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Baseline Psychopathology and Relationship to Longitudinal Functional Outcome in Attenuated and Early First Episode Psychosis

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Abstract

Background: As efforts intensify to intervene early among those at risk for psychosis, examination of the relationship between presenting psychopathology and long-term functional outcome may guide treatment decision-making and offer a means to prevent or reduce chronic disability.

Methods: Data were collected through the Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP), a multisite national trial testing the efficacy of an early intervention for youth at risk of developing psychosis. Participants were followed prospectively and completed comprehensive evaluations at 6, 12, and 24 months, including the Structured Interview for Prodromal Syndromes (SIPS) and the Global Social and Role Functioning Scales. The present analyses included 327 participants and examined the relationships between baseline symptoms and longitudinal global social and role functioning using a linear mixed modeling approach.

Results: Higher baseline negative symptoms and deteriorated thought process predicted worse social and role functioning in the follow-up period. The effect of negative symptoms on social functioning, however, was moderated by positive symptoms, and the relationship between positive

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symptoms and social functioning changed over time. Baseline positive symptoms, distress, and level of symptom severity were not predictors of either social or role functioning.

Conclusions: Baseline negative symptoms and thought disorder appear to predict functional outcome for up to two years among adolescents and young adults at risk for psychosis. Developing effective interventions to target these symptoms may be critical to promote functional recovery among those experiencing attenuated symptoms or a first episode of psychosis.

Keywords

clinical high risk; attenuated psychosis; positive symptoms; negative symptoms; functioning

1. Introduction

Given the chronic disability and poor functional outcome often associated with schizophrenia and other psychotic disorders, much attention has shifted in recent years to early detection and intervention among those at risk for psychosis. Originally conceptualized as a 'prodromal' phase of illness, current terminology describes individuals as "clinical high risk" (CHR), "ultra-high risk" (UHR) or "at risk mental state" (ARMS), all essentially referring to the same condition. Although 10–35% of people with the risk syndrome go on to develop full psychosis within 2 to 2 ½ years, conversion rates continue to increase linearly over lengthier periods (Cannon et al., 2008; Fusar-Poli et al., 2012; Nelson et al., 2013). Worldwide efforts have focused on developing an evidence base for a variety of interventions for adolescents and young adults at risk for or following a first episode of psychosis. Family-aided Community Treatment (FACT) is one such intervention for CHR individuals, while Coordinated Specialty Care (CSC) is intended for individuals experiencing a first episode of psychosis. These programs are team-based, collaborative, and recovery-oriented approaches that typically involve intensive case management, family psychoeducation, individual or group psychotherapy, supported employment and education, and selective antipsychotic treatment. In the United States, the Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP) found positive effects for a broad range of symptoms and global outcomes for FACT (McFarlane et al., 2015). Similarly, the NIMH Recovery After an Initial Schizophrenia Episode (RAISE) research initiative determined that comprehensive care improved some aspects of functional and clinical outcomes over two years, with more pronounced effects among individuals with a shorter duration of untreated psychosis (Kane et al., 2016). Therefore, with increasing recognition of the benefit of these types of programs, thorough examination of the relationships between baseline presenting psychopathology and longitudinal functional outcome may help refine treatment decision-making and offer a means to prevent or reduce chronic disability.

Among individuals identified as CHR, some evidence suggests that negative and disorganized symptoms are associated with functional outcome. For example, Meyer and colleagues (2014) found that negative symptoms mediated the relationship between neurocognition and social and role functioning at baseline and 12-month follow-up among CHR individuals in the first phase of the North American Prodrome Longitudinal Study. Similarly, a 2015 study demonstrated that negative symptom severity was uniquely predictive of social functioning, beyond depression/anxiety and neurocognition (Schlosser et

al., 2015). In addition, both duration and severity of negative symptoms at baseline have been found to significantly predict social outcome (Carrión et al., 2016). Furthermore, Yung and colleagues recently reported that persistent negative symptoms were associated with poorer psychosocial functioning over a lengthy follow-up period, regardless of transition to psychosis (Yung et al., 2018). Regarding disorganized symptoms, a 2014 study concluded that disorganized symptoms were highly predictive of functional outcome over a 6-year follow-up interval (Ziermans et al., 2014). Disorganized symptoms at baseline also predicted social functioning in another CHR sample (Carrión et al., 2013).

