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Running Title: Prodromal psychosis screening
ABSTRACT

**Background:** Research has identified a syndrome conferring ultra-high risk (UHR) for psychosis, although UHR interviews require intensive staff training, time, and patient burden. Previously, we developed the Prodromal Questionnaire (PQ) to screen more efficiently for UHR syndromes. **Aims:** This study examines the concurrent validity of the PQ against UHR status and preliminary predictive validity for later psychotic disorder.

**Method:** We assessed a consecutive patient sample of 408 adolescents who presented to psychiatry clinics in Helsinki, Finland seeking mental health treatment, including 80 participants who completed the Structured Interview for Prodromal Syndromes (SIPS).

**Results:** A cut-off score of 18 or more positive symptoms on the PQ predicted UHR diagnoses on the SIPS with 82% sensitivity and 49% specificity. Three of fourteen (21%) participants with high PQ scores and SIPS UHR diagnoses developed full psychotic disorders within one year. **Conclusions:** Using the PQ and SIPS together can be an efficient two-stage screening process for prodromal psychosis in mental health clinics.

**Key words:** assessment, prodrome, psychosis, schizophrenia, high risk
INTRODUCTION

Clinical research on the psychosis prodrome has burgeoned over the past decade, due in large part to the development of semi-structured interviews that operationalized the definition of “ultra-high-risk” (UHR) or “prodromal” syndromes for psychosis. These syndromes are primarily defined by the presence of attenuated positive psychotic symptoms without full conviction that the experiences are real. For example, a young person with a UHR syndrome may intermittently hear voices, but is unsure whether they are real or a product of his imagination or may wonder if other people can read his mind. Attenuated symptoms must have started or worsened recently and are associated with concern or distress. The Structured Interview for Prodromal Syndromes (SIPS)\(^1\) and the Comprehensive Assessment of At-Risk States (CAARMS)\(^2\) are two interviews that diagnose these prodromal syndromes in similar ways, identifying a population with an approximate 35% risk of developing full psychosis within 2.5 years, when used within UHR referral settings\(^3\text{--}^5\). While useful in diagnosing UHR status, these clinician-administered interviews require substantial patient participation, staff training and staff time. Although university research clinics may have the resources to interview each potential participant for several hours, this is not common practice in the community, nor do general mental health practitioners have an easy way to identify potential prodromal symptoms in order to refer young people to appropriate treatment. In fact, it often takes several years for help-seeking youth with prodromal syndromes to be properly identified\(^6\).
In order to streamline the process of identifying at-risk youth most in need of an interview-based evaluation, we previously developed the Prodromal Questionnaire (PQ) as a self-report screen for prodromal symptoms in adolescents and young adults. The PQ is a 92-item questionnaire that covers four symptom clusters that are parallel to the symptom dimensions assessed in the SIPS: positive, negative, disorganized and general (affective and functioning) symptoms. In a sample of youth referred to a prodromal research clinic at the University of California, Los Angeles, the PQ discriminated between subjects with prodromal and fully psychotic SIPS diagnoses versus no SIPS diagnoses with 90% sensitivity and 49% specificity. In addition, a brief (21-item) form of the PQ has been developed with comparable predictive validity in UHR clinical contexts. Although the PQ may be useful in a specialty early psychosis clinic, only a small number of such clinics exist around the world, and most youth do not have access to them. The PQ would be more useful if it could function as a screen to identify symptomatic, help-seeking UHR youth where they first present for help – in general mental health clinics. Therefore, the purpose of this study was to examine the concurrent validity of the PQ against a “gold-standard” SIPS diagnosis in a general adolescent psychiatry sample.

METHODS

Participants & Assessments.

As part of the on-going Helsinki Prodromal Study, we administered a Finnish-language version of the PQ to two consecutive samples of adolescents (total N=408) who presented to any public psychiatric clinic in Helsinki, Finland. All young people aged 15-18 within
the Helsinki catchment area who presented to a psychiatric clinic for the first time between January 1, 2003 and March 31, 2004 or between March 1, 2007 and November 7, 2007 were asked to complete the PQ at their first or second clinic visit. Subjects’ average age was 16.5 years and 67% were female. Participants were required to speak Finnish fluently and could not have received psychiatric treatment within the previous two years or a psychotic disorder diagnosis at intake. The latter requirement ensured that our screening targeted individuals with a recent onset of symptoms or previously unidentified symptoms.

