, Bonoldi I, Carpenter W, Yung A, McGuire P

At Risk for Schizophrenic or Affective Psychoses? A Meta-Analysis of DSM/ICD Diagnostic Outcomes in Individuals at High Clinical Risk

Schizophrenia Bulletin 2013; 39(4): 923-932

View review abstract online

Comparison	**Diagnostic outcomes of people who were assessed as being at high risk for psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a higher risk of a diagnosis of schizophrenia than affective psychosis in people who transitioned to psychosis, particularly older people and people assessed using the basic symptoms approach.**

Diagnosis

23 studies, N = 2182, mean follow-up period = 2.35 years

Around one third (26%) of the overall sample transitioned to psychosis.

Males were more likely to transition to psychosis than females;

RR 1.82, 95% CI 1.33 to 2.49, $p < 0.001$

More people who transitioned to psychosis were given a diagnosis of schizophrenia than a diagnosis of affective psychosis;

RR 5.43, 95% CI 3.35 to 8.83, $p < 0.001$, I^2 42%, $p < 0.001$

This effect was significantly more pronounced in people assessed for risk using the basic symptoms criteria than using the ultra-high risk criteria;

Basic symptoms criteria: RR = 17.07

Ultra-high-risk criteria: RR = 3.81

Q_B 21.108, $p < 0.001$ *This effect increased significantly with increased mean study age;* $b = 0.14$, 95% CI 0.04 to 0.23, $p = 0.005$ There were no moderating effects according to diagnostic outcome tool (ICD vs. DSM), medication (treated vs. untreated), publication year, duration of follow-up, or study quality. Authors report no evidence of publication bias.

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P

Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk

Archives of General Psychiatry 2012; 69(3): 220-229

View review abstract online

Comparison	**Rates of transition to psychosis in people at high clinical risk due to having attenuated or prodromal symptoms of psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, appears precise, direct) indicates the mean risk of transition to full psychotic episode in clinical high-risk groups is around 29.2% over 31 months, with transition rate increasing over time.** **Studies with older samples reported higher transition rates than studies with younger samples, and more recent publications reported lower transition rates than older publications. Studies using the basic symptoms approach reported higher transition rates compared to studies using the ultra-high-risk approach.** **Studies of people receiving psychosocial treatments (e.g. cognitive behavioral therapy) reported lower transition rates than studies of people receiving standard care (e.g. case management), and studies of people receiving antipsychotics reported lower transition rates than studies of people not receiving antipsychotics.**

	No differences were reported between studies defining "high risk" or "transition to psychosis" using the Structured Interview for Prodromal Syndromes (SIPS) or the Comprehensive Assessment of At-Risk Mental States (CAARMS).
Rates of transition	
27 studies, N = 2502, mean follow-up period = 31 months *Transition to psychosis occurred in about one third of people identified as being at risk;* Transition rate: 29.2%, 95%CI 27.3% to 31.1%, I^2 = 83.11%, $p < 0.001$ Removing low quality studies resulted in a decrease in the overall estimate to 22%. *The risk of transition to psychosis increased with time;* 6 months after initial presentation, transition rate: 18% 1 year after initial presentation, transition rate: 22% 2 years after initial presentation, transition rate: 29% 3 years after initial presentation, transition rate: 36% *Increasing mean age of study participants was related to increased rate of transition;* β = 0.07, 95%CI 0.05 to 0.09, $p < 0.001$ *Studies using the basic Symptoms approach reported significantly higher transition rates than studies using the Ultra-high risk approach;* Basic symptoms: 2 studies, 48.5%, 95%CI 41.9% to 55.9% Ultra-high Risk: 22 studies, 27.7%, 95%CI 25.6% to 29.9% Q_B = 46.56, $p < 0.001$ There were no significant differences in transition rates between studies using the SIPS or the CAARMS. *Studies using ICD-10, DSM-III, or DSM-IV diagnostic criteria for psychosis reported a transition rate of around half of the study samples;* 51.1%, 95%CI 43.4% to 58.7% *More recent publications reported lower transition rates;* β = -0.15, 95%CI -0.17 to -0.11, $p < 0.001$ *Studies of people receiving psychosocial treatments (e.g. cognitive behavioural therapy) reported lower transition rates than studies of people receiving standard care (e.g. case management);* Cognitive behavioural therapy: 24.9%, 95%CI, 23.2% to 28.0% Standard care: 32.8%, 95% CI, 29.5% to 36.2% Q_B = 11.69, $p < 0.001$ *Studies of people on antipsychotics reported lower mean transition risk than studies of people not*	

