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Symptom trajectories and psychosis onset in a clinical high-risk cohort: the relevance of subthreshold thought disorder

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Abstract

Background—Prior studies have implicated baseline positive and negative symptoms as predictors of psychosis onset among individuals at clinical high risk (CHR), but none have evaluated latent trajectories of symptoms over time. This study evaluated the dynamic evolution of symptoms leading to psychosis onset in a CHR cohort.

Method—100 CHR participants were assessed quarterly for up to 2.5 years. Latent trajectory analysis was used to identify patterns of symptom change. Logistic and proportional hazards

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Contributors

Jordan DeVlyder developed the hypotheses and analyses to evaluate trajectories of symptoms in the CHR cohort, conducted the literature review, and wrote a series of drafts, which were reviewed and edited by the other authors. Felix Muchomba conducted the trajectory analyses, provided general statistical consultation, and reviewed and edited drafts. Kelly Gill and Shelly Ben-David collected and cleaned the data and managed the dataset. Deborah Walder and Dolores Malaspina contributed to drafts in terms of expertise on psychosis risk. Cheryl Corcoran was the director of the cohort study and designed the research methods; she oversaw the ascertainment and characterization of CHR patients, leading consensus on SIPS/SOPS ratings, and did primary editing of successive drafts.

Conflict of Interest

None.

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models were employed to evaluate the predictive value for psychosis onset of baseline symptoms and symptom trajectories.

Results—Transition rate to psychosis was 26%. Disorganized communication (i.e., subthreshold thought disorder) presented an increased hazard for psychosis onset, both at baseline (Hazard Ratio (95% CI) = 1.4 (1.1–1.9)) and as a trajectory of high persistent disorganized communication (Hazard Ratio (95% CI) = 2.2 (1.0–4.9)). Interval clinical data did not improve the predictive value of baseline symptoms for psychosis onset.

Conclusions—High baseline disorganized communication evident at ascertainment tended to persist and lead to psychosis onset, consistent with prior behavioral and speech analysis studies in similar cohorts. Remediation of language dysfunction therefore may be a candidate strategy for preventive intervention.

Keywords

schizophrenia; disorganized communication; longitudinal; latent trajectory analysis; clinical high risk; ultra high risk

1. Introduction

The clinical high-risk (CHR) state for psychosis is characterized by attenuated psychotic symptoms, i.e. subthreshold delusions (unusual thought content, suspiciousness, grandiosity), subthreshold hallucinations (perceptual disturbances) and subthreshold thought disorder (disorganized communication) (Miller et al., 2003). Individuals who meet CHR criteria also have profound negative symptoms, related to their poor function (Corcoran et al., 2011). Prior large ($N > 100$) CHR cohort studies have examined the predictive value of positive symptoms obtained at ascertainment for psychosis onset within 1–2 years (~15–25%), finding baseline severity of subthreshold thought disorder and subthreshold delusions, and variably negative symptoms, to be associated with later psychosis onset (Cannon et al., 2008; Demjaha et al., 2012; Lemos-Giraldez et al., 2009; Nelson et al., 2013; Ruhrmann et al., 2010).

The clinical high-risk state, however, is likely dynamic over time, and interval data may be informative in quantifying risk for psychosis outcome. As yet, two research groups have examined interval clinical data, finding correlations of symptoms with contemporaneous transition to psychotic disorder. One study ($N = 138$) assessed symptoms and potential psychosis onset at baseline, six months, and one year in CHR participants, finding that persistent negative symptoms were associated with the development of psychosis (15%) (Piskulic et al., 2012). Another study ($N = 61$) assessed symptoms and potential psychosis onset at baseline, one year and three years, finding that consistently elevated positive and negative symptoms were present at all three time points among CHR participants who developed psychosis (Lemos-Giraldez et al., 2009). We build on these prior studies, which had three assessment points, by increasing the number of assessments (quarterly for up to 2.5 years) in order to assess if there are heterogeneous trajectories of different “prodromal” symptoms (Fusar-Poli et al., 2014) associated with psychosis outcome.

