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Current Status Specifiers for Patients at Clinical High Risk for Psychosis

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Abstract

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Contributors

All authors contributed to the design of the NAPLS-1. Dr Woods took the lead on defining the current status specifiers, analyzing the data, and writing the first draft. All authors contributed to and approved the final manuscript.

Conflict of interest

Dr. Woods reports that within three years of beginning this work he has received investigator-initiated research funding support from UCB Pharma, Eli Lilly, Janssen, Pfizer, and Bristol-Myers Squibb and has consulted to Otsuka and Schering-Plough. He has also served as an unpaid consultant to DSM-5. Drs. Walsh, Addington, Cadenhead, Seidman, Tarbox, Tsuang, and Walker report no actual or potential conflict of interest. Dr. Cannon reports that within three years of beginning this work he has served as a consultant for Janssen Pharmaceuticals and Eli Lilly. Dr. Cornblatt reports that within three years of beginning this work she has served as a consultant for Lilly, Bristol-Meyers Squibb and Janssen Pharmaceuticals and has received unrestricted educational grants from Janssen. Dr. Heinssen is an employee of the US National Institutes of Health. Dr. Perkins reports that within three years of beginning this work she has received research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Otsuka Pharmaceutical Co. Ltd, Eli Lilly and Co., Janssen Pharmaceutica Products, and Pfizer Inc.; and consulting and educational fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Eli Lilly and Co., Janssen Pharmaceuticals, GlaxoSmithKline, Forest Labs, Pfizer Inc, and Shire. Dr. McGlashan reports that within three years of beginning this work he has received investigator-initiated research funding support from Eli Lilly Company. He has also served as a consultant for Lilly, Pfizer, Solvay/Wyeth, and Roche pharmaceuticals and as an unpaid consultant to DSM-5.

Background—Longitudinal studies of the clinical high risk (CHR) syndrome for psychosis have emphasized the conversion vs non-conversion distinction and thus far have not focused intensively on classification among non-converters. The present study proposes a system for classifying CHR outcomes over time when using the Structured Interview for Psychosis-risk Syndromes and evaluates its validity.

Method—The system for classifying CHR outcomes is referred to as "current status specifiers," with "current" meaning over the month prior to the present evaluation and "specifiers" indicating a set of labels and descriptions of the statuses. Specifiers for four current statuses are described: progression, persistence, partial remission, and full remission. Data from the North American Prodromal Longitudinal Study were employed to test convergent, discriminant, and predictive validity of the current status distinctions.

Results—Validity analyses partly supported current status distinctions. Social and role functioning were more impaired in progressive and persistent than in remitted patients, suggesting a degree of convergent validity. Agreement between CHR current statuses and current statuses for a different diagnostic construct (DSM-IV Major Depression) was poor, suggesting discriminant validity. The proportion converting to psychosis within a year was significantly higher in cases meeting progression criteria than in those meeting persistence criteria and tended to be higher than in those meeting full remission criteria, consistent with a degree of predictive validity.

Discussion—CHR syndrome current status specifiers could offer a potentially valid and useful description of current clinical status among non-converters. Study in additional samples is needed.

Keywords

psychosis; clinical high risk; risk syndrome; current status; course of illness

1. Introduction

A prodromal period before the onset of frank schizophrenia has been recognized for at least a century (Bleuler, 1911; Klosterkotter et al., 2008), and over the past two decades a growing body of work has sought to diagnose a prodromal syndrome prospectively (Fusar-Poli et al., 2013). One approach has been to define clinical high risk (CHR) criteria, also known as at-risk mental state or ultra-high risk or risk syndrome (Schultze-Lutter et al., 2011) criteria. Two structured diagnostic interviews, the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2004) and the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010) have demonstrated reliability and validity (Addington et al., 2007; Fusar-Poli et al., 2012b; Woods et al., 2009; Woods et al., 2010; Yung et al., 2008; Yung et al., 2005).

While CHR criteria consistently have been statistically significant predictors of conversion, it has become more clear over the past decade that the majority of patients meeting the criteria do not go on to become psychotic (Cannon et al., 2008; Fusar-Poli et al., 2012a; Nelson et al., 2013; Ruhrmann et al., 2010). Some of the non-converting patients remain symptomatic over time, and others become symptom-free (Addington et al., 2011). At present, however, existing diagnostic criteria have paid relatively little attention to follow-up classification.