on antipsychotics; Antipsychotics: 22.9%, 95% CI 20.5% to 25.5% No antipsychotics: 36.5%, 32.1% to 41.3% $Q_B = 28.32$, $p < 0.001$ *There was no effect of sex on rates of transition;* $\beta = 0.002$, 95%CI -0.08 to 0.12, $p = 0.88$	
Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Lee TY, Lee J, Kim M, Choe E, Kwon JS

Can we predict psychosis outside the clinical high-risk state? A systematic review of non-psychotic risk syndromes for mental disorders

Schizophrenia Bulletin 2018; 44: 276-85

View review abstract online

Comparison	**3-year risk of transition to psychosis vs. transition to non-psychotic mental disorders in people at clinical high risk for non-psychotic mental disorders (i.e. those with sub-threshold or mild symptoms).**
Summary of evidence	**Moderate to high quality evidence (large samples, unable to assess consistency, appears precise, direct) suggests rates of transition to non-psychotic disorders are three times higher than rates of transition to psychotic disorders in people at clinical high risk for non-psychotic disorders (13.1% vs. 3.9% 3-year incidence). Obsessive-compulsive risk syndrome is associated with higher risk of transition to psychosis than bipolar risk syndrome, with depression risk syndrome showing the lowest risk.** **Subgroup analysis showed the high-risk for psychosis syndrome was associated with a higher risk of transition to psychosis (492-fold than the general population) than samples seeking help at clinical high risk for psychosis services (284-fold than the general population), which was higher than in samples with risk syndromes for non-psychotic disorders (77-fold than the general population), which was higher than in samples that did not meet**

	clinical high risk for psychosis (30-fold than the general population).
Rates of transition	
Transition to psychosis is about 1/3 of the rate of transition to non-psychotic disorders in people at clinical high risk for non-psychotic disorders; Transition to psychosis: 4 prospective studies, N = 1,051, incidence = 12.9 per 1,000 person-years (3.9% 3-year incidence), 95%CI 4.3 to 38.6 Transition to non-psychotic disorders: 3 prospective studies, N = 538, incidence = 43.5 per 1,000 person-years (13.1% 3-year incidence), 95%CI 30.9 to 61.3 Subgroup analysis showed obsessive-compulsive risk syndrome was associated with a higher risk of transition to psychosis (33.7 per 1,000 person-years) than bipolar risk syndrome (24.1 per 1000 person-years) and depression risk syndrome (4.4 per 1000 person-years). Subgroup analysis showed the high-risk for psychosis syndrome was associated with a higher risk of transition to psychosis (492-fold than the general population), which was higher than in samples seeking help at clinical high risk for psychosis services (284-fold than the general population), which was higher than in samples with risk syndromes for non-psychotic disorders (77-fold than the general population), which was higher than in samples that did not meet clinical high risk for psychosis (30-fold than the general population).	
Consistency in results	Unable to assess; no measure of consistency is provided.
Precision in results	Appears imprecise.
Directness of results	Direct

Mark W, Toulopoulou T

Psychometric Properties of "Community Assessment of Psychic Experiences": Review and Meta-analyses

Schizophrenia Bulletin 2016; 42(1): 34-44

View review abstract online

Comparison	**Exploratory factor analysis and internal reliability of the Community Assessment of Psychic Experiences (CAPE).**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests the CAPE has good internal reliability, with 3 factors; positive, negative and**

