Is the Clinical High-Risk State a Valid Concept? Retrospective Examination in a First-Episode Psychosis Sample

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Objective: One reason for worldwide interest in the clinical high-risk (CHR) state for psychosis is its potential as a target for prevention. However, the feasibility and utility of early intervention initiatives that are focused on this stage involve an untested assumption: that most patients with a first episode of psychosis (FEP) experience earlier CHR symptoms. The objective of this study was to identify and characterize the proportion of FEP patients who had experienced such symptoms prior to the onset of their psychosis.

Methods: Semistructured interviews of 351 patients and families with the Circumstances of Onset and Relapse Schedule were supplemented by chart reviews in a catchment area–based sample of FEP patients. Information was extracted regarding pathways to care and psychiatric and behavioral changes over time. Experts (N=30) working in FEP and CHR settings identified which of 27 early signs and symptoms constitute attenuated positive or subthreshold psychotic symptoms (APSPS) if they appear prior to a syndromal-level psychotic episode.

Results: Nine early signs and symptoms were endorsed by the experts as representing APSPS. More than half of consenting patients, and two-thirds (68%) of those who completed all assessments, had experienced at least one such sign or symptom prior to their FEP. The groups with and without APSPS were similar in social, demographic, and clinical characteristics.

Conclusions: Most consenting patients with an FEP had experienced previous signs and symptoms consistent with a CHR state prior to the onset of threshold-level psychotic symptoms, although a substantial minority had not. This finding validates the viability of the CHR construct as a potential target for early case identification and preventive and therapeutic interventions.

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The occurrence of psychiatric signs and symptoms prior to a psychotic disorder has been noted as far back as 1861 (1). However, recent years have seen more intensive documentation of these signs and symptoms among young people in the early stages of psychotic illness (2–4), including the nonpsychotic symptoms that are frequent but relatively insensitive for predicting psychosis (5). In particular, Birchwood's (6) identification of a critical period for detection and intervention around the first episode of psychosis (FEP) catalyzed a wave of investigations into the psychosis "prodrome"—a common (1,7) phase of continuous affective, anxiety, subthreshold psychotic, and other symptoms (often coupled with decreased functioning) that immediately precedes an FEP (8). Yet because the symptoms that constitute the prodrome frequently resolve without development of a full-blown psychosis, the existence of a prodrome can be determined only retrospectively—that is, if and when a psychosis emerges directly from it (9).

As a result, individuals are now identified in a well-defined "clinical high risk" (CHR) state (10,11) or "at-risk mental state" (12) that is proximal to the FEP. Young people experiencing a CHR state have a substantially higher risk of developing a syndromal-level psychosis than is observed in the general population (13). There is understandable excitement and some evidence that early identification and intervention efforts during the CHR period can improve risk prediction and delay or even prevent the development of an FEP (14,15). However, the potential impacts and effectiveness of such resource-intensive interventions are complicated by the fact that only a minority of persons in the CHR phase transition to FEP, while the overall rates of transition from CHR to FEP have actually decreased over the past one to two decades (16,17).

Furthermore, the current literature is largely based on patients who were assertively recruited to specially designed clinics based on meeting CHR criteria at the time of initial assessment. It is not known how commonly a CHR state

precedes an FEP, making it premature to draw conclusions about one state on the basis of information from the other. Assuming that persons in a CHR state are merely experiencing "schizophrenia lite" may therefore be misguided (18). Conversely, however, understanding what proportion of cases of FEP could be prevented by identifying or targeting individuals in CHR states will begin to inform the planning and feasibility of public mental health efforts.

The utility of targeting the CHR state to prevent FEP depends on a key assumption: that the FEP is actually preceded by a CHR stage involving identifiable attenuated positive or subthreshold psychotic symptoms (APSPS). Previous analyses have searched for general prodromal symptoms rather than for the more specific subthreshold psychotic symptoms that characterize the CHR state, or they have focused on selected populations, such as inpatients, socially disadvantaged persons, or those with nonaffective psychosis (1,7). Schultze-Lutter and colleagues (19) recently found that fewer than half of adults hospitalized for psychosis reported CHR symptoms prior to the onset of an FEP. However, they wondered whether this finding was an underestimate of the phenomenon; also, because their sample consisted solely of inpatients, there was a potential bias toward more severe manifestations of psychosis.