The subset of adolescents with PQ positive symptom scores in the top 20% of the distribution (the criterion being a PQ positive symptom score of 18 or more, based on the pilot sample described below) who had not already received a psychotic disorder diagnosis were invited to complete the SIPS, as were 12.5% of the remaining sample, chosen by permuted block randomization (one out of every eight subjects scoring 17 or lower), blocked by arrival order. Subjects in both outpatient and inpatient clinics participated, with inpatient participants accounting for 13% of the PQ sample and 16% of the SIPS-assessed sample.

Participants completed diagnostic assessments with trained research staff in the Department of Mental Health and Alcohol Research, National Public Health Institute of Finland (KTL), who were blind to subjects’ PQ scores. Written informed consent was obtained from all assessed subjects before their inclusion in the study, and parents notified in the case of minors, as required by Finnish law. Study procedures were approved by the Joint Authority for the Hospital District of Helsinki and Uusimaa, the KTL IRB and the University of California at Los Angeles IRB.
Diagnostic and Reliability Procedures. In September 2002, all screening staff members completed a 3-day SIPS training workshop with Dr. Rachel Loewy, in line with the training protocol previously conducted at UCLA by Dr. Tandy Miller, one of the authors of the SIPS. Screening staff rated four videotaped interviews and 4 written vignettes, and achieved extremely high inter-rater agreement of .92 to .99 on intra-class correlations of SOPS items averaged by scale and nearly perfect agreement for SIPS diagnoses (kappa=.97). In addition, several interview transcripts were translated into English and co-rated by UCLA staff to ensure reliability was maintained across sites. Final SOPS scores and SIPS diagnoses were assigned by team consensus. Staff had been previously trained to high standards of reliability on the Structured Clinical Interview for DSM-IV (SCID) by senior researcher Jaana Suvisaari, MD. The alcohol and substance use sections were administered to all subjects who completed the SIPS, and the full SCID was administered to a subsample of fourteen UHR patients followed over time.

Measures.

PQ. The Prodromal Questionnaire (PQ) is a 92-item self-report questionnaire that takes approximately 20 minutes to complete. The items are answered True/False and sum to form four major symptom scales, which are parallel to the scales of the SIPS. Items assess positive symptoms (39 items) such as unusual thinking and perceptual abnormalities, negative symptoms (19 items), including flat affect and social isolation, disorganized symptoms (19 items) such as disorganized thinking and behavior and general symptoms (15 items) that include depression, anxiety and problems with role functioning.
**SIPS.** The SIPS is semi-structured interview designed to be administered by a trained clinician. The interview begins with a biopsychosocial history and then assesses symptoms along four major dimensions on the Scale of Prodromal Symptoms (SOPS): positive symptoms (e.g. unusual thinking and perceptual disturbances), negative symptoms (e.g. anhedonia and flat affect), disorganized symptoms (e.g. conceptual disorganization and odd behavior) and general symptoms (e.g. depression and problems with role functioning). The SIPS also includes an assessment of family history of psychiatric diagnoses and requires the assignment of a score on the Global Assessment of Functioning Scale (GAF).

The SIPS diagnoses three types of prodromal syndromes, listed in order of sample prevalence: 1) Attenuated Positive Symptom Prodromal Syndrome: Attenuated positive psychotic symptoms present at least once per week, started or worsened in that past year (unusual thought content/delusional ideas, suspiciousness/ persecutory ideas, grandiosity, perceptual abnormalities/distortions, and conceptual disorganization; 2) Brief Intermittent Psychosis Prodromal Syndrome: Brief and intermittent fully psychotic symptoms that have started recently; 3) Genetic Risk and Deterioration Prodromal State: Either a family history of a psychotic disorder in any first-degree relative and a decline of at least 30% in the past 12 months on the GAF scale, or, meets criteria for schizotypal personality disorder and had a decline of 30% on the GAF in the past year. A person meeting any of these three sets of criteria is considered to be at ultra-high-risk for psychosis. The SIPS was translated into Finnish by 3 Finnish psychiatric researchers (Markus Heinimaa, MD, Ulla Mustonen MSW, and Liisa Varonen, PhD) and backtranslated into English by Dr. Jyrki Heikkilä.
Development of the Finnish-language PQ.