This paper proposes a new classification system for CHR patients when using the SIPS over time. The system is based on diagnostic criteria that establish eligibility for classification and specifiers of current status that may vary over follow-up. Data from the first phase of the North American Prodrome Longitudinal Study (Addington et al., 2007) (NAPLS-1) are used to evaluate the validity of the current status distinctions.

2. Methods

In the term "current status specifiers," "current" refers to the month prior to the present evaluation and "specifiers" to a set of labels and descriptions of possible statuses. Although conversion to psychosis could also be considered a current status, the focus of the present paper is not upon the existing SIPS definition of conversion but on new specifiers of current status for patients who have not converted or who have not converted yet. The proposed current status specifiers are influenced by the severity/psychosis/remission specifiers used for affective disorder diagnoses (American Psychiatric Association, 1987, 1994, 2013) and remission criteria proposed for schizophrenia (van Os et al., 2006).

2.1 Current status specifiers

The SIPS identifies three CHR syndromes: Attenuated Psychotic Symptoms Syndrome (APSS), Brief Intermittent Psychosis Syndrome (BIPS), and Genetic Risk and Deterioration (GRD), all originally articulated by the Melbourne group (Yung et al., 1996b). In previous versions of the SIPS, criteria for each CHR syndrome required recent worsening, and each was scored only as currently present vs not currently present. Different ways of not meeting current worsening criteria (features present but no longer worsening, features no longer present, features never present) were not distinguished.

For each CHR syndrome Figure 1 outlines criteria for four current status specifiers: progression, persistence, partial remission, and full remission. The current status specifiers may be applied to patients meeting syndromal diagnostic criteria, also in Figure 1. The syndromal criteria and the current status specifiers are intended to be used together, at initial evaluation and/or at any follow-up assessment. The syndromal diagnosis would apply across course while the current status could vary (for example: APSS currently progressive, or GRD currently in partial remission).

Figure 1 shows that for APSS and BIPS a CHR diagnosis depends on a history of at least one positive symptom meeting severity, frequency, and attribution criteria. APSS or BIPS progression requires that these criteria be met currently as well as recent worsening: these APSS or BIPS progression criteria are identical to our previously proposed SIPS criteria for APSS and BIPS current presence yes vs no. APSS or BIPS persistence are similar to APSS or BIPS progression in requiring that syndromal criteria be met currently but differ in that worsening criteria cannot. For APSS or BIPS partial remission two pathways were considered appropriate, following the format for DSM affective disorders in partial remission. For the first pathway, no positive symptom can meet severity and attribution criteria, but for no longer than 6 months. For the second pathway, one or more positive symptoms do currently meet severity and attribution criteria but not frequency criteria. Patients meeting criteria for this second route could potentially remain in partial remission

for an indefinite period of time. For APSS or BIPS full remission, no positive symptom has met severity and attribution criteria for longer than 6 months. GRD syndromal and current status criteria are based on indices of genetic risk and changes in global functioning. Criteria for GRD progression differ slightly from our previous criteria for GRD current presence (rationale in supplementary data).

When patients meet criteria for a current status for one CHR syndrome (e.g. GRD partial remission) but also criteria for a different current status for another CHR syndrome (e.g. APSS progression), the overall CHR syndrome current status is defined according to the rule "progression trumps persistence trumps partial remission trumps full remission." The supplementary data include pages from SIPS 5.6 providing detail on how syndromal assessments and current status assessments are scored.

2.2 Subjects

NAPLS-1 methods have been described in detail previously (Addington et al., 2007). All subjects provided written informed consent, and protocols were approved by institutional review boards at each site. Symptomatic subjects from three groups according to the earlier classification (Woods et al., 2009) were eligible for the present analyses if all 5 SIPS positive symptoms were rated for severity either at baseline, 6 months, and 12 months or at 12, 18, and 24 months. Figure 2 shows the flow diagram of eligible subjects and reasons for ineligibility.

2.3 Classification

Eligible subjects were then classified at each timepoint based as closely as possible on the current status specifier scheme shown in Figure 1. NAPLS-1 data, however, were not collected prospectively to map onto this criterion set, and therefore certain criteria either could not be applied or required estimation methods. Early versions of the SIPS did not provide for symptom specific frequency ratings, and therefore symptom frequency data were unavoidably missing for some cases. Simple exclusion of these cases would introduce bias (supplementary data) and so was not the preferred option. To avoid such bias, we placed **s**ymptomatic but **m**issing **f**requency cases into a separate "Smf" category (see Figure 2). We then made use of data from the symptomatic patients who did have frequency ratings (Table S1) to estimate percentages for current status specifiers among the Smf group, as detailed in the supplementary data.

