# AT RISK OR NOT AT RISK? META-ANALYSIS OF THE PROGNOSTIC ACCURACY OF PSYCHOMETRIC INTERVIEWS FOR PSYCHOSIS PREDICTION.

Fusar-Poli P[1,21], Cappucciati M[1], Rutigliano G[1], Schultze-Lutter F[3], Bonoldi I[1], Borgwardt S[4],

Riecher-Rossler A[4], Addington J[5], Perkins D[6], Woods SW[7], McGlashan TH[7], Lee J[8],

Klosterkötter J[9], Yung AR[10*] , McGuire P[1,2*] .


1. King's College London, Institute of Psychiatry, London, United Kingdom;

2. OASIS service, South London and the Maudsley NHS Foundation Trust, London, United Kingdom;

3. University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland;

4. University of Basel Psychiatric Clinics, Switzerland;

5. Hotchkiss Brain Institute, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada;

6 Department of Psychiatry, University of North Carolina, Chapel Hill, NC;

7. Department of Psychiatry, Yale University, New Haven, CT, USA;

8 Department of General Psychiatry, Institute of Mental Health, Singapore, Singapore.

9. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany;

10. Institute of Brain, Behaviour and Mental Health, University of Manchester, UK;

*Joint last authors

Endnote : CAARMS_SIPS

Word count

Abstract: 251

Text: 4453

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[1] Corresponding author Dr. Paolo Fusar-Poli, Department of Psychosis Studies, Institute of Psychiatry PO63, De Crespigny Park, SE58AF London UK. Phone ++44 (0) 20 7848 0900; e-mail: paolo.fusar-poli@kcl.ac.uk

**ACRONYMS, ABBREVIATIONS**

CHR+, at clinical high risk for psychosis

CHR-, not at clinical high risk for psychosis

CAARMS, Comprehensive Assessment of At-Risk Mental States

SIPS, Structured Interview for Prodromal/Psychosis-Risk Symptoms

SPI-A, Schizophrenia Proneness Instrument, Adult version

AUC, Area Under the Curve

SROC, Summary Receiver Operating Characteristic

Se, Sensitivity

Sp, Specificity

**ABSTRACT**

**Background**

An accurate detection of individuals at clinical high risk of psychosis (CHR hereafter) is a prerequisite for effective preventative treatments. Several prognostic psychometric interviews are available, but their comprehensive prognostic accuracy is unknown.

**Methods**

Prognostic accuracy meta-analysis of psychometric interviews was employed to examine referrals to high risk services. Index test was the CHR diagnostic psychometric instrument used to identify subjects with (CHR+) and without CHR (CHR-). The reference index was psychosis onset over time in both CHR+ and CHR-. Data were analysed with MIDAS (STATA13). Area Under the Curve, Summary Receiver Operating Characteristics curves, quality assessment, likelihood ratios, Fagan's nomogram and probability modified plots were computed.

**Results**

Eleven independent studies were included with a total of 2519 help-seeking, predominately adult subjects (CHR+: n = 1359; CHR-: n= 1160) referred to high risk services. Mean follow-up was 38 months. The AUC was excellent (0.90; 95%CI: 0.87 - 0.93), and comparable to other tests in preventative medicine, suggesting clinical utility in subjects referred to high risk services. Meta-regression analyses revealed an effect for exposure to antipsychotics and no effects for type of instrument, age, gender, follow-up time, sample size, quality assessment, proportion of CHR+ in the total sample. Fagan's nomogram indicated a low positive predictive value (5.74%) in the general non-help seeking population.

**Conclusions**

Albeit the clear need to further improve prediction of psychosis, these findings support the use of psychometric prognostic interviews for CHR as clinical tool for an indicated prevention in subjects seeking help at high risk services worldwide.

## INTRODUCTION

Treatments for psychosis have been in wide use for nearly half a century, yet there is little evidence that they have substantially improved outcomes[1]. Therefore, indicated preventative treatment in psychosis is the main paradigm yielding new hope for impacting the course of psychosis[2]. However, preventative treatment of psychosis requires first an accurate diagnosis of individuals at clinical high risk (CHR hereafter) that relies on the use of accurate prognostic tools to detect psychosis as early as possible so that its progress can be arrested and, if possible, reversed.

Prognostic testing is commonly used in preventative medicine[3]. While a screening test should identify all individuals who may develop the disease[4], a prognostic test is used to predict the presence or absence of the future disease when a patient shows some heralding signs or symptoms of the disease. Examples of predictive testing in somatic medicine include fasting glucose and oral glucose tolerance test and glycated haemoglobin to detect subjects at high risk for diabetes (prediabetes or intermediate hyperglycaemia)[5]. Prediabetes closely resembles the CHR state in that only about 5–10% of people per year will progress to diabetes, with the same proportion converting back to normoglycaemia[5]. Since no biological test such as those used to detect prediabetes are available in clinical psychiatry[6], for an indicated prevention of psychosis, prognostic testing is usually accomplished by administration of specific psychometric interviews, which assess validated CHR criteria[7]. These instruments include the Comprehensive Assessment of At Risk Mental State (CAARMS)[8, 9], the Structured Interview for Psychosis-Risk Syndrome (SIPS)[10] and the Basel Screening Instrument for Psychosis (BSIP)[11] for the assessment of 'ultra-high risk' (UHR) criteria[12], and the Bonn Scale for the Assessment of Basic Symptoms (BSABS)[13] and, developed from it, the Schizophrenia Proneness Instruments (Adult Version, SPI-A[14], and Child & Youth version, SPI-CY[15]) for the assessment of basic symptom (BS) criteria[16]. The UHR criteria include attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and trait vulnerability plus a marked decline in psychosocial functioning (Genetic Risk and Functional Deterioration Syndrome: GRFD). The two partially overlapping BS criteria rely on

subjectively experienced disturbances of perception, thinking, language and attention[17].

