Predictors of Functional and Clinical Outcome in Early-Onset First-Episode Psychosis: The Child and Adolescent First Episode of Psychosis (CAFEPS) Study

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ABSTRACT

Objective: The objective of this study was to study baseline clinical and biological predictors of 2-year outcome in a cohort of children and adolescents with a first episode of psychosis.

Method: Standard instruments were used to evaluate symptoms and functioning in 110 children and adolescents (mean age = 15.47 years) with first episode of psychosis at admission (between 2003 and 2005) and after 2-year follow-up. Clinical assessments included diagnostic assessment to yield *DSM-IV* diagnosis, developmental, premorbid, and past-year data, together with structural neuroimaging and other biological parameters (genetics and oxidative stress). Eighty-three subjects had assessments at baseline (including the Strauss-Carpenter Outcome Scale [SCOS]) and at 2-year follow-up. Association and multistep regression analyses were conducted to show correlates and predictors of primary outcome measures: functional outcome (Children's Global Assessment Scale [CGAS]), improvement (CGAS change), and primary negative symptoms (Proxy for the Deficit Syndrome Scale).

Results: The SCOS predicted 27.46% ($P < .001$) of the variance in CGAS score at 2 years. Baseline severity (measured by CGAS) predicted 30.9% ($P < .001$) of CGAS improvement after 2 years, and SCOS total score predicted an added 24.1% ($P < .001$). A diagnosis of nonaffective psychosis, primary negative symptoms, and less white matter at baseline predicted more primary negative symptoms at follow-up. The prediction of functional outcome was not increased by genetic, oxidative stress, or neurostructural markers.

Conclusions: Baseline clinical assessments have a better predictive value than biological assessments for 2-year follow-up functioning of children and adolescents with a first episode of psychosis. Patients with primary negative symptoms at baseline continue to have negative symptoms 2 years later, and neurostructural markers predict these. Clinicians must still rely on clinical variables to judge the functional prognosis of early-onset first psychotic episodes.

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It is difficult to predict the clinical outcome of a first episode of psychosis, particularly in early-onset cases, as very few studies have included these populations.[1] The course of illness is typically heterogeneous after a first episode,[2] and the supposedly worse outcome of early-onset versus later-onset schizophrenia is not clear when psychosis other than schizophrenia and adolescent onset (in addition to childhood onset) is included.[3–5] Only about 20% of subjects presenting with a psychotic episode in adolescence receive a specific diagnosis such as schizophrenia or bipolar disorder at the time of the first episode. Those diagnosed with schizophrenia or bipolar disorder at baseline have very stable diagnoses, whereas the stability of those with a diagnosis different from schizophrenia or bipolar disorder—roughly 80% of subjects—is very low.[6] In addition, full symptomatic recovery has been shown in 8%–17% of young subjects with a first episode of psychosis.[1,6]

Baseline premorbid functioning, duration of untreated psychosis, insidious onset, and cognitive functioning are usually reported as predicting general outcome in adult samples.[7–16] In addition, differential patterns of clinical and functional deterioration have recently been described.[15] Poor premorbid social adjustment and significant premorbid social deterioration have been associated with a negative course,[10,17] while longer duration of untreated psychosis has been associated with poorer functional outcome.[10] Gray matter reduction is associated with conversion to psychosis in high-risk individuals and with poor outcome in adolescent first episode of psychosis.[18,19] Oxidative stress–mediated pathology may be a contributor to the physiopathology of schizophrenia and other neurodevelopmental disorders by being a downstream mechanism between gene and environmental risk factors and clinical symptoms of severe mental disorders.[20,21] Oxidative stress has been shown to damage the cell membrane, to contribute to the physiopathology of schizophrenia, and to be associated with its clinical course.[22] A few specific polymorphisms have been associated with risk liability for psychosis and very

Clinical Points

- Prodromal features (during the year before onset of psychosis) and duration of untreated psychosis are core to predicting functional outcome.
- Early detection and treatment may improve functional outcome of recent-onset psychosis.
- Biological measurements are important for research but still lack clinical usefulness.

few with clinical outcome.[23] However, most studies focus on clinical and demographic variables or biomarkers, and very few include all of those within the same study.

The aim of this study was to assess the differential predictive value of clinical and biological data at the emergence of early-onset first episode of psychosis. In view of the existing literature, we hypothesized that (1) more baseline negative symptoms, worse premorbid adjustment, longer duration of untreated psychosis, poorer insight, reduced cognitive functioning, and reduced frontal gray matter volume would predict worse global functioning at 2 years; (2) the nonaffective, nonschizophrenic psychosis group would improve more than the other 2 groups; and (3) more baseline negative symptoms, worse cognitive functioning, worse infancy adjustment, and reduced frontal gray matter volume at baseline would predict primary negative symptoms at 2 years.