For data analyses, we used latent trajectory analysis, which offers the opportunity to use interval clinical data between baseline characterization and psychosis onset (or censoring) to examine symptom trajectories as potential predictors of psychosis onset, i.e. latent groups that vary qualitatively by pattern of symptom change (Jones et al., 2001). For more trait-like symptoms of schizophrenia, such as thought disorder, latent trajectory analysis can determine whether there is any added predictive value of trajectories beyond that of baseline severity. In psychiatry, latent trajectory analyses have been used to evaluate the patterns of symptoms in autism onset (N = 52) (Ozonoff et al., 2011), in disparate types of mood episodes in bipolar disorder (N= 118) (M'Bailara et al., 2013), and in response to antipsychotic medications in first-episode psychosis patients (N = 161) (Pelayo-Teran et al., 2014).

Latent class cluster analysis has been used to identify baseline negative symptoms and baseline functional impairment as predictive of psychosis onset (N = 318) (Valmaggia et al., 2013). Latent trajectory analysis, however, has not yet been utilized previously in CHR cohorts. Herein, we evaluated prodromal symptom trajectories in CHR participants assessed on a quarterly basis for up to 30 months until psychosis onset or censoring, to assess the predictive value of clinical trajectories for psychosis. It was hypothesized that latent symptom trajectories exist that have predictive value for psychosis outcome, including time to onset.

2. Experimental/Materials and methods

2.1 Participants

This prospective CHR cohort study was ascertained from 2004 through 2012 at the New York State Psychiatric Institute at Columbia University Medical Center. Participants were 100 English-speaking, help-seeking youths between the ages of 12 and 30 years (at study entry) who were referred from schools and clinicians, or self-referred through the research program website, and who were ascertained as at clinical high-risk for using the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS; (Miller et al., 2003)). Exclusion criteria included history of threshold psychosis or Axis I psychotic disorder, risk of harm to self or others incommensurate with outpatient care, any major medical or neurological disorder, and IQ < 70. Additionally, attenuated positive symptoms could not have occurred solely in the context of substance use or withdrawal, or have been better accounted for by another Axis I disorder (i.e. a mood disorder). All adult participants provided written informed consent; participants under the age of 18 provided written assent, with written informed consent provided by a parent. This study was approved by the Institutional Review Board at the New York State Psychiatric Institute at Columbia University.

Of note, participants were assessed quarterly in person for up to 2½ years (defined specifically as fewer than or equal to 958 days, or 30 months + 1.5 month acceptable window for the final assessment), or until time of transition to psychosis. For those participants who did not develop psychosis or complete the full 2½ years of assessments, their longitudinal symptom data were considered censored for survival analyses with their

last in-person interview, but their outcome with respect to transition by 2½ years was assessed through telephone interview, for the purposes of logistic regression analyses.

2.2 Measures

Demographic information (self-reported age, gender, ethnicity, and education/employment status) was recorded at time of enrollment in the study, as was the use of medications (separate dichotomous variables indicating yes/no for use of antidepressants, yes/no for use of antipsychotics) and cannabis use (yes/no, determined using timeline follow-back procedures for the prior month). The use of other medications and other substances was reported too infrequently for consideration in data analyses.

The SIPS/SOPS was used for ascertainment, and for ratings of prodromal symptoms at baseline and then quarterly for up to 2.5 years, with transition to psychosis determined using its “presence of psychosis” criteria (at least one positive symptom at threshold level (i.e. rating = 6) present several times per week for one month, or for a full day if disorganizing or dangerous). The research design of quarterly clinical ratings was established to characterize symptom trajectories toward psychosis onset. The SIPS/SOPS was administered by trained masters-level clinicians, and ratings were achieved by consensus with the senior author (CMC), who was certified multiple times in its administration by investigators at Yale University, and who has maintained excellent inter-rater reliability with other clinical high-risk programs (intraclass correlation coefficients (ICCs) >0.70 for individual scale items and 1.00 for syndrome ratings).