In this study, we take advantage of a catchment area–based sample of inpatient and outpatient FEP service users to test the assumption that the FEP is preceded by symptoms consistent with a CHR stage. Although not an exhaustive list of all persons with FEP in an area, a catchment-based service presents the opportunity to examine a relatively representative clinical population—in this case, to determine the proportion of persons who had experienced a CHR phase prior to the threshold-level FEP for which they sought treatment. Our aims were threefold: to identify a subset of features that reflect APSPS prior to an FEP, to assess what proportion of persons with FEP do and do not experience such symptoms, and to determine whether baseline differences exist between patients who do and do not experience APSPS prior to their FEP.

METHODS

Setting

This study was carried out at a specialized early intervention (SEI) program in an urban setting in Canada (20), known as the Prevention and Early Intervention Program for Psychosis (PEPP-Montréal). The program provides assessment, treatment, and follow-up over a two-year period to youths ages 14 to 35 who are experiencing an FEP within a geographically defined catchment area of roughly 300,000 individuals. Notably, the program is a publicly funded service, as are all mental health services in Canada; no other competing public or private FEP treatment facilities exist in the region. It is thus expected that the service receives most persons identified as having an FEP who are seeking treatment in the catchment area. The program admits an average of 60 new patients each year, suggesting a treated incidence rate of 20 per 100,000. Patients are accepted from all referral sources, including emergency departments, hospital inpatient units, general practitioner and other outpatient clinics, schools, family and other support, and self-referrals (20). All patients are asked to provide written informed consent to participate in an evaluation and care protocol as part of various longitudinal FEP outcomes studies. This protocol was approved by the Douglas Hospital Research Center's Research Ethics Board.

Study Population

Of the 568 patients with an FEP admitted to PEPP between 2003 and 2013, 482 (85%) provided consent for the overall PEPP research protocol. Of these, 351 (73%) completed required assessments regarding the early signs and symptoms they experienced prior to an FEP. Inclusion criteria for the program are age 14–35 at the time of referral, diagnosis of an affective or nonaffective psychotic illness with the Structured Clinical Interview for DSM-IV (SCID) (21), and fluency in either English or French. In the context of an FEP, patients accepted to the program had to have received antipsychotic medications for no more than 30 days prior to referral. Exclusion criteria were IQ <70, psychotic illness solely related to substance intoxication or withdrawal, or an organic mental disorder. Patients with a concurrent substance use disorder were not excluded. All patients included in this analysis signed informed consent; those under age 18 assented with consent provided by a parent or guardian.

Instruments and Assessments

The SCID was administered by trained staff, and primary and secondary diagnoses were confirmed through consensus with a senior research psychiatrist (RJ or AKM). Diagnostic assessment was repeated one year later. The Circumstances of Onset and Relapse Schedule (CORS) (22,23) was similarly administered by a trained evaluator within a patient's first three months of entry into the program; this included detailed interviews with the patient and (whenever possible) with a close family member, as well as a review of all available health and educational records. From these sources, information regarding patients' pathways to care was extracted, including early changes in behavior, initial psychiatric changes (as opposed to lifelong behaviors or early childhood conditions, such as autism or attention-deficit hyperactivity disorder), ongoing symptoms, symptoms that appeared and later resolved, the onset of symptoms that were or were not contiguous with the FEP, the timing of onset of frank psychosis, and the beginning of adequate treatment. As done by Compton and colleagues (7), we cross-referenced the timeline of psychopathology generated by these data with conventions of key milestones or anchors in order to pinpoint exactly the dates of important changes or events. These were recorded once consensus was achieved at a regular meeting chaired by one of the authors (RJ or AKM).