METHOD

Procedure

This is a prospective cohort study of an initial sample of 110 children and adolescents with a first episode of psychosis, followed for 2 years (the Child and Adolescent First Episode of Psychosis [CAFEPS] study). Prediction of 2-year outcome from baseline data, which is the primary objective of the study, is reported for 83 subjects for whom clinical data were available at 2 years. Sample data were collected between 2003 and 2005. Patients were recruited from 6 different sites by attending psychiatrists. The complete procedure has been published elsewhere.[24] Sites were not homogeneous in number of patients included, their diagnoses, mean age, and other clinical or brain structure variables.[24,25] Basic inclusion criteria were 9–17 years of age and a first episode of psychosis (*DSM-IV*) of less than 6 months' duration. Basic exclusion criteria were mental retardation (per *DSM-IV* criteria) or pervasive developmental disorder, drug-induced psychosis, neurologic disorders or history of head trauma, and presence of *DSM* comorbid diagnoses. Children and adolescents consecutively treated for a first episode of psychosis were enrolled if they fulfilled inclusion but not exclusion criteria and they and their parents/guardians signed an informed consent form after the procedures of the study were fully explained; subjects under 12 years of age gave assent.

An age- and gender-matched control group (n = 98) was also recruited in the CAFEPS study.[24] For the purposes of this article, the control group was used only to standardize the neurocognitive and neuroimaging data.

The 6 institutional review boards (IRBs) of the participating centers approved the study.

Primary Outcome Variables

Outcome variables at 2-year follow-up were (1) global functioning, (2) functional improvement, and (3) presence of primary negative symptoms (not secondary to affective or other general psychopathology).

Clinical and Neuropsychological Measurements

Global functioning was assessed by means of the Children's Global Assessment Scale (CGAS),[26] which measures global severity by rating patient psychological, social, and occupational functioning and has been validated for children and adolescents. Functional improvement was the change in global functioning (2-year CGAS score minus baseline CGAS score). The CGAS and the Positive and Negative Syndrome Scale (PANSS)[27] were administered both at baseline and at 2 years. We calculated primary negative symptoms, ie, negative symptoms not secondary to affective or other general psychopathology, using the Proxy for the Deficit Syndrome Scale (PDS),[28] which consists of combining PANSS item scores as follows: PDS = (blunted affect + poverty of speech) – (hostility + anxiety + guilt + depression). A high score means a high number of negative symptoms and an absence of dysphoria typical of deficit patients.[28] The PANSS was used as the measure of psychopathology given its ample use in the literature, the absence of instruments validated for children/adolescents that permit the same kind of evaluation, and the fact that the sample is mainly composed of adolescents, all with acute episodes, which makes the clinical picture very similar to that of adults. The fact that the instrument is administered by clinicians (not self-rated) also minimizes the shortcomings of using an instrument not validated in children and adolescents.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)[29] was administered at baseline and at 2 years. At 2 years, the researcher administering the K-SADS-PL was blinded to the initial diagnosis. The Clinical Global Impressions (CGI) Scale,[30] the childhood subscale of the Cannon-Spoor Premorbid Adjustment Scale (PAS),[31] the Scale to Assess Unawareness of Mental Disorders,[32] the Strauss-Carpenter Outcome Scale (SCOS),[33] the Neurological Evaluation Scale,[33,34] and the Lewis-Murray Obstetric Complications Scale[35] were administered at baseline. Duration of untreated psychosis was the time in days from the onset of any positive symptom to the baseline assessment. All scales were administered by experienced psychiatrists (PANSS reliability: within-class correlation coefficients higher than 0.8). The information was gathered from interviews with subjects and parents, medical records, and other relevant informants.

A comprehensive neuropsychological assessment was conducted at baseline by 7 trained research psychologists, with interrater reliability in administering and scoring the preestablished tests of > 0.85 (interclass correlation

coefficient).[36,37] Raw test scores were converted to *z* scores (mean = 0, SD = 1) based on the performance of the control group. To derive the *z* scores, the sample was divided into 3 age groups (9–14, 15–16, and 17 years), minimizing the effect of age and education. The *z* scores were truncated at ±4 to avoid outlying variables and calculated in such a way that higher scores always reflected better performance. Summary scores were calculated for executive functioning and prefrontal cognitive functioning, using mean *z* scores derived from the neuropsychological test variables listed in footnotes *b* and *c* of Table 1. We also checked if either prefrontal cognition or executive functioning correlated with age, and neither the results for the whole sample nor the results by diagnosis did so (whole sample: age × prefrontal cognition, Spearman $r = 0.128$, $P = .247$; executive functioning, $r = 0.688$, $P = .247$; schizophrenia: age × prefrontal cognition, Spearman $r = 0.240$, $P = .147$; executive functioning, $r = 0.142$, $P = .395$; bipolar: age × prefrontal cognition, Spearman $r = 0.018$, $P = .940$; executive functioning, $r = 0.042$, $P = .859$; other psychosis: age × prefrontal cognition, Spearman $r = 0.020$, $P = .924$; executive functioning, $r = 0.274$, $P = .185$). Estimated intelligence quotient was calculated with the block design and vocabulary subtests of the Wechsler Intelligence Scale for Children-revised (WISC-R) or Wechsler Adult Intelligence Scale (WAIS) accordingly, based on the method proposed by Sattler and Ryan.[38]

All clinical assessments were conducted by child and adolescent psychiatrists with experience in early-onset psychosis and with reliability in the K-SADS-PL and PANSS (interrater intraclass correlation coefficient > 0.80).

