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Dissecting the functional outcomes of first episode schizophrenia spectrum disorders: a 10-year follow-up study in the PAFIP cohort‡

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Original Article

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Abstract

Background. The aim of the current study was to examine the heterogeneity of functional outcomes in first episode psychosis (FEP) patients and related clinical, neurocognitive and sociodemographic factors using a cluster analytic approach.

Method. A large sample of FEP patients ($N = 209$) was functionally reassessed 10 years after the first contact with an early intervention service. Multiple baseline, 3-year and 10-year follow-up variables were explored.

Results. The cluster analysis emphasized the existence of six independent clusters of functioning: one cluster was normal overall (42.16%), two clusters showed moderate interpersonal (9.63%) or instrumental (12.65%) deficits, two clusters showed more severe interpersonal (12.05%) or interpersonal and instrumental (13.85%) deficits and there was a significantly overall impaired cluster (9.63%). Cluster comparisons showed that several baseline and follow-up factors were differentially involved in functional outcomes.

Conclusions. The current study demonstrated that distinct clusters of functioning in FEP patients can be identified. The fact that a variety of profiles was observed contributes to a better understanding of the nature of the heterogeneity characterizing FEP patients and has clinical implications for developing individualized treatment plans.

Introduction

The improvement of everyday functioning of individuals with schizophrenia over the long term is the main outcome measure for determining optimal levels of quality of life in the real world and should be considered to be the real challenge of schizophrenia treatment. Despite recent developments in its clinical management, schizophrenia spectrum disorders (SDDs) are still associated with an uncertain long-term functional prognosis (McGorry, 2015). Patients repeatedly have difficulties in attaining their functional milestones in educational, residential, social and vocational domains (Harvey *et al*., 2012). This also raises the question of accurately measuring multiple domains of function as essential for assessing the effectiveness of treatment strategies on the course of the illness (Harvey and Bellack, 2009).

Early intervention (EI) programs provide an extensive multidisciplinary clinical management during the early phases of the illness, with the major aim of achieving recovery (McGorry *et al*., 2008). They have demonstrated their benefits in reducing the short-term adverse impact of SDD and improving function (De Maio *et al*., 2015; Csillag *et al*., 2017). The superiority of EI over treatment as usual regarding all outcomes was evident at the 2-year follow-up (Correll *et al*., 2018). However, whether these gains are maintained or vanish over the long term, after patients are discharged from specialized EI programs to routine outpatient mental healthcare services, or whether they may provide (as presently designed) a real improvement only for particular subgroups of patients, is still under debate. The success of EI programs broadly varies and has usually been assessed by taking into account group averages and accepting a one-size-fits-all scenario. Therefore, understanding this diversity in outcomes might help to sort out individuals or subgroups of individuals who will benefit from intensive EIs (Austin *et al*., 2015; Velthorst *et al*., 2017).

The long-term outcome assessment in SDD is much more challenging. Apart from the multidimensional nature of outcomes, there are methodological concerns about how best to compare results from studies with different inclusion criteria and different durations of

follow-up (e.g. 5 *v.* 25 years), questioning the validity of comparing between studies with different follow-up periods (McGrath, 2008). Even when comparing prospective EI cohorts with similar long-term follow-up (10 years) (Secher *et al.*, 2015; Chan *et al.*, 2018) several issues concerning outcomes have been left unanswered.

In that context, there is a growing interest in depicting the heterogeneity and subtyping the outcomes, which makes cluster analyses a useful exploratory tool that provides the opportunity to group individuals using a data-driven approach rather than a predetermined set of grouping criteria (Lewandowski *et al.*, 2014; Laloyaux *et al.*, 2018). Follow-up naturalistic studies of first episode of psychosis (FEP) cohorts allow cluster analyses to identify patient characteristics that merit specific intervention.