2.3 Data analyses

Demographics and baseline use of medications/cannabis were evaluated for association with transition to psychosis, using Student t-tests, χ^2 analyses and proportional hazards models; any identified as such were included as covariates in further analyses. Stepwise logistic regression and Cox proportional hazards models, with forward selection based on likelihood-ratio estimates, were then used to evaluate the association of any baseline positive symptoms with psychosis transition (yes/no and time to onset, respectively), as well as the predictive value of the sums of both positive and negative symptom scores. Odds ratios (OR) and hazard ratios (HR), with 95% confidence intervals (CI), were calculated using logistic regression and Cox regression analyses, respectively. Alpha (two-tailed) was set at 0.05 for all analyses.

Positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were calculated for each of the baseline variables that were significantly associated with psychosis onset. Baseline symptom measures which presented a statistically significant hazard for psychosis onset were evaluated serially as dichotomous variables (i.e. low/high) divided at each possible score (from 1 through 5) in order to determine the optimal cutpoint to maximize the area under curve (AUC) for receiver operator characteristic (ROC) curves. The Youden index was calculated as the maximal value for sensitivity + specificity – 1 (Ruopp et al., 2008) at this optimal cutpoint.

Trajectory analyses were used to identify clusters of participants following similar trajectories in symptoms over time using the “TRAJ” module of STATA (Jones et al., 2001). First, trajectory analyses were conducted for each symptom item that at baseline presented a statistically significant hazard for psychosis onset, with resulting trajectories evaluated for their own predictive power. Trajectories were fit using unadjusted censored normal models to account for clustering of scores at the scales’ minima and maxima. The optimal number of trajectory groups and shape of each trajectory was selected using the Bayesian Information Criterion (BIC) (Schwarz, 1978), which penalizes complex models and thus attains a balance between model parsimony and fit to the data. Allowing for more than five trajectory groups did not improve any of the models and thus only models with five or fewer trajectory groups were considered. Additionally, the highest order polynomial considered for each trajectory was the cubic polynomial since higher order polynomials did not significantly improve model fit. All terms were significant with alpha set at 0.05 in the BIC-selected models. For exploratory analyses, STATA TRAJ was also used to examine trajectories for sum scores for positive and negative symptoms (Hawkins et al., 2004), and also for each SIPS/SOPS item.

Symptom trajectories evaluated for prediction of psychosis were also compared in terms of demographics and baseline use of medication/substances, which if significantly different, were included in tests of association with psychosis onset and time to onset. Symptom trajectories were tested for association with psychosis onset using χ^2 -square tests, with alpha set at 0.05, with identified trajectories then evaluated in terms of sensitivity, specificity, and positive and negative predictive value, with the Youden Index reported for the optimal trajectory (Ruopp et al., 2008). Survival analyses were done for these same symptom trajectories using Kaplan-Meier analysis, with differential survival determined using the log-rank test, whereas hazard ratios, with 95% confidence intervals, were calculated using Cox proportional hazards models.

3. Results

3.1 Baseline predictors

The cohort was predominantly male (76%) and ethnically diverse, with low levels of baseline medication and substance use (Table 1). Twenty-six of the 100 participants transitioned to psychosis, primarily schizophrenia or schizoaffective disorder (> 90%), during the 30-month follow-up period, with mean (standard error) survival = 729.8 (39.0) days. In forward stepwise regression with all demographic and baseline clinical variables (individual positive and negative symptoms) entered as predictors, only disorganized communication (i.e., subthreshold thought disorder) was related to increased risk for psychosis, Wald $\chi^2_{1df} = 4.83$, $p = 0.03$, Odds Ratio (95% CI) = 1.43 (1.04–1.97), and to shorter time to psychosis onset, Wald $\chi^2_{1df} = 6.80$, $p = 0.009$, Hazard Ratio (95% CI) = 1.43 (1.09–1.87) (Table 1). Baseline disorganized communication was significantly predictive of transition when dichotomized using either 2, 3 or 4 as the cut-off scores, with increasing PPV and specificity for higher cut-off scores and greater NPV and sensitivity for lower cut-off scores (Table 2). Visual inspection of the ROC curve (AUC = 0.64, SE = 0.06), which bows towards optimal sensitivity and specificity in the 2 through 4 range, supports the use of