Ratings of symptom causal attribution were not added to the SIPS until after NAPLS-1 data collection ended, and thus these data were never collected and this requirement had to be waived.

Progression for APSS and GRD at follow-up was assessed by direct comparison of ratings to those from one year previously. Evaluation of BIPS progression criteria utilized fields in the SIPS that asked whether positive symptoms had progressed to a 6 in the past 3 months.

2.4 Validity

We investigated the validity of the current status specifiers in three analyses. A convergent validity analysis asked whether social or role functioning differed across current status. The social and role functioning variables (Cornblatt et al., 2007) did not contribute to the CHR syndrome diagnosis or to the current status specifier definitions. A discriminant validity analysis evaluated the degree to which CHR current status was independent from DSM-IV current status specifiers for comorbid major depression. Among comorbidities in CHR patients (Fusar-Poli et al., 2014; Rosen et al., 2006; Salokangas et al., 2012; Woods et al., 2009), major depression is perhaps the most frequent and among the most severe and also is described by established (American Psychiatric Association, 1994, 2013) current status specifiers. Lastly, predictive validity analyses asked whether the rate of conversion to psychosis during a 12-month interval differed by current status at interval start. We chose 12 months as the shortest interval whose outcome did not depend on unmeasured information, such as positive symptom or GAF data before baseline. The starting points of each available 12-month interval were lined up to provide a "snapshot" of the 12-month conversion rate.

2.5 Effects of treatment on conversion or progression after remission

In the NAPLS-1 cohort, some patients received psychotropic medication or psychosocial treatment, either clinically during naturalistic research follow-along or in prospective research trials, as previously described (Cadenhead et al., 2010; Cannon et al., 2008; Walker et al., 2009; Woods et al., 2013). We thus also investigated the extent to which cases converting or meeting progression criteria after having achieved remission could potentially be accounted for by discontinuation of treatment.

2.6 Statistical methods

Analyses were conducted using SPSS, version 19. Convergent validity analyses employed one-way ANOVA, with post-hoc pairwise testing by Student's t-test. Discriminant validity analyses employed Cohen's kappa. Predictive validity analyses utilized Fisher's exact tests.

3. Results

3.1 Availability of data

The NAPLS-1 database contains 624 symptomatic nonpsychotic patients at baseline (Woods et al., 2009). Of these, 435 (70%, see Figure 2) were classifiable according to Figure 1, including 58 who met the criteria for Persistence at baseline. At one year, 172/435 were classifiable (40%) and at two years, 44/172 (26%). The primary reason for inability to classify at baseline was that the information collected did not permit identification of whether CHR had ever been present before baseline. The primary reason at follow-up was the absence of visits (Figure 2). Differences between the present sample and samples in other reports on the NAPLS-1 cohort are discussed in the supplementary data.

3.2 Current status determinations for individual CHR syndromes

Table S2 shows the degree of overlap between current status specifiers for the three CHR syndromes among visits that ended intervals in Figure 2. As in previous studies the large

majority of patients met criteria for APSS. In the relatively few cases where more than one syndrome was present, the current statuses agreed about 40% of the time, with the "trumps rule" coming into play otherwise (supplementary data).

3.3 Validity

Convergent validity—Tables 1 and S3–4 show that social and role functioning both differed across the spectrum of CHR current status specifiers. Pairwise findings were also similar for social and role functioning. For patients with either progressive or persistent status, functioning was significantly lower than for patients in either partial or full remission. Functioning did not differ significantly between progression and persistence statuses or between partial and full remission. Statistical power was <0.80 for partial vs full remission (Table S3).

Discriminant validity—Table 2 shows how current status specifiers for CHR syndrome overlapped with those for DSM-IV Major Depression. Sixty-two percent of cases in a known CHR status did not meet criteria for a major depression diagnosis. If these patients with no major depression diagnosis are not considered, along with the 39 in Table 2 whose major depression was coded as status unspecified (296.20 or 296.30), Table 2 can be collapsed into a 2x2 categorization: either in partial/full remission or not, for each syndrome. Among unremitted CHR cases (n=105), depression was remitted in 58 (55%). Among remitted CHR cases (n=18), depression was not remitted in 4 (22%). Kappa for agreement was 0.10 (less than 0.40 poor (Fleiss, 1981)).