The current study aims to investigate the heterogeneity of function and outcomes over long term by examining a large epidemiological sample of individuals with non-affective psychosis, 10 years after their inclusion in an EI program. We sought to (1) describe subtypes of functional outcomes according to clinical, neurocognitive and sociodemographic characteristics and (2) examine likely associations of these clusters with other areas of function, such as living independently, occupational/vocational status and active social interactions.

Method

Setting

Data for the current study were obtained from a large cohort of patients representative of the general population of individuals suffering from an FEP in an epidemiological catchment area, which is the autonomous community of Cantabria, located in the Northern coast of Spain (Pelayo-Teran *et al.*, 2008*a*). FEP patients were treated in a longitudinal intervention program (Programa de Atención a Fases Iniciales de Psicosis, PAFIP) conducted at the University Hospital Marqués de Valdecilla (Crespo-Facorro *et al.*, 2005; Crespo-Facorro *et al.*, 2006; Pelayo-Teran *et al.*, 2008*b*). Referrals to the PAFIP came from the inpatient unit and emergency room at the, from outreach mental health services, and from other health-care workers throughout the region of Cantabria. After the initial contact by a qualified psychiatric nurse, an experienced psychiatrist carried out a formal interview for a full assessment of the patient and confirmed the presence of schizophrenia and other primary psychotic disorders (F20–F29). PAFIP includes inpatient and outpatient care and provides multidisciplinary (psychiatric nursing, psychology, psychiatry and social work) and specific and personalized clinical attention from the first contact with PAFIP staff up to 3 years. It has a strong track record with FEP subjects that has included a longitudinal component with multiple assessments. Considering that the PAFIP constitutes the only alternative form of mental health care for FEP, we could defend that the included sample constitutes an epidemiological representation of the population of patients with FEP occurring in the entire region of Cantabria. Accordingly, the patients included in the PAFIP reached an age-corrected (16–60) incidence rate for SDD of 1.38 per 10 000, a figure that is equivalent to the one reported in most epidemiological studies (Crespo-Facorro *et al.*, 2005).

PAFIP-10 is a long-term follow-up study at 10 years (range between 8 and 12 years) of individuals with an FEP who were initially included in PAFIP from February 2001 to July 2008. All patients included in the referred period were invited for a reassessment, which comprised the 10-year follow-up study group.

Ethics

The program, which is fully publicly funded by the regional Mental Health Services, was approved by the local institutional review board (ethics committee for clinical research, CEIC-Cantabria) in accordance with international standards for research ethics (clinical trial numbers NCT0235832 and NCT02534363). Patients who met criteria and provided written informed consent, along with their families, were entered into PAFIP and PAFIP-10 for reassessment.

Baseline inclusion criteria

All referrals to PAFIP were screened against the following inclusion criteria: were 15–60 years of age; lived in the catchment area; experienced their first episode of psychosis; and were antipsychotic medication naïve, or if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks. Meeting the DSM-IV criteria for drug or alcohol dependence, having an intellectual disability and having a history of neurological disease or head injury were exclusion criteria. The diagnoses were confirmed through the use of the Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.*, 1996) conducted by an experienced psychiatrist within 6 months of the baseline visit.

Baseline assessment and intervention at PAFIP

Sociodemographic information was recorded from interviews with patients, their relatives and from medical records on admission. Premorbid social adjustment was measured by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor *et al.*, 1982). Age at psychosis onset [defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred], duration of untreated illness [DUI, defined as the time from the first nonspecific symptom related to psychosis (i.e. with no return to previous level of functioning) to antipsychotic treatment onset], and duration of untreated psychosis [DUP, defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment] were obtained.

The initial social functioning assessment was taken at first contact and 3 months later, when the participants were no longer in the hospital. Thus, the 3-month assessment was used as the starting point.