The Topography of Psychotic Episode (TOPE) (2,4), derived from the Instrument for the Retrospective Assessment of

TABLE 1. Characteristics of participants with a first episode of psychosis who completed all assessments and those who did not (nonparticipants) and of participants with and without attenuated positive or subthreshold psychotic symptoms (APSPS)[a]

	Nonparticipants (N=117)		Participants (N=351)			With APSPS (N=238)		Without APSPS (N=113)		
Characteristic	N	%	N	%	p	N	%	N	%	p
Age at program entry (M±SD)	23.54±4.83		23.35±4.34		.697	23.24±4.24		23.59±4.57		.483
Age at onset of psychosis for presenting episode (M±SD)	22.54±4.87		22.46±4.41		.880	22.31±4.24		22.79±4.77		.364
Age at onset of prodrome (M±SD)	20.71±5.57		20.73±4.99		.977	20.38±4.81		21.47±5.30		.054
Age at first APSPS (M±SD)						19.04±5.72				
Male	86	74	248	71	.637	172	72	76	67	.380
Race					.908					.145
Caucasian	71	65	224	66		144	63	80	71	
Non-Caucasian	38	35	117	34		85	37	32	29	
Single marital status	100	87	319	91	.202	217	92	102	91	.841
High school or less	60	60	166	49	.068	118	51	48	45	.351
Primary diagnosis of schizophrenia spectrum disorder	75	68	257	73	.275	181	76	76	68	.120
Secondary diagnosis of a substance use disorder	62	63	190	55	<.001	135	57	55	51	.554
SAPS total score (M±SD)[b]	36.29±13.74		33.68±15.36		.110	33.82±15.45		33.38±15.22		.802
SANS total score minus attention items (M±SD)[c]	25.07±13.10		24.95±13.72		.933	24.81±13.47		25.25±14.30		.783
PANSS total score (M±SD)[d]	90.21±17.62		84.51±17.55		.005	83.67±16.96		86.38±18.64		.187
BPRS total score (M±SD)[e]	69.90±14.68		66.01±12.83		.009	65.98±12.94		66.07±12.67		.949
SOFAS (M±SD)[f]	38.29±12.54		42.88±13.27		.002	42.87±13.47		42.92±12.92		.975
GAF (M±SD)[f]	28.13±8.98		29.76±8.02		.087	29.98±8.16		29.29±7.72		.455

[a] An independent-samples t test or Mann-Whitney U test was used to compare means, and proportions were compared with a chi-square test. The numbers may not sum to 117, 351, 238, or 113 because of missing data.
[b] Possible total scores on the Scale for the Assessment of Positive Symptoms (SAPS) range from 0 to 150, with higher scores indicating more severe symptoms.
[c] Possible total scores on the Scale for the Assessment of Negative Symptoms (SANS) range from 0 to 90 after removal of the items for attention, with higher scores indicating more severe symptoms.
[d] Possible total scores on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) range from 30 to 210, with higher scores indicating more severe symptoms.
[e] Possible total scores on the Brief Psychiatric Rating Scale (BPRS) range from 24 to 168, with higher scores indicating more severe symptoms.
[f] Possible total scores on the Social and Occupational Functioning Assessment Scale (SOFAS) and the Global Assessment of Functioning (GAF) range from 0 to 100, with higher scores indicating greater functioning.

Onset of Schizophrenia (24), is a subset of the CORS that allows for a retrospective assessment of 27 potential early signs and symptoms of psychosis. Specifically, as part of administering the CORS, a trained interviewer established which of the 27 features had occurred, beginning with the first ever psychiatric change up to the onset of frank psychosis. Training in administering the CORS included orientation, rating videotapes, role playing, and conducting the interview itself under supervision, followed by estimation of pertinent dates for each event. Interrater reliability was based on the cases of 12 randomly selected individuals rated separately by three raters (intraclass correlation coefficient=.81–.98).

Expert Consensus

International experts (N=30) who were practicing psychiatrists or doctoral-level psychologists were identified as senior authors from publications involving the early phases of psychotic illness. They were contacted via e-mail by one of the authors (AC or JLS) between 2011 and 2013. Experts were asked to complete an anonymous online survey that provided a full list of the 27 early signs and symptoms; respondents were asked to state (as either yes or no) which of them would "constitute attenuated positive symptoms/subthreshold psychotic symptoms, if they appeared at a time when an individual would not have met criteria for a syndromal level psychotic episode."