	depressive symptoms.
Exploratory factor analysis; identifies the underlying relationships between measured variables **Internal reliability; the degree to which items on the scale measure the same construct**	
Factor analysis confirmed a 3-factor model consisting of positive, negative, and depressive subscales, which accounted for 93.1% of the variance in scores; The Positive dimension consisted of bizarre experiences, delusional ideations, and perceptual anomalies. The Negative dimension consisted of social withdrawal, affective flattening, and avolition/lack of motivation. *CAPE showed good internal reliability;* 18 samples, N ~ 77,191 CAPE-42 full scale reliability mean = 0.91 CAPE-positive subscale reliability mean = 0.84 CAPE-negative subscale reliability mean = 0.81 CAPE-depressive subscale reliability mean = 0.76 Subgroup analysis of sample age revealed CAPE-positive and CAPE-negative subscales had greater internal reliability in younger samples (≤ 25 years old) than in older samples (> 25 years old), with no differences on the full scale CAPE or CAPE-depressive subscale.	
Consistency in results	Unable to assess; no measure of consistency is provided.
Precision in results	Unable to assess; no measure of precision is provided.
Directness of results	Direct

Oliver D, Reilly TJ, Baccaredda Boy O, Petros N, Davies C, Borgwardt S, McGuire P, Fusar-Poli P

What Causes the Onset of Psychosis in Individuals at Clinical High Risk? A Meta-analysis of Risk and Protective Factors

Schizophrenia Bulletin 2020; 46: 110-20

View review abstract online

Comparison	**Early indicators of transition to psychosis in people at clinical**

	high risk.
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests higher risk of transition to psychosis in people at clinical high risk with attenuated positive symptoms, negative symptoms, disorganized and cognitive symptoms, and poor global functioning.**
Transition to psychosis	
Small to medium-sized effects of higher risk of transition in people at high risk with; Attenuated positive symptoms: 49 studies, N = 1,163, SMD = 0.348, 95%CI 0.280 to 0.415, $p < 0.05$, $I^2 = 70\%$ Negative symptoms: 49 studies, N = 1,374, SMD = 0.393, 95%CI 0.317 to 0.469, $p < 0.05$, $I^2 = 63\%$ Disorganised/cognitive: 18 studies, N = 503, SMD = 0.317, 95%CI 0.172 to 0.461, $p < 0.05$, $I^2 = 77\%$ Total symptoms: 29 studies, N = 675, SMD = 0.307, 95%CI 0.148 to 0.467, $p < 0.05$, $I^2 = 72\%$ Global functioning: 49 studies, N = 1,560, SMD = -0.291, 95%CI -0.370 to -0.211, $p < 0.05$, $I^2 = 76\%$	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Oliver D, Kotlicka-Antczak M, Minichino A, Spada G, McGuire P, Fusar-Poli P

Meta-analytical prognostic accuracy of the Comprehensive Assessment of at Risk Mental States (CAARMS): The need for refined prediction

European Psychiatry 2018; 49: 62-8

View review abstract online

Comparison 1	**2-year prognostic accuracy of the CAARMS for predicting transition to psychosis in help-seeking people referred to high-risk services.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, appears precise, direct) suggests the CAARMS has excellent sensitivity but poor specificity. This indicates the CAARMS is a valuable tool for correctly identifying individuals who will develop psychosis by 2 years follow-up (although only 16% did), but not**

	as good at identifying individuals who will not develop psychosis by 2 years follow-up.
Transition to psychosis	
The CAARMS showed excellent sensitivity but poor specificity for predicting transition to psychosis, although the overall test performance was good; 6 studies, N = 1876 Sensitivity = 0.86, 95%CI 0.76 to 0.92 Specificity = 0.55, 95%CI 0.48 to 0.63 AUC = 0.79, 95%CI 0.75 to 0.83, I^2 = 93% 16.4% of those identified as being at risk of transition to psychosis developed psychosis by the 2 year follow-up, while 3.38% of those identified as not being at risk of transition to psychosis developed psychosis by the 2 year follow-up.	
Comparison 2	**2-year prognostic accuracy of the SIPS vs. the CAARMS for predicting transition to psychosis in help-seeking people referred to high-risk services.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, appears precise, direct) suggests the SIPS has significantly better sensitivity and comparable specificity to the CAARMS.**
Transition to psychosis	
The SIPS showed excellent sensitivity but poor specificity for predicting transition to psychosis; 5 studies, N = 1143 Sensitivity = 0.95, 95%CI 0.91 to 0.99 Specificity = 0.45, 95%CI 0.38 to 0.53 Authors report that sensitivity was significantly higher for the SIPS than the CAARMS, while specificity was similar.	
Consistency in results	Inconsistent for CAARMS, unable to assess SIPS (not reported).
Precision in results	Appears precise.
Directness of results	Direct