All participants received 3 years of evidence-based phase-specific individual interventions: pharmacotherapy (the lowest effective dose of antipsychotic as maintenance dosage, monitoring for clinical response and side effects, such as prevent weight gain), psychoeducation, addictions' treatment, vocational and education plans, and group interventions for patients and their families, as well as crisis intervention services, main components of FEP services (Addington *et al.*, 2013), tracking the process of outcome with the expectation of a full recovery. In addition to routine visits, patients were telephonically contacted to schedule face-to-face appointments at 1- and 3-year follow-ups for research purposes.

Tracing and long-term follow-up procedures

Baseline and 10-year characteristics, such as years of education, education level ('only elementary education' *v.* 'other'), socioeconomic status derived from the parents' occupation ('low qualification worker' *v.* 'other'), living area ('urban' *v.* 'rural', defined as

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more or less than 10 000 inhabitants, respectively), relationship status ('married/cohabiting' *v.* 'single/divorced/separate or widowed'), living status ('alone' *v.* 'other'), employment status ('employed' *v.* 'unemployed'), and first degree family history of psychosis, which was based on the subject and family reports ('yes' *v.* 'no'), as well as tobacco, alcohol and cannabis consumption as dichotomous (no/yes) measures were recorded. Information on suicidal behaviors, i.e. 'potentially self-injurious behavior for which the person intended to kill himself/herself' (Silverman *et al.*, 2007*a*, 2007*b*), which encompasses suicide attempts and suicide completions, were collected.

Based on follow-up information, diagnoses stability *v.* change was considered at 10 years reassessment by means of SCID-I information.

Symptom assessment

Clinical data were collected at four different points throughout the 10-year period. The same senior consultant psychiatrist (BC-F) interviewed patients at the baseline, 1-year, 3-year and 10-year follow-up. Respondents completed face-to-face interviews. Clinical symptoms of psychosis were assessed by the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). SANS-SAPS dimensions of positive (scores for hallucinations and delusions), disorganized (scores for formal thought disorder, bizarre behavior and inappropriate affect) and negative (scores for alogia, affective fattening, apathy and anhedonia) symptoms were calculated (Grube *et al.*, 1998). Manic symptoms were assessed with the Young Mania Rating Scale (YMRS) (Young *et al.*, 1978), general psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) (Flemenbaum and Zimmermann, 1973), and depressive symptom severity was measured using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington *et al.*, 1992).

Neurocognition measures

The WAIS-III vocabulary subtest, a proven measure of crystallized intelligence, was used to estimate premorbid IQ. A measure of global cognitive functioning (GCF) was calculated in accordance with previous methodology (Reichenberg *et al.*, 2009). Scores on the seven cognitive domains fundamentally impaired in psychosis were converted to *T*-scores derived from a healthy comparison sample and converted to deficit scores that reflected the presence and severity of cognitive deficit in each cognitive domain. Deficit scores were then averaged to create the GCF measure at baseline and the 3-year and 10-year follow-up assessments.

Measures of 10-year functional outcomes

Ten-year functional outcomes were measured by three widely used scales: the Disability Assessment Scale (DAS) Spanish version (Mañá *et al.*, 1998), the Global Assessment of Function (GAF) (Pedersen *et al.*, 2007) and the Quality of Life Scale (QLS) (Heinrichs *et al.*, 1984).

The DAS is a semistructured interview that assesses several areas of functioning: self-care, social withdrawal, participation in the household, relationship with spouse or partner, occupational role and general interest. These areas are rated on a 6-point scale: 0, no disability; 1, minimum disability; 2, obvious disability; ⩾3, serious to maximum disability.

The GAF is a numeric scale (0 through 100) used by mental health professionals to subjectively rate social, occupational and psychological functioning. The highest ratings are 91–100, 'Superior functioning in a wide range of activities', and the lowest ratings 10–1, 'Persistent inability to maintain minimal personal hygiene'.

