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Prediction of Functional Outcome in Individuals at Clinical High Risk for Psychosis

Ricardo E. Carrión, PhD, Danielle McLaughlin, MA, Terry E. Goldberg, PhD, Andrea M. Auther, PhD, Ruth H. Olsen, BS, Doreen M. Olvet, PhD, Christoph U. Correll, MD, and Barbara A. Cornblatt, PhD, MBA

Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, Glen Oaks, New York (Carrión, McLaughlin, Goldberg, Auther, Olsen, Olvet, Correll, Cornblatt); Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, North Shore–Long Island Jewish Health System, Manhasset, New York (Carrión, Goldberg, Olvet, Correll, Cornblatt); Department of Psychiatry and Molecular Medicine, Hofstra North Shore–LIJ School of Medicine, Hempstead, New York (Correll, Cornblatt)

Abstract

Importance—A major public health concern associated with schizophrenia and psychotic disorders is the long-term disability that involves impaired cognition, lack of social support, and an inability to function independently in the community. A critical goal of early detection and intervention studies in psychosis is therefore to understand the factors leading to this often profound impairment.

Objective—To develop a predictive model of functional (social and role) outcome in a clinical high-risk sample for psychosis.

Design—Prospective, naturalistic, longitudinal 3- to 5-year follow-up study.

Corresponding Author: Ricardo E. Carrión, PhD, Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd St, Glen Oaks, NY 11004 (rcarrion@nshs.edu).

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Author Contributions: *Study concept and design:* Carrión, McLaughlin, Auther, Cornblatt.

Acquisition of data: Carrión, McLaughlin, Auther, Olsen, Cornblatt.

Analysis and interpretation of data: Carrión, Goldberg, Olvet, Correll, Cornblatt.

Drafting of the manuscript: Carrión, Olvet, Cornblatt.

Critical revision of the manuscript for important intellectual content: Carrión, McLaughlin, Goldberg, Auther, Olsen, Correll, Cornblatt.

Statistical analysis: Carrión, Goldberg, Olvet.

Administrative, technical, or material support: McLaughlin, Auther, Olsen, Cornblatt.

Study supervision: Correll, Cornblatt.

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Setting—The Recognition and Prevention Program in New York, a research clinic located in the Zucker Hillside Hospital in New York.

Participants—One hundred one treatment-seeking patients at clinical high risk for psychosis. Ninety-two (91%) were followed up prospectively for a mean (SD) of 3 (1.6) years.

Intervention—Neurocognitive and clinical assessment.

Main Outcomes and Measures—The primary outcome variables were social and role functioning at the last follow-up visit.

Results—Poor social outcome was predicted by reduced processing speed (odds ratio [OR], 1.38; 95% CI, 1.050-1.823; $P = .02$), impaired social functioning at baseline (OR, 1.85; 95% CI, 1.258-2.732; $P = .002$), and total disorganized symptoms (OR, 5.06; 95% CI, 1.548-16.527; $P = .007$). Reduced performance on tests for verbal memory (OR, 1.74; 95% CI, 1.169-2.594; $P = .006$), role functioning at baseline (OR, 1.34; 95% CI, 1.053-1.711; $P = .02$), and motor disturbances (OR, 1.77; 95% CI, 1.060-2.969; $P = .03$) predicted role outcome. The areas under the curve for the social and role prediction models were 0.824 (95% CI, 0.736-0.913; $P < .001$) and 0.77 (95% CI, 0.68-0.87; $P < .001$), respectively, demonstrating a high discriminative ability. In addition, poor functional outcomes were not entirely dependent on the development of psychosis, because 40.3% and 45.5% of nonconverters at clinical high risk had poor social and role outcomes, respectively.

Conclusions and Relevance—Results from this study support the increasing emphasis on functional decline as a critically important outcome that parallels conversion to psychosis and suggest that both psychosis and long-term functional disability are equally important targets for prevention. Reduced neurocognitive performance, functional impairments, and nonpositive attenuated symptoms at baseline were associated with an increased risk of poor functional outcomes in our sample. Poor functional outcomes were not entirely dependent on positive symptoms and the development of psychosis, further highlighting the need for intervention at this early stage of development for those who do and do not convert to a full-blown psychotic disorder.

The burden of schizophrenia and psychotic disorders to patients, family members, friends, and wider society is largely due to deficits in functioning.¹⁻⁵ Impairments in functioning reduce independence, lower productivity, limit educational attainment, and decrease quality of life.⁶ Subsequently, this often profound disability imposes a substantial economic burden on society, with estimated indirect costs of the illness in the United States, specifically related to functional disability, being as high as \$30 billion annually, accounting for 52% of all schizophrenia-related costs.⁷ Impairments in social and role functioning are particularly problematic, because patients consistently have difficulty developing and maintaining many traditional societal roles, such as friend, spouse, parent, student, or worker.⁸⁻¹¹ Even with optimal medication treatment and remission of positive symptoms, functional outcomes are poor during the early years of the illness.¹²⁻¹⁴ A critical goal is therefore to understand the factors leading to long-term disability in psychotic disorders.