These CHR instruments show excellent reliability in trained raters: the overall inter-rater agreement for the SIPS was 0.95[18], for the CAARMS 0.85[12] and for the SPI-A 0.91[19]. Yet, their prognostic accuracy is still uncertain. For an ideal instrument, all subjects actually about to develop psychosis should be classified as "at risk" (CHR+) while those suffering from other complaints not leading to frank psychosis should be classified as "not at risk" (CHR-). This prognostic accuracy of a test can be quantified by different measures: Sensitivity (Se), Specificity (Sp), Summary Receiver-Operating-Characteristic (SROC) curves or Area Under the Curve (AUC); whose evaluation requires follow-up not only of CHR+ but also of CHR- subjects. So far, no robust meta-analysis has addressed the consistency and magnitude of the prognostic accuracy of psychometric CHR testing; and the few available studies reported inconsistent prognostic accuracy findings[20, 21]. Because of this, the overall clinical utility (i.e. predictive value) of psychometric interviews in help-seeking and non help-seeking subjects is still unknown. Indeed, predictive values are not fixed indicators of a test performance but are affected by the prevalence of the condition[4]. Within help-seeking CHR+ samples, the ability of above psychometric instruments used towards identification of true positives is accumulating to 29% at 2-year follow-up[22, 23] – a finding comparable to other preventative approaches in medicine[24]. Conversely, the predictive value and potential clinical utility of these instruments in samples with a lower prevalence of the condition, such as the general population, still await results from follow-ups[25-27]. Similarly, the predictive value in other samples with a variable psychosis risk such as unselected psychiatric adolescents[28], subjects accessing public treatment services, psychiatric patients in forensic units[29], primary care patients, genetic high risk samples, prisoners, post-partum women, 22q11.2 deletion syndrome, users of high potency cannabis, military, black ethnic minorities, refugees, borderline personality disorders or epilepsy is still largely unknown.

To overcome this lack of knowledge, we conducted the first robust meta-analysis to examine

the consistency and magnitude of the prognostic accuracy of instruments used for psychosis prediction while at the same time investigating its potential clinical utility in help-seeking samples of high risk services, in the general population and across other groups.


**METHODS**

*Search strategy*

Two investigators (MC, GR) conducted a two-step literature search. At a first step, the Web of Knowledge[SM] database by Thomson Reuters® was searched, incorporating both the Web of Science[SM] and MEDLINE®. The search was extended until March 2015, including abstracts in English language only. The electronic research adopted several combinations of the following keywords: "at risk mental state", "psychosis risk", "prodrome", "prodromal psychosis", "ultra-high risk", "high risk", "help-seeking", "diagnostic accuracy", "sensitivity", "specificity", "psychosis prediction", "psychosis onset" and name of the possible CHR assessment instruments. The second step involved the use of Scopus® to investigate citations of previous systematic reviews on transition outcomes in CHR subjects and a manual search of the reference lists of the retrieved articles. Articles identified through these two steps were then screened for the selection criteria on basis of abstract reading. The articles surviving this selection were assessed for eligibility on basis of full-text reading. To achieve a high standard of reporting, we adopted the MOOSE checklist[30] (available from the authors on request).


*Selection criteria*

Studies were eligible for inclusion if the following criteria were fulfilled: (a) were original articles, written in English or in German; (b) have screened the same pool of referrals with an established CHR psychometric instrument (index test)[7] (i.e. APS, BLIPS, GRFD or BS); (c) have followed up both CHR+ and CHR for psychosis onset (reference index) with established international diagnostic manuals (ICD/DSM); (d) have reported sufficient prognostic accuracy data. With respect to the latter point, when data were not directly presented they

were indirectly extracted from associated data. Additionally, we contacted all corresponding authors to request additional data when needed.

Exclusion criteria were: (a) abstracts, pilot datasets, reviews, articles in language other than English and German; (b) articles that were not interviewing the same pool of referrals or that used an external CHR- group of healthy controls; (c) articles with overlapping datasets. Specifically, in case of multiple publications deriving from the same study population, we selected the articles reporting the largest and most recent data set. Literature search was summarized according to the PRISMA guidelines[31].

*Recorded variables*

Data extraction was independently performed by two investigators (MC, GR): author, year of publication, characteristics of CHR samples (baseline sample sizes, mean age and age range, proportion of females), the CHR diagnostic instrument used, exposure to antipsychotics, diagnostic criteria used at follow-ups to assess the psychotic outcome, follow-up time, prognostic accuracy data (number of true and false positives, true and false negatives or associated data) and quality assessment conducted with the QUADAS checklist[32].

**Statistical analysis**

The statistical analysis followed the Cochrane Guidelines for Systematic Reviews of Diagnostic Test Accuracy Version 1.0[33] and the Methods Guide for Authors of Systematic Reviews of Medical Tests by the Agency for Healthcare Research and Quality (chapter 8) [34]. Briefly, evaluating test accuracy requires knowledge of two quantities, the test's Se and Sp. Meta‑analysis methods for diagnostic test accuracy thus have to deal with two summary statistics simultaneously rather than one[33]. Methods for undertaking analyses which account for both Se and Sp, the relationship between them, and the heterogeneity in test accuracy, require fitting advanced hierarchical random effects models[33].

For each study we constructed a two-by-two table, which included true positive, false-positive, true-negative, and false-negative values. When studies reported different data at

different follow-up time, we used data from the longest follow-up (please see below). The baseline sample size was conservatively used as the base reference to avoid a bias towards overly high transition risks at longer follow-ups and related higher drop-out rates of transition-negatives.

Data were then analysed with MIDAS (Meta-analytical Integration of Diagnostic Accuracy Studies)[35], a comprehensive program of statistical and graphical routines for undertaking meta-analysis of diagnostic/prognostic test performance in STATA 13 software. The index tests of CHR status (CHR+ or CHR-) and reference tests of transition to psychosis according to international diagnostic manuals (ICD/DSM as gold standard) were dichotomous. Primary data synthesis was performed within the bivariate mixed-effects regression framework for the logit transforms of Se and Sp[35]. In addition to accounting for study size, the bivariate model estimates and incorporates the intrinsic negative correlation that may arise between Se and Sp within studies (threshold effect)[36] as a result of differences in the test threshold between studies[37]. The bivariate model allows for heterogeneity beyond chance as a result of clinical and methodological differences between studies[37]. We estimated the summary Se and Sp and the estimated hierarchical SROC curves[33]. A SROC graph across each predictor, with the y-axis representing the predictor's Se and the x-axis representing 1-specificity, was used to plot around the summary estimates a 95% confidence region and a 95% prediction region to illustrate the precision with which the summary values were estimated (confidence ellipse of a mean) and to show the amount of between-study variation (prediction ellipse; the likely range of values for a new study). We also estimated the AUC. Finally, for sensitivity analyses of the impact of follow-up times, supplementary analyses were conducted by grouping the data at each specific time point of 6, 12, 24 and $\geq$30 months.