The QLS is a 21-item scale rated from a semistructured interview providing information on four domains (interpersonal relations, instrumental role, intrapsychic foundations, common objects and activities) on a 7-point scale (0–1, severe impairment, to 5–6, normal or unimpaired functioning). The specific descriptors vary among items, but the high end of the scales (scores of 5 and 6) reflects normal or unimpaired functioning, and the low end of the scales (scores of 0 and 1) reflects severe impairment of the function in question.

Assessment interviews were performed by two experienced raters (psychiatrist and psychologist) per subject. An overall judgment was established with a full consensus rating reached together with the psychiatric nurse and the social worker.

Recovery, comprising symptomatic remission and adequate psychosocial function at 1, 3 and 10-year follow-ups, was determined by scores of 2 or less in the corresponding items of the SANS and the SAPS scales, as established by the remission work group (Andreasen *et al.*, 2005), and a score of 1 or less in the DAS scale.

Data analyses

The data were analyzed using the R statistical computer program (R Development Core Team, 2010), version 3.5.1 (http://www.r-project.org). Cluster analyses were performed using R packages (script available upon request).

The possible relationships between the functional characteristics were explored using principal component analysis (PCA) and hierarchical clustering (HC) applied to the mean-centered and SD-scaled (*z*-transformed) data. The HC analysis was based on the Euclidean distance and Ward's linkage method. The results were visualized by means of dendrograms and a PCA biplot of the first two principal components.

The number of clusters examined was selected by visual inspection of the dendrograms and confirmed by discriminant function analysis. Clusters (using *K*-means results) were then compared on sociodemographic, clinical and cognitive variables using analysis of variance (ANOVA) or χ^2. Post-hoc *t* tests with Bonferroni correction were conducted to examine pairwise relationships between clusters.

Results

Study description

Out of the 307 patients assessed at baseline, from February 2001 to July 2008, 10 patients died, including four deaths from suicide, during the follow-up period. Out of the 297 eligible participants who took part in the PAFIP study, 209 (70.4%) completed the 10-year follow-up reassessment (PAFIP-10). Attrition within the analysis sample seemed random; that is, the number of assessments was not associated with age, sex, negative symptoms, positive symptoms, employment, independent living, financial support or diagnosis (data available upon request).

Out of the 209 participants reassessed at the 10-year follow-up, 183 completed face-to-face interviews and 26