Studies of adults with psychosis have shown that multiple factors are linked to poor functional outcomes, including a long duration of untreated psychosis¹⁵ and poor premorbid functioning.¹⁶ In addition, there is considerable evidence that cognitive dysfunctions are

associated with impaired functioning in schizophrenia and first-episode psychosis.¹⁷⁻³¹ However, these findings are tempered by chronic illness and prolonged treatment, because the functional outcomes of adults with psychotic disorders are influenced by relapse, multiple episodes, medication treatment, and repeated hospitalizations.^{32,33} For these reasons, it would be ideal to intervene when individuals are less functionally impaired, optimally prior to the onset of illness, and at a point where social, academic, and occupational skills are acquired and generalized, which typically takes place during adolescence and early adulthood.^{33,34}

Although adolescence is the period when social and occupational problems become apparent,³⁵⁻⁴⁰ few early intervention studies in psychosis have extended the preventive approach and developed criteria for ascertaining individuals at risk for functional impairments, along with risk for psychosis. While progression to full-blown psychosis assumes primary importance in early detection and intervention studies,⁴¹⁻⁴³ it is becoming increasingly clear that prevention models should also aim to improve the prediction of poor functional outcomes. In light of recent evidence that a large proportion of individuals at clinical high risk (CHR) do not develop full-blown psychosis,⁴⁴ the identification of predictors that reliably differentiate between CHR patients at high and low risk for functional impairments may provide a pathway to prevent the disability associated with the illness. Moreover, this approach may lead to better understanding of the underlying mechanisms of functional impairments at a critical phase in the illness and improved treatments and services for those at an increased risk for functional disability.

Previous findings from prospective CHR studies suggest that it may be possible to identify predictors of functional outcomes before the influence of long-term illness and prolonged treatment. Previous work from our group⁴⁵ demonstrated that the relationship between reduced neurocognitive performance and functional impairments at baseline exists prior to psychosis and is not solely an outcome of chronic illness. Recent data⁴⁶ indicate that impairments in social and role functioning are stable over time and independent from positive symptoms. This suggests that rather than predicting psychosis, preillness functional impairments may be a critical predictor of long-term disability and that baseline characteristics can be used to develop a prediction model for risk of functional impairments in CHR samples, independent of positive symptoms and the development of psychosis.

The present study aimed to identify baseline predictors of poor functional outcome in a large, prospective, longitudinal sample of treatment-seeking adolescents and young adults at CHR for psychosis. To our knowledge, no prospective studies have developed a prediction model for poor functional outcome, independent of positive symptoms and the development of psychosis. In addition, this report also focuses on the identification of predictors across specific domains of functioning, rather than relying on traditional global outcomes scores. Several prospective CHR studies have linked reduced baseline neurocognitive performance with poorer functioning at follow-up.⁴⁷⁻⁴⁹ For example, Lin et al⁴⁷ recently reported that baseline verbal memory deficits were the strongest predictor of poor functional outcome. These studies have been limited, however, by small sample sizes, lack of healthy comparison groups, and inclusion of symptom-based global functioning (ie, Global Assessment of Functioning Scale). In the current study, social and role (academic/

occupational) functioning were measured with the Global Functioning: Social (GF:Social) and Role (GF:Role) scales, developed specifically for use with adolescents and young adults at CHR for psychosis.⁵⁰ We addressed the following questions: (1) What are the social and role outcomes of CHR individuals with 3 to 5 years of follow-up? (2) How is baseline neurocognitive performance associated with long-term academic and social functioning in individuals at CHR for psychosis? (3) What are baseline predictors of poor functional outcome, independent of psychosis?

Methods

All procedures were approved by the institutional review board at North Shore–Long Island Jewish Health System. Written informed consent (with assent from participants younger than 18 years) was obtained from all participants.

Participants

The original intake sample consisted of 101 participants who met criteria for CHR positive derived from the Scale of Prodromal Symptoms (SOPS).⁵¹⁻⁵³ Inclusion criteria were based on the presence of 1 or more moderate, moderately severe, or severe (scores of 3, 4, or 5) SOPS-rated (scale of 0-6) attenuated positive symptoms. A score of 6 (severe and psychotic) on any item was exclusionary for the CHR group. In this article, subjects in the CHR group are broadly comparable with those considered “prodromal” in most other studies in North America and internationally.⁵⁴

Healthy control (HC) subjects (n = 68) were recruited through announcements in local newspapers and within the medical center. Inclusion criteria required participants to be between the ages of 12 and 22 years. Exclusion criteria were (1) schizophrenia spectrum diagnosis; (2) non-English speaking; (3) a medical or neurological disorder; and (4) estimated IQ <70. Healthy controls were excluded if they had a first-degree relative with a diagnosed Axis I psychotic disorder.

The data reported herein were collected as part of the larger Recognition and Prevention (RAP) Program, an ongoing longitudinal investigation initiated in 1998 and funded by the National Institute of Mental Health in 2000. This article reports follow-up data for participants reported in a previous baseline study⁴⁵ and recruited during phase 1 of the RAP Program (January 1998-February 2006). Patient referrals were made to the RAP Program by affiliated outpatient and inpatient psychiatry departments, local mental health providers, or school psychologists or counselors or patients were self-referred.