Data Analysis

Basic descriptive statistics were compiled for sociodemographic and clinical variables, including t tests, analyses of variance, and chi-square tests as appropriate. Comparisons of demographic and clinical characteristics were made between patients included in this study and patients for whom adequate data were not available. For expert responses, the threshold for agreement on each putative APSPS was set a priori at a positive response of 60% or more. Basic statistics for the early signs and symptoms meeting this threshold criterion were also computed. All statistical analysis used SPSS, version 23.

RESULTS

Sample Characteristics

Of the 482 patients who signed consent after entry to the SEI program, 351 (73%) completed the TOPE. Sociodemographic and clinical information, along with ages at key time points, for this full sample are presented in Table 1. Relevant data were available for 117 of the 131 remaining patients who did

not complete the TOPE, and a comparison of these patients with the 351 patients in the study is also presented in Table 1. Those who did not complete the TOPE had lower scores on the Social and Occupational Functioning Assessment Scale, indicating lower functioning, and higher scores on the Positive and Negative Syndrome Scale for Schizophrenia and Brief Psychiatric Rating Scale, indicating more severe symptoms; noncompleters were also more likely to have a comorbid substance use disorder.

APSPS per Expert Group

All 27 early signs and symptoms included in the TOPE are presented in Table 2, along with the frequency of endorsement by the expert group of psychiatrists and psychologists. The percentage of experts endorsing symptoms as APSPS ranged from 5% (change in appetite or weight and self-harm) to 100% (unusual perceptual experiences, not clearly psychotic). The upper portion of Table 2 lists the nine early signs and symptoms that were endorsed as having met criteria for APSPS (endorsed by at least 60% of the experts surveyed). They are, in order of decreasing frequency among the 351 patients, suspiciousness or odd ideas of reference (44%); odd or bizarre ideas that are not delusional (33%); odd, unusual, or eccentric behavior (19%); unusual perceptual experiences that are clearly psychotic (19%); disorganized or odd speech (16%); inappropriate affect (11%); subthreshold hallucinations (4%); subthreshold delusions (4%); and passivity experiences (3%).

TABLE 2. Expert endorsement of early signs and symptoms as constituting attenuated positive or subthreshold psychotic symptoms and their frequency among patients experiencing a first episode of psychosis

	Experts endorsing (N=30)		Frequency among patients (N=351)		
Early sign or symptom	N	%	N with data	N	%
Endorsed by ≥60% of experts					
Suspiciousness or odd ideas of reference	20	95	347	151	44
Odd or bizarre ideas (not delusional)	19	90	346	115	33
Odd, unusual, or eccentric behavior	17	81	344	65	19
Unusual perceptual experiences (not clearly psychotic)	21	100	349	65	19
Disorganized or odd speech	20	95	348	57	16
Inappropriate affect	13	62	350	37	11
Hallucinations (subthreshold)	16	76	340	15	4
Delusions (subthreshold)	16	76	339	13	4
Passivity experiences	14	67	351	10	3
Endorsed by <60% of experts					
Depression	2	10	348	248	71
Anxiety	3	14	349	229	66
Impaired role functioning	8	38	346	228	66
Social withdrawal	12	57	348	210	60
Impaired concentration	8	38	347	197	57
Sleep disturbance	3	14	349	190	54
Decreased energy and initiative	5	24	349	188	54
Irritability or aggressiveness	4	19	347	167	48
Change in appetite or weight	1	5	350	156	45
Restlessness	2	10	348	89	26
Blunted or flat affect	6	29	350	87	25
Memory problems	2	10	347	86	25
Mood elation	4	19	345	74	21
Poor hygiene or grooming	9	43	349	54	15
Self-harm	1	5	351	37	11
Obsessive-compulsive symptoms	2	10	345	33	10
Altered motor behavior (extrapyramidal symptoms)	6	29	350	21	6
Altered motor behavior (catatonia)	7	33	350	14	4

Subpopulation With APSPS

Of the 351 participants, 238 (68%) reported having experienced at least one of the nine early signs and symptoms selected by the expert group, and 113 (32%) had not experienced any; 42% had experienced two or more such symptoms (Table 3). In this group of 238, the first such symptom appeared at a mean±SD age of 19.10±5.61, and the onset of psychosis was at 22.40 years±4.41.