The literature on the effect of positive symptoms on functioning among CHR individuals, however, is inconsistent. Although the presence of attenuated positive symptoms is a main criterion for CHR classification, and logically predicts conversion to psychosis as a clinical outcome, several studies have found that positive symptoms are not strongly or significantly predictive of functional outcome (Carrión et al., 2016; Meyer et al., 2014; Ziermans et al., 2014). Other research suggests, though, that those with more severe positive symptoms at baseline take considerably longer to achieve both symptomatic and functional remission (Lee et al., 2014). It is possible that the effect of positive symptoms on outcome changes over the course of illness or interacts with other symptom dimensions; thus, relationships with outcome cannot be readily revealed by examining its main effect only, as has been the case in previous studies.

While these studies provide useful preliminary information regarding the effect of baseline symptom severity on functional outcome, many were limited by small sample sizes and either narrow measurement of functioning (e.g., examining only social functioning) or use of a global functioning scale that combines symptom-based information with functional status, thereby confounding clinical and functional data. To address some of these limitations, the present study included a larger sample of individuals at varying levels of risk for developing psychosis who were followed longitudinally for up to two years. Specifically, the sample included those with psychosis-like experiences or functional decline, individuals meeting standard criteria of Psychosis-Risk Syndromes, and individuals in the earliest phases of onset of frank psychosis. We tested four empirically derived symptom factors at baseline as predictors of functional outcome, which was separately assessed for social and role functioning (apart from clinical symptom severity). This study also used linear mixed modeling, a type of regression useful for longitudinal data in which observations are not independent. This approach allows for the examination of whether predictors interact with one another and if their predictive value changes over time. Overall, this large sample, longitudinal study aimed to add to the limited existing evidence base by focusing on symptomatic predictors of functional outcome among CHR individuals, rather than conversion to psychosis. Achieving a better understanding of the long-term functional consequences of presenting symptomatology may allow for more precise allocation of treatment resources at service entry, enhance a personalized medicine approach, and guide the discovery of the relevant neurobiology influencing both symptoms and functioning.

We hypothesized that greater baseline negative symptoms and thought disorganization would significantly predict worse functional outcome. We also conducted exploratory analyses based on the literature in schizophrenia suggesting that the relationship between

negative symptoms and functional outcome would interact with positive symptoms and distress. Negative symptoms in schizophrenia are often separated into *primary* negative symptoms, reflecting a core disability linked to poor outcome, and *secondary* negative symptoms, reflecting depression, paranoid withdrawal, extrapyramidal symptoms, etc. (Galderisi et al., 2018; Strauss and Cohen, 2017). The assessment of negative symptoms using standardized instruments in CHR cannot easily distinguish between the two, so we hypothesized that positive symptoms and distress would moderate the effect of negative symptoms on outcome (for example, if negative symptom ratings picked up withdrawal due to paranoia or depression, that would be a secondary negative symptom and not predictive of poor outcome).