these cutoff values in order to maximize the utility of this item in predicting psychosis onset (Figure 1). The Youden Index (maximal value for sensitivity + specificity – 1) (Ruopp et al., 2008) was .24 with the optimal cutpoint of a score of 3 for baseline disorganized communication.

3.2 Trajectory analyses

Given the predictive value for psychosis onset of baseline disorganized communication, we next conducted trajectory analyses to determine if the pattern of expression over time for disorganized communication added to its predictive value beyond baseline severity. We identified four trajectory groups for disorganized communication (Figure 2); these four trajectories did not vary on demographic features, education, employment, substance use, or medications. The trajectory describing high persistent disorganized communication had a transition rate to psychosis of 34.1%, compared with 28.6%, 20.0%, and 15.8% for the other trajectories (in descending order of baseline severity of disorganized communication).

The sensitivity and specificity for this trajectory of high persistent disorganized communication in terms of psychosis risk was comparable to that determined by a cutoff of 3 for the baseline value of high disorganized communication (Table 2), with a slightly lower Youden Index = .19 (vs. .24). Notably, the group with baseline disorganized communication scores of 3 or greater (i.e. 3+) largely overlapped with the persistently elevated trajectory group for disorganized communication (37/44 of members (84.1%) of each group overlapped, $\chi^2_{1df} = 53.3, p < 0.001$). Further, this trajectory of high persistent disorganized communication was associated with a shorter time to onset of psychosis (Figure 3), mean survival (standard error) = 652.4 (63.8) days vs. 788.7 (46.9) for the combined group of the other three trajectories, and Hazard Ratio (95% CI) = 2.23 (1.01–4.93), log-rank $\chi^2_{1df} = 4.2, p = 0.04$, with a trend for prediction of psychosis in bivariate analysis $\chi^2_{1df} = 2.67, p = 0.10$. Of note, the mean(se) change in disorganized communication from baseline to last evaluation was small at –0.33 (0.11) for the full cohort, and was independent of psychosis outcome.

Exploratory trajectory analyses of sums for positive and negative symptom scores yielded two and four trajectories, respectively (supplementary figure, online), none of which were associated with risk for psychosis onset or time to psychosis onset, using χ^2 analyses (total positive symptom score: $\chi^2_{1df} = 0.3, p = 0.58$; total negative symptom score: $\chi^2_{3df} = 3.6, p = 0.31$) or Kaplan-Meier analyses (total positive symptom score: log rank $\chi^2_{1df} = 0.0, p = 0.93$; total negative symptom score: log-rank $\chi^2_{3df} = 1.5, p = 0.69$). Exploratory trajectory analyses for all SIPS/SOPS items also did not yield any trajectories associated with risk for psychosis or time to psychosis onset (data not shown).

4. Discussion

In the present study, baseline severity of subthreshold thought disorder, indicated by the SIPS/SOPS symptom of “disorganized communication,” was associated with transition to psychosis, primarily in the schizophrenia spectrum, consistent with prior studies in CHR cohorts (Bearden et al., 2011; Cannon et al., 2008; Demjaha et al., 2012; Haroun et al., 2006; Klosterkotter et al., 2001; Nelson et al., 2013; Ruhrmann et al., 2010). No other