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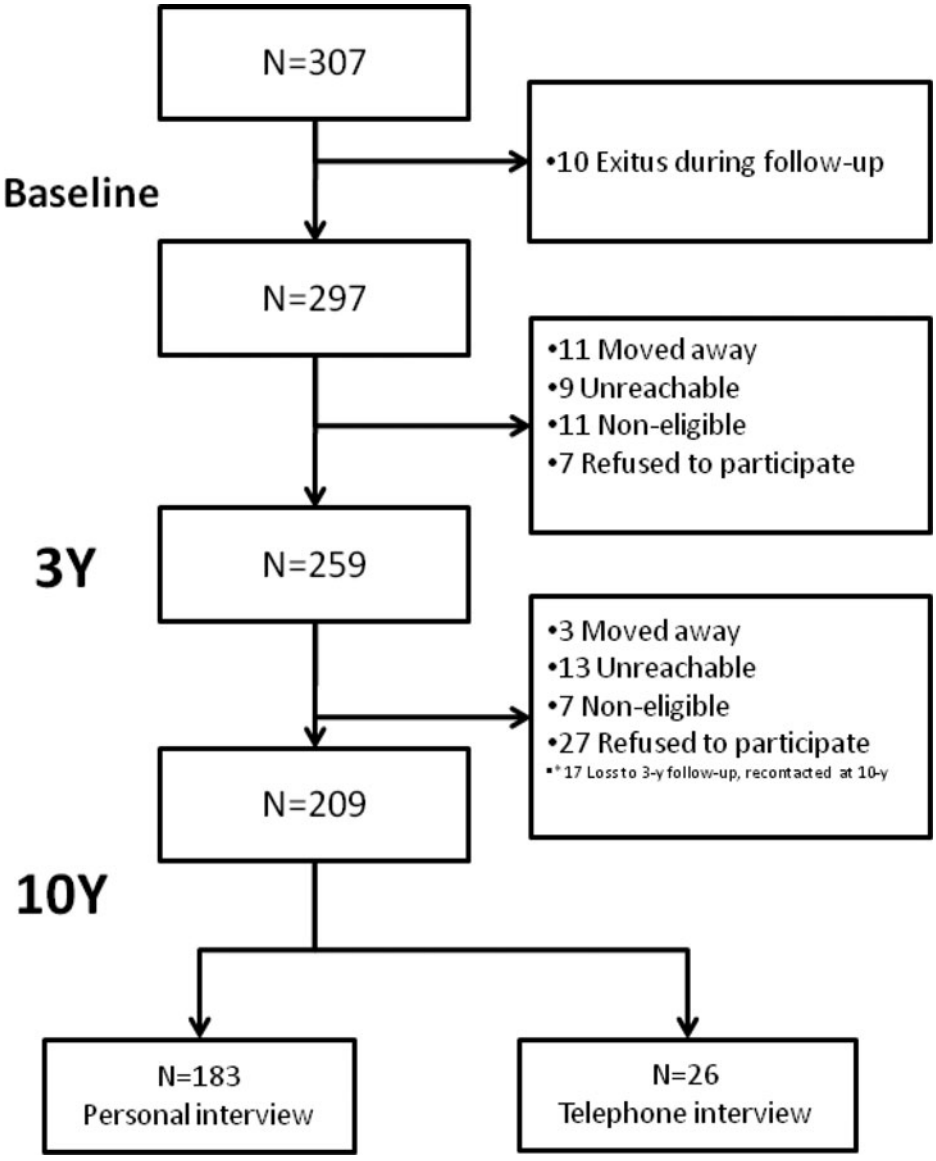

Fig. 1. Flowchart depicting the inclusion of 10-year FEP patients in the study.

completed telephone interviews. The nonresponse rate was primarily accounted for by refusal to participate and loss to follow-up (see flowchart in Fig. 1). Among the 183 patients who had face-to-face, 10-year follow-up reassessments, 131 (71.6%) maintained the initial diagnosis. The dropouts did not differ from the analyzed sample in terms of sex, age or diagnosis (all $p = 0.05$).

Establishing clusters of functional outcomes

A cluster analysis was conducted and included the following variables: the DAS score, the GAF score and scores in the four domains of the QLS (intrapsychic foundations, interpersonal relations, instrumental role and common objects and activities). The agglomeration schedule suggested a six-cluster solution. The first two principal components explained 85.83% of the variability. Cluster membership was then determined (see Fig. 2).

The six clusters were as follows: cluster 1 (42.2% of the patients) was characterized by high scores on function (GAF and QLS), and low scores on disability (DAS), and was labeled 'Normal overall'; cluster 2 (9.6%) demonstrated low scores on DAS, high scores on the GAF and all QLS measures except for intermediate scores in the interpersonal relationships domain and was labeled 'Interpersonal intermediate'; cluster 3 (12.7%) demonstrated low scores on DAS, and high scores on the GAF and all QLS measures except for intermediate scores in the instrumental role domain and was labeled 'Instrumental intermediate'; cluster 4 (12%) was characterized by high scores on QLS intrapsychic foundations, common objects and activities, and interpersonal relationships, intermediate scores on the GAF and DAS measures, but low scores in the QLS instrumental role domain, and was labeled 'Instrumental severe'; cluster 5 (13.9%) was characterized by intermediate scores on the GAF, DAS and QLS intrapsychic foundations and common objects and activities domains, but low scores in the interpersonal relationships and instrumental role domains, and was labeled 'Instrumental and interpersonal severe'; cluster 6 (9.6%) was characterized by low scores on GAF and QLS, and high scores on DAS and was labeled 'Overall impaired'. The profile of each cluster is depicted in Fig. 3.