Biological Measurements

Genetics. The polymorphisms analyzed were Val158Met (catechol-*O*-methyltransferase [*COMT*]); C677T (methylenetetrahydrofolate reductase [*MTHFR*]); Taq1A (D_2 dopamine receptor gene [*DRD2*]); Ser9Gly (D_3 dopamine receptor gene [*DRD3*]); −1438G>A, T102C, and His452Tyr (5-hydroxytryptamine receptor 2_A, [*HTR2A*]); and Cys23Ser (*HTR2C*), serotonin-transporter-linked polymorphic region (*5-HTTLPR*), and STin2 VNTR (solute carrier family 6, member 4 [*SLC6A4*]). They were chosen at the time of the initial analyses of the study from among those polymorphisms that were replicated in schizophrenia and informative (including polymorphisms of the dopamine receptors and metabolism enzymes, serotonin receptors, and transporter and methylation processes) and taking into account the sample available, which limits the quantity of variables to study.[39–41]

Oxidative metabolism. Total antioxidant status, lipid peroxidation, antioxidant enzyme activities (catalase, superoxide dismutase, and glutathione peroxidase), and total glutathione levels were determined at baseline. Immediately after enrollment, blood samples were taken in heparin tubes and processed per standard procedures. Blood cells and plasma were immediately frozen at −80°C, and all samples were tested at one time. All tests were conducted by standard methods, which are explained elsewhere.[42]

Neuroimaging. Magnetic resonance imaging (MRI) was conducted within 3 months of the baseline assessment, as soon as the patient was symptomatically controlled enough to tolerate the procedure. Five different scanning facilities contributed data to the study, which were then processed at 1 site. Two axial MRI sequences were acquired for each subject, a T1-weighted 3D gradient echo (voxel size = 1 × 1 × 1.5 mm) and a T2-weighted turbo spin echo (voxel size = 1 × 1 × 3.5 mm). To minimize the effect of the multicenter design, we matched the sample of patients and controls within each of the 5 contributing institutions. Total and regional (frontal, parietal, temporal, and occipital) brain volumes, total and regional gray matter, white matter, and cerebrospinal fluid data were obtained, with semiautomated segmentation of the brain based on the Talairach proportional grid system[43] and then processed and quantified with locally devised, validated methodology.[44] Full details about the acquisition parameters and procedures at each site and the comparability among machines for this study are provided in Reig et al.[45]

A principal components analysis was conducted with all the total and regional brain, gray matter, and white matter volumes, corrected by total brain volume and age. Four variables (total gray matter, total white matter, bilateral frontal, and lateral ventricle volumes) explained 60% of the variance in the imaging data and represented relevant anatomic and clinical domains and were therefore included in subsequent analyses.

Analyses

Standard association analyses were conducted to explore the relationship between baseline putative predictive variables and outcome variables. Normality of continuous variables was assessed with the Kolmogorov-Smirnov test. Parametric or nonparametric tests were correspondingly applied. A repeated-measures analysis of variance test was used to assess the change in psychopathology and global functioning over the follow-up period. As we confirmed significant variations in some clinical assessments across sites (CGAS at 2 years: $F = 3.253$, $P = .01$; primary negative symptoms at 2 years: $F = 6.002$, $P < .001$), site was used as a confounding variable in the analyses.

Linear regression analyses were conducted to ascertain the predictive value of baseline variables on outcome variables. For the multiple regressions, we used a combination of standard and hierarchical approaches. Preliminary linear regressions were conducted to ensure no violation of the assumptions of linearity, independence, homoscedasticity, normality, and multicollinearity. We first included all variables that yielded significant results in the bivariate analyses and those hypothesized to influence a given outcome. Then, we repeated regression analyses excluding those variables that reduced the number of subjects and did not contribute to the model. Finally, we calculated the independent contribution of each independent variable to the final model by squaring its part correlations. Analyses were performed using SPSS (version 18; IBM Corp).

RESULTS

Eighty-three of the initial 110 patients (69% male) were followed from baseline to 2 years, with valid clinical measurements and diagnoses (75.45% attrition). The diagnoses were considered valid if they were stable (made or confirmed at least 1 year after the initial assessment). Age, gender, global functioning, and severity of psychopathology (PANSS) did not differ between those patients available at 2 years and those unavailable (data not shown). Baseline characteristics of the sample are presented in Table 1.