Baseline Neurocognitive Assessment

Estimated full-scale IQ scores were derived from the vocabulary and block design subscales of the Wechsler Intelligence Scale for Children, Third Edition⁵⁵ for subjects younger than 16 years and from the Wechsler Adult Intelligence Scale, Revised⁵⁶ for subjects 16 years or older. In addition, the battery included neuropsychological tests that assessed 8 cognitive domains: processing speed, verbal memory, executive function, working memory, visuospatial processing, motor speed, sustained attention, and language. Domain construction was based on (1) rational criteria derived from clinical neuroscience and

neuropsychological literature; (2) previous work by our group and others that demonstrated the content validity of the domains^{45,57}; and (3) findings of separable factors in the schizophrenia cognitive architecture, including processing speed.^{28,58} The internal reliability (Cronbach α) for these domains was good (eTable 1 in Supplement) to minimize the possibility of identifying spurious differences across domains.^{59,60}

Baseline Clinical Assessment

Axis I diagnoses were assessed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version.⁶¹ Axis II diagnoses were assessed using the Structured Interview for *DSM-IV* Personality.⁶² Prodromal symptoms were assessed by the Structured Interview for Prodromal Syndromes and the companion SOPS.⁵² Conversion to psychosis was defined as the presence of a psychotic-level positive symptom (SOPS score of 6). The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version was used to confirm diagnoses in those participants whose symptoms developed into full psychotic disorders.

Social and role functioning was assessed using the GF:Social and GF:Role scales.⁵⁰ These rater-scored measures were designed to represent parallel, well-anchored scales that account for age and phase of illness and detect functional changes over time.⁵⁰ In addition, the scales avoid confounding functioning with psychiatric symptoms. The GF:Social Scale assesses peer relationships, peer conflict, age-appropriate intimate relationships, and involvement with family members. The GF:Role Scale rates performance and amount of support needed in one's specific role (ie, school or work). For both scales, scores range from 1 to 10 (10 = superior functioning to 1 = extreme dysfunction). Ratings for each of the 2 GF scales were based on best source of available clinical information, derived from all information available, which included clinician reports, telephone interviews, and in-person follow-up interviews. High interrater reliabilities were reported²² using this approach, along with construct and predictive validity.^{41,50}

Functional Outcome

The primary outcome variable for this study was functional outcome at the last follow-up visit. Good outcome was defined as current functioning scores of 7 and higher, indicating mild impairments to superior functioning. Poor outcome was defined as current functioning scores of 6 and lower (moderate impairments to extreme dysfunction). The GF:Social and Role scores at outcome were dichotomized based on the following considerations: (1) Ratings of 7 and higher on the scales were specifically anchored to reflect levels of functioning within the normal/healthy range and scores of 6 and lower, to reflect impaired functioning.⁵⁰ (2) The median rating of CHR individuals has consistently been shown to be a score of 6. (3) Social functioning at baseline (score ≥ 6) was found to be an independent predictor of conversion to psychosis,⁴¹ thus supporting the predictive validity of dichotomized good vs poor functioning. Along with the Structured Interview for Prodromal Syndromes, the GF:Social and GF:Role scales⁵⁰ were re-administered approximately 6 months after entry to the RAP Program and regularly every 6 to 9 months, as well as at termination of treatment or conversion to psychosis. For the latter, patients were also reassessed whenever the study team became aware of a major event potentially indicating

clinical worsening/conversion, such as an inpatient admission or patient or caregiver outreach to the program.

Of the initial 101 CHR subjects, 92 (91%) had follow-up clinical ratings. Nine subjects were excluded (1 died, 5 declined to continue participation, and 3 could not be located), leaving a final sample of 92 participants. The mean follow-up period (time to conversion to psychosis or last follow-up) was 3.0 years (SD = 1.6 years; median = 2.8).

Statistical Analyses

All analyses were conducted using SPSS version 16.0 (SPSS Inc). Comparisons of demographic and clinical characteristics were performed with *t* tests for continuous variables, Pearson χ^2 or Fisher exact tests for categorical variables, and Kolmogorov-Smirnov *z* for 1 ordinal variable (2-tailed, $P < .05$).

Prior to neurocognitive domain construction, raw test scores were transformed into standard *z* scores using age-stratified means and standard deviations of the demographically matched sample of healthy subjects to control for age-related change in cognitive performance. When applicable, tests were reverse scored so that lower scores always reflected worse performance. Domain scores were then computed by averaging each subject's *z* scores on tests assessing the same neurocognitive domain (eTable 1 in Supplement). The *z* scores for each domain were then restandardized using the mean and standard deviation of the domain scores of the HC group.

Multivariate analysis of covariance was used to evaluate the profile of baseline neurocognitive performance among the groups, with group (HC, good outcome, and poor outcome) as the between-subject factor and neurocognitive domain scores as within-subject factors. Multivariate analysis of covariance was used to assess the effects of race since HC and CHR subjects differed on this variable. Post hoc comparisons were performed with Bonferroni corrections ($P = .05/3 = .017$).