2. Methods

2.1 Participants

Participants for these analyses were enrolled in EDIPPP, a multisite national trial testing the efficacy of FACT as early intervention for youth at risk of developing psychosis (McFarlane et al., 2012; McFarlane et al., 2015). Specific inclusion criteria were: (1) age 12–25, (2) living in the site's defined catchment area, and (3) receiving a score of ≥ 1 on any Positive Symptom Scale or ≥ 3 on any Negative Symptom Scale of the Scale of Prodromal Symptoms (SOPS; defined below in Measures). Potential participants were excluded if they (1) were experiencing a current psychotic episode (i.e., a score of 6 on any Positive Symptom Scale for longer than 30 consecutive days), (2) had a prior episode of psychosis or had received antipsychotic medication for 30 days or more at a dosage appropriate to treat a psychotic episode, (3) had an IQ less than 70, (4) did not speak English fluently, (5) were currently a prisoner in the criminal justice system, or (6) had psychotic symptoms due to an acute toxic or medical etiology. It should be noted that EDIPPP employed a risk-based classification, different from traditional CHR criteria. SOPS positive scores were used to classify participants into one of three groups: clinical low-risk (CLR; n=86; sum of positive scores on the SOPS < 7), CHR (n=197; sum of SOPS positive scores ≥ 7, but not meeting threshold for psychosis), and early first episode psychosis (EFEP; n=44; < 30 days of positive symptoms meeting the threshold for psychosis as determined by the Presence of Psychotic Symptoms or POPS criteria of the SOPS). Participants included in the present analyses (N=327) were 17 years old on average, and the majority were male and Caucasian. Table 1 includes demographic and clinical characteristics of the sample.

2.2 Procedures

EDIPPP study procedures have been fully described elsewhere (McFarlane et al., 2012). Briefly, six participating clinical sites representing ethnically and geographically diverse populations provided community outreach and education, intake assessments, and prospective follow-up visits for two years. Using a risk-based allocation design, CHR and EFEP participants were provided FACT, and CLR participants were provided monthly phone monitoring. Participants completed comprehensive evaluations at 6, 12, and 24 months.

2.3 Measures

Among others, measures included the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan et al., 2010) and specifically one of its constituent sections called the Scale of Prodromal Symptoms (SOPS). As developed, the SOPS includes sections assessing positive symptoms, negative symptoms, disorganization, and general symptoms (examples below). Previous analysis including 334 EDIPPP participants at baseline identified four empirical factors of the SOPS: positive symptoms (i.e., unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, bizarre thinking), distress (i.e., sleep disturbance, dysphoric mood, impaired tolerance to normal stress), negative symptoms (i.e., social anhedonia, avolition, expression of emotion, experience of emotions and self, odd behavior or appearance, impairment in personal hygiene), and deteriorated thought process (i.e., disorganized communication, ideational richness, occupational functioning, trouble with focus and attention) (Tso et al., 2017). These factor scores were used in the present analyses, which are favorable because they assign the empirical weight to each item, rather than assigning equal weight as with calculating a mean or summed score. Functional outcome was measured with the Global Functioning: Social (GF Social) and Global Functioning: Role (GF Role) Scales (Cornblatt et al., 2007). As outlined by Cornblatt and colleagues (2007), these scales provide clinician-rated single overall scores between 1 and 10, with 1 indicating extreme dysfunction and 10 representing superior functioning. The scales are rated regardless of etiology of functional impairment or level of clinical symptomatology. Both scales include detailed anchor points designed to be relevant to an adolescent/young adult population; for example, the GF Role scale anchor points refer to performance in school, work, or as a homemaker, depending on age. It also takes into account the individual's overall performance in the role given the level of support required. The GF Social scale assesses the quantity and quality of peer relationships, level of peer conflict, age-appropriate intimate relationships, and involvement with family members (though social contacts outside the family are emphasized).

Of note, two items of the SOPS, social anhedonia (N1) and occupational functioning (N6), clearly overlap with the content of the GF Social and GF Role scales, respectively. To avoid this confound, these two items were removed from the dataset when computing the baseline negative symptoms and deteriorated thought process scores for the current analyses.