Heterogeneity across studies was assessed using the $I^2$, with values of 25%, 50%, and 75% representing mild, moderate, and severe inconsistency, respectively[38]. Within MIDAS, forest plots and heterogeneity statistics can be created for each test performance parameter individually or may be displayed as paired plots. Sub-groups analyses and meta-regressions were used to examine the influence of CHR instruments used, mean age, gender (% of

females), follow-up time, sample size, exposure to antipsychotics, and quality assessment (QUADAS) on meta-analytical estimates. To control for biases associated with imbalanced datasets[39], we further tested the impact of the proportion of CHR+ in the overall samples (i.e. CHR+ and CHR-). The meta-regressions were used if there was substantial heterogeneity ($I^2 > 50\%$)[40]. Model diagnostic analyses included quantile plot of residual based goodness-of fit; Chi-squared probability plot of squared Mahalanobis distances for assessment of the bivariate normality assumption; spike plot for checking for particularly influential observations using Cook's distance; a scatter plot for checking for outliers using standardized predicted random effects (standardized level-2 residuals)[35]. Sensitivity analyses (i.e. exclusion of outliers and rerunning of the model) were conducted to further explore heterogeneity. We did not test publication bias[41], because no proven statistical method exists for this type of meta-analysis[42].

In a second step we employed the probability-modifying plot and the Fagan's nomogram to estimate the clinical or patient-relevant utility of the CHR interview in subjects seeking help at early detection services, in the general population as well as in other samples (i.e. genetic high risk samples, prisoners, post-partum women, 22q11.2 deletion syndrome, users of high potency cannabis, military, black ethnic minorities, borderline personality disorders or unselected psychiatric samples). The clinical utility was evaluated using the positive and negative likelihood ratios (LR+ and LR-) to calculate post-test probability (PostTP) based on Bayes' theorem as follows with pre-test probability (PrePT)= prevalence of condition in target population: $PostTP = LR \times PreTP/[(1 - PreTP) + (PreTP \times LR)]$[35]. Specifically, the probability-modifying plot[35], is a graphical sensitivity analysis of the test's predictive values across a baseline psychosis risk continuum in people seeking help at early detection services. It depicts separate curves for positive and negative tests and uses general summary statistics (i.e., unconditional positive and negative predictive values, NPV and PPV, which permit underlying psychosis risk heterogeneity) to evaluate the effect of the CHR assessment on predictive values[43]. The PreTP probability of psychosis risk in subjects seeking help at early

detection services was computed in the current dataset as the proportion of subjects developing psychosis on the total baseline sample (CHR+ plus CHR-)[35]. Fagan's nomogram, a two-dimensional graphical tool for estimating how much the result of a test changes the pre-test probability that a patient will develop psychosis, was used to estimate the clinical value of psychometric CHR diagnostic interview in the general population and in the other samples. Again, the clinical value is calculated on the LR+ and LR- obtained from the current meta-analysis[44] and using the pre-test psychosis risk in the different samples as estimated from the available literature.

Statistical tests were two-sided and statistical significance was defined as p-values <0.05.

## RESULTS

### Database

The literature review (PRISMA flow-chart available from the authors upon request) produced 11 independent studies that met the inclusion criteria, for a total of 2519 (CHR+: n=1359; CHR-: n=1160) subjects referred to high risk services (Table 1). Proportion of CHR+ in the total sample (CHR+ and CHR-) was 0.54 revealing an overall balanced dataset. Four studies employed the CAARMS, three the SIPS, one the BSIP, one the BSABS, and two both the SIPS and SPI-A. The mean follow-up time was 37.72 months (SD 27.81, median=33). QUADAS ratings ranged from 2.5 to 14 (equals highest possible score), main reasons for a non-optimal rating were (partial) exposure to antipsychotics and unsatisfactory reporting of results.


*** TABLE 1 ABOUT HERE ***


### Prognostic accuracy of CHR interview

Across the 11 studies interviewing help-seeking subjects for CHR symptoms, the summary meta-analytical estimate of Se and the AUC were outstanding, while the estimate of Sp was poor (Figure 1). There was moderate to substantial heterogeneity for Se ($I^2$=51, p=0.02) and

severe heterogeneity for Sp ($I^2$=95, p<0.001), 17% of which was due to threshold effects. Sensitivity analyses revealed that the two studies with the highest proportion of CHR- in the total sample had the highest Sp[45, 46], while the two studies with the lowest proportion of CHR- had the lowest Sp[47, 48]. However, meta-regression analyses showed that the proportion of CHR+ in the total sample had no impact on the overall AUC[39]. Across SIPS samples (n=5)[47, 49-51] Se was 0.96 (95%CI: 0.88–0.99) and Sp 0.39 (95%CI: 0.32–0.46). Across CAARMS samples (n=4)[45, 46, 48, 52] Se was 0.96 (95%CI: 0.82–0.99), Sp 0.56 (95%CI: 0.38-0.73). There were not enough data to perform subgroups meta-analyses in BSIP samples (n=1)[11], BSABS/SPI-A samples (n=3)[53 47, 51] and in samples combining the SIPS and SPI-A (n=1)[47]. Meta-regression analyses revealed no significant effects for mean age, gender, follow-up time, sample size and quality assessment (QUADAS), but there was a significant effect for exposure to antipsychotics at baseline (p=0.04). This effect was driven by a significant decrease of Se (0.94) in studies (n=5) where subjects were exposed to antipsychotics as compared to studies (n=6) were subjects were not exposed (Se=0.98). Model diagnostics revealed a good fit of the model and indicated that one study was close to the outlier threshold[45]. Sensitivity analyses confirmed a very good AUC (0.84) after this study was removed from the dataset.

*** FIGURE 1 ABOUT HERE ***

Finally, supplementary analyses were conducted grouping the available samples at specific time points of 6, 12, 24 and ≥ 30 months. The AUCs were outstanding at each time point: at 6 months (7 samples, AUC=0.97, 95%CI: 0.95–0.98), at 12 months (6 samples, AUC=0.94, 95%CI: 0.92–0.96), at 24 months (8 samples, AUC=0.94, 95%CI: 0.92–0.96), at more than 30 months (7 samples, AUC=0.91, 95%CI: 0.88–0.93).

**Clinical utility of psychometric CHR interviews in subjects seeking help at high risk services**

The 38-month psychosis risk in the 2519 help-seeking subjects was 15% (95%CI: 0.9%-24%). On the basis of this prior distribution, the continuous relationship between PreTP and PostTP probability is summarized in in Figure 2. Being CHR+ was associated with a 26% (95%CI: 23%-30%) risk of developing psychosis within 38 months, yet a small LR+ of just 1.82 (95%CI: 1.52-2.18)[54], while being CHR- was associated with a 1.56% (CI95%: 0.7%−2.42%) risk of developing psychosis and a large LR- of 0.09 (CI95%: 0.04-0.18)[54].