In addition, a multivariable model was constructed to predict functional outcome. A broad range of potential predictor variables were available from the baseline assessment, including neuropsychological, clinical, sociodemographic, substance use, and treatment (ie, medication)-related factors (see eTable 2 in Supplement for a complete list of domains and variables). Potential predictors were selected in several stages.^{41,42}

In the first stage of variable selection, all potential variables were computed individually in univariable logistic regression analyses ($P < .15$).⁶³ The -2 log-likelihood ratio test was used to test the overall significance of the predictive equation. Wald χ^2 statistics were used to assess the significance of the individual variables. Variables that remained after the initial screening procedure were entered into a best-subset logistic regression analysis ($P < .05$).^{63,64} Best-subset regression finds the best subset or combination of these variables.⁶⁵ Model selection was guided by the Mallows Cp criterion⁶⁶ and bias-corrected Akaike Information Criterion.^{67,68} Both the Mallows Cp criterion and bias-corrected Akaike Information Criterion determine the optimal number of input variables by defining the optimal tradeoff between model size and accuracy by penalizing models with an increasing

number of parameters. One model was built for social and role functioning at outcome. The final models were adjusted for the possible confounding effects of individuals who developed psychosis over the follow-up period.

Overall performance of the final models was measured with the Nagelkerke pseudo R^2 statistic (R^2_N). The Nagelkerke statistic is an approximate measure of the proportion of explained variation.⁶⁹ Model discrimination and diagnostic accuracy were determined with the area under the receiver operating characteristic curve⁷⁰ (eAppendix in Supplement).

Missing data were handled using expectation-maximization estimates.^{71,72} Overall, 4.9% of the data (392 of 8004 values) were missing. No significant relationship was found between the patterns of missing data and functional outcome results.

Results

Sample Characteristics

Healthy controls and CHR subjects did not differ significantly on baseline age, education level, sex ratio, parental socioeconomic status, handedness, or ethnicity (eTable 3 in Supplement). However, HCs had higher estimated current IQs and a lower proportion of white males compared with the CHR group. Of the 92 CHR patients, 44 (47.8%) had a poor social outcome, whereas 48 patients (52.2%) were classified as having a good social outcome. Forty-five (48.9%) had a poor role outcome, whereas 47 patients (51.1%) were classified as having a good role outcome. Overall, 32.6% ($n = 30$) of the sample had both a poor social and role outcome, while 35.9% ($n = 33$) of the patients had a good outcome in both domains.

Table 1 summarizes baseline demographic and clinical characteristics of individuals with poor and good social and role outcomes, respectively. In both samples, good and poor outcome groups did not differ significantly on any demographic feature, including age at testing, estimated current IQ, education level, sex ratio, handedness, socioeconomic status, race, or ethnicity. At baseline, the good and poor outcome groups did not differ in rates of mood, anxiety, and substance-related disorders. In addition, for both functional domains, medications at baseline testing did not differ between the good and poor outcome groups. Patterns of medication treatment over the follow-up period indicated that antipsychotics were prescribed to 39 patients (42.4%), antidepressants to 58 patients (63.0%), anxiolytics to 17 patients (18.5%), mood stabilizers to 12 patients (13.0%), and stimulants to 13 patients (14.3%), and 21 patients (22.8%) received no medication. We further evaluated the effects of follow-up medication treatment on functional outcome and found that antipsychotics had no effects on the findings, while the effects of antidepressants were variable and uninterpretable.

The good and poor outcome groups did not differ significantly on baseline positive symptoms. However, patients with poor social outcome showed higher negative and disorganized symptoms and poorer social functioning at baseline compared with those with good social outcome. Patients with poor role outcome also had lower role functioning scores at baseline compared with the good role outcome group.

There was also a difference in percentage of change in functioning between the functional outcome groups, because a good outcome in social or role functioning was associated with modest improvements in functioning over the follow-up period. In contrast, patients in the poor outcome groups displayed impairments in functioning that were consistent over time. Patients with good social outcome showed a modest improvement in social functioning compared with those with poor social outcome (23.6% vs -5.0%; $t_{90} = 5.34$; $P < .001$). Patients with good role outcome also had a higher percentage of change in role functioning over time compared with the poor role outcome group (61.4% vs -9.1%; $t_{90} = 3.65$; $P < .001$).

Neurocognitive Performance and Functional Outcome

For social outcome, multivariate analysis of covariance revealed a significant overall group effect (Wilks $\lambda = 0.65$; $F_{16,290} = 4.43$; $P < .01$) and significant group differences on all 8 neurocognitive domains, with the largest effect-size differences on processing speed (Table 2) Race was not a significant covariate (Wilks $\lambda = 0.95$; $F_{8,145} = 0.96$; $P = .44$). As shown in Table 2, post hoc comparisons indicated that at baseline patients with poor social outcome performed at levels significantly lower than those with good social outcome in verbal memory, processing speed, executive function, motor speed, and language ($P < .017$). Moreover, compared with HCs, the poor outcome group displayed significant deficits in all 8 neurocognitive domains. In contrast, patients with good social outcomes were only impaired, relative to the HC group, in processing speed, verbal memory, and attention (Table 2).