Olsen KA, Rosenbaum B

Prospective investigations of the prodromal state of schizophrenia:

assessment instruments

Acta Psychiatrica Scandinavica 2006; 113(4): 273-82

View review abstract online

Comparison	**Assessment of instruments for screening and assessing at risk mental states.**
Summary of evidence	**Low quality evidence (all small samples, unable to assess consistency or precision) is unsure of the reliability and validity of instruments for screening and assessing at risk mental states.**

Screening

Reliability and Validity

PRODscreen

1 study (N = 132 mixed sample of research subjects) correctly identified a SIPS-defined at-risk mental state in 77% of the sample, showing good concurrent validity.

Sensitivity is 80% and specificity is 75%.

PQ

1 study (N = 113 subjects referred to an early detection and intervention clinic) - good concurrent validity of PQ-positive subscale against SIPS.

With a cut-off at 8 or more items of positive symptoms - sensitivity is 90%, specificity 49%, and with a cut-off at 14 or more items of positive symptoms - sensitivity is 71% and specificity is 81%.

Y-PARQ

1 study (N = 74 adolescents potentially displaying at risk mental states) - PPV of a CAARMS defined at-risk mental state = 82.4%, showing good concurrent validity.

SIPS screen

1 study (N = 36 sample of subjects referred for evaluation of at-risk mental state). Sensitivity is 90% and 100% is specificity

Assessing the early prodromal state - Basic symptoms approach (BS)

Reliability and Validity

BSABS

1 study (N = 110 out-patients with at least one BS) found 70% developed schizophrenia in an average follow-up of 9.6 years. In the control group, the absence of BS excluded schizophrenia with a probability of 96%. Two items on the BSABS were particularly diagnostically relevant; thought pressure and decreased ability to discriminate between ideas/perception and phantasy/true memory.

SPI-A

1 study (N = 147) 17% who have reported experiencing at least one BS have developed schizophrenia within an average of 12 months.

Preliminary results indicate good inter-rater reliability (89%) and ‘good’ construct validity.

Assessing the late prodromal state - attenuated positive symptoms approach (APS)	
Reliability and Validity CAARMS 1 study (N = 150 non-psychotic, help-seeking individuals), 6 month follow-up; sensitivity = 83%, specificity = 74%, PPV = 12%, NPV = 99%. Inter-rater reliability (N = 34, UHR) range of 0.62–0.93 SIPS 1 study (N= 13 with a SIPS-defined prodromal state), 46% developed psychosis within 6 months, 54% within 12 months. Agreement on prodromal/non-prodromal status of 18 subjects = 93%. Another larger study (N = 34, treatment seeking sample) has reported preliminary data on transition rates at 6, 12, 18 and 24 months: 43%, 50%, 62% and 67% respectively (sensitivity 100%, specificity 73% at 24 months).	
Assessing at risk mental state – other instruments	
ERIraos This instrument has not yet been published and is currently being validated. EASE This scale was not specifically developed for the assessment of an at-risk mental state, however it explores phenomenological aspects in the pre-onset phase focusing on experiential anomalies of self-awareness and disorders in the subjective experience. *Reliability and Validity* EASE Inter-rater reliability – 1 study (N = 14 in-patients) - Kappa reliability 0.6 to 1.0. Test–retest reliability is under evaluation.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Savill M, D'Ambrosio J, Cannon TD, Loewy RL

Psychosis risk screening in different populations using the Prodromal Questionnaire: A systematic review

Early Intervention in Psychiatry 2018; 12: 3-14 View review abstract online	
Comparison	**Diagnostic accuracy of the PQ.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests the PQ was found to be a reasonably accurate predictor of ultra-high-risk diagnosis.**
Diagnostic accuracy	
PQ was found to be a reasonably accurate predictor of ultra high risk diagnosis; 14 studies, N = 2551, AUC range = 0.71 (95%CI 0.57 to 0.85) to 0.95 (95%CI 0.94 to 0.95) 45 studies used PQ as a screening tool; higher cut-off points were required in non-help-seeking samples relative to general help-seeking populations, which in turn were higher than those needed in samples of UHR participants.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Schmidt A, Cappucciati M, Radua J, Rutigliano G, Rocchetti M, Dell'Osso L, Politi P, Borgwardt S, Reilly T, Valmaggia L, McGuire P, Fusar-Poli P