*** FIGURE 2 ABOUT HERE ***


**Estimated clinical utility of psychometric CHR interviews in the general population and in other samples**

Based on a lifetime prevalence of all non-organic psychotic disorders of 3.27%[60] and the above LRs, Fagan's nomogram revealed only limited clinical utility for CHR instruments in the general population by estimating testing positive for CHR was associated with a 5.74% lifetime risk of developing psychosis, while testing negative was associated with hardly any such risk (0.26%).


*** FIGURE 2 ABOUT HERE ***


Corresponding figures for other clinical and non-clinical samples are displayed in Table 2.

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*** TABLE 2 ABOUT HERE ***


**DISCUSSION**

This is the first study to present a robust and elaborated meta-analytical estimate of the prognostic accuracy of psychometric CHR interviews for psychosis prediction. Assessing help-seekers referred to a high risk service with a CHR interview generally revealed an excellent overall prognostic performance in terms of the AUC at three years (38 months)

follow-up (values of 0.9-1.0 are considered outstanding, of 0.8-0.9 excellent and of 0.7-0.8 acceptable[55]), which was comparable to other preventative approaches in medicine. However, excellent AUC values were mainly mediated by an excellent ability of the instruments to rule out psychosis (i.e., very satisfyingly low LR- and high Se), at an expense of their ability to rule in psychosis (i.e., unsatisfyingly low LR+ and only moderate overall Sp), which indicates some need to further improve prediction. Conversely, the clinical utility of current CHR instruments in non-help-seeking subjects in the general population was estimated to be low

Our first aim was to investigate at meta-analytical level the overall prognostic accuracy of CHR instruments in determining the risk of developing psychosis at three years (38 months) in young help-seeking subjects referred to high risk services. We first estimated the AUC, which serves as a global measure of test performance and indicates the overall goodness of a diagnostic tests. Thereby, we adopted a robust methodological approach following international guidelines for diagnostic/prognostic accuracy meta-analysis, to avoid the serious flaws observed in a previous meta-analytical attempt, such as overlapping samples, missing studies and lack of control for several moderators[56, 57]. Our finding of consistent prognostic accuracy across CHR instruments is particularly important, given the significant differences of operationalization criteria[58]. This finding of a negligible role of the CHR assessment instrument (i.e. CAARMS vs SIPS) is in line with our previous meta-analysis which found no differences in pooled annual transition risks between these instruments[22]. This finding was also confirmed by a second independent meta-analysis by the EPA taskforce[23]. We further revealed that despite an excellent overall prognostic accuracy there is a need to specifically improve the ability to rule in subsequent psychosis, i.e., to improve LR+ and Sp, while preserving the outstanding ability to rule it out. This is particularly relevant given that interviewing subjects seeking help at high risk services is particularly difficult: these individuals are assumed to lay on an upper mid-range of a symptomatic continuum by showing mild and often infrequent symptoms of yet some clinical significance already[25]. However, differentiating between such gradual symptoms with specific tests or interviews is

not a problem specific to psychosis prevention or other preventive approaches in psychiatry. For example in case of the at-risk state of diabetes, the WHO proposed the use of the term "intermediate hyperglycaemia" (i.e. pre-diabetes) to accurately reflect the observation that glucose is a continuous variable and that their defined categories are based on somewhat arbitrary decisions on where to draw a line between normality and abnormality[59]. Similarly to the different cut-offs and operationalization criteria used to identify CHR subjects, the definition of pre-diabetes is based on cut-off points for glucose[5] to that there are different diagnostic operationalisations (e.g. by WHO and by the American Diabetes Association[5]). Furthermore, as for the CHR state[7], progression to diabetes is not inevitable in pre-diabetes; some individuals, in the absence of any intervention may remain in that state or even revert to normoglycaemia[5]. Because of this, various risk assessment tools based on sociodemographic or questionnaire data are available to identify subjects with pre-diabetes, and their overall prognostic accuracy is comparable to our meta-analytical estimates such as the AUC=0.76 reported for the Cambridge risk score[60]. More broadly, the overall prognostic accuracy of the CHR instruments was comparable if not superior to various other medical tests used for an indicated prevention (Table 3). However, it is important to highlight that the high AUC of CHR instruments is secondary to an accurate training of raters and on-going close supervision provided by expert clinicians[7]. Thus, the recent EPA guidance on the early detection of psychosis explicitly recommends their CHR assessment in specialized centres by well-trained raters and/or clinical supervision by such raters.[23]

*** TABLE 3 ABOUT HERE ***

The imbalance between an excellent Se (0.96) and an only modest Sp (0.47) may have some relevant clinical indications, when considering that we have selectively included only studies discriminating CHR+ from CHR- within the same pool of help-seeking subjects referred to early detection services. Since these patients were seeking help at or were subsequently referred to early detection services and frequently presented also with psychosocial and

functional impairment[61] and other non-psychotic symptoms[62] and disorders[63] (along with CHR symptoms), the use of CHR assessments should not be thought of as identifying and treating an unselected and asymptomatic group at risk of a poor outcome (universal prevention)[64]. Rather, the use of CHR assessment follows the approach of an indicated prevention, which is concerned with detecting a disease in its earliest stages, before frank symptoms appear, and with intervening to slow or stop its progression into the full-blown medical picture. Therefore, recent EPA guidance explicitly restricts CHR assessment to the clients of mental health services[23]. With regard to the potential CHR+ misdiagnosis of persons who do not in fact develop psychosis, or the potential CHR- misdiagnosis of persons who will develop psychosis, the low Sp suggests a stepped and multi-component strategy. In a first sensitivity-preserving step, CHR instruments could be used to rule out true negatives, i.e. subjects who are unlikely to develop psychosis. In a second step, additional clinical, neurocognitive, biological or combined models of risk stratification could be applied to the CHR+ group with the aim of increasing Sp and prognostic reliability. This would enable risk stratification and personalized treatments accordingly[65, 66].