For role outcome, multivariate analysis of covariance revealed a significant overall group effect (Wilks $\lambda = 0.66$; $F_{16,290} = 4.22$; $P < .001$) and significant group differences on all neurocognitive domains, except for motor speed, with the largest effect-size differences found on verbal memory (Table 3) Race was not a significant covariate (Wilks $\lambda = 0.94$; $F_{8,145} = 1.18$; $P = .32$). Post hoc testing indicated that the poor role outcome group functioned at levels significantly lower than the good role outcome group in verbal memory, executive function, sustained attention, and language (Table 3). In addition, the poor role outcome group displayed impairments in all neurocognitive domains, except for motor speed, relative to the HC group. Participants with good role outcome, however, only displayed deficits in processing speed compared with the HC group.

Prediction of Functional Outcome

Table 4 and Table 5 show the final logistic regression models for social and role outcome. Baseline processing speed, social functioning, and SOPS total disorganization subscale score more than 4 were significant predictors of social outcome (Table 4). The final model accounted for 39% of the variance ($R^2_N = 0.393$). Participants with poor social functioning, impaired processing speed, and a SOPS total disorganization sub-scale score more than 4 at baseline were more likely in the poor social outcome group. The area under the curve for this model was 0.824 (95% CI, 0.736-0.913; $P < .001$), indicating a good discriminative ability, with a sensitivity of 72.7% and specificity of 75.0% (eFigure, A, in Supplement).

Verbal memory, role functioning, and motor disturbances were significant predictors of role outcome (Table 5). The final model accounted for 32% of the variance ($R^2_N = 0.320$). Participants with poor role functioning, impaired verbal memory, and increased motor disturbances at baseline were more likely in the poor role outcome group. The area under the curve for this model was 0.77 (95% CI, 0.68-0.87; $P < .001$), with a sensitivity of 62.2% and a specificity of 72.3% (eFigure, B, in Supplement).

Functional Outcome and Conversion to Psychosis

To examine the independence of functional outcome from conversion to psychosis, we added conversion status to the prediction models. Individuals who developed psychosis over the follow-up period may have confounded the association between the baseline predictors and functional outcome, because converters typically display, for example, lower neurocognitive performance and poorer functioning at baseline compared with individuals who do not go on to develop psychosis. Compared with nonconverters ($n = 77$), converters ($n = 15$) were more likely to have a poor social outcome (40.3% vs 86.7%; $\chi^2 = 10.84$; $P < .001$). In contrast, nonconverters and converters had similar role outcomes (45.5% vs 66.7%; $\chi^2 = 2.26$; $P = .16$).

Predictors of role outcome were independent of conversion to psychosis ($\beta = 0.65$; SE = 0.73; $P = .38$), because role functioning (odds ratio [OR], 1.35; 95% CI, 1.05-1.72; $P = .02$), verbal memory (OR, 1.66; 95% CI, 1.10-2.49; $P = .02$), and motor disturbances (OR, 1.85; 95% CI, 1.09-3.14; $P = .02$) continued to predict poor role outcome.

In contrast, conversion to psychosis was significantly related to poor social outcome (OR, 8.74; 95% CI, 1.30-58.78; $P = .03$). In addition, the impact of processing speed on social outcome was reduced (OR, 1.26; 95% CI, 0.92-1.73; $P = .15$) after accounting for conversion. Conversion to psychosis alone did not account solely for social outcome, however, because social functioning (OR, 1.93; 95% CI, 1.26-2.95; $P = .002$) and a SOPS total disorganization subscale score more than 4 (OR, 5.52; 95% CI, 1.60-19.09; $P = .007$) continued to contribute significantly to the equation, after adjusting for the development of psychosis.

Discussion

Our study yielded 4 main findings. First, initial CHR classification is associated with persistent and long-standing functional difficulties, lasting years after ascertainment. Second, lower neurocognitive performance at baseline was associated with poorer social and role outcome. Third, neurocognitive performance and functioning at baseline were key predictors of long-term functioning, suggesting that predictors of poor functional outcomes can be identified in adolescence, before illness onset, and perhaps limit the progression to long-term disability. Fourth, poor functional outcomes were not entirely dependent on the development of psychosis, further highlighting the need for intervention at this early stage for those who do and do not convert to a full-blown psychotic disorder.

At the conclusion of the study, we found that a substantial portion of the CHR subjects in our sample had poor social and role outcomes. Almost half of the sample experienced either

a poor social (47.8%) or role (48.9%) outcome. In addition, one-third (32.6%) of the sample had both a poor social and role outcome, which is similar to recently reported transition rates to psychosis of 19% to 35%.^{41,42,44} These findings support prior studies showing persistent functional impairments in subjects initially meeting criteria for prodromal syndromes.^{47,74} These adolescents and young adults are both at risk for psychosis and functional disability. Thus, prevention is needed for emerging psychosis, as well as for helping these individuals cope with persistent relationship and school/work difficulties.