The PQ was translated into Finnish for the purposes of the present study by 8 Finnish investigators (Dr. Matti Huttunen, Dr. Hely Kalska, Maija Lindgren, Marko Manninen, Ulla Mustonen, Riitta Salmensaaari, Sebastian Therman, and Liisa Varonen), and backtranslated by licensed translator Ari Penttilä. Discrepancies between the original English and backtranslated versions were flagged and discussed by the Finnish and American investigators; the revised items were then again backtranslated into English by Sebastian Therman. In 2001-2002, the PQ was administered to 53 adolescent psychiatric inpatients and 60 adolescent psychiatric outpatients in the Helsinki health care district. The first 64 patients (51 outpatients and 11 inpatients) were asked to elaborate on their responses to the PQ items. The Finnish and American investigators then discussed these comments and, where appropriate, made changes to the Finnish items in order to ensure that the meaning of the items was consistent with the original English content.

In 2002, this revised PQ was administered to a pilot sample of 175 adolescent psychiatric outpatients from the Helsinki catchment area. In the overall sample, the distribution of scores on the positive symptom scale (mean=9.9, SD=8.2) was comparable to that obtained in the UCLA patient sample (mean=12.1, SD=7.9). For a subset of patients (N=41), treating psychiatrists reported detailed diagnostic and demographic information, including age, gender, medication, previous care, entry diagnosis, current diagnoses, medical history, and family psychiatric history. Among these, adolescents who answered positively to at least 18 of the positive symptoms items were five times more likely to be assigned a psychotic disorder diagnosis by their clinicians.
Statistical Analyses.

A total of 408 participants completed the PQ in the initial screening phase of the study, of which 99 participants, selected according to the criteria outlined above (i.e., highest scoring 20% plus 10% of the remainder), also completed the SIPS. Subjects were excluded from further statistical analyses if they received a diagnosis of a psychotic syndrome on the SIPS (N= 8) or current substance abuse/dependence on the SCID module (N=9) or incomplete data (N=2). Therefore, the selected interviewed sample available for statistical analyses includes 56 subjects with high PQ scores and 24 subjects with low PQ scores, for a total sample of 80 subjects.

Concurrent validity was examined by assessing the agreement between PQ scores and SIPS diagnoses (UHR or no SIPS diagnosis) in the selected sample. Logistic regressions assessed the ability of PQ scale scores to predict SIPS diagnosis. A receiver operating characteristic (ROC) curve was generated and area under the curve (AUC) calculated in order to examine the ability of the PQ selection criteria to discriminate between diagnostic groups.

Mann-Whitney U tests compared SOPS scores for high- and low-scoring PQ subjects selected to complete the SIPS (a non-parametric method used to compare groups with markedly different sample sizes). Correlation analyses were performed between PQ scores (major scales and total score) and the corresponding SOPS scores for all subjects who completed both measures, using Spearman’s correlation coefficient. Cronbach’s
coefficients alpha was used to examine internal consistency of the PQ scales. Statistical analyses were computed using SPSS 14.0\textsuperscript{10} and MedCalc 8.2.0.3.\textsuperscript{11}

**RESULTS**

Participants with high PQ scores (PQ positive symptoms ≥ 18) were rated as having higher SOPS scores compared to PQ low-scorers on all scales, including positive symptoms (U=225, p< .001, med=10, 2), negative symptoms (U=442, p= .02, med=12, 8), disorganized symptoms (U=362, p< .001, med=6, 2), general symptoms (U=359, p< .001, med=11, 7), and total symptoms (U=301, p< .001, med=38, 19.5). PQ scales showed strong internal consistency as reflected by high Cronbach’s alpha scores for positive symptoms (α=.90), negative symptoms (α=.82), disorganized symptoms (α=.85), general symptoms (α=.85), and for all items (α=.95).