We further estimated the clinical utility of CHR assessments in other clinical and non-clinical populations as clinical utility is affected by the underlying psychosis risk in a population. In particular, the conditional probability of a condition given a positive or negative test result, the so-called PPV and NPV values are critically important for clinical applications, and the PPV tends to be highest in settings with a high prevalence of the disorder[4]. We found that testing positive for CHR was associated with a 26% risk of developing psychosis within three years (38 months), a number comparable with our previous meta-analysis (95CI% 23 – 35)[22] of transition risks in CHR+ subjects. This was due to a small LR+ of 1.82[54]. We could also show here for the first time that being CHR- was associated with only a 1.56% risk of developing the illness, corresponding to a large LR- of 0.09. It is important to note that the PostTP, as estimated from the likelihood ratio and PreTP, is generally more accurate than if estimated from the PPV of the test. In fact, with help of these two measures (LR+ and LR-), it

was possible to estimate the PostTP in different settings characterized by a variable PrePT of psychosis risk, which however will nevertheless require empirical studies. We clearly estimated for the first time a limited clinical utility of CHR interviews in the general population, revealing only small and inadequate PPV of 5.74%. Our estimate of limited clinical utility is in line with meta-analytical results indicating that self-reported psychotic-like experiences in the young non help-seeking general population are associated with a negligible risk of transitioning to psychotic disorders over time[67]. Yet, as self-reported psychotic experiences are only a poor estimate of clinician-assessed CHR symptoms, these findings might not reflect on the true predictive power of CHR criteria in the community{Schultze-Lutter, 2014 #248}. Similarly, it appears there is no scope to assess psychometric CHR interviews in 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. The latter finding is in line with a recent study indicating that the CHR state does not predict psychosis in adolescent delinquent samples[29]. Conversely, our estimates provide some support for the clinical utility of CHR assessments in subjects with two psychotic relatives, in patients with 22q11.2 deletion syndrome and in subjects using high potency cannabis, as well as for preventative trials already proposed in some of these clinical samples[68]. The additional novel finding is that our probability-modifying plot allows future power calculation studies in variable samples characterized by an underlying variable psychosis risk that is ranging from 0 to 1. For example, with our plot available, the researchers may draw a vertical line from the selected pre-test probability of the sample to the appropriate likelihood ratio line and then reads the post-test probability off the vertical scale.

Some limitations should be acknowledged. First, because of limited statistical power, we were unable to directly compare the prognostic accuracy of different psychometric instruments. However, subgroups analyses revealed comparable SIPS vs CAARMS AUCs. Furthermore, two independent meta-analyses[22, 23] did not reveal any significant impact of the

type of psychometric instrument employed on risk estimates. Also, we were unable explain all the observed heterogeneity across individual studies. However, some of this was explained by threshold effects and by the effect of antipsychotics exposure on Se. An effect of age, with lower transition risks in younger CHR+ subjects was observed in our first meta-analysis[22] and recently confirmed in another re-analysis[23]. Such an age effect might have missed in our analyses, as only the by far smallest of the included studies with an only 6-month follow-up[58] was on minors only. Furthermore, the individual studies included here varied with respect to follow-up time, however, meta-regression did not reveal any significant effect. We additionally conducted supplementary analyses at each specific time points, and these analyses confirmed exceptional AUCs. Furthermore, there is new meta-analytical evidence that, in UHR samples, transition to psychosis is most likely to occur within the first 2 years after presentation to clinical services with a stable plateau after 36 months[69]. Since our mean follow-up time (38 months) falls in this plateau period, follow-up had no significant impact on the meta-analytical estimates across samples mainly at risk for UHR criteria.

**CONCLUSIONS**

The current prognostic accuracy meta-analysis indicated that currently used interviews for psychosis prediction have an excellent overall prognostic performance. This supports their use as clinical tool for an indicated prevention in subject seeking help at mental health services worldwide, provided raters have undergone adequate training, while discouraging their use for prevention in non-help-seeking subjects in the general population.

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**Table 1**. *Independent studies included in the meta-analysis (studies n=11, subjects n=2519; CHR+: n=1359, CHR-: n= 1160)*

| Study | QUADAS score (14=max.); exposure to antipsychotics at baseline | Predictor (Index test) | Psychosis diagnosis (Reference standard) | Age (mean±SD, range) | Gender (% females) | Follow-up (months) | CHR+ (baseline) | CHR- (baseline) |
|---|---|---|---|---|---|---|---|---|
| 1. Klosterkötter, et al. 2001[53] (a) | 14; NO | BSABS (BS) | DSM-IV | 29.3±10.0 (15-53) | 47.5 | 0, ≥30 | 110 | 50 |
| 2. Yung, et al. 2008[46] | 12; YES (Na) | CAARMS, before 2006 (UHR) | CAARMS | 18.1 (15-24) | 51.0 | 0, 6 (b), 24 | 119 | 173 |
| 3. Riecher-Rössler, et al. 2008[11] | 13.5; NO | BSIP (UHR plus 4th criterion) | BPRS | 26.8±8.9 (18-60) | 41.4(c) | 0, 6, 12, 24, ≥30 | 58 | 32 |
| 4. Woods, et al. 2009 (NAPL-1)[49](d) | 13.5; YES (11.6%) | SIPS (UHR) | DSM-IV or medical records | 17.8±4.4 (12-36) | 39.5 | 0, 6, 12, 24 | 259 | 111 |
| 5. Woods, et al. 2009 (PREDICT)[49](d) | 13.5; YES (1.8%) | SIPS (UHR) | DSM-IV | 19.76±4.5 (12-31) | 47.8 | 0, 6, 12, 24 | 172 | 100 |
| 6. Liu, et al. 2011[50] | 2.5; YES (79.7%)(c) | SIPS (UHR) | DSM-IV | 21.4±4.0 (16-24) | 47.7 | 0, 24 | 59 | 48 |
| 7. Simon, et al. 2012[51] | 6; NO | SIPS / SPI-A (e) (BS / UHR) | DSM-IV | 21.0 (14-40) | 32.4 | 0, 12, 24 | 99 | 49 |
| 8. Lee, et al. 2013[45](d) | 13; NO | CAARMS before 2006 (UHR) | DSM-IV | 21.6±3.5 (14-29) | 39.9 | 0, 6, 12, 24, ≥30 | 173 | 494 |
| 9. Schultze-Lutter, et al. 2014[47] | 13; YES (13.8%) | SPI-A / SIPS (e) (BS / UHR) | DSM-IV | 24.9±6.0 (15-39) | 37.0 | 0, 6, 12, 24, ≥30 | 194 | 52 |
| 10. Kotlicka-Antczak et al 2014[48](d) | 11.5 YES (10.2%) | CAARMS (UHR) | ICD-10 | 19.05±3.6 (15-29) | 51.1 (c) | ≥30 | 94 | 33 |
| 11. Spada, et al. 2015[52] | 11; NO | CAARMS (UHR) | DSM-IV | 15.8±1.7 (12-17) | 47.5 | 0, 6 | 22 | 18 |

UHR, Ultra High Risk; BS, Basic Symptoms, BSABS, Bonn Scale for the Assessment of Basic Symptoms; BPRS, Brief Psychiatric Rating Scale; BSIP, Basel Screening Instrument for Psychosis; CAARMS, Comprehensive Assessment of At Risk Mental State; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; SIPS, Structured Interview for Prodromal Syndromes; SPI-A, Schizophrenia Proneness Instrument; Na, not available; a) at least 1 BS; b) 6 months data reported in Yung et al 2006[70]; c) CHR+ only; d) updated follow-up data provided by the authors; e) different combinations of SPI-A and SIPS criteria reported in this article.