Improving Prognostic Accuracy in Subjects at Clinical High Risk for Psychosis: Systematic Review of Predictive Models and Meta-analytical Sequential Testing Simulation

Schizophrenia Bulletin 2017; 43: 375-88

View review abstract online

Comparison	**Predictive models for transition to psychosis in people at clinical high risk for psychosis.**
Summary of evidence	**Moderate quality evidence (large sample overall, unable to assess consistency or precision, direct) suggests the model with the highest PPV (86%) was a clinical model including odd beliefs, marked impairment in role functioning, blunted affect, auditory hallucinations, and anhedonia/asociality. A biological model using grey matter volume, and a neurocognitive model using IQ, verbal**

	memory, executive functioning, attention, processing speed, and speech perception, both had a PPV of 83%. An environmental predictive model with a PPV of 63% involved urbanicity, social-sexual aspects, and social/personal adjustment. The best combination model had a PPV of 82% involved disorganised communication, suspiciousness, verbal memory deficit, and decline in social functioning.
Transition to psychosis	
25 studies, N = 2811 *Clinical predictive models* The highest PPV was 86% in a model with measures of odd beliefs, marked impairment in role functioning, blunted affect, auditory hallucinations, and anhedonia/asociality. This model yielded a sensitivity of 84%, specificity of 86%, and negative predictive value of 84%. *Biological predictive models* The highest PPV was 83% in a model with gray matter volumes, which produced a sensitivity of 76%, specificity of 85%, and negative predictive value of 78%. *Neurocognitive predictive models* The highest PPV was 83% in a model with IQ, verbal memory, executive functioning, attention, processing speed, and speech perception, which produced a sensitivity of 75%, specificity of 80%, and negative predictive value of 71%. *Environmental predictive models* The highest PPV was 63% in a model with urbanicity, social-sexual aspects, and social/personal adjustment, which produced a sensitivity of 63%, specificity of 88%, and negative predictive value of 88%. *Combinations of predictive models* The highest PPV was 82% in a model with disorganised communication, suspiciousness, verbal memory deficit, and decline in social functioning, which produced a sensitivity of 60%, specificity of 97%, and negative predictive value of 93%.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Tor J, Dolz M, Sintes A, Munoz D, Pardo M, de la Serna E, Puig O, Sugranyes G, Baeza I

Early detection

Clinical high risk for psychosis in children and adolescents: a systematic review

European Child & Adolescent Psychiatry 2018; 27: 683-700

View review abstract online

Comparison	**Transition to psychosis and other clinical features in children and adolescents at clinical high risk for psychosis.**
Summary of evidence	**Moderate quality evidence (large sample overall, unable to assess consistency or precision, direct) suggests conversion to psychosis in children and adolescents assessed as being at clinical high risk was between 17% and 20% by 1 year follow-up and between 7% and 21% at 2 year follow-up. 36% recovered from their clinical high-risk status by 6-year follow-up, and 40% continued to meet clinical high risk criteria. Children presented with mostly perceptual abnormalities and suspiciousness, and frequently also had depressive and anxiety disorders. Compared to healthy controls, they presented with lower general intelligence and no structural brain changes.**
Clinical features	
48 studies, N >3000 Authors report that conversion to psychosis was between 17% and 20% at 1 year follow-up and between 7% and 21% at 2 year follow-up. 36% of patients recovered from their clinical high-risk status at 6-year follow-up, and 40% still met clinical high risk criteria. Children and adolescents assessed as being at clinical high risk presented with attenuated positive-symptoms, mostly perceptual abnormalities and suspiciousness. They also frequently had comorbid depressive and anxiety disorders. Children and adolescents assessed as being at clinical high risk presented with lower general intelligence and no structural brain changes compared with controls.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