positive or negative symptom or subscale scores were predictive of psychosis onset in this cohort. Further, latent trajectory analysis demonstrated that sustained elevated disorganized communication also predicted psychosis outcome, primarily in the schizophrenia spectrum, as well as time to onset. However, there was significant overlap between this trajectory group and the subcohort who had elevated scores for disorganized communication at baseline. In fact, the predictive power (i.e. Youden Index = maximal sensitivity + specificity - 1) for the trajectory of persistent disorganized communication (Youden Index = .19) was slightly less than that of baseline symptoms, in both this cohort (Youden Index = .24) and in similar risk cohorts (i.e. Youden Index = .25) in North America (Cannon et al., 2008). Thus, there does not seem to be added benefit or utility in conducting frequent (i.e. quarterly) comprehensive assessments in a clinical high-risk cohort for predicting eventual psychosis outcome.

Overall, clinically relevant subthreshold thought disorder evident at ascertainment in high-risk participants tended to persist and eventually lead to psychosis onset, primarily schizophrenia. These data support the concept of disorganized communication as a potential endophenotype or stable trait marker for schizophrenia risk, consistent with the finding that disorganized communication aggregates in family members of individuals with schizophrenia (Levy et al., 2010) and predicts psychosis onset also in genetic high-risk individuals (Ott et al., 2002). Of note, the relevance of subthreshold thought disorder for emergent schizophrenia and related psychotic disorders is evident also from studies of 1) speech analysis, using audio recordings and transcripts, in both clinical high risk (Bearden et al., 2011) and genetic high risk (Gooding et al., 2012; Gooding et al., 2013) cohorts; and 2) studies of speech illusion (the tendency to find spurious meaning in the noise of overlapping speech), which is increased in those CHR participants who go on to develop psychosis (Hoffman et al., 2007).

The specific neural correlates of disorganized communication have not yet been identified among at-risk participants, though as a *forme fruste* of thought disorder, it would be expected to be related to pathology in the left superior temporal gyrus, including reduction in its gray matter volume (Barta et al., 1997; Menon et al., 1995; Sans-Sansa et al., 2013; Shenton et al., 1992; Weinstein et al., 2007) and in its functional activity (Kircher et al., 2001; Sans-Sansa et al., 2013; Weinstein et al., 2007). The left superior temporal gyrus is a biologically plausible neural substrate for disorganized communication as it is critical for language comprehension and production. As dopamine antagonists reverse volume loss in the superior temporal gyrus in first-episode schizophrenia (Keshavan et al., 1998), they might have efficacy in treating disorganized communication and preventing psychosis onset in CHR participants; however, their utility in at-risk cohorts has been limited by side effects and subsequent noncompliance and dropout (McGorry et al., 2009). Remediation strategies to improve communication in CHR participants have not yet been evaluated.

Neither baseline negative symptoms nor a trajectory of negative symptoms was associated with hazard or risk for psychosis onset in the current study. Disparate results across studies may be related to differences in methodology. Prior studies which found baseline negative symptoms to be predictive of psychosis onset (Demjaha et al., 2012; Nelson et al., 2013; Riecher-Rossler et al., 2009; Valmaggia et al., 2013; Velthorst et al., 2009; Yung et al.,

2005) generally used alternative scales, specifically the Comprehensive Assessment of At-Risk Mental States (Yung et al., 2005) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1982). Prior studies that used the SIPS/SOPS, as we did, have generally not found negative symptoms to be significantly predictive of psychosis onset (Cannon et al., 2008; Haroun et al., 2006; Lemos-Giraldez et al., 2009; Riecher-Rossler et al., 2009; Ruhrmann et al., 2010; Walder et al., 2013) (but see (Piskulic et al., 2012)). Disparate results from prior studies may also be related to differences in ascertainment, and resultant cohort differences, as our sample had prevalent schizophrenia outcome, and greater severity of negative symptoms (Corcoran et al., 2011) than the prior study that found SIPS negative symptoms to be predictive of psychosis onset (Piskulic et al., 2012).