At baseline, 8 patients (9.6%) were diagnosed with schizophrenia, 10 (12%) with bipolar disorder, and 65 (78.3%) with "other psychosis." At follow-up, 38 patients (45.8%) had schizophrenia diagnosis, 20 (24.1%) had bipolar disorder, and 25 (30.1%) had other psychosis. Within "other psychosis," the diagnoses were 7 schizoaffective disorders, 5 schizophreniform disorders, 1 acute reactive psychosis, 5 depressive episodes with psychotic symptoms, and 7 psychosis not otherwise specified. There were no psychopathology or global functioning differences between diagnostic groups at baseline (see Supplementary eTable 1). There were 8 patients (9.6%) with a 2-year CGAS score less than or equal to 40, corresponding to severe global functioning impairment, and 22 patients (26.8%) with adequate functioning in all areas (CGAS score > 80). At follow-up, primary negative symptoms were more prominent in the schizophrenia group ($F = 0.331$, $P < .001$; schizophrenia vs bipolar, $P = .009$; and schizophrenia vs other psychosis, $P < .001$).

Changes in global functioning and psychopathology from baseline to 2 years are presented in Table 2.

Associations between baseline variables and global functioning, functioning change, and primary negative symptoms at 2 years are presented in Table 3.

Global Functioning

Global functioning at 2 years was better in older patients, those with shorter duration of untreated psychosis, better baseline prefrontal cognition, better prognostic features (total score on the SCOS), and better adjustment in childhood (Table 3). Within the SCOS items, better academic status, more social contacts and fullness of life in the year before psychosis onset, later onset of any psychiatric symptom, absence of conduct disorders, and shorter duration of psychotic symptoms were positively associated with better functioning at 2 years (all with $P = .001$). Blunted affect in the previous month correlated negatively with CGAS at 2 years ($P = .02$).

Functional Improvement

Functional improvement was greater for those with higher levels of baseline severity (higher CGI and lower CGAS), shorter duration of untreated psychosis, better prognostic features (SCOS score), and better adjustment in childhood (Table 3). Several independent SCOS items were associated with change in CGAS, specifically quantity and quality of social contacts in the past year (more contacts associated with more improvement) and independence for basic needs and fullness of life; later onset of any psychiatric symptoms, absence of conduct problems after age 12 years, and less presence and duration of psychotic psychopathology (all P values < .001).

Table 1. Baseline Characteristics of the Sample (n = 83)

Characteristic	n	Mean	SD
Age, y	83	15.47	1.80
Parent studies, y	80	11.60	3.83
Birth weight, g	70	3,259.64	449.76
Estimated IQ[a]	81	81.00	18.33
Executive functioning[b]	83	−0.91	0.84
Prefrontal cognition[c]	83	−0.69	0.93
CGAS	83	33.39	15.53
CGI	83	5.58	1.08
DUP, d	83	64.54	52.25
PANSS			
Positive score	83	23.94	6.09
Negative score	83	19.93	9.25
General score	83	44.87	11.26
Total score	83	88.73	20.78
Deficit syndrome	83	−5.80	4.31
Total SCOS	83	52.84	7.70
PAS infancy	83	7.43	4.86
SUMD	82	3.23	1.52
Gray matter volume[d]	71	−16.66	34.40
White matter volume[d]	71	0.30	1.67
Bilateral frontal volume[d]	71	−0.21	17.44
Lateral ventricles CSF[d]	71	2.27	6.01
Total NES	83	25.48	9.90

[a]Estimated IQ was calculated using the block design and vocabulary subtests of the Wechsler Adult Intelligence Scale or Wechsler Intelligence Scale for Children (see Method).
[b]Executive functioning is a composite score (arithmetic mean) obtained from those measures (*z* scores) considered to be related to executive functioning: total errors, perseverative errors, and conceptual-level responses on the Wisconsin Card Sorting Test; Stroop Test interference score; number of correct words on the Controlled Verbal Fluency Task; and time to complete and number of errors on Trail Making Test-B.
[c]Prefrontal cognitive functioning is a summary score (arithmetic mean) obtained from the summary scores of attention (reaction time and correct responses on the Continuous Performance Test II; Digit Span Forward, Trail Making Test-A; Stroop Test words and colors), working memory (Wechsler Adult Intelligence Scale, Digit Span Backward, and Letter-Number Sequencing), and executive functioning (*z* scores; see Method).
[d]Regression residuals.
Abbreviations: CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impressions, CSF = cerebrospinal fluid, DUP = duration of untreated psychosis, PANSS = Positive and Negative Syndrome Scale, NES = Neurological Evaluation Scale, PAS = Premorbid Adjustment Scale, SCOS = Strauss-Carpender Outcome Scale, SUMD = Scale to Assess Unawareness of Mental Disorders.