Of note, no significant differences were found in early or baseline social, demographic, or clinical variables between the groups with and without APSPS at the point of entry to PEPP (Table 1).

DISCUSSION

There was considerable agreement among experts in the field as to what constitutes APSPS. Using a semistructured interview-based instrument (CORS) with FEP patients and their caregivers and aided by detailed chart reviews, we found that at least half of all consenting patients in this catchment area–based clinical sample, and two-thirds (68%) of those who completed all assessments, recalled experiencing one or more APSPS prior to their FEP. Although each of the nine APSPS identified by the experts were individually present in a minority of patients, the most common early signs and symptoms reported in the overall assessments of the FEP patients were, in fact, depression, anxiety, and impaired role functioning. Overall, those with and without APSPS were similar in social, demographic, and clinical features at baseline.

With the exception of inappropriate affect, the nine early signs and symptoms identified by the experts readily map onto the various subscales of the Comprehensive Assessment of At-Risk Mental States (CAARMS) (10) and the Structured Interview for Psychosis-Risk Syndrome (SIPS) (11), both widely accepted instruments documenting the CHR construct (25). Odd or bizarre ideas, passivity experiences, subthreshold delusions, and suspiciousness (included in the TOPE) are accounted for by the unusual thought content, delusional ideas, suspiciousness or persecutory ideas,

TABLE 3. Patients (N=351) reporting attenuated positive or subthreshold psychotic symptoms prior to their first episode of psychosis

N of symptoms	N	%
0	113	32
1	91	25
2	71	20
3	36	10
4	22	6
5	12	3
6	3	1
7	3	1
≥1	238	68
≥2	147	42
≥3	76	22
≥4	40	12
≥5	18	5
≥6	6	2
≥7	3	1

and grandiose ideas of the SIPS and the unusual thought content and nonbizarre ideas of the CAARMS. Unusual perceptions (not clearly psychotic) and subthreshold hallucinations (TOPE) reflect perceptual abnormalities or hallucinations of the SIPS and perceptual abnormalities of the CAARMS. Disorganized or odd speech (TOPE) is represented by disorganized communication (SIPS) and disorganized speech (CAARMS). Finally, the TOPE's odd or unusual behavior is described in both the unusual thought content and the perceptual abnormalities scales of the SIPS and CAARMS.

Despite excitement about the CHR stage, it has been unclear whether most individuals with a FEP pass through an identifiable CHR phase. This knowledge gap has emerged in part because interventions for the high-risk state are largely organized around CHR research clinics, where patients are assertively recruited and followed on the basis of defined CHR criteria. In contrast to those prospective longitudinal studies of CHR youths, this study is the first to provide evidence that at least half of FEP patients, and 68% of those who completed all assessments, recalled experiencing early APSPS consistent with the CHR state. A key advantage of our analysis is its catchment area–based sample, which included both inpatients and outpatients with any form or severity of FEP. It supports Schultze-Lutter and colleagues' speculation that their own report may have underestimated the prevalence of CHR symptoms prior to an FEP (19).

This work also has important consequences from a population health and service-planning perspective. Because only a minority of persons in a CHR state transition to FEP (17), arguments for the feasibility and relevance of targeting the CHR state (via early identification, prevention, or other intervention efforts) presume that this state is in fact a frequent pathway en route to the FEP. In other words, if most patients with a psychosis had not actually experienced APSPS and had only nonspecific (non-CHR) early signs and symptoms prior to their FEP, then case identification or other interventions targeting the CHR phase would have limited relevance or utility for delaying or preventing FEP. In contrast, our conclusion that a majority of consenting FEP patients (68% of those who completed all assessments) reported experiencing early APSPS provides an important validation of the CHR state's relevance for mental health service planning and strengthens the clinical utility of CHR for case identification and indicated prevention initiatives.

Such arguments must bear in mind potential risks, such as the labeling of individuals as being at risk of psychosis when most of them will not in fact develop a FEP. Furthermore, the finding that many individuals with FEP did not pass through a CHR phase underscores the fact that multiple forms of psychopathology occur en route to an FEP and that a sole focus on interventions for CHR may ignore other pathways to FEP.