Consistent with previous findings in individuals at CHR,^{47,48} these data reveal that early neurocognitive impairments are associated with social and educational/occupational functioning at follow-up. For example, in a recent study with long-term follow-up of CHR subjects,⁴⁷ poor functioning at outcome was related to baseline impairments in verbal learning/memory, verbal fluency, and, to a lesser degree, processing speed. Niendam et al⁴⁸ reported that short-term social functioning was linked to baseline processing speed. Our study revealed a similar differential pattern of baseline neurocognitive performance in high-risk individuals, because those with poor outcomes performed lower than HCs across all neurocognitive domains. Moreover, those with poor outcomes were especially compromised in processing speed, verbal memory, and executive function compared with those with good outcomes. Impairments in verbal memory and processing speed have also been well documented in studies of patients with chronic illness⁷⁵⁻⁷⁹ and have been found to be related to functional outcome.^{20,47,80} These findings add to a growing body of evidence that cognitive heterogeneity is present prior to the onset of the illness⁸¹ and could be used as a differential predictor of functional as well as psychotic outcomes.

Neurocognition and functioning at baseline were key predictors for both social and role outcome, providing a link between baseline functional achievement and cognitive performance, and long-term functional outcome in CHR subjects. Specifically, processing speed and social functioning predicted social outcome. Predictors of role outcome included verbal memory and role functioning. In addition, nonpositive attenuated symptoms, namely disorganized behavioral symptoms and motor disturbances, were associated with functional outcome. This finding was independent of conversion status, indicating that functional outcome is independent of the development of a full-blown psychosis.⁴⁶

In the present study, certain neurocognitive abilities were more sensitive to specific domains of functioning at outcome. Baseline processing speed performance appeared important for maintaining social relationships, while verbal memory was related to successful academic and work achievement. Slowing in understanding and reaction to incoming information might be debilitating in multiple domains of real-world functioning, such as the ability to select and maintain conversational topics.⁷⁵ In an academic or work setting, verbal memory is essential for the encoding and recall of facts, formula, and homework assignments. Taken together, these findings suggest that researchers using current cognitive training interventions for individuals at CHR should consider examining specific cognitive abilities as they relate to different domains of functioning.

Baseline functioning also made a significant independent contribution to the prediction of functional outcome. Premorbid functioning is generally considered to be one of the strongest

predictors of functional outcome in both patients with chronic illness^{82,83} and those with first-episode illness.⁸⁴ Our findings are consistent with the growing body of evidence that preillness social problems and school difficulties emerge in adolescence, long before the onset of psychosis.³⁵⁻⁴⁰ This is particularly problematic because functional impairments at an early stage of development can limit functional recovery once the disorder is established.³⁹

The importance of disorganized behavioral symptoms has also been found in previous CHR studies.^{49,85} In the present study, the odds of poor social outcome were nearly 5 times greater in patients with a SOPS total disorganization subscale score more than 4. The contribution of disorganized behavioral symptoms to social outcome highlights the importance of nondelusional and nonhallucinatory psychopathology and behavioral disorganization in patients' ability to maintain friendships and relationships.

Our results demonstrate that a preventive approach to psychosis should be extended to include relevant functional outcomes, because these markers provided relevant discrimination between individuals with poor and good outcomes, as indicated by an area under the curve of 0.82 for social and 0.78 for role outcome. However, these markers are not intended to replace or modify the current inclusion criteria, but rather to provide information that can guide selection of CHR individuals who warrant intervention for risk factors other than increasing positive symptoms, such as poor hygiene, cognitive impairments, and deficits in social functioning.

Starting more than a decade ago, the RAP program was one of the earliest prevention programs in North America. As a result, the initial emphasis was on positive symptoms and emergence of psychosis. Over time, there have been modifications introduced to the field that have broadened the scope of social and role risk factors in individuals at CHR. As such, the current findings should be interpreted in the context of the limitations of measures available at the time. The RAP phase 1 database does not include social cognition, measures of functional capacity, stigma, and other factors that may further contribute to the development of functional impairment. Second, the study design is underpowered for examining the predictors of all possible combinations of social and role outcomes, for example, an individual who had poor social and role functioning at last assessment. In all likelihood, individuals with the poorest outcomes are at the greatest risk of future disability. However, our study has the advantage of using separate measures of social and role functioning rather than global measures, such as the Global Assessment of Functioning Scale, which confounds functioning with clinical symptoms. The current findings indicate that using a global measure of functional outcome is likely to conceal the ability to predict specific developmental patterns that are linked to different domains of functioning.

Finally, future research should continue to refine and cross-validate these findings to confirm the ability of the prediction models to prospectively identify risk of functional impairments in CHR samples. The prediction of poor functioning, possibly prior to the emergence of psychosis, is increasingly important because treatments aimed at the factors related to early functional difficulties may limit future disability. We also plan further research to better understand the role of pharmacological treatments on short-term and long-

term social and role functioning in individuals at CHR for psychosis. Such research will result in a greater understanding of the role of pharmacological treatment on these important functional domains and determine whether medication before the onset of psychosis is effective for treating functional impairments.