Table 2. Changes in Global Functioning and Psychopathology From Baseline to 2 Years

	Baseline (n = 83)		2 Years (n = 82)				
Measure	Mean (range)	SD	Mean (range)	SD	Statistic	*P* Value	*df*
CGAS	33.49 (5–85)	14.836	66.66 (15–95)	19.307	−7.415[a]	< .001	80
PANSS							
Total	88.830 (30–146)	20.891	56.768 (30–42)	21.681	10.931[b]	< .001	81
Positive	23.976 (7–40)	6.122	12.292 (7–37)	6.181	13.079[b]	< .001	81
Negative	20.085 (7–38)	9.191	15.988 (7–39)	7.736	3.928[b]	< .001	81
General	44.768 (16–74)	11.292	28.488 (16–66)	10.795	10.344[b]	< .001	81

[a]Wilcoxon rank test.
[b]Repeated-measures *t*.
Abbreviations: CGAS = Children's Global Assessment Scale, PANSS = Positive and Negative Syndrome Scale.

Table 3. Associations Between Baseline Variables and Global Functioning at 2 Years and Functional Change Between Baseline and 2 Years

	2-Year CGAS			CGAS Change			2-Year PNS		
Baseline Data	Statistic	*P* Value[a]	*df*	Statistic	*P* Value[a]	*df*	Statistic	*P* Value[a]	*df*
Recruitment site	$F=3.253$	**.010**	76,5	$F=4.482$	**.001**	76,5	$F=6.002$	**<.001**	76,5
Age	$r=0.253$	**.022**	81	$r=0.137$	.102	81	$r=0.084$	.453	81
Gender	$t=-0.014$	.989	81	$t=1.012$	.315	81	$t=-0.157$	.876	81
Parental education (y)	$r=0.066$	.564	78	$r=-0.049$	.664	78	$r=-0.005$	.964	78
Baseline diagnosis	$F=1.045$	.357	79,2	$F=1.769$	.177	79,2	$F=5.737$	**.005**	79,2
Birth weight	$r=0.202$	.093	68	$r=0.076$	.375	68	$r=-0.112$	.357	68
OCS delivery	$t=-1.315$	.172	75	$t=-0.143$	.887	75	$t=0.233$	.816	75
Estimated IQ	$r=0.097$	.393	79	$r=-0.038$	.739	79	$r=-0.109$	.336	79
Prefrontal cognition	$r=0.382$	**<.001**	78	$r=0.118$	.290	78	$r=-0.003$	.976	78
Executive functioning	$r=0.028$	.803	80	$r=0.056$	.643	80	$r=0.038$	.754	80
CGAS baseline	$r=0.019$	.868	80	$r=-0.593$	**<.001**	80	$r=-0.085$	.447	80
DUP (d)	$r=-0.347$	**.001**	81	$r=-0.428$	**<.001**	81	$r=0.058$	.604	81
CGI	$r=-0.143$	.2	81	$r=0.260$	**.003**	81	$r=-0.069$	.537	81
PANSS									
Positive score	$r=-0.09$	.460	80	$r=-0.098$	.418	80	$r=-0.116$	.338	80
Negative score	$r=-0.0124$	.305	80	$r=-0.156$	.196	80	$r=0.155$	.199	80
General score	$r=0.030$	.804	80	$r=-0.094$	.440	80	$r=-0.242$	**.043**	80
Total score	$r=-0.002$	.989	80	$r=0.035$	.758	80	$r=-0.113$	**.311**	80
PNS	$t=-0.024$	.981	81	$t=0.508$	.617	81	$t=0.247$	**.025**	81
Total SCOS	$r=0.603$	**<.001**	81	$r=0.535$	**<.001**	81	$r=0.073$	.516	81
PAS infancy	$r=-0.292$	**.008**	80	$r=-0.269$	**.014**	80	$r=0.073$	.515	80
SUMD	$r=-0.214$	.055	80	$r=-0.018$	.834	80	$r=0.005$	.965	80
Gray matter volume	$r=0.190$	.114	69	$r=0.068$	.575	69	$r=0.109$	.368	69
White matter volume	$r=0.025$	.835	69	$r=-0.187$	.121	69	$r=-0.363$	**.002**	69
Bilateral frontal volume	$r=0.006$	.959	69	$r=0.087$	.475	69	$r=0.029$	.809	69
Lateral ventricle CSF	$r=0.026$	.828	69	$r=0.046$	.576	69	$r=-0.118$	.332	69
Total NES	$r=-0.210$	.058	81	$r=-0.099$	.374	81	$r=-0.108$	.333	81
Glutathione (μmol/L)	$r=0.197$	.180	46	$r=0.109$	.460	46	$r=-0.070$	.639	46
Total antioxidant status (mmol/L)	$r=-0.135$	.361	46	$r=-0.231$	.115	46	$r=0.002$	.991	46
Lipid peroxidation (μmol/L)	$r=0.104$	.516	46	$r=0.055$	.731	46	$r=-0.144$	.368	46

[a]Significant results are indicated in boldface.
Abbreviations: CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impressions, CSF = cerebrospinal fluid, DUP = duration of untreated psychosis, NES = Neurological Evaluation Scale, OCS = Obstetric Complicactions Scale, PANSS = Positive and Negative Syndrome Scale, PAS = Premorbid Adjustment Scale, PNS = primary negative symptoms, SCOS = Strauss-Carpenter Outcome Scale, SUMD = Scale to Assess Unawareness of Mental Disorders.