**Figure 1.** Meta-analytical Summary Receiver Operating Characteristics (SROC) curve of CHR instruments for psychosis onset in 2519 help-seekers at high risk services reported in 11 studies (follow-up 38 months). Legend: Se, sensitivity; Sp, specificity; AUC, area under the curve; 1 Klosterkötter, et al. 2001[53] ; 2 Yung, et al. 2008[46]; 3 Riecher-Rössler, et al. 2008[11]; 4 Woods (NAPLS-1), et al. 2009[49]; 5 Woods (PREDICT), et al. 2009[49], 6 Liu, et al. 2011[50]; 7 Simon, et al. 2012[51]; 8 Lee, et al. 2013[45]; 9 Schultze-Lutter, et al. 2014[47]; 10. Kotlicka-Antczak et al 2014[48], 11 Spada, et al. 2015[52].
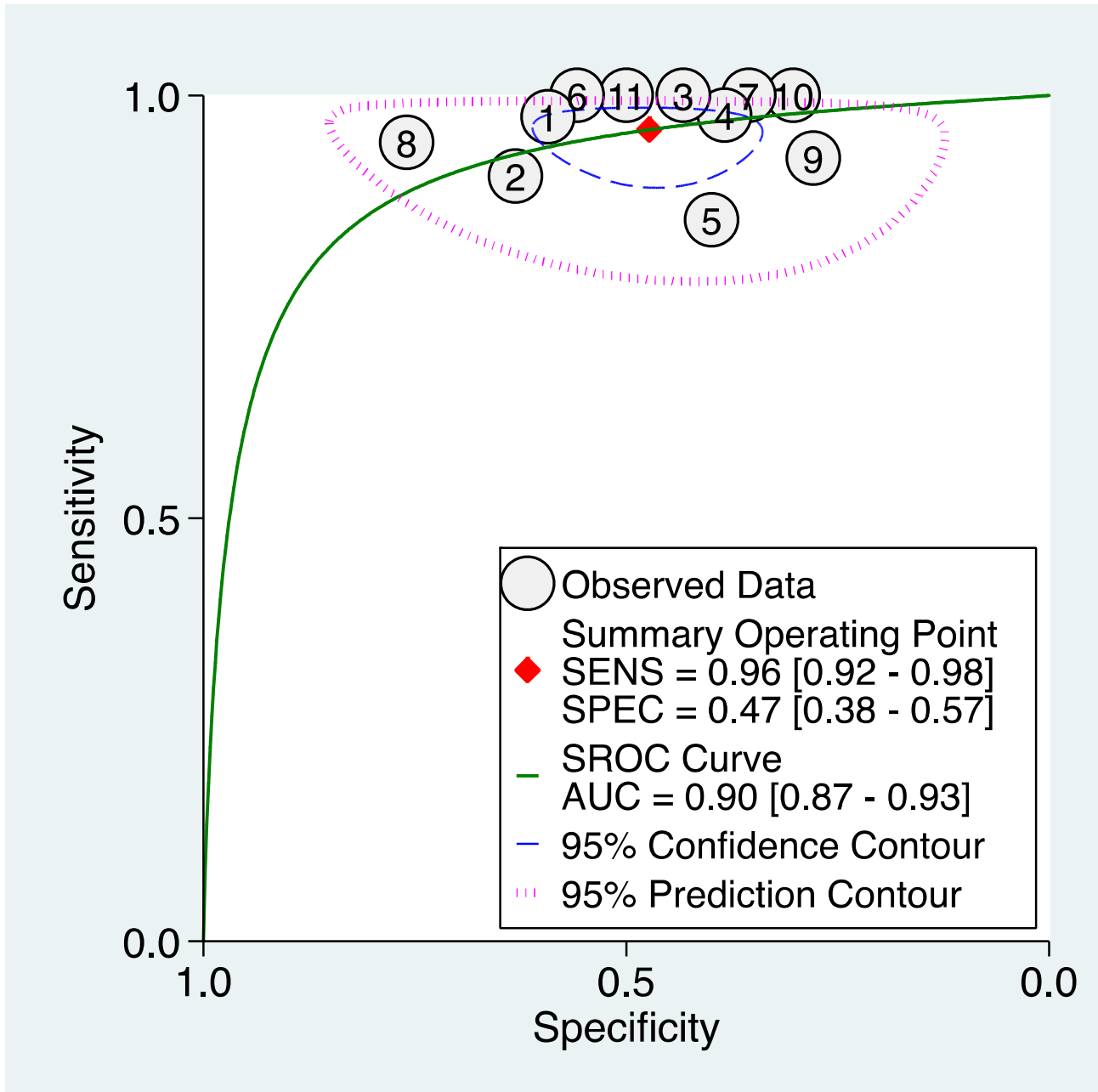
**Figure 2.** *Meta analytical probability modifying plot* for illustration of the relationship between PerTP (9% to 24% psychosis risk at 38 months in subjects seeking help at early detection services) and PostTP (psychosis risk at 38 months in help-seeking subjects based on CHR instruments) computed as the likelihood of a positive (above diagonal line; LR+) or negative (below diagonal line, LR-) test result over the 0-1 range of PreTP.
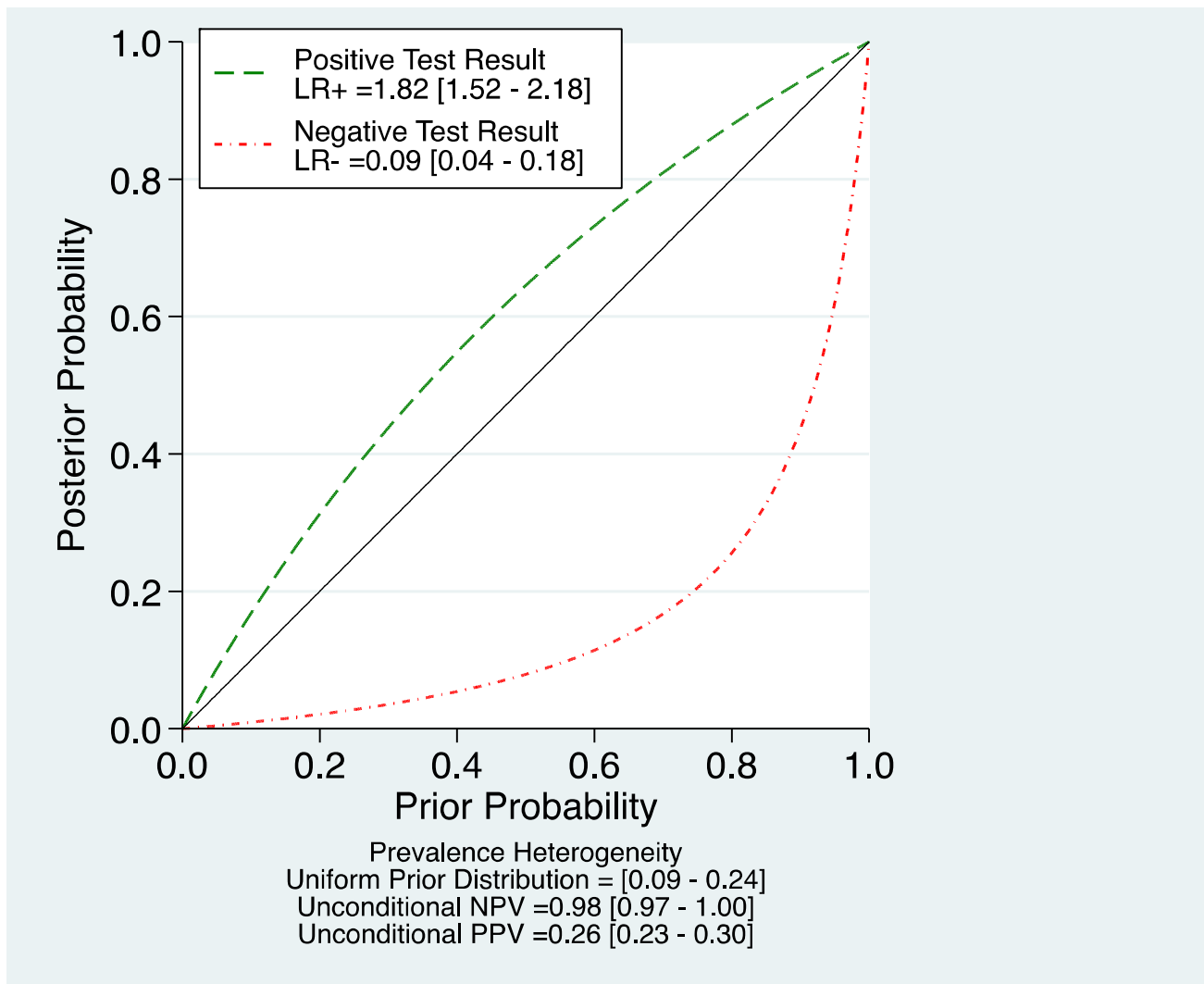
**Figure 3.** Fagan's nomogram illustrating the meta-analytical (subjects n=2519) clinical value (post-test probability) of psychometric CHR interview in the general population in order to predict 38 months risk of psychosis, given an assumed psychosis risk (pre-test probability) of 3.27%, as reported in a nationally representative sample (n= 8028) of the general population subjects of age 30-44 year [71].
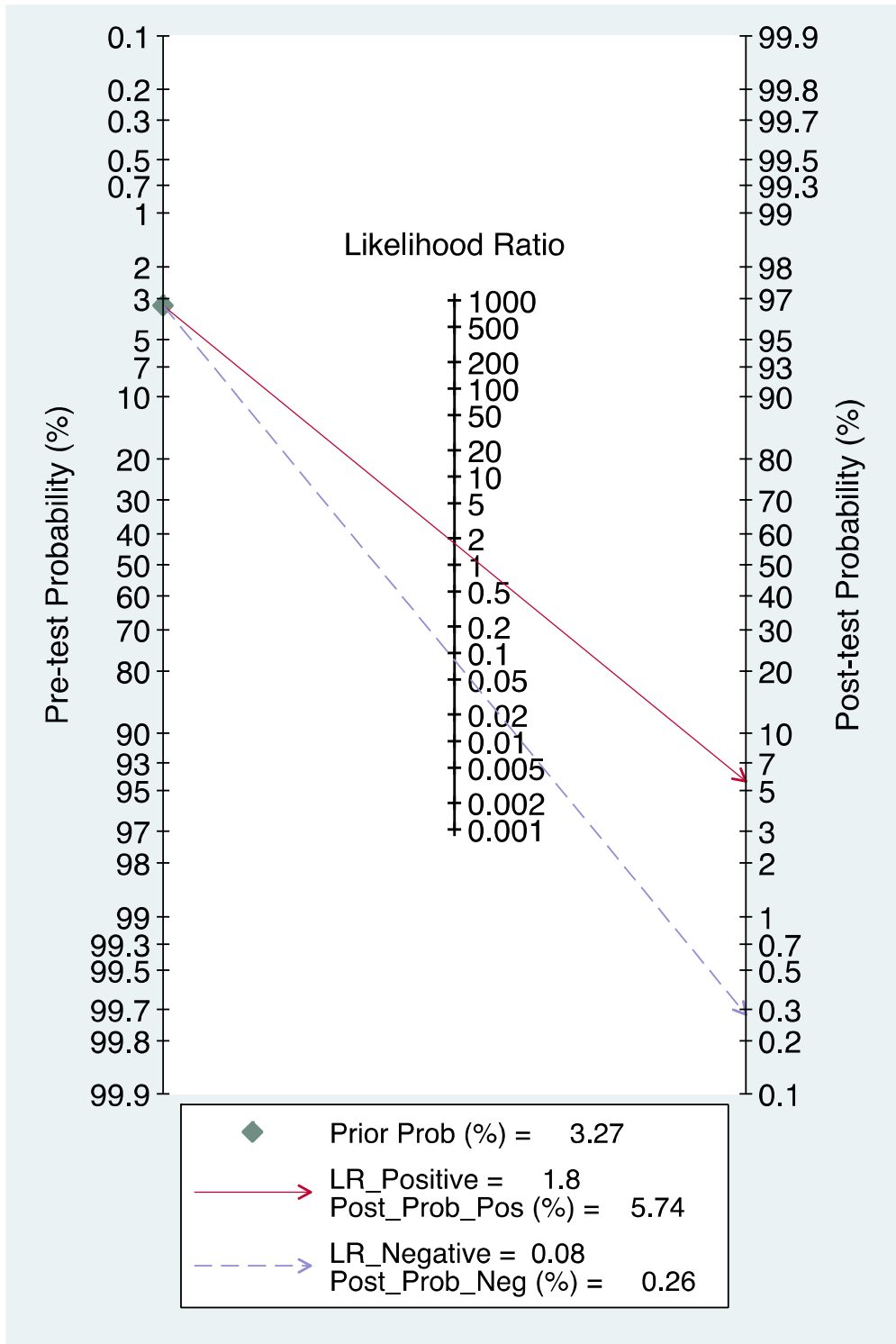
**Table 2**. Estimated clinical utility of CHR instruments for psychosis prediction in different populations

