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

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CRD summary
This review concluded that ultra-high-risk and basic-symptoms criteria were useful in predicting the development of schizophrenia in high-risk populations. The potential for missed studies, lack of comparison with other index tests, and the restriction of studies to specialist clinics, limits the reliability and wider applicability of the authors' conclusions; the recommendation for further research seems appropriate.

Authors' objectives
To evaluate the predictive validity of prodromal criteria (early symptom or set of symptoms) in identifying individuals at high risk of developing schizophrenia.

Searching
CINAHL, EMBASE, MEDLINE and PsycINFO were searched from inception up to 2010; search terms were reported, which included diagnostic filters. Reference lists of articles obtained were also searched.

Study selection
Prospective studies, including cohort and cross-sectional designs, that investigated the predictive validity of prodromal criteria in people with and without prodromal symptoms of schizophrenia were eligible for inclusion. Studies had to reassess the prodromal criteria after a period of follow-up to allow a comparison with baseline to determine whether schizophrenia had developed. The reference standard used was the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM–IV). Studies that recruited people with a psychotic disorder or known organic cause of presentation and/or intellectual disability were excluded.

The included studies evaluated a wide range of assessment tools with various cut-off values. All the included studies were conducted in specialised early detection assessment settings. Where reported, the mean age of participants ranged from 17 to 20 years, and the proportion of women from 24% to 53%; participant details were poorly reported in the studies.

Two reviewers screened titles and abstracts; it was unclear whether this was conducted independently. One reviewer screened full papers.

Assessment of study quality
Study quality was assessed by one reviewer using the STARD statement and the 14-point QUADAS tool.

Data extraction
Two reviewers independently extracted data to construct 2x2 tables of test performance, from which sensitivity, specificity, positive and negative likelihood ratios, and the diagnostic odds ratio were calculated. Study authors were contacted for missing data.

Methods of synthesis
Summary estimates of sensitivity and specificity, with 95% confidence regions, were produced using a bivariate model; studies were weighted by sample size. Results were presented as summary estimates and 95% confidence intervals. Heterogeneity was assessed using $I^2$ of the pooled diagnostic odds ratio ($I^2$ of 75% was considered to show high heterogeneity).

Results of the review
Thirteen studies met the inclusion criteria (2,091 participants, range 30 to 638). None of the studies reported whether interpreters of tests were blinded. Six studies did not detail the number, training, and expertise of interpreters of tests. Three studies did not enrol people who tested negative to the prodromal criteria. Only three studies were considered to
have had sufficient sample sizes and well-defined control groups. Follow-up ranged from 6 to 84 months.

For ultra-high-risk criteria (12 studies; 1,918 participants), sensitivity was 66% (95% CI 61 to 70), specificity was 73% (95% CI 71 to 75), positive likelihood ratio was 3.53 (95% CI 2.66 to 4.69), and negative likelihood ratio was 0.33 (95% CI 0.22 to 0.51); when the diagnostic odds ratio was pooled, heterogeneity was considered low ($I^2=35.5\%$). When two outliers that did not systematically enrol people who tested negative to the prodromal criteria were excluded, sensitivity was 81% (95% CI 76 to 85) and specificity was 67% (95% CI 64 to 70); there was no heterogeneity ($I^2=0\%$).

For basic-symptoms criteria (one study; 160 participants), sensitivity was 97% (95% CI 91 to 100), specificity was 59% (95% CI 48 to 70), positive likelihood ratio was 2.39 (95% CI 1.84 to 3.12) and negative likelihood ratio was 0.04 (95% CI 0.01 to 1.17).

**Authors' conclusions**
Both ultra-high-risk criteria and basic-symptoms criteria were useful in predicting the development of schizophrenia among high-risk populations.

**CRD commentary**
The review addressed a clear question supported by reproducible inclusion criteria. Several relevant sources were searched for published studies. It was unclear whether language restrictions were applied, and unpublished studies were not sought. Therefore, publication and language bias could not be ruled out. In addition, diagnostic filters were used in the search strategy, so it was likely that studies were missed. Although data extraction was conducted in duplicate, similar methods to reduce error and bias were not employed during the selection of full papers or the assessment of study quality.

Appropriate criteria were used to assess study quality, but the results of the assessment were poorly reported. It seemed that appropriate methods of synthesis were employed, although the authors did not specify that a random-effects model was used. Given the lack of a comparison with other available index tests, the conclusion that the ultra-high-risk criteria may be useful in clinical practice was difficult to assess, as the estimates of accuracy presented seem low. Although the accuracy for the basic criteria were higher, these estimates were based on a single study. The authors acknowledged that the generalisability of the results of the review to non-specialist settings was uncertain.

The potential for missed studies, lack of comparison with other index tests, and the restriction of studies to specialist clinics, limits the reliability and generalisability of the authors’ conclusions; the recommendation for further research seems appropriate.

**Implications of the review for practice and research**

**Practice**: The authors did not state implications for practice.

**Research**: The authors stated that more long-term studies needed to be undertaken using the ultra-high-risk criteria to eliminate the possibility of false positives given the possible long duration of a prodromal state. They also stated that further research applying the basic-symptoms criteria in different settings and cultures was required.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
22045944

**DOI**
10.1192/bjp.bp.110.086868
Original Paper URL
http://bjp.rcpsych.org/content/199/5/361.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Diagnostic and Statistical Manual of Mental Disorders; Disease Susceptibility; Epidemiologic Studies; False Positive Reactions; Humans; Predictive Value of Tests; Schizophrenia /epidemiology; Schizophrenic Psychology; Statistics as Topic; Time Factors

AccessionNumber
12012000452

Date bibliographic record published
13/02/2012

Date abstract record published
20/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.