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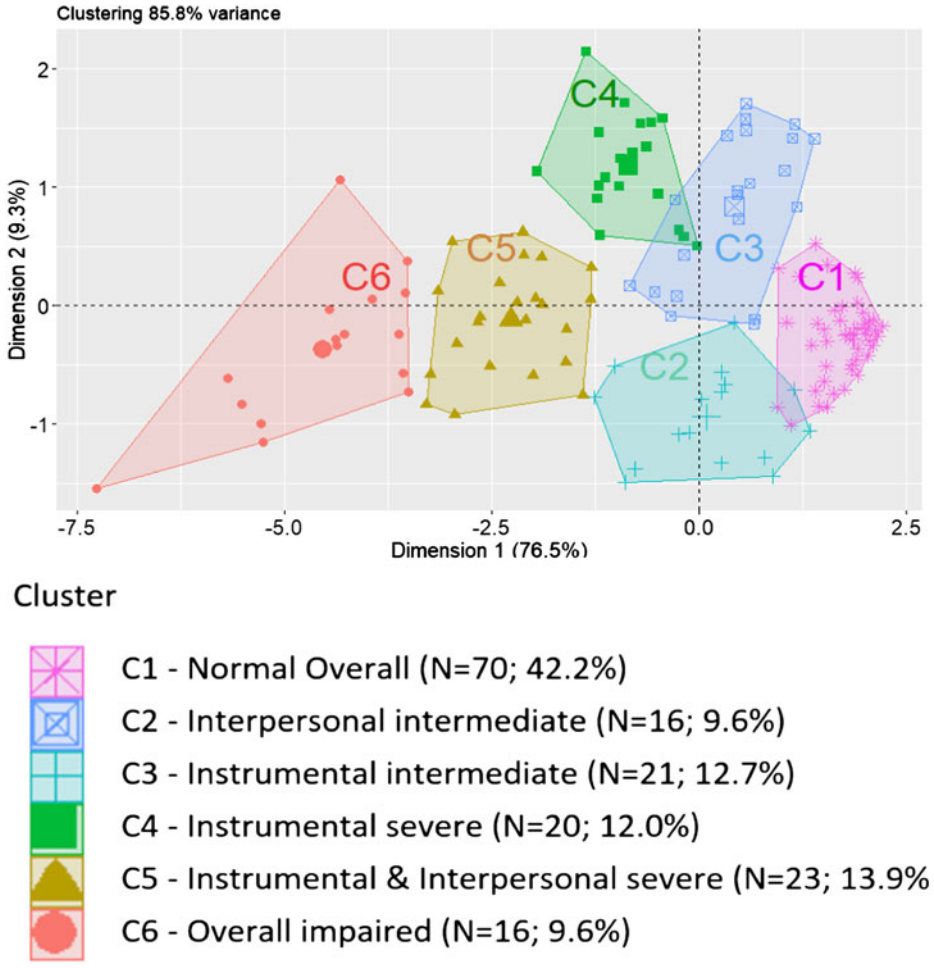

Fig. 2. Cluster membership.

Comparisons between clusters

The results of ANOVAs revealed significant effects of cluster membership on several variables. Descriptive statistics for each cluster and ANOVAs for sociodemographic, clinical and cognitive variables, including the results of the post-hoc analyses, are reported in Tables 1–3. Post-hoc comparisons of clusters with larger effects are summarized below:

- *Cluster 1*. The patients in cluster 1 had significantly better premorbid adjustment in childhood, early and late adolescence and adulthood than cluster 6, and better adjustment in early adolescence than cluster 5. They showed less severe symptomatology (lower BPRS scores) than clusters 4 and 6, particularly less severe negative symptoms (lower SANS scores) and better functioning (higher GAF scores) than clusters 4, 5 and 6, less severe positive symptoms than cluster 6 and less severe negative symptoms (negative dimension) than cluster 2 at the 10-year follow-up. This cluster showed significantly better GCF than cluster 6 at the 10-year follow-up. These patients were also more frequently in a working/studying occupational status than clusters 5 and 6 at baseline and the 3-year follow-up and clusters 3, 4, 5 and 6 at the 10-year follow-up; they were also more frequently married or in a relationship 10 years later (47.1%) and showed functional recovery (95.7%), remission (91.4%) and stability (92.9%). In this cluster, 19 patients (27.1%) were not prescribed antipsychotic treatment.
- *Cluster 2*. The patients in cluster 2 showed a similar functional outcome to patients in cluster 1. However, they presented measurably worse baseline global functioning (GAF at first contact) than cluster 1, with more premorbid social disabilities (premorbid DAS) than clusters 3, 4 and 5. Their premorbid IQ was significantly higher than that in cluster 6, and they had also reached significantly more years of education than the patients in clusters 5 and 6. This subgroup presented less severe positive symptoms than cluster 6 at the 10-year follow-up and less severe negative symptoms at the 3- and 10-year follow-ups.
- *Cluster 3*. The patients in cluster 3 showed less frequent functional recovery than patients in cluster 1, which was characterized by a significantly higher unemployment rate (42.9%), disability status (71.4%) and/or financial state support rate (81%) than cluster 1 at the 10-year follow-up. Similar to patients in cluster 2, their premorbid IQ was significantly higher than that of patients in cluster 6, and they presented less severe positive symptoms than cluster 6 at the 10-year follow-up and less severe negative symptoms than cluster 6 at the 3- and 10-year follow-ups.
- *Cluster 4*. The patients in cluster 4 did not achieve functional recovery relative to clusters 1 and 2 and had more frequent suicidal behaviors. These patients were more frequently unemployed and on disability and/or dependency conditions

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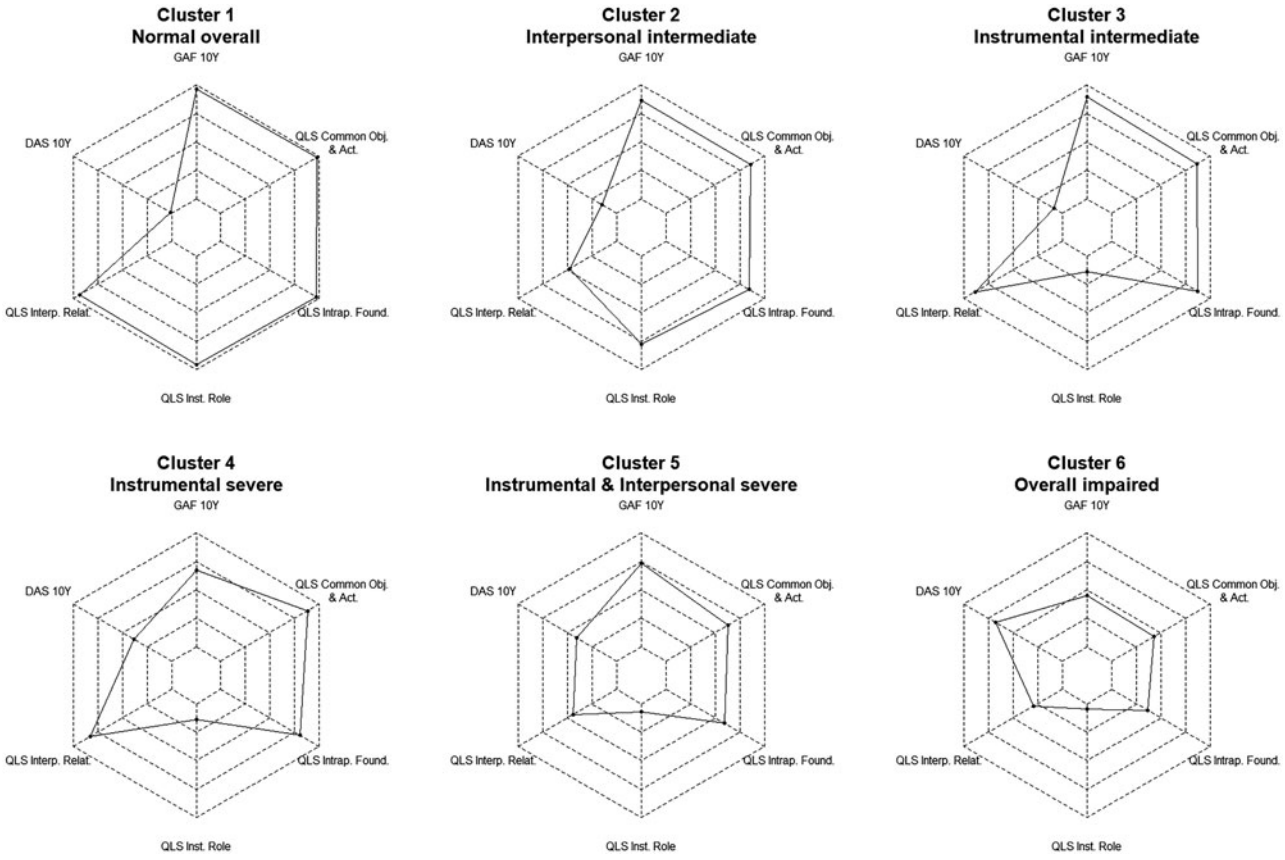