Blunted affect in the previous month also correlated with less functional improvement ($P=.012$).

No association was found between genetic, biochemical, or baseline neuroimaging variables and 2-year functioning or improvement.

Primary Negative Symptoms

Primary negative symptoms at 2 years were greater in patients with a baseline diagnosis of schizophrenia compared with the other 2 diagnostic groups ($P=.002$ compared with bipolar disorder and $P=.003$ compared with other psychosis) and in patients with lower baseline levels of general psychopathology or higher primary negative symptoms score. Larger white matter volume was associated with fewer primary negative symptoms at follow-up (Table 3).

Prediction Analyses

The regression models that better explained the outcome measures (CGAS, CGAS change, and primary negative symptoms), including the individual contributions of each variable with a significant predictive value, are presented in Table 4.

Global functioning at 2 years was better explained by baseline SCOS total score (Table 4). This variable explained 27.46% of the variance in functioning. A small percentage of the variance in global functioning was explained by prefrontal cognitive functioning. Up to 58.6% of the variance in improvement in global functioning was explained by severity at baseline (the worse the functioning and more severe the disorder at baseline, the larger the improvement) and SCOS total score. Primary negative symptoms at 2 years were better explained by a model that included primary negative symptoms at baseline, baseline diagnosis, white matter volume, and belonging to site 3. These variables together explained 36% of the variance of primary negative symptoms at 2 years.

DISCUSSION

The main result of this study is that clinical variables predicted 2-year follow-up outcome better than selected biomarkers in a sample of children and adolescents with a first episode of psychosis. Specifically, (1) the SCOS was a good predictor of functioning and improvement, (2) patients with greater illness severity experienced higher levels of improvement, (3) primary negative symptoms at baseline had continuity over 2 years, and (4) biological tests did not add significant prognostic value to clinical assessments.

Table 4. Predictive Value of Baseline Characteristics of the Sample on Clinical Outcome at 2-Year Follow-Up

Variable	Nonstandardized Coefficients: B	Nonstandardized Coefficients: Standard Error	Standardized Coefficients, β	Correlations Part	Corrected R^2	Variance Explained, %	Change in *F*	*P* Value (change in *F*)	n	Model *P* Value
CGAS at 2 y										
(constant)	−1.543	12.415			0.40				81	<.001
PCF	4.891	1.861	0.235	0.157		2.47	13.667	<.001		
Total SCOS	1.353	0.225	0.539	0.524		27.46[a]	38.318	<.001		
CGAS change										
(constant)	−19.338	12.774			0.586				82	<.001
Baseline CGAS	−0.859	0.110	−0.558	−0.556		30.9	43.925	<.001		
Baseline total SCOS	1.536	0.224	0.493	0.491		24.1[b]	47.166	<.001		
Deficit syndrome										
(constant)	−4.161	1.113			0.360				70	<.001
Baseline PNS	0.170	0.088	0.188	0.186		3.5	3.391	.070		
Baseline WM	−0.360	0.235	−0.168	−0.147		2.16	11.706	.001		
Site 3	−6.019	1.682	−0.392	−0.345		12	12.714	.001		
Baseline diagnosis	3.278	1.531	0.258	0.206		4.2	0.173	.679		
Schizophrenia	3.136	1.036	0.361	0.291		8.4	9.160	.004		
Other psychosis	−4.161	1.113		0.186		3.4	3.391	.070		

[a]Including the individual items of the SCOS in the model; academic status (item 1B of SCOS) and fullness of life (item 17 of SCOS) in the past year contributed up to 10% of the new general emergent model and total duration of severe psychiatric symptoms before baseline contributed 2.83% (item 11B of SCOS).

[b]Including the individual items of the SCOS in the model; again, academic status (item 1B of SCOS) and fullness of life (item 17 of SCOS) in the past year contributed significantly to the model, explaining up to 11.89% of the variance of new emerging model, and total duration of psychotic symptoms before baseline contributing 2.16%.

Abbreviations: CGAS = Children's Global Assessment Scale, PCF = prefrontal cognitive functioning, PNS = primary negative symptoms, SCOS = Strauss-Carpenter Outcome Scale, WM = white matter.

Total SCOS score for prediction of functioning in this sample is consistent with data from adult samples.[9] SCOS comprises a series of domains assessing mainly social and academic/vocational functioning in the year prior to assessment, lifelong presence of any psychopathology, and subjective feelings of fullness of life prior to baseline assessment. In this study, SCOS total score also significantly predicted improvement. Academic functioning (SCOS item 1B) in the year before the psychotic episode was particularly significant for both outcome measures. General feelings of fullness of life in the past year also predicted outcome, and age at onset of any psychiatric symptom predicted improvement, with patients who had onset before 15 years of age improving less than those with onset after age 16.