In a stepwise logistic regression, SIPS diagnosis was significantly predicted by PQ positive symptoms (p=.006) but the model was not significantly improved by adding the negative, disorganized or general PQ scale scores (variables retained at p<.05). PQ scale scores were moderately to highly correlated with the corresponding SOPS scale scores for positive symptoms (r = .57, p< .001), negative symptoms (r = .50, p< .001), disorganized symptoms (r = .41, p< .001), general symptoms (r = .51, p< .001) and total symptoms (r = .63, p< .001). When conceptual disorganization was shifted to the positive symptom scale (as it is classified on the SIPS/SOPS), the correlation was similar for positive symptoms (r=.57, p<.001) and slightly higher for disorganized symptoms (r=.45, p< .001). Next, an
ROC curve (Figure 1) was calculated for the prediction of SIPS diagnosis by PQ positive symptom score (AUC= .72, p<.001).

At the pre-selected cutoff of 18 or more positive symptoms, the PQ showed good agreement; with 82% sensitivity and 49% specificity (see Table 1). Within the low-scoring PQ group, 22% of subjects were diagnosed with a UHR syndrome on the SIPS, while 41% of high-PQ scorers received a SIPS diagnosis.

A small group of subjects with high PQ scores (≥ 18), who were diagnosed with UHR syndromes on the SIPS were followed to assess predictive validity (N=14). By 6-month follow-up, one subject had developed a full psychotic disorder (7%), and two more had developed full psychosis by 12 months (21%). One additional subject developed a new onset of bipolar disorder without psychotic features by 12 months. These conversion rates are comparable to other samples that follow SIPS-diagnosed patients over time.³⁶
DISCUSSION

In this study, the PQ discriminated moderately well between adolescents in general mental health clinics judged to have UHR diagnoses on the SIPS/SOPS versus those with no SIPS diagnosis (82% sensitivity, 49% specificity). The PQ performed slightly better in the UCLA prodromal clinic sample, with a cutoff of 8 or more positive symptoms producing 90% sensitivity and 49% specificity. Together, these results suggest that the PQ performs similarly in both clinic-referred and general mental health samples, although the criterion for selecting patients for interviews may vary by setting, depending on the purpose of the screening.

Practically speaking, these results correspond to interviewing roughly 20% of a general clinic sample, with approximately one out of two interviewed subjects meeting UHR criteria, and missing about one out of six true UHR cases who screen out with low scores on the PQ. For the purposes of recruiting UHR participants for research, this two-stage method could be highly efficient compared to current referral-based practices. The interviews would likely be too burdensome, however, for routine clinical use. Of note, the PQ is only meant to be used in a two-stage screening process with clinical interview. As the distinctions of frequency and severity are quite time-consuming even during interviews, we chose not to assess onset, frequency, distress or insight on the PQ.

However, in order to further improve accuracy and efficiency, we later developed a brief version of the PQ (PQ-B) that shows greater specificity in a specialty-clinic referred sample through use of a distress/impairment criterion. The PQ-B has not yet been tested in a general mental health treatment setting.
Based on published reports, the total sample and UHR-diagnosed sample for this study appear to be comparable to other outpatient groups and UHR research samples, respectively. The total sample obtained PQ scores consistent with those of help-seeking adolescents in the US.\textsuperscript{13} The 12-month rate of conversion to psychosis in this sample (21\%) was generally consistent with other SIPS-diagnosed samples. Therefore, we believe that patients with high PQ scores and SIPS-derived prodromal diagnoses are, in fact, at very high risk for developing a psychotic illness. Six subjects who had not been previously identified as psychotic by the outpatient clinics were diagnosed with DSM-IV psychotic disorders at their baseline study evaluation, suggesting that the PQ may also help to screen for fully psychotic individuals in outpatient settings.

Screening for psychosis risk requires careful consideration of the stigma and distress that can accompany this designation, especially in false positive cases. First, we recommend only using the PQ in the context of two-stage screening with a clinical interview. Second, ethical responsibility dictates that clinicians conduct sensitive and thoughtful discussions with clients and families about the accuracy of assessment measures and a description of what “risk” really means, balancing potential stigma and fear with a normalizing perspective that recognizes attenuated psychotic symptoms alone do not fully predict eventual disorder\textsuperscript{14,15}.