Predictive validity—Table 3 summarizes outcomes of CHR cases by current status at interval start. These same data may be traced in Figure 2. The proportion converting to psychosis was significantly higher in cases meeting progression criteria than in those meeting persistence criteria at interval start and tended to be higher than in those meeting full remission criteria (Table S5). Proportions converting in the other pairwise comparisons did not differ, but statistical power was low (Table S5).

3.4 Effects of treatment on conversion or progression after remission

Table 3 shows that four remitted patients then converted or met criteria for progression over the next year. These outcomes generally did not appear to be accounted for by discontinuation of treatment. Treatment data were complete, and a medication or psychosocial treatment present at remission was discontinued before conversion/progression in only one of these cases.

4. Discussion

This report presents nomenclature and criteria for syndromal diagnosis and current status assessment for clinical high risk (CHR) patients. Data from the NAPLS-1 dataset provide partial support for the validity of the current status designations.

4.1 Validity of the current status definitions

Taken together, the convergent, discriminant, and predictive validity analyses are supportive of the validity of the CHR current status specifiers as defined in Figure 1. These data must be interpreted cautiously, however, because neither the convergent validity nor the predictive validity analyses fully distinguished each current status specifier from all others. The criteria in Figure 1 will need to be applied to additional samples to evaluate validity fully. Persistence was distinguished from progression in the predictive validity analyses (conversion events in Table 3) but not in the convergent validity analysis of functioning (Table 1). The low functioning scores for patients in a persistent CHR status suggest the need for longer follow-up to determine the likelihood of functional improvement in this group. Partial remission was not significantly distinguished from full remission in either analysis, although numerically patients in full remission did show higher functioning scores and lower conversion rates than those in partial remission. The discriminant validity analysis in Table 2, which suggests substantial independence between the course of the CHR syndrome and the course of comorbid major depression, speaks to the validity of the CHR syndrome as a whole in addition to the validity of the current status specifiers.

4.2 Utility of current status specification

The definitions shown in Figure 1 improve upon the SIPS assessment of CHR syndrome in three ways. First, the definitions address a previous limitation with the use of the SIPS. Previously, patients with continuing but no longer progressive symptoms had to be classified as “not currently CHR” whereas now they can be coded “CHR, currently persistent.” There may be applications where the present classification could be used for baseline eligibility determination; for example, recruitment of patients coded as “ CHR, currently in full remission” could be useful as entry criteria for clinical trial designs investigating whether treatments sustain remission. Second, the definitions address ambiguities with the use the term “remission” of CHR syndrome over the past few years (Addington et al., 2011; Schlosser et al., 2012; Simon et al., 2012; Simon and Umbricht, 2010; Velthorst et al., 2011; Ziermans et al., 2011), wherein it has not always been clear whether patients with persistent symptoms qualified as remitted (because they no longer met the previously articulated CHR current presence criteria). Meta-analyses of remission rates (Simon et al., 2013) would be facilitated by consistent definition. In addition, remission from the less common BIPS and GRD syndromes has not previously been addressed in the literature to our knowledge. Third, the current status specifiers provide a richer description of the nonconverting patients. Future studies could determine whether treatments differentially alter rates of continued progression, persistence, or remission as well as conversion rates, and ordinal regression analyses incorporating current statuses may be statistically more powerful in detecting treatment effects than analyses of dichotomous conversion vs non-conversion.

The present data suggest that most remissions are generally stable over the next year (Table 3); however, a few patients did not remain in remission but converted to psychosis or met criteria for progression. Analyses of treatment data suggest that in at least some cases the loss of sustained remission can be unrelated to discontinuation of previous treatment. These observations are consistent with a previously recognized course pattern wherein the original occurrence of progression can sometimes constitute an “outpost syndrome” (Yung and

McGorry, 1996a) followed by remission and then later recurrence of illness. Future studies should focus on the course of remitted patients and on predictors of sustaining remission.