2.4 Analyses

The present analyses included 327 participants with baseline SOPS factor scores derived by Tso and colleagues (2017) and functional ratings for at least one time point. Functioning data were available for 318 participants at baseline, 239 at 6-month follow-up, 236 at 12-month follow-up, and 217 at 24-month follow-up. Linear mixed effect modeling with maximum likelihood estimation was used to examine the relationship between baseline symptoms and social & role functioning over time. For each outcome variable (GF Social and GF Role), successive models were built: first, an unconditional mean model (Model 1) was estimated to compute the intraclass correlation coefficient and confirm the utility of modeling a growth curve. Next, an unconditional linear growth curve model (Model 2) added only visit (time) as a continuous predictor variable. Third, the four baseline symptom predictors were added, as well as two dummy coded clinical group variables to examine any

effect related to clinical classification (i.e., CLR vs. CHR vs. EFEP) (Model 3). Non-significant fixed effects were then removed; for initial model-building, alpha for significance was set to $p \leq 0.10$ for each predictor to lean towards broader inclusion, and for the final model a more stringent criterion of $p \leq 0.05$ was used. Then, interaction terms including visit by each of the four symptom predictors were added to examine whether the predictive value of baseline symptoms changed over time. Again, non-significant effects ($p \geq 0.10$) were removed. Two additional interaction terms were then added based on a priori hypotheses regarding the effects of symptom dimensions on one another: positive symptoms by negative symptoms and distress by negative symptoms. Non-significant effects were removed until all remaining predictors were statistically significant at $p < 0.05$. For each model, three indices were used to compare fit: −2 Log Likelihood, Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC). Random effects included intercept and visit (time), and the covariance matrix was unstructured. The final models were those with the lowest −2 Log Likelihood, AIC, and BIC values.

3. Results

Figure 1 illustrates mean social and role functioning scores at each time point for the three clinical groups.

3.1 Social Functioning

The unconditional mean model yielded an intraclass correlation coefficient of 0.46, indicating that 46% of the variance in social functioning ratings were due to interindividual differences and exceeding the suggested minimum cutoff of 25% for the utility of growth curve modeling (Shek and Ma, 2011). Ultimately, nine models were compared (Supplementary Table 1). The best-fitting model included main effects for Negative Symptoms and Deteriorated Thought Process, and Negative × Visit, Positive × Visit, and Positive × Negative interactions (Table 2). Specifically, more severe negative symptoms and deteriorated thought process significantly predicted worse social functioning. The Negative × Visit interaction indicated that the relationship between negative symptoms and social functioning differed over time, such that more negative symptoms always predicted worse social functioning, though the effect lessened over the follow-up period. Positive symptoms alone were not a significant predictor, but the interaction with visit occurred because the effect of positive symptoms on social functioning differed over time. At baseline, more positive symptoms predicted worse social functioning, although at follow-up time points, more baseline positive symptoms predicted better social functioning. The significant interaction between positive symptoms and negative symptoms indicated that the effect of negative symptom severity on social functioning depended on severity of positive symptoms. More specifically, higher positive symptoms at baseline lessened the deleterious effect of negative symptoms on social functioning.

3.2 Role functioning

The unconditional mean model yielded an intraclass correlation coefficient of 0.49, suggesting that 49% of the variance in role functioning ratings was due to interindividual differences and again exceeding the suggested minimum cutoff for growth curve modeling

(Shek and Ma, 2011). Ultimately, six models were compared (Supplementary Table 2). The best-fitting model included significant main effects for visit, negative symptoms, and deteriorated thought process; there were no interactions with time or among symptom types (Table 3). While in general role functioning improved over time, higher baseline negative symptoms and deteriorated thought process predicted worse role functioning. Model fit worsened with the inclusion of visit by symptom interactions as well as the hypothesized interactions between positive and negative symptoms, and distress and negative symptoms. This suggests that the predictive value of baseline symptoms did not change over time, and did not change based on other-symptom severity.