It is perhaps surprising that there were no significant sociodemographic or clinical differences (including both baseline symptoms and functioning [Table 1]) between the groups with and without APSPS at the point of help seeking for an FEP. This finding suggests that the form of symptoms can change substantially between the prepsychotic period and emergence of an FEP. APSPS are not required in a prodrome but can occur prior to the prodrome (9); there was a trend toward earlier age at onset of the prodrome in the group that had experienced APSPS compared with the group without APSPS. However, no difference was found in the age at onset of psychosis between the two patient groups. Furthermore, our results indicate that even though the prodrome is a concept linked to schizophrenia, individuals with a history of APSPS did not differ in their rate of development of affective versus nonaffective (schizophrenia spectrum) FEP (Table 1). Intriguingly, recent work supports the view that early APSPS may be of limited consequence; the presence of subthreshold positive symptoms among CHR youths followed prospectively is not related to functioning either initially or over time (26).

Strengths of our study included the agreement across multiple continents by internationally recognized experts in the early psychosis field and the use of semistructured interviews followed by consensus decision making about symptom onset and key time points. Our methodology also enabled us to capture distress, help-seeking behavior, and APSPS that emerged prior to the prodrome (for example, APSPS that were followed by a period of full symptom resolution, then by either more APSPS or nonspecific symptoms that evolved into an FEP). Potential explanations for the higher rates of APSPS seen in our sample are the inclusion of younger patients and those from both inpatient and outpatient settings, in many cases capturing psychosis onset in the community prior to initiation of psychosocial or pharmacological treatment. Also, because our sample was derived from a catchment-based FEP program with no

competing services, our data likely reflect real-world diversity in intensity and severity of illness onset.

Limitations included the fact that some individuals receiving FEP care did not consent to their data being used for research purposes, meaning that they could not be included in this sample. In addition, many who consented did not complete all assessments required for the analysis. There were significant differences in symptoms and functioning between the 351 study completers and the 131 noncompleters (Table 1). As a result, the 68% of study completers who experienced at least one APSPS could be an over- or underestimate of APSPS in the total FEP population.

Furthermore, our list of 27 early signs and symptoms was shorter and less detailed than the more than 100 symptoms included in other instruments, such as the Interview for the Retrospective Assessment of the Onset of Schizophrenia (24). Two of the nine identified features (inappropriate affect and passivity experiences) were endorsed by only slightly more than the 60% threshold of experts (Table 2), and inappropriate affect does not readily map onto elements screened for in prospective CHR diagnostic instruments. A more rigorous survey of experts could have used higher thresholds; more intensive approaches, including feedback; or a push toward convergence, as is typically done in studies using Delphi methods. Recall bias is a limitation of any instrument that is based on recollection of symptoms and behaviors, and such bias may have persisted even when data from family members and other caregivers were integrated and despite multiple probes and anchors provided in the CORS and TOPE (birthdays, milestones, and major events). Further investigation of the psychometric properties of both the CORS and the TOPE is required. Finally, although the baseline sample represented patients with relatively untreated FEP, the ≥30-day exclusion criterion regarding use of antipsychotic medications may have excluded those who received such medications for more than one month before referral to PEPP-Montréal.

CONCLUSIONS

This report provides the first evidence that in a catchment area–based sample, at least half of consenting youths with an FEP, and over two-thirds of all study completers, had experienced a prior phase of APSPS resembling the operationalized CHR state. Even though patients with and without APSPS had similar baseline sociodemographic and clinical characteristics, our finding that APSPS preceded development of an FEP in a substantial proportion of patients is an important validation of the population-level feasibility and relevance of the CHR construct for FEP. It also supports the CHR state's viability as a target for early intervention, such as through case identification or indicated prevention approaches. Finally, it lends credence to a clinical staging model (27) in which later and more differentiated forms of illness are sometimes—but not always—preceded by subthreshold syndromes.