4.3 Limitations

A number of limitations are recognized. The most important limitation is the relative paucity of visits where patients could be classified in persistent, partial remission, or full remission status, and especially the limited number of one-year intervals beginning with those statuses. This limitation applies to the convergent validity analysis in Table 1 and particularly to the predictive validity analyses in Table 3 and led to low statistical power in both analyses (Tables S3 and S5). Larger samples are needed of patients in these current statuses. We underscore that in retrofitting current status classifications to the NAPLS-1 data it was never possible fully to apply the attribution criterion shown in Figure 1, since this criterion was not added to the SIPS formally until after NAPLS-1 data collection ended. Site training in the SIPS did include the understanding that attenuated positive symptoms due to another disorder did not qualify for a CHR syndrome diagnosis, but there are no fields in the NAPLS-1 dataset to document application of this criterion. Another limitation is that symptom frequency ratings were often not present in the NAPLS-1 dataset, due to their introduction into the SIPS with version 4.0 in 2003, while the sites' collection of data occurred between 1998 and 2005. For intervals classifiable at start that required frequency ratings to apply Figure 1 criteria at interval end, the needed frequency ratings were missing 50% of the time (supplementary data). Consequently the follow-up proportions of progression, persistence, and partial remission statuses in Table 3 had partly to be estimated. It also should be emphasized that inter-rater reliability remains to be established.

Lastly, it is not yet clear for how long a diagnosis of CHR remains appropriate after full remission has been achieved and continuously sustained. Future research may permit recommendations for a definition of recovery or for use of a term such as "past history of a CHR diagnosis."

4.4 Implications

Current status distinctions (progression, persistence, partial remission, full remission) for CHR patients appear to be valid and potentially useful. Their application to additional samples may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Addington J, Cadenhead KS, Cannon TD, Cornblatt B, McGlashan TH, Perkins DO, Seidman LJ, Tsuang M, Walker EF, Woods SW, Heinssen R. North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. Schizophr Bull. 2007; 33(3): 665–672. [PubMed: 17255119]

Addington J, Cornblatt B, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang M, Walker EF, Woods SW, Heinssen R. At risk for psychosis: Outcome for false-positives. Am J Psychiatr. 2011; 168(8):800–805. [PubMed: 21498462]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Arlington, VA: American Psychiatric Association; 1987. Revised

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington DC: American Psychiatric Association; 1994.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. Arlington, VA: American Psychiatric Association; 2013.

Bleuler, E. Dementia Praecox or the Group of the Schizophrenias. New York: International Universities Press; 1911.

Cadenhead KS, Addington J, Cannon T, Cornblatt B, McGlashan T, Perkins D, Seidman L, Tsuang M, Walker E, Woods S, Heinssen R. Treatment history in the psychosis prodrome: characteristics of the North American Prodrome Longitudinal Study Cohort. Early Interv Psychiatr. 2010; 4(3):220–226.

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatr. 2008; 65(1):28–37. [PubMed: 18180426]

Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophr Bull. 2007; 33(3):688–702. [PubMed: 17440198]

Fleiss, JL. Statistical Methods for Rates and Proportions. 2. New York: John Wiley & Sons; 1981.

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatr. 2012a; 69(3):220–229. [PubMed: 22393215]

Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkotter J, McGuire P, Yung A. The psychosis high-risk state: A comprehensive state-of-the-art review. Jama Psychiatr. 2013; 70(1):107–120.

Fusar-Poli P, Hobson R, Raduelli M, Balottin U. Reliability and validity of the Comprehensive Assessment of the at Risk Mental State, Italian version (CAARMS-I). Curr Pharm Des. 2012b; 18(4):386–391. [PubMed: 22239569]

Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis. Schizophr Bull. 2014; 40:120–131. [PubMed: 23180756]

Klosterkotter J, Schultze-Lutter F, Ruhrmann S. Kraepelin and psychotic prodromal conditions. Eur Arch Psychiatr Clin Neurosci. 2008; 258:74–84.

McGlashan, TH.; Walsh, BC.; Woods, SW. The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-up. New York: Oxford University Press; 2010.

Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, Broussard C, Simmons M, Foley DL, Brewer WJ, Francey SM, Amminger GP, Thompson A, McGorry PD, Yung AR. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: The PACE 400 Study. Jama Psychiatr. 2013; 70(8):793–802.