4. Discussion

This study used linear mixed modeling to examine the relationships between baseline symptom severity and longitudinal functional outcome for up to 24 months among individuals at varying levels of risk for psychosis or in the very early stage of a first psychotic episode; how these effects change over time and interact with one another were also tested. In general, and consistent with our hypothesis, worse negative symptoms at baseline were robustly associated with worse social and role functioning across time points; the same was true for deteriorated thought process. This finding adds to the existing literature in schizophrenia that negative symptom severity is significantly associated with functioning, and contributes to a ‘deficit’ or ‘persistent’ clinical subtype characterized by poor functional outcome and subsequent disability (Ahmed et al., 2015, 2018). Over time, the association between negative symptoms and social functioning decreased slightly, which may represent a treatment effect. Interestingly, the relationship between positive symptoms and social functioning reversed over time, where baseline positive symptoms were related to worse current social functioning but better social functioning at all three follow-up time points. This finding may reconcile some of the mixed literature on the relationship between positive symptom severity and functioning, since cross-sectional analyses or exclusion of interaction terms would not reveal the changing relationship over time. It may also reflect a treatment effect, in that positive symptoms may have responded better to treatment and resulted in better social functioning.

Moreover, these results supported the hypothesis that positive symptoms and negative symptoms interact to affect social functioning, where individuals with more severe positive and negative symptoms at baseline demonstrated better social functioning over time than those with only high negative symptoms. The moderating effect of positive symptoms on the relationship between negative symptoms and social functioning was in line with our prediction, possibly reflecting that the assessment of negative symptoms for those with high positive symptoms included secondary negative symptoms, not necessarily associated with poor outcome in the schizophrenia literature (Ahmed et al., 2018). It is also possible that high symptoms on both dimensions may indicate the development of a disorder other than schizophrenia, but with a better prognosis, such as bipolar disorder or PTSD. In contrast, the hypothesis that distress at baseline would also moderate the relationship between negative symptoms and functioning was not supported. In terms of role functioning at school, work, or home, the relationships between negative symptoms and deteriorated thought process and role functioning were consistent over time (i.e., there were no interactions with time).

Interestingly, neither positive symptoms nor distress at baseline were associated with social or role functioning ratings at follow-up. This appears consistent with the literature in individuals with chronic schizophrenia, in which positive symptoms may be disturbing and attract attention clinically but are not strongly associated with functioning (Rabinowitz et al., 2012). It is also notable that there was no significant effect of clinical group (CLR versus CHR versus EFEP), indicating that these relationships hold regardless of current clinical designation. This also suggests that the finding would hold if treatment were entered as a covariate, since by design the CHR and EFEP groups received active treatment and the CLR group did not.

Overall, these results suggest that negative symptoms and thought disorder are significantly related to functional outcome for up to two years among adolescents and young adults at risk for psychosis. These findings have important implications for researchers and clinicians working with youth at risk for psychosis, particularly as the clinical emphasis shifts from merely preventing ‘conversion’ to full psychosis to improving functional outcomes regardless of diagnosis, severity, or level of risk. For example, there is growing evidence that psychosocial interventions like Cognitive Behavioral Therapy (CBT) and family psychoeducation are efficacious at reducing symptoms in this population (Devoe et al., 2018; Kane et al., 2016; McFarlane et al., 2015). Although CBT for psychosis often focuses on positive symptoms like delusional ideation or hallucinatory experiences, it could also address defeatist performance beliefs thought to contribute to the development and maintenance of negative symptoms (Campellone et al., 2016; Granholm et al., 2018). Similarly, family psychoeducation emphasizes behavioral activation strategies and family-based behavioral experiments to challenge negative performance expectations on the part of the individual or the family. Although there is minimal description in the literature regarding interventions for thought disorder specifically, there is some evidence that Cognitive Therapy may reduce the likelihood of transition to psychosis among those at high risk, where transition was partially defined by the severity of conceptual disorganization (Morrison et al., 2007, 2004). It is reasonable to think that consistent participation in structured and goal-directed cognitive psychotherapy could improve disordered thought processes leading to functional deterioration. Moreover, as pharmacological and nutritional agents continue to be developed and tested for this population, focusing on negative symptoms and disorganized thinking as treatment targets in clinical trials may prove to be more beneficial to long-term outcome. In addition, given the widely reported relationship between cognitive deficits and disorganized thinking, one particular avenue for future research would be to include cognitive enhancement therapies that may improve disorganization and ultimately be associated with better functional outcomes.