b = correlation coefficient, BS = Basic Symptoms, BSABS = Bonn Scale for the Assessment of Basic Symptoms, BSIP = Basel Screening Instrument for Psychosis, CAARMS = Comprehensive Assessment of At-Risk Mental States, CAPE = Community Assessment of Psychic Experiences, CI = confidence interval, DSM = Diagnostic and Statistical Manual of Mental Disorders, ERIraos = Early Recognition Inventory EASE = Examination of Anomalies in Self-experience, ICD = International Classification of Diseases, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NPV = negative predictive value - the proportion of patients with negative test results who are correctly diagnosed, PANSS = Positive and negative syndrome scale, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PPV = positive predictive value - proportion of patients with positive test results who are correctly diagnosed, PQ = Prodromal Questionnaire, PRODscreen = Prodromal screening test, Q = Q statistic for the test of heterogeneity, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RR = relative risk, SIPS = Structured Interview of Prodromal Syndromes, SMD = standardised mean difference, SPI-A = Schizophrenia Prediction Instrument – Adult version, UHR = Ultra High Risk for psychosis, Y-PARQ = Youth Psychosis At Risk Questionnaire, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Early detection

Explanation of technical terms

*Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[16].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[16].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[17]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[18].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Early detection

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Olsen KA, Rosenbaum B (2006): Prospective investigations of the prodromal state of schizophrenia: assessment instruments. *Acta Psychiatrica Scandinavica* 113: 273-82.
4. Chuma J, Mahadun P (2011): Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria. *British Journal of Psychiatry* 199: 361-6.
5. Fusar-Poli P, Bechdolf A, Taylor MJ, Bonoldi I, Carpenter WT, Yung AR*, et al.* (2013): At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophrenia Bulletin* 39: 923-32.
6. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L*, et al.* (2012): Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry* 69: 220-9.
7. Fusar-Poli P, Cappucciati M, Rutigliano G, Schultze-Lutter F, Bonoldi I, Borgwardt S*, et al.* (2015): At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World Psychiatry* 14: 322-32.
8. Mark W, Toulopoulou T (2016): Psychometric Properties of "Community Assessment of Psychic Experiences": Review and Meta-analyses. *Schizophrenia Bulletin* 42: 34-44.
9. Fusar-Poli P, Schultze-Lutter F, Cappucciati M, Rutigliano G, Bonoldi I, Stahl D*, et al.* (2016): The Dark Side of the Moon: Meta-analytical Impact of Recruitment Strategies on Risk Enrichment in the Clinical High Risk State for Psychosis. *Schizophrenia Bulletin* 42: 732-43.
10. Oliver D, Kotlicka-Antczak M, Minichino A, Spada G, McGuire P, Fusar-Poli P (2018): Meta-analytical prognostic accuracy of the Comprehensive Assessment of at Risk Mental States (CAARMS): The need for refined prediction. *European Psychiatry* 49: 62-8.
11. Savill M, D'Ambrosio J, Cannon TD, Loewy RL (2018): Psychosis risk screening in different populations using the Prodromal Questionnaire: A systematic review. *Early Intervention in Psychiatry* 12: 3-14.
12. Schmidt A, Cappucciati M, Radua J, Rutigliano G, Rocchetti M, Dell'Osso L*, et al.* (2017): Improving Prognostic Accuracy in Subjects at Clinical High Risk for Psychosis: Systematic Review of Predictive Models and Meta-analytical Sequential Testing Simulation. *Schizophrenia Bulletin* 43: 375-88.
13. Tor J, Dolz M, Sintes A, Munoz D, Pardo M, de la Serna E*, et al.* (2018): Clinical high risk for psychosis in children and adolescents: a systematic review. *European Child & Adolescent Psychiatry* 27: 683-700.
14. Lee TY, Lee J, Kim M, Choe E, Kwon JS (2018): Can we predict psychosis outside the clinical high-risk state? A systematic review of non-psychotic risk syndromes for mental disorders. *Schizophrenia Bulletin* 44: 276-85.
15. Oliver D, Reilly TJ, Baccaredda Boy O, Petros N, Davies C, Borgwardt S*, et al.* (2020): What Causes the Onset of Psychosis in Individuals at Clinical High Risk? A Meta-analysis of Risk and Protective Factors. *Schizophrenia Bulletin* 46: 110-20.
16. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
17. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
18. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*