Rosen JL, Miller TJ, D'Andrea JT, McGlashan TH, Woods SW. Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. Schizophr Res. 2006; 85(1–3):124–131. [PubMed: 16650735]

Ruhrmann S, Schultze-Lutter F, Salokangas RKR, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkoetter J. Prediction of psychosis in adolescents and young adults at high risk: Results from the Prospective European Prediction of Psychosis Study. Arch Gen Psychiatr. 2010; 67(3):241–251. [PubMed: 20194824]

Salokangas RKR, Ruhrmann S, von Reventlow HG, Heinimaa M, Svirskis T, From T, Luutonen S, Juckel G, Linszen D, Dingemans P, Birchwood M, Patterson P, Schultze-Lutter F, Klosterkoetter J. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: Prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr Res. 2012; 138(2–3):192–197. [PubMed: 22464922]

Schlosser DA, Jacobson S, Chen Q, Sugar CA, Niendam TA, Li G, Bearden CE, Cannon TD. Recovery from an at-risk state: Clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. Schizophr Bull. 2012; 38(6):1225–1233. [PubMed: 21825282]

Schultze-Lutter F, Schimmelmann BG, Ruhrmann S. The near Babylonian speech confusion in early detection of psychosis. Schizophr Bull. 2011; 37(4):653–655. [PubMed: 21558142]

Simon AE, Borgwardt S, Riecher-Rossler A, Velthorst E, de Haan L, Fusar-Poli P. Moving beyond transition outcomes: Meta-analysis of remission rates in individuals at high clinical risk for psychosis. Psychiatr Res. 2013; 209(3):266–272.

Simon AE, Graedel M, Cattapan-Ludewig K, Gruber K, Ballinari P, Roth B, Umbricht D. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. Schizophr Res. 2012; 142(1–3):108–115. [PubMed: 23025995]

Simon AE, Umbricht D. High remission rates from an initial ultra-high risk state for psychosis. Schizophr Res. 2010; 116(2–3):168–172. [PubMed: 19854621]

van Os J, Burns T, Cavallaro R, Leucht S, Peuskens J, Helldin L, Bernardo M, Arango C, Fleischhacker W, Lachaux B, Kane JM. Standardized remission criteria in schizophrenia. Acta Psychiatr Scand. 2006; 113(2):91–95. [PubMed: 16423159]

Velthorst E, Nieman DH, Klaassen RMC, Becker HE, Dingemans PM, Linszen DH, de Haan L. Three-year course of clinical symptomatology in young people at ultra high risk for transition to psychosis. Acta Psychiatr Scand. 2011; 123(1):36–42. [PubMed: 20712825]

Walker EF, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Woods SW, Heinssen R. The relation of antipsychotic and antidepressant medication with baseline symptoms and symptom progression: a naturalistic study of the North American Prodrome Longitudinal Sample. Schizophr Res. 2009; 115(1):50–57. [PubMed: 19709859]

Woods SW, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Mathalon DH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Psychotropic medication use in youth at high risk for psychosis: Comparison of baseline data from two research cohorts 1998–2005 and 2008–2011. Schizophr Res. 2013; 148(1–3):99–104. [PubMed: 23787224]

Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Validity of the prodromal risk syndrome for

psychosis: findings from North American Prodrome Longitudinal Study. Schizophr Bull. 2009; 35:894–908. [PubMed: 19386578]

Woods SW, Walsh BC, Saksa JR, McGlashan TH. The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. Schizophr Res. 2010; 123:199–207. [PubMed: 20832249]

Yung, A.; Phillips, L.; McGorry, PD. Treating Schizophrenia in the Prodromal Phase. London: Taylor & Francis; 2004.

Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996a; 22(2):353–370. [PubMed: 8782291]

Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. Schizophr Bull. 1996b; 22(2):283–303. [PubMed: 8782287]

Yung AR, Nelson B, Stanford C, Simmons MB, Cosgrave EM, Killackey E, Phillips LJ, Bechdolf A, Buckby J, McGorry PD. Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. Schizophr Res. 2008; 105(1–3):10–17. [PubMed: 18765167]

Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J. Mapping the onset of psychosis: The comprehensive assessment of at-risk mental states. Austral N Z J Psychiatr. 2005; 39(11–12):964–971.

Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. Schizophr Res. 2011; 126(1–3):58–64. [PubMed: 21095104]

Term Defined		APSS Syndrome	BIPS Syndrome	GRD Syndrome
Syndromal Diagnosis		Attenuated pos sx ever met criteria for: -severity (rated 3-5 at some time), -frequency (≥ 1x/week the same month), -attribution (not due to other disorder).	Positive sx ever met criteria for: -severity (rated 6 in some month), -frequency (≥ 1x/mo), -attribution (not due to other disorder).	FHx psychosis, or ever SPD. Hx of current or past p
Current Status Specifiers	Progression	≥1 positive sx meets severity, frequency, attribution, and progression (≥1 point more than 12 mos ago) criteria.	≥1 positive sx meets severity, frequency, attribution, and progression (≥1 point more than 3 mos ago) criteria.	GAF meets current pr criteria (≥30% lowe 12 mos ago).
	Persistence	≥1 positive sx meets severity, frequency, and attribution but not progression criteria.	≥1 positive sx meets severity, frequency, and attribution but not progression criteria.	GAF <90% of 12 months prior to first progression.
	Partial Remission	No positive sx have met severity and attribution criteria ≤6 months, OR ≥1 positive sx meet severity and attribution, but not frequency criteria.	No positive sx have met severity and attribution criteria ≤6 months, OR ≥1 positive sx meet severity and attribution, but not frequency criteria.	GAF ≥90% of 12 months prior to first progression, for ≤6 months.
	Full Remission	No positive sx have met severity and attribution criteria >6 months.	No positive sx have met severity and attribution criteria >6 months.	GAF ≥90% of 12 mos prior to first progression, for >6 months.

Figure 1.

Definitions for clinical high risk syndrome and current status specifiers when using the SIPS.

SIPS--Structured Interview for Psychosis-risk Syndromes, APSS--Attenuated Psychotic Symptoms Syndrome, BIPS--Brief Intermittent Psychosis Syndrome, GRD--Genetic Risk and functional Decline, pos--positive, sx--symptoms, FHx--family history of, SPD--schizotypal personality disorder, Hx--history of, GAF--Global Assessment of Functioning.

N.B. When a patient meets criteria for two or more specific CHR syndromes now meets criteria for one at a higher level than another (e.g. both APSS progressive and GRD persistent), the higher level current status is given as the overall CHR syndrome status. To be explicit, “progression trumps persistence trumps partial remission trumps full remission.”

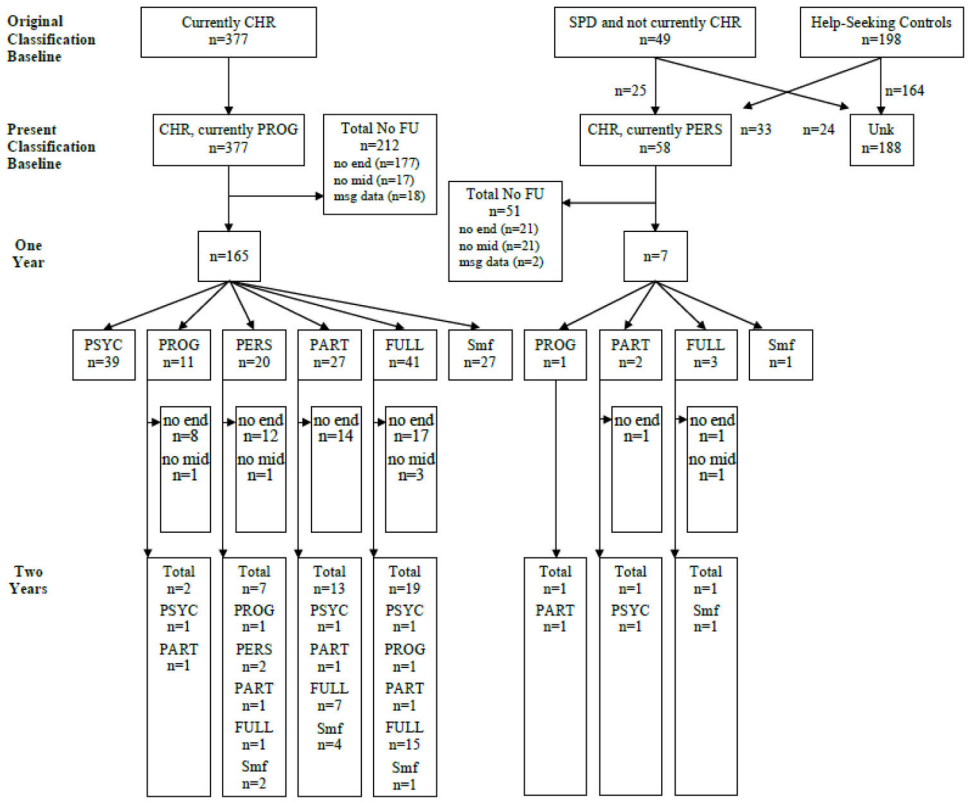

Figure 2.