In this study, time before baseline assessment (the proxy for duration of untreated psychosis used in this study) and premorbid (childhood) assessment were associated with outcome but not independently of total SCOS score. Numerous studies show a correlation between duration of untreated psychosis and psychosis outcome.[7,10,41] However, when duration of untreated psychosis is analyzed in conjunction with other putative predictive factors such as past adjustment, results vary.[10,12,42,45] In this study, all patients were assessed shortly after onset of psychosis (less than 6 months, per inclusion criteria), which may explain the lack of a predictive effect of this measurement.

Worse premorbid adjustment (up to 1 year before onset) has been consistently shown to be an independent predictor of worse outcome in previous studies.[7,46,47] Although PAS score did not appear to predict functional outcome or negative symptoms independently in our sample, poor baseline educational functioning did. However, we cannot conclude from our data that educational impairment was there before the prodromal period. In this sample, PAS was lower in patients than in controls ($U = 2245.5$, $P < .001$; C.A., unpublished data, 2005). Other studies have shown a deterioration in academic functioning in subjects with schizophrenia, particularly with a deficit course, by assessing PAS from childhood to adolescence.[17] In this sample, although prefrontal cognition at baseline was associated with global functioning at 2 years, once the effect of time with untreated psychosis and other prodromal prognostic factors were taken into account, only a small effect was seen in the final model. Cognitive performance was quite low in this sample compared with other samples of first episodes of psychosis. The mean estimated intelligence quotient in this sample was 81 and was not different between diagnostic groups. This homogeneous low functioning may explain the absence of a greater predictive effect of prefrontal cognition.

Patients with more severe symptoms have more room for improvement, and that seems to have been the case in this sample. As expected,[48] not only the CGAS but all measures of positive, negative, and general psychopathology improved over the course of the 2 years after the first episode. In fact, a quarter of the patients had good functioning 2 years after the episode.

Primary negative symptoms showed stability over the first 2 years of the schizophrenia course, in line with our and others' data.[6,49,50] However, we did not find a relationship between premorbid adjustment and negative symptoms, as other studies do.[10,47] Total white matter volume at baseline had some predictive value in this sample. A few recent diffusion tensor imaging studies[51,52] have shown that poor integration of white matter in psychosis or in high-risk

individuals predicts a poor outcome, but there are no data in the literature to assess whether the structural volumetric abnormalities found in our study are consistently associated with prognosis. In addition, the physiological significance of a global measure of white matter volume is not clear.

As shown, laboratory variables yielded very little predictive value in this study. Although oxidative stress and genetic polymorphisms have been associated with outcome in other samples,[42,53,54] the intensity of the effect, particularly for individual polymorphisms, may not be large enough to be tested with our sample. In addition, our gene selection may not have been optimal. In this sample, only the *MTHR* gene (which mediates DNA methylation) turned out to be associated with a baseline diagnosis of psychosis in a previous analysis,[55] but other genes not analyzed here, such as *DISC*, *NRG*, and *HLA* have proven to be better candidates for liability to schizophrenia. However, their predictive value for illness outcome is still largely unknown. The lack of relevant predictive value for biological variables in this study was consistent with the literature.[8]

With regard to the main limitations of the study, a small sample size for the number of variables considered and the heterogeneity in terms of diagnosis of the sample are 2 important ones. However, heterogeneity is inevitable, as this is a first episode of psychosis sample, and we wanted to evaluate the differential weight of the available measurements at psychosis onset in a prognostic evaluation. Biological tests available at the time of the study have changed a great deal, and results may have varied if we had included newly associated candidate risk polymorphisms. However, the capacity to predict outcome in studies of individual polymorphisms has not rendered much profit yet. Despite the small size and heterogeneity of the sample, this is the largest sample of first episode of psychosis in children and adolescents followed prospectively and providing a structured assessment of clinical and biological aspects in order to predict functional outcome. The dropout rate (24.5%), mainly due to patients' refusal to continue participating in the study (14%), although significant, was no higher than in other equivalent studies (follow-up studies with patients after a first episode of psychosis).[55] Patients who dropped out and patients who completed the protocol did not differ in main clinical variables.[6] In addition to the aforementioned limitations, the lack of absolute blinding at the 2-year assessment (only for the diagnostic assessment) may have biased the results. Finally, given the number of variables included in this study, we had to choose among many possible dependent variables, and we may have left out potential confounders, including but not limited to pharmacologic treatment. We chose not to include pharmacologic treatment because previous studies with this sample have shown no effect on clinical, cognitive, or brain structure measurements.

We believe that the data presented here are very representative of the Spanish general population (with more than 90% of the patients Caucasian and 7% Hispanic). Early-onset psychosis is a rare condition, and the 6 sites where the recruitment took place include the main clinical centers in the country and most of the inpatient beds for adolescents. Therefore, most adolescents with a psychotic episode are admitted to one of the sites participating in this study.