Limitations of the current study include a reliance solely on behavioral measures, specifically clinician ratings of subjective symptoms and observable behavioral signs, with only one measure of negative symptoms used. Nonetheless, symptom ratings were conducted on a longitudinal basis, with frequent assessments in a cohort enriched with cases of emergent schizophrenia and related psychotic disorders. Also, the cohort size was modest (i.e. $N = 100$), which may increase risk for Type 2 error, though it falls within the range (i.e. $N = 52-161$) of cohort sizes in prior studies that evaluated trajectories of symptoms in autism, bipolar disorder and psychosis (M'Bailara et al., 2013; Ozonoff et al., 2011; Pelayo-Teran et al., 2014). Future studies including longitudinal assay of structural and functional integrity of the left superior temporal gyrus and its connectivity with other nodes relevant to language, as well as analysis of speech transcripts (Bearden et al., 2011; Gooding et al., 2012; Gooding et al., 2013) and speech interpretation (Hoffman et al., 2007), may carry added benefit. In addition, therapeutics beyond dopamine antagonists, that similarly target the superior temporal gyrus and related neuroanatomic regions (such as noninvasive brain stimulation and/or language-based remediation strategies) may also be considered in conjunction with putative neuroimaging and/or speech analysis biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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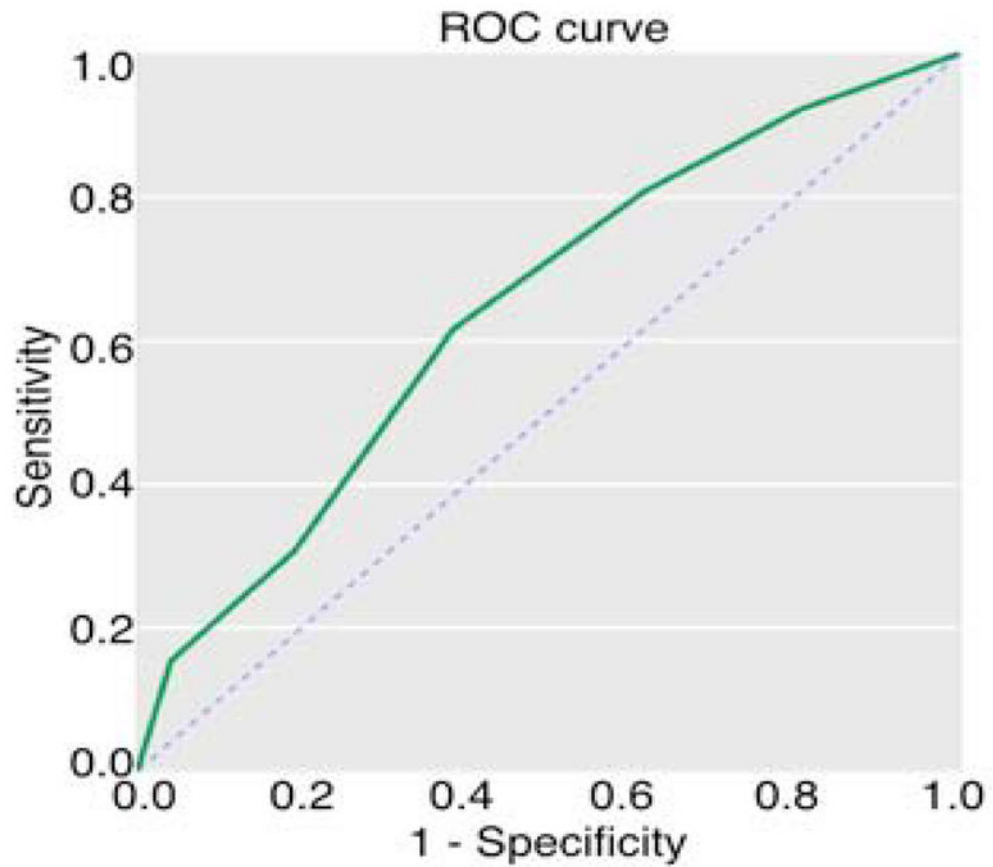


Figure 1. Baseline disorganized communication and psychosis onset. Receiver operator characteristic (ROC) is indicated by the solid black line, plotted as sensitivity (y-axis) versus 1-specificity (x-axis). The dashed line indicates the line of no-discrimination.