Overall, the results of the present study reveal that conversion alone did not account for poor functional outcome, supporting the relative independence of functioning from positive symptoms and psychotic outcomes. Baseline functioning and nonpositive attenuated symptoms continued to predict functional outcome, even after adjusting for conversion status. Consistent with recent findings,⁴⁶ these results suggest that functional impairments are long-standing vulnerability traits, can potentially contribute to prediction of psychosis,^{41,86} and therefore have an important position in the treatment of disability. Furthermore, these results emphasize the need for a flexible perspective on outcome in at-risk individuals. Functional disability is not solely dependent on the progression of full-blown psychosis, because many individuals who did not convert continued to present with impairments in social and role functioning.

Taken together, these results support the presence of an underlying developmental vulnerability core for the illness that is thought to be the major source of later functional difficulties, independent of emerging positive symptoms.⁸⁷ Cornblatt and colleagues⁸⁷ hypothesized that the prodromal period of the illness is characterized by an underlying developmental vulnerability core for the illness, determined by genetic vulnerability and perinatal biological insults, consisting of cognitive deficits, affective disturbances, social isolation, and school failure (ie, CASIS). While this core vulnerability is not sufficient to lead to schizophrenia, the presence of these distal risk factors may lead to a variety of functionally related disorders⁸⁷ and therefore appear to be particularly good targets for future interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Characteristic	No. (%)						P Value
	Social Outcome			Role Outcome			
	Good (n = 48)	Poor (n=44)	P Value	Good (n = 47)	Poor (n = 45)	P Value	
Role	5.92 (2.04)	5.27 (2.00)	.13	6.23 (2.05)	4.96 (1.83)	.002	
Global assessment of functioning score, mean (SD)	47.52 (8.73)	44.70 (7.40)	.10	47.64 (8.67)	44.64 (7.48)	.08	
<i>DSM-IV diagnoses</i>							
Mood ^b	33 (68.8)	25 (56.8)	.28	34 (72.3)	24 (53.3)	.08	
Anxiety ^c	28 (58.3)	25 (56.8)	>.99	29 (61.7)	24 (53.3)	.53	
Substance ^d	6 (12.5)	3 (6.8)	.49	3 (6.4)	6 (13.3)	.31	
<i>Medication at testing</i>							
No medication	26 (54.2)	22 (50.0)	.85	24 (51.1)	24 (53.3)	.84	
Antipsychotics	9 (18.8)	10 (22.7)	.80	11 (23.4)	8 (17.8)	.61	
Antidepressants	13 (27.1)	15 (34.1)	.50	17 (36.2)	11 (24.4)	.26	
Anxiolytics	5 (10.4)	4 (9.1)	>.99	5 (10.6)	4 (8.9)	>.99	
Mood stabilizers	3 (6.2)	1 (2.3)	.62	2 (4.3)	2 (4.4)	>.99	
Stimulants	2 (4.2)	1 (2.3)	>.99	1 (2.1)	2 (4.4)	.61	
Other medications ^e	0	1 (2.3)	.48	0	1 (2.2)	.49	
Time to last follow-up, y, mean (SD)	3.12 (1.60)	2.80 (1.61)	.34	2.90 (1.63)	3.03 (1.60)	.70	

Abbreviations: NOS, not otherwise specified; SES, socioeconomic status; SOPS, Structured Interview for Prodromal Symptoms.

^aHollingshead Four-Factor Index of Socioeconomic Status, where scores of 1 to 3 are “high” and scores of 4 and 5 are “low.”

^bDSM-IV–defined diagnosis of major depressive disorder, dysthymic disorder, mood disorder NOS, or depressive disorder NOS.

^c *DSM-IV*-defined diagnosis of panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, anxiety disorder NOS, or phobias including simple phobias and social phobia.

^d *DSM-IV*-defined diagnosis of alcohol, amphetamine, cocaine, hallucinogen, nicotine, opioid, or polysubstance-related disorder.

^e The category “other medications” included the following: anticholinergic, anticonvulsant, antihypertensive, and sedative-hypnotic medication.

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Table 2
Scores on the Neurocognitive Domains for Clinical High-Risk Subjects With Good and Poor Social Outcome

Score	Mean (SD)		$F_{2,152}$ Value	P Value	Cohen f^2	Post hoc Contrasts ^b
	Good Social (n = 48)	Poor Social (n = 44)				
Verbal memory	-0.51 (1.13)	-1.43 (1.39)	19.94	<.001	0.50	HC>PO, GO; PO>GO
Working memory	-0.42 (1.17)	-0.92 (1.28)	9.05	<.001	0.33	HC>PO
Executive function	-0.25 (1.29)	-1.63 (2.9)	11.37	<.001	0.39	HC>PO; PO>GO
Sustained attention	-0.35 (1.18)	-0.99 (1.4)	9.35	.003	0.34	HC>PO, GO
Processing speed	-1.08 (2.03)	-2.02 (2.44)	18.18	<.001	0.46	HC>PO, GO; PO>GO
Motor speed	-0.39 (1.22)	-0.42 (1.38)	2.92	.002	0.16	HC>PO; PO>GO
Visuospatial processing	-0.62 (1.34)	-0.87 (1.78)	5.56	.005	0.26	HC>PO
Language	-0.43 (1.46)	-1.12 (1.58)	9.08	<.001	0.34	HC>PO; PO>GO

Abbreviations: GO, good outcome; HC, healthy controls; PO, poor outcome.