There are limitations to this study that should be considered. First, although this was a large sample recruited from geographically diverse locations in the United States, there was not sufficient sample size in each racial category to examine them individually or enable comparisons between groups; future studies may benefit from strategic recruitment of racially and ethnically diverse participants. In addition, not all study participants received the same intervention; for example, individuals designated as clinical low-risk did not receive the FACT intervention, and medication was provided based on protocol-driven clinician judgment (and could have contributed to secondary negative symptoms). Thus,

heterogeneity of treatment may have contributed to variance in functional outcome and obscured or magnified these results. Another methodological limitation is that the same examiners used their judgment in rating both symptoms and functioning, which could introduce bias or score similarity related to measure invariance; ideally, future studies would include multiple methods of assessing functioning, for example through use of performance-based functional tasks. It should also be noted that CLR participants were recruited on the basis of both positive and negative symptoms, which failed to meet a predefined threshold; this group should not therefore be considered a healthy comparison group. In fact, these findings suggest that those in the CLR group with high negative symptoms would actually be at risk for functional impairment. In addition, many participants were lost to follow-up, and for unknown reasons; it is possible that some had improved and did not wish to continue participation, or that they worsened clinically and were no longer able to participate. Although unavoidable in a longitudinal study, sample selection bias at the follow-up time points could have affected these results. Moreover, the absence of a cross-validation sample limits conclusions about the stability of the final model and the estimates that were generated to compare relative model fits; confirmation of these results in an independent sample would be helpful. We also acknowledge that the assessment of negative symptoms overlaps with social and role functioning impairment. If negative symptoms and poor functioning reflect the same underlying deficit, to state that symptoms “predict” functioning could be problematic and misleading. To minimize this potential misinterpretation, we limited the use of “predict” to the description of the regression models and their results in the Methods and Results sections. In our interpretation of the findings, we used words indicating associations without implying causal direction.