Fig. 3. Profile of each cluster.

at the 10-year follow-up when compared with patients in cluster 1. All patients in this cluster were maintained on antipsychotic treatment (20 out of 20) and received financial state support; the percentage of patients using community-based rehabilitation resources (30%) was similar to that observed in cluster 6 (31.3%).

– *Cluster 5*. The patients in cluster 5 were characterized by the presence of more severe negative symptoms than the patients in clusters 1, 2 and 3 at the 10-year follow-up. The absence of occupational activities at baseline, 3-year and 10-year follow-ups was significant when compared to clusters 1 and 2, with larger proportions on disability (69.6%) and receiving financial state support (73.9%) for their condition.
– *Cluster 6*. The patients in this group showed significantly more severe positive and manic symptoms than the patients in the other clusters. The severity of positive symptoms (related to not achieving remission, stability or recovery) was particularly significant in this cluster at the 10-year follow-up. For negative symptoms, the severity in this cluster was significant when compared with all clusters at the 10-year assessment. The patients were characterized by their poor premorbid adjustment in early and late adolescence and adulthood, the low level of education and the persistent absence of occupational activities (not been working or engaged in any other activity such as formal studying). Ten years later, these patients were less frequently without a partner (81.3%) and were more likely to be receiving financial state support (16 out of 16), presenting a disability (75%), being in a dependence situation (43.8%), and using community-based rehabilitation resources (31.3%).

Discussion

Summary of findings

Mental health is defined as 'a state of welfare in which the individual realizes his own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his community' (WHO, 2008). This definition expresses what constitutes good functional outcome after an FEP. It is very good news that our results showed that 42.2% of FEP patients, those considered with normal overall functioning, showed good outcomes, and only 9.6%, those overall impaired, experienced poor long-term functional outcomes. A systematic review carried out in 2012 (Clemmensen *et al.*, 2012), including studies published between 1980 and 2012, showed that only 15.4% of early onset schizophrenia patients showed a good outcome, while 60.1% experienced poor outcomes. However, Clemmensen and colleagues remarked that the rate of poor outcomes was significantly higher in the low attrition samples compared to the high-attrition samples (rates ranging from 20% to 60%) and that these types of findings depended on