In conclusion, our data show differential predictive variables for functioning and clinical outcomes. The SCOS results shown here point to the importance of the year before positive symptom onset on later functioning (particularly general and academic functioning), thus emphasizing the need for identification of symptoms and treatment very early in the course of the illness, as some groups are already doing.[57,58] Severity and later onset of psychopathology predict improvement, and primary negative symptoms at baseline show continuity in the long term. Clinical as opposed to biological assessments have better general predictive value and, in particular, the regular use of outcome scales such as the SCOS might be useful for clinical purposes.

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Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

Supplementary material follows this article.

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Supplementary Material

Article Title: Predictors of Functional and Clinical Outcome in Early-Onset First-Episode Psychosis: The Child and Adolescent First Episode of Psychosis (CAFEPS) Study

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List of Supplementary Material for the article

1. eTable 1 Baseline characteristics of the sample by diagnostic (2-years) group

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Baseline characteristics of the sample by diagnostic (2-years) group

	ESQ (N=38)	Bipolar (N=20)	OP (N=25)	ANOVA		Kruskal-Wallis	
				$F_{2;82}$	Sig.	X2	Sig.
Age m (SD), median	15.18 (1.98) 16	16.1 (1.41) 16.5	15.4 (1.71) 15			3.53	0.17
Parent studies (years)	11.92 (3.54)	11 (2.83)	11.56 (4.85)			0.47	0.79
Birth Weight	3322.21 (430.98)	3123 (634.19)	3255.95 (298.68)	1.02	0.37		
Estimated-IQ [a]	80.71 (15.66)	81.05 (20.83)	81.42 (20.82)	0.01	0.99		
Prefrontal Cognition [b]	-0.82 (0.96)	-0.56 (0.83)	-0.6 (0.96)	0.69	0.50		
Executive Functioning [b]	-0.84 (0.85)	-0.94 (0.74)	-1 (0.92)	0.28	0.756		
C-GAS	32.37 (14.15)	30.75 (16.73)	37.04 (16.5)			1.32	0.52
CGI	5.74 (0.79)	5.6 (1.27)	5.32 (1.14)			1.68	0.43
DUP (days)	71.76 (52.17)	51.65 (48.82)	63.88 (54.99)			1.63	0.44
PANSS Positive Score	23.95 (4.82)	25.35 (7.59)	22.8 (6.52)	0.97	0.38		
PANSS Negative Score	22.92 (9.26)	16.15 (9.54)	18.4 (7.71)	**4.33**	**0.016**		
PANSS General Score	45.29 (9.38)	46.65 (13.88)	42.8 (11.73)	0.69	0.50		
PANSS Total Score	92.16 (17.24)	88.15 (26.09)	84 (20.88)	1.18	0.31		
PNS	-3.92 (4.13)	-7.3 (2.96)	-7.44 (4.47)	**7.72**	**0.001**		
Total Strauss Carpenter	51.63 (8.46)	53.5 (6.66)	54.16 (7.24)	0.91	0.41		
PAS infancy	8.24 (5.07)	6.1 (3.45)	7.28 (5.38)	1.3	0.28		
SUMD	3.59 (1.46)	3.2 (1.61)	2.72 (1.43)			5.25	0.07
Total NES	24.68 (8.28)	26.05 (9.45)	26.24 (12.52)	0.23	0.80		
Grey Matter Volume [c]	-18.2 (36.54)	-22.57 (31.24)	-8.8 (33.69)	0.82	0.44		
White Matter Volume [c]	0.01 (1.38)	1.04 (2.01)	0.12 (1.65)	2.47	0.09		
Bilateral Frontal Volume [c]	-3 (15.68)	6.9 (16.95)	-2 (19.63)	2.09	0.13		
Lateral Ventricles CSF [c]	2.45 (5.64)	0.8 (2.71)	3.28 (8.36)	0.82	0.44		

C-GAF: Children- Global Assessment Scale; CGI: Clinical Global Impression; CSF: cerebrospinal Fluid; DUP: Duration of Untreated Psychosis; IQ: Intelligent Quotient; NES: Neurological Examination ScalePANSS: Positive and Negative Symptom Scale; PAS: Past Adjustment Scale; PNS: Primary Negative Symptoms; SUMD: Insight into having a mental disorder.

a. Estimated intelligence quotient was calculated with Wechsler Intelligence Scale block design and vocabulary subtests

b. Executive Functioning (EF), a composite that included Wisconsin Card Sorting Test total errors, perseverative errors, and conceptual-level responses, Stroop test interference score, number of correct words on the Controlled Verbal Fluency Task, and time to complete and number of errors on Trail Making Test-B, and 2) Prefrontal Cognitive Functioning (PCF), an index grouping the results of attention tests (reaction time and correct responses on the Continuous Performance Test II; Digit Span Forward, Trail Making Test A; Stroop test words and colors), working memory (Wechsler Adult Intelligence Scale Digit Span Backward and Letter-Number Sequencing), and adding the composite score for EF itself. Standardized z-scores.

c. Regression residuals.