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REFERENCES

1. Hafner H: Prodrome, onset and early course of schizophrenia; in The Epidemiology of Schizophrenia. Edited by Murray RM, Jones PB, Susser E, et al. Cambridge, United Kingdom, Cambridge University Press, 2003
2. Iyer SN, Boekestyn L, Cassidy CM, et al: Signs and symptoms in the pre-psychotic phase: description and implications for diagnostic trajectories. Psychological Medicine 38:1147–1156, 2008
3. Woodberry KA, Serur RA, Hallinan SB, et al: Frequency and pattern of childhood symptom onset reported by first episode schizophrenia and clinical high risk youth. Schizophrenia Research 158:45–51, 2014
4. Norman RMG, Scholten DJ, Malla AK, et al: Early signs in schizophrenia spectrum disorders. Journal of Nervous and Mental Disease 193:17–23, 2005
5. Fusar-Poli P, Yung AR, McGorry P, et al: Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. Psychological Medicine 44:17–24, 2014
6. Birchwood M, Todd P, Jackson C: Early intervention in psychosis: the critical period hypothesis. British Journal of Psychiatry. Supplement 172:53–59, 1998
7. Compton MT, Goulding SM, Walker EF: Characteristics of the retrospectively assessed prodromal period in hospitalized patients with first-episode nonaffective psychosis: findings from a socially disadvantaged, low-income, predominantly African American population. Journal of Clinical Psychiatry 71:1279–1285, 2010
8. Yung AR, McGorry PD: The initial prodrome in psychosis: descriptive and qualitative aspects. Australian and New Zealand Journal of Psychiatry 30:587–599, 1996
9. Yung AR, McGorry PD: The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophrenia Bulletin 22:353–370, 1996
10. Yung AR, Yuen HP, McGorry PD, et al: Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Australian and New Zealand Journal of Psychiatry 39: 964–971, 2005
11. Miller TJ, McGlashan TH, Rosen JL, et al: Prodromal assessment with the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin 29:703–715, 2003

12. McGorry PD, Singh BS: Schizophrenia: risk and possibility; in Handbook of Preventive Psychiatry. Edited by Raphael B, Burrows GD. Amsterdam, Elsevier, 1995
13. Fusar-Poli P, Bonoldi I, Yung AR, et al: Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry 69:220–229, 2012
14. Thompson E, Millman ZB, Okuzawa N, et al: Evidence-based early interventions for individuals at clinical high risk for psychosis: a review of treatment components. Journal of Nervous and Mental Disease 203:342–351, 2015
15. Cannon TD, Yu C, Addington J, et al.: An individualized risk calculator for research in prodromal psychosis. American Journal of Psychiatry 173:980–988, 2016
16. Yung AR, Yuen HP, Berger G, et al: Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophrenia Bulletin 33:673–681, 2007
17. Fusar-Poli P, Borgwardt S, Bechdolf A, et al: The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70:107–120, 2013
18. van Os J, Murray RM: Can we identify and treat "schizophrenia light" to prevent true psychotic illness? BMJ 346:f304, 2013
19. Schultze-Lutter F, Rahman J, Ruhrmann S, et al: Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. Social Psychiatry and Psychiatric Epidemiology 50:1831–1841, 2015
20. Iyer S, Jordan G, MacDonald K, et al: Early intervention for psychosis: a Canadian perspective. Journal of Nervous and Mental Disease 203:356–364, 2015
21. First M, Spitzer R, Gibbon M, et al: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York, New York State Psychiatric Institute, Biometric Research, 2002
22. Payne J, Malla A, Norman R, et al: Status of first-episode psychosis patients presenting for routine care in a defined catchment area. Canadian Journal of Psychiatry 51:42–47, 2006
23. Malla AK, Norman RMG, Joober R: First-episode psychosis, early intervention, and outcome: what have we learned? Canadian Journal of Psychiatry 50:881–891, 2005
24. Häfner H, Riecher-Rössler A, Hambrecht M, et al: IRAOS: an instrument for the assessment of onset and early course of schizophrenia. Schizophrenia Research 6:209–223, 1992
25. Fusar-Poli P, Cappucciati M, Rutigliano G, et al: Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. Psychiatry Journal (Epub ahead of print, May 30 2016)
26. Cotter J, Drake RJ, Bucci S, et al: What drives poor functioning in the at-risk mental state? A systematic review. Schizophrenia Research 159:267–277, 2014
27. Scott J, Leboyer M, Hickie I, et al: Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. British Journal of Psychiatry 202:243–245, 2013