**Sample-dependent conversion rates**

Some investigators have suggested that the rate of conversion to full psychosis in UHR samples varies depending on the method of ascertainment, consistent with the
dependence of the validity of disease risk screening on the prevalence rate in a particular sample. This issue raises the question of how useful a general screening approach would actually be in common practice. When the CAARMS criteria were applied to adolescents in a general outpatient mental health setting, only 10% of patients diagnosed as UHR developed a psychotic disorder within six months and 16% by two years. This is a lower conversion rate than those previously reported in samples of young people referred specifically for UHR evaluation. The authors of that study raise the possibility that using the CAARMS in a general outpatient sample may result in a higher proportion of false-positives. However, that study was conducted in a community where the average clinician is now quite familiar with the concept of the prodromal syndrome and the importance of early diagnosis and intervention, due to successful education and outreach campaigns that have been in operation over the past decade. Furthermore, clinicians in that community may be more familiar with using effective interventions during the prodromal phase, and young people may be identified more quickly after the onset of attenuated psychotic symptoms. In fact, youth referred specifically for a suspected UHR syndrome who met CAARMS criteria have more recently shown a similarly low conversion rate of just 17% at 2 years. These results argue that the lower conversion rates are specific to a region with highly effective public education and intervention models in place. In other communities, where conversion rates remain high, screening in general outpatient settings may be a more effective and efficient way to identify at-risk youth. Longitudinal studies with larger samples will be required to fully evaluate the two-stage screening.
Limitations

One caveat to these conclusions is that there may be linguistic and/or cultural differences between the Finnish and English-speaking samples that affect the results. However, the similarity in its performance across countries suggests that the PQ may be useful in identifying at-risk youth in a variety of nations. In a sample of 100 first-visit outpatients in Taiwan, a Chinese version of the PQ showed excellent sensitivity (97%) against clinician diagnoses at a cutoff of 8 or more positive symptoms, but poor specificity (30%). A higher cutoff or selection of specific items may be more appropriate for that population.\textsuperscript{18}

The small sample size (N=14) of patients followed longitudinally requires cautious interpretation, and the conversion rates should be considered preliminary outcomes. Future studies will need to follow larger samples over time to determine the true predictive validity of combined PQ-SIPS screening. Following both high- and low-scoring patients to assess later psychiatric diagnoses is necessary to assess the true predictive validity of screening.

Future Directions

Ultimately, the performance of the PQ must be assessed in each type of population where it may be used to determine its validity. Our results highlight the importance of conducting studies to validate both the PQ and predictive validity of UHR diagnoses in a variety of settings, including unselected samples.
In future studies, we plan to follow larger samples over time in order to examine the ability of the PQ to directly predict conversion to psychosis. While important research is currently being conducted to identify neurobiological markers of increased psychosis risk within a UHR group, no biomarker has yet been identified that truly predicts psychosis. In most countries, mental health diagnoses are based on patients’ symptom report, and more costly screening techniques are not used in general help-seeking samples. Therefore, we hope the development of the PQ can promptly aid efficient, early identification of psychosis risk in a range of settings and countries. As evidence for effective UHR treatment accumulates\textsuperscript{19-25}, early identification of prodromal syndromes becomes increasingly important.

ACKNOWLEDGEMENTS

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Table 1. Agreement of PQ with concurrent SIPS diagnosis

<table>
<thead>
<tr>
<th>Sample</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV^a</th>
<th>NPV^a</th>
<th>AUC^a</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Helsinki</td>
<td>PQ Positive symptoms ≥ 18</td>
<td>82%</td>
<td>49%</td>
<td>51%</td>
<td>81%</td>
<td>0.72</td>
<td>0.61 – 0.81*</td>
</tr>
<tr>
<td>UCLA</td>
<td>PQ Positive symptoms ≥ 8</td>
<td>90%</td>
<td>49%</td>
<td>78%</td>
<td>69%</td>
<td>0.79</td>
<td>0.70 – 0.86*</td>
</tr>
</tbody>
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^a PPV = Positive predictive value, NPV = Negative predictive value, AUC = Area Under the Curve, * p < .001
Figure 1. Receiver operating characteristic (ROC) curve of PQ positive symptoms predicting SIPS diagnosis.