In summary, these results provide additional evidence that baseline negative symptoms and deteriorated thought processes are suggestive of adverse social and role functioning up to two years later. Careful assessment of these features among adolescents and young adults at risk for psychosis, as well as provision of effective interventions targeting these symptom dimensions, may be helpful to reduce their long-term functional impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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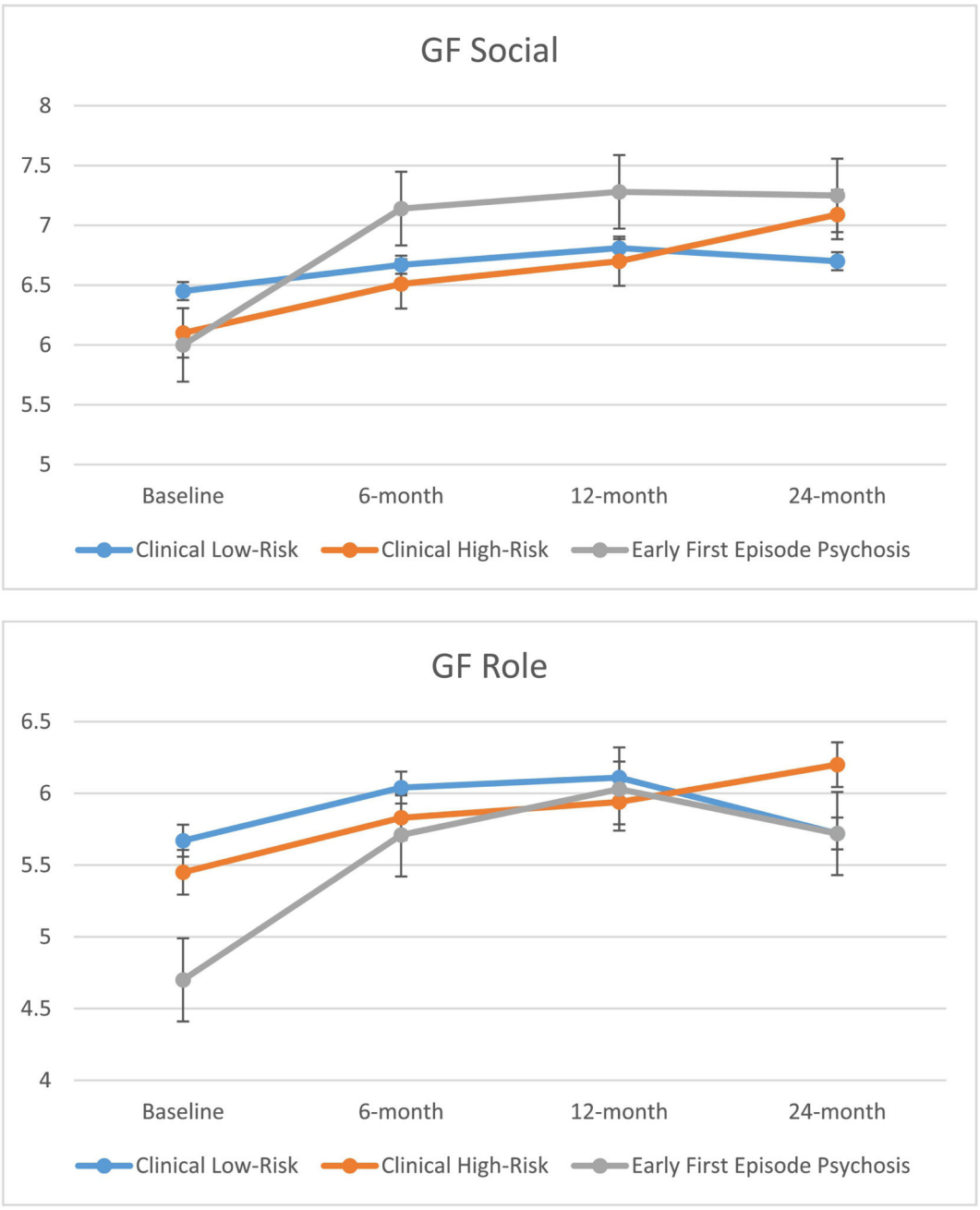

Figure 1.
GF Social and GF Role ratings at each time point

Table 1.

Demographic and Clinical Characteristics of the Sample

Variable	Mean / N	SD / %
Age	16.96	3.3
Male	198	60.6
Race		
Caucasian	201	61.5
African American	31	9.5
Asian American	13	4.0
American Indian/Alaska Native	4	1.2
Native Hawaiian/Pacific Islander	2	0.6
More than one Race	37	11.3
Other Race	24	7.3
GF Social	6.18	1.5
GF Role	5.41	2.4
SOPS Positive score	10.94	5.7
SOPS Negative score	13.37	6.1
SOPS Disorganized score	5.52	3.4
SOPS General score	10.42	4.5

Note. Fifteen participants (5%) were missing racial demographic data. GF and SOPS values reflect baseline scores.

Table 2.

Social Functioning Final Model

Parameter	Estimate (Std Error)	df	t	p
Intercept	7.39(0.16)	348.08	46.88	<0.001
Negative symptoms	−0.66(0.11)	344.80	−6.15	<0.001
Deteriorated thought process	−0.21 (0.07)	320.12	−3.10	0.002
Visit*Positive symptoms	0.01 (0.00)	267.49	2.51	0.013
Visit*Negative symptoms	0.01 (0.00)	262.37	3.39	0.001
Positive symptoms*Negative symptoms	0.098 (0.03)	362.08	3.31	0.001

Table 3.

Role Functioning Final Model

Parameter	Estimate (Std Error)	df	t	p
Intercept	6.88 (0.26)	338.40	26.58	<0.001
Visit	0.02 (0.01)	253.46	2.89	0.004
Negative symptoms	−0.36(0.12)	316.76	−3.00	0.003
Deteriorated thought process	−0.40(0.11)	318.71	−3.61	<0.001