^a Indicates a measure of effect size that provides the standardized mean difference between groups and can be interpreted using the following categories⁷³: small = 0.10, medium = 0.25, large = 0.40.

^b Bonferroni-corrected post hoc contrast ($P < .017$).

Table 3
Scores on the Neurocognitive Domains for Clinical High-Risk Subjects With Good and Poor Role Outcome

Score	Mean (SD)		F _{2,152} Value	P Value	Cohen's <i>f</i> ^a	Post hoc Contrasts ^b
	Good Role (n = 47)	Poor Role (n = 45)				
Verbal memory	-0.58 (1.01)	-1.33 (1.56)	19.12	<.001	0.47	HC>PO; PO>GO
Working memory	-0.40 (1.24)	-0.96 (1.25)	8.75	<.001	0.35	HC>PO
Executive function	-0.18 (1.29)	-1.76 (2.87)	11.36	<.001	0.45	HC>PO; PO>GO
Sustained attention	-0.48 (1.26)	-0.68 (1.45)	6.15	.003	0.24	HC>PO; PO>GO
Processing speed	-0.75 (1.29)	-2.44 (2.91)	17.56	<.001	0.58	HC>PO, GO
Motor speed	-0.09 (1.04)	-0.81 (1.50)	3.32	.06	0.31	...
Visuospatial processing	-0.62 (1.31)	-0.86 (1.79)	5.54	.01	0.27	HC>PO
Language	-0.34 (1.27)	-1.31 (1.77)	8.95	<.001	0.42	HC>PO; PO>GO

Abbreviations: GO, good outcome; HC, healthy controls; PO, poor outcome.

^a Indicates a measure of effect size that provides the standardized mean difference between groups and can be interpreted using the following categories⁷³: small = 0.10, medium = 0.25, large = 0.40.

^b Bonferroni-corrected post hoc contrast (*P* < .017).

Table 4

Logistic Regression Model Predicting Social Outcome

Variable	β	SE	Wald	OR (95% CI)	P Value	AUC ^a (SE) [95% CI]	R ² _N	Sensitivity	Specificity
Processing speed ^b	0.324	0.141	5.31	1.38 (1.050-1.823)	.02				
Social functioning ^b	0.617	0.198	9.72	1.85 (1.258-2.732)	.002	0.824 (0.045) [0.736-0.913]	0.393	0.727	0.750
SOPS total disorganization subscale score (>4)	1.621	0.604	7.20	5.06 (1.548-16.527)	.007				

Abbreviations: AUC, area under the curve; OR, odds ratio; R²_N, Nagelkerke pseudo R² statistic; SE, standard error; SOPS, Scale of Prodromal Symptoms.

^aThe AUC values can range from 0.5 (indicates that an instrument can discriminate between groups no better than chance) to 1.0 (represents perfect discriminatory performance) and can be interpreted using the following categories: acceptable = 0.70, good = 0.80, and excellent = 0.90.

^bTo keep all coefficients positive, Global Functioning: Social and Global Functioning: Role scores have been inverted (subtracting 1) so that a higher number indicates poorer functioning (eg, a score of 10 equals 1). Processing speed and verbal memory scores were also inverted (multiplied by -1) so that a larger z score indicates worse performance.

Table 5

Logistic Regression Model Predicting Role Outcome

Variable	β	SE	Wald	OR (95% CI)	P Value	AUC ^a (SE) [95% CI]	R ² _N	Sensitivity	Specificity
Verbal memory ^b	0.555	0.203	7.45	1.74 (1.169-2.594)	.006				
Role functioning ^b	0.294	0.124	5.67	1.34 (1.053-1.711)	.02	0.77 (0.048) [0.68-0.87]	0.32	0.622	0.723
Motor disturbances	0.573	0.263	4.76	1.77 (1.060-2.969)	.03				

Abbreviations: AUC, area under the curve; OR, odds ratio; R²_N, Nagelkerke pseudo R² statistic; SE, standard error.

^aThe AUC values can range from 0.5 (indicates that an instrument can discriminate between groups no better than chance) to 1.0 (represents perfect discriminatory performance) and can be interpreted using the following categories: acceptable = 0.70, good = 0.80, and excellent = 0.90.

^bTo keep all coefficients positive, Global Functioning: Social and Global Functioning: Role scores have been inverted (subtracting 1) so that a higher number indicates poorer functioning (eg, a score of 10 equals 1). Processing speed and verbal memory scores were also inverted (multiplied by -1) so that a larger z score indicates worse performance.