| Sample | Psychosis risk | Positive Test Result | Negative Test Result |
|---|---|---|---|
| 1 Unselected psychiatric adolescent samples | 3.13%[28] (12mo) | 3.13% | 0.29% |
| 2 Subjects in contact with public treatment services | 0.35%[72] (lifetime) | 0.63% | <0.001% |
| 3 Psychiatric patients in forensic units | 74%[73] (lifetime) | 83.38% | 20.39% |
| 4 Primary care patients | 0.045%[74] (per year) | <0.001% | <0.001% |
| 5 Prisoners | 3.90% [75] (lifetime) | 6.87% | 0.36% |
| 6 Post-partum women | 4%[76] (12mo) | 7.04% | 0.37% |
| 7 22q11.2 deletion syndrome | 16% [77] (48mo) | 25.74% | 1.68% |
| 8 Familial risk for psychosis | 12% [78] (30mo) | 19.88% | 1.21% |
| 9 Users of high potency cannabis | 24% [79] (lifetime) | 36.49% | 2.76% |
| 10 Military | 0.014% [80] (per year) | <0.001% | <0.001% |
| 11 Black ethnic minority | 1.45 % [81] (lifetime) | 2.60% | 0.13% |
| 12 Refugees | 3.3%[82] (lifetime) | 5.84% | 0.31% |
| 13 Epilepsy | 5.6%[83] (lifetime) | 9.74% | 0.53% |