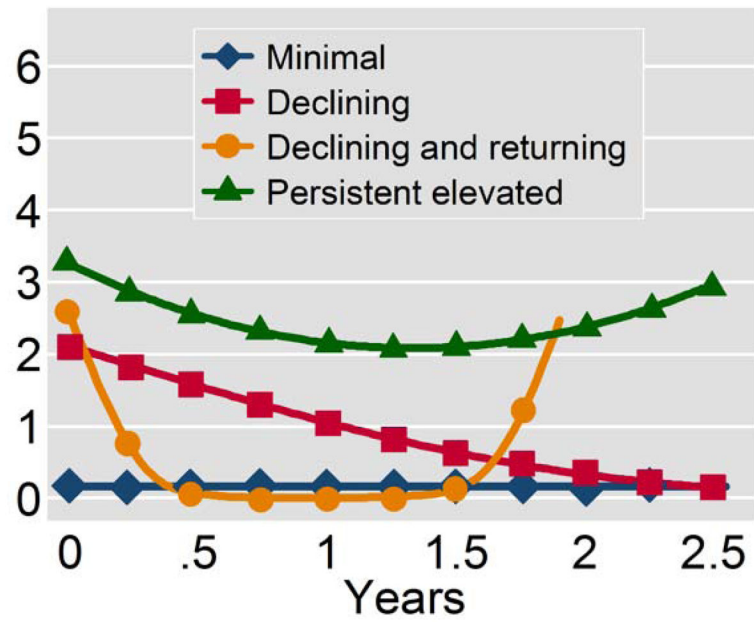


Figure 2. Latent trajectories of disorganized communication (SOPS) over the course of follow-up. Time (years) is presented on the x-axis and symptom severity (Scale of Prodromal Symptoms disorganized communication score) on the y-axis. Curves were derived from fitting cubic splines to trajectory model estimates.

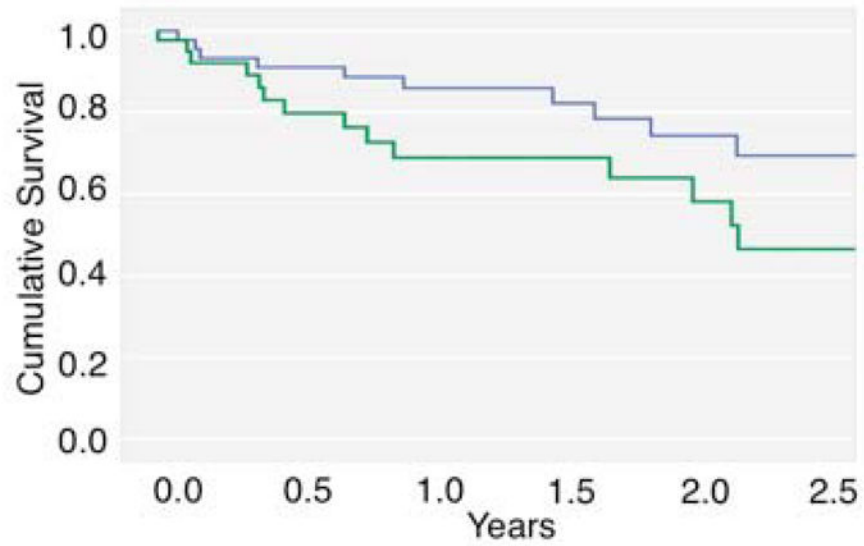


Figure 3. Survival (in years) plotted as a function of disorganized communication trajectory group. The thick black line indicates the persistently elevated symptom group and the thin gray line indicates the remaining three groups.