Subject flow diagram of NAPLS-1 sample in the present analysis.

Classifications shown at baseline with the Structured Interview for Psychosis-risk Syndromes (SIPS) under the original classification scheme and for assessments as per the present paper for syndroinal diagnosis and current status specification, at baseline, one year, and two years.

CHR–clinical high risk. SPD–schizotypal personality disorder. PROG–progressive current status; of CHR syndrome. No FU–no follow-up classification possible, no end–did not have a study visit at the endpoint of the one-year interval, no mid–did not have a study visit at the midpoint of the one-year interval, msg data–study visits occurred but severity data for one or more positive symptoms were missing. PERS–persistent current status of CHR syndrome. Unit–unknown CHR history, PSYCH–transitioned to frank psychosis. PART–partial remission current status of CHR syndrome. FULL–fell remission current status of CHR syndrome. Smf–currently symptomatic but cannot be classified as PROG vs PERS vs PART due to missing symptom frequency data.

Table 1

Comparison of current status specifiers* on social and role functioning.

Specifier Measure	Progression	Persistence	Partial Remission	Full Remission	F	p
Social Functioning	6.17±1.53^{a,b} (390)	5.96±1.41^{c,d} (79)	7.00±1.53^{a,c} (34)	7.21±1.41^{b,d} (65)	12.8	0.000
Role Functioning	6.08±1.71^{a,b} (391)	6.23±1.39^{c,d} (79)	7.15±1.68^{a,c} (34)	7.47±1.28^{b,d} (64)	16.6	0.000

mean±SD (n). Scales range from 1–10, with 10 indicating superior functioning, 7 mild problems, 6 moderate impairment, and 1 extreme impairment.

a-d groups with the same letter differ from each other $p<0.05$

* CHR specifiers and functioning each assessed at the same timepoint. Timepoints included are baseline, 12, or 24 months. Symptomatic patients unclassifiable into a CHR current status due to missing frequency ratings (Smf in Figure 2) not shown.

Table 2

Current status specifiers* for CHR syndrome and DSM-IV Major Depression.

Current status		Major Depression							
		Severe	**Moderate**	**Mild**	**Partial Remission**	**Full Remission**	**Unspecified**	**None**	**Total**
CHR syndrome	Progressive	15 (5%)	18 (6%)	9 (3%)	19 (6%)	34 (11%)	27 (9%)	180 (60%)	302
	Persistent	1 (2%)	4 (7%)	0 (0%)	4 (7%)	1 (2%)	9 (15%)	40 (68%)	59
	Partial Remission	1 (4%)	0 (0%)	0 (0%)	2 (8%)	2 (8%)	2 (8%)	18 (72%)	25
	Full Remission	2 (5%)	1 (2%)	0 (0%)	6 (14%)	4 (9%)	1 (2%)	29 (67%)	43
	Total	19	23	9	31	41	39	267	429

*CHR syndrome and major depression each assessed at the same timepoint. Timepoints included are baseline, 12, or 24 months. Symptomatic patients unclassifiable into a CHR current status due to missing frequency ratings (Smf in Figure 2) not shown.

Table 3

Twelve-month outcomes by CHR syndrome current status at interval start*.

Outcome Interval Start	Psychosis	Progression	Persistence	Partial Remission	Full Remission	Smf [a]	Total
Progression	40 (24%)	11 (10%)[b]	20 (23%)[b]	29 (19%)[b]	41 (24%)	27	168
Persistence	0 (0%)	2 (26%)[b]	2 (21%)[b]	3 (24%)[b]	4 (29%)	3	14
Partial Remission	2 (14%)	0 (24%)[b]	0 (0%)[b]	1 (12%)[b]	7 (50%)	4	14
Full Remission	1 (5%)	1 (13%)[b]	0 (0%)[b]	1 (7%)[b]	15 (75%)	2	20
Total	43	14	22	34	67	36	216

*interval start either at baseline or at 12 months.

[a]Smf -- patients with one or more positive symptoms in the CHR syndrome severity range, but who could not be classified because of missing symptom frequency ratings

[b]estimated percentages, calculated by estimating classifications for Smf cases based on results in symptomatic cases whose frequency ratings were not missing (please see Table S1 and estimation methods in data supplement).