1. Unselected sample of adolescent psychiatric patients (n=161);
2. National psychosis survey in representative sample of adults with psychotic disorders in contact with public treatment services (n=1642);
3. Population based consecutive cohort of forensic psychiatric patients (n=125)
4. Longitudinal patient records from a national primary care database (n=4164794)
5. Prisoners (n=33 588) in unselected prison samples worldwide assessed;
6. Past-year pregnant and postpartum women (n=14549) in the United States;
7. Children and young adults (n=125) with 22q11.2 deletion syndrome;
8. Young adults (n=163) with two relatives with schizophrenia;
9. Patients with first-episode psychosis (n=470) and matched population controls (n=370);
10. A 2000-2009 sample of US military (n=1976) admitted with a first episode of schizophrenia;
11. UK individuals (n=549) of black ethnic minority background;
12. Randomly selected participants screened by household representative (n = 748) and individual (n = 315) interviews
13. Meta-analysis of 58 studies reporting risk of psychosis in patients with epilepsy

**Table 3.** Prognostic accuracy of indicated prevention tests in clinical medicine

| At-risk population | Outcome | Diagnostic test | Sensitivity (follow-up) | Specificity (follow-up) | AUC (follow-up) |
|---|---|---|---|---|---|
| Patients presenting for CHR evaluation | Psychosis | CHR interview | 0.96 (2y) | 0.47 (2y) | 0.89 (2y) |
| Men at risk for prostate cancer[a] | Prostate cancer | PSA | 0.69[84] (5y) | 0.89[84] (5y) | 0.88[85] (5y) |
| Men at risk for colorectal cancer | Colorectal cancer | Risk prediction model[f] | Na† (5y) | Na (5y) | 0.80[86] (5y) |
| Women at risk for colorectal cancer | Colorectal cancer | Risk prediction model[g] | Na (5y) | Na (5y) | 0.73[86] (5y) |
| Patients with transient ischemic attack | Stroke | ABCD2 Score[j] | 0.57[87] (30 days) | 0.32[87] (30 days) | 0.72[88] (7 days) |
| Patients with stable coronary disease | Coronary event[h] | Framingham Risk Score[i] + number of diseased vessels | Na (8.5y) | Na (8.5y) | 0.67[89] (8.5y) |
| Prediabetes[k] | Diabetes | 30-min plasma glucose | 0.91[90] (9y) | 0.39[90] (9y) | 0.67[90] (9y) |
| Mild cognitive impairment | Alzheimer's disease | ADAS-cog subscale[l] | 0.62[91] (1y) | 0.73[91] (1y) | 0.67[91] (1y) |
| Women at risk for breast cancer[c] | ER[d]- positive invasive breast cancer | Gail model[e] | 0.50[92] (5y) | 0.65[92] (5Y) | 0.60[92] (5y) |

*AUC, Area Under the Curve;

†Na, Not Available.

[a] Age: 55-70; [b] PSA, Prostate-Specific Antigen; [c] Postmenopausal women, age: 50-79; [d] ER, Estrogen Receptor; [e] Age, ethnicity, age at menarche, age of the mother at the birth of her first live child, number of first-degree relatives with breast cancer (0, 1 or > 1), number of previous breast biopsy examinations (0, 1 or >1), and the presence or absence of atypical hyperplasia in the biopsy specimen; [f] Age, height, family history for cancer, BMI, and amount of alcohol consumed; [g] Age, height, family history of cancer, fasting glucose, meat consumption frequency; [h] Cardiac death, non-fatal myocardial infarction or unstable angina pectoris requiring unplanned coronary revascularization; [i] Age (≥45 years for men, ≥55 years for women), hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication), smoking, diabetes, elevated cholesterol (cholesterol ≥240 mg/dL or LDL-C ≥160 mg/dL), and HDL-C <35 mg/dL; [j] Age≥60, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg), clinical features (unilateral weakness, speech impairment), symptom duration (greater than 60 min, 10-59 minutes), diabetes; [k] Impaired Fasting Glucose (IFG), fasting plasma glucose levels of 100–125 mg/dL, or Impaired Glucose Tolerance (IGT), 2-h PG 140-199 mg/dL, or Combined Glucose Intolerance (CGI), or HbA1c 5.7-6.4% (American Diabetes Association 2010); [l] Alzheimer Disease Assessment Scale-cognitive part.