Table 1

Demographics and baseline clinical characteristics

	Total CHR N =100	CHR+ N = 26	CHR– N = 74
Demographics			
	Mean (SD)	Mean (SD)	Mean (SD)
Age (mean (SD))	20.1 (3.8)	20.0 (3.9)	20.1 (3.8)
	N/%	N (%)	N (%)
Male	76 (76)	21 (81)	55 (74)
Ethnicity (self-reported) ¹			
Caucasian	43 (43)	8 (31)	35 (47)
Latino	32 (32)	9 (35)	23 (31)
African-American	13 (13)	4 (15)	9 (12)
Asian-American	9 (9)	4 (15)	5 (7)
More than one	3 (3)	1 (4)	2 (3)
Full time employment/education	63 (63)	13 (50)	50 (68)
Antipsychotic use at baseline	14 (14)	4 (15)	10 (14)
Antidepressant use at baseline	22 (22)	4 (15)	18 (24)
Cannabis use	23 (23)	6 (23)	17 (23)
Symptoms			
	Mean (SD)	Mean (SD)	Mean (SD)
Positive symptoms (SIPS/SOPS)			
Total	13.0 (4.5)	13.5 (4.9)	12.8 (4.4)
Unusual thought content	3.5 (1.3)	3.7 (1.4)	3.4 (1.2)
Suspiciousness	3.0 (1.4)	3.0 (1.5)	3.0 (1.5)
Grandiosity	1.7 (1.6)	1.3 (1.7)	1.9 (1.5)
Perceptual abnormalities	2.6 (1.6)	2.7 (1.9)	2.6 (1.5)
Disorganized communication *	2.2 (1.5)	2.8 (1.5)	2.0 (1.5)
Negative symptoms (SIPS/SOPS)			
Total	13.8 (6.6)	15.4 (7.4)	13.3 (6.3)
Social isolation and withdrawal	3.2 (1.8)	3.7 (1.8)	3.0 (1.8)
Avolition	2.7 (1.7)	2.8 (1.6)	2.7 (1.8)
Decreased expression of emotion	1.5 (1.6)	1.8 (1.8)	1.4 (1.6)
Decreased experience of emotion	1.6 (1.5)	1.8 (1.6)	1.5 (1.5)
Decreased ideational richness	1.2 (1.4)	1.4 (1.5)	1.1 (1.4)
Deterioration in role function	3.6 (1.8)	3.9 (1.7)	3.5 (1.9)

Note: CHR+ are clinical high-risk patients who developed psychosis and CHR– are clinical high-risk patients who did not develop psychosis, within 2.5 years following baseline assessment.

* indicates significant in stepwise logistic and Cox regression tests, $p < 0.05$, two-tailed.

¹ Ethnic differences in risk for psychosis were tested by comparing ethnic minority to Caucasian respondents, due to limited statistical power when considering each ethnic group separately.

Table 2

Disorganized communication as a predictor of psychosis onset

	<i>n</i>	Survival		Binomial classification		
		HR (95% CI)	PPV	NPV	Sensitivity	Specificity
Baseline						
Disorganized communication, 1+	83	2.15 (0.51–9.09)	.29	.88	.92	.19
Disorganized communication, 2+	66	2.73 (1.03–7.27)	.33	.85	.81	.38
Disorganized communication, 3+	44	2.63 (1.18–5.85)	.36	.82	.62	.62
Disorganized communication, 4+	22	2.43 (1.04–5.69)	.36	.77	.31	.81
Disorganized communication, 5+	7	2.47 (0.84–7.27)	.57	.76	.15	.96
Trajectories						
Disorganized communication, elevated	44	2.23 (1.01–4.93)	.34	.80	.58	.61

Note: Bold indicates significant hazard ratio by Cox regression, $p < 0.05$.

PPV = positive predictive value

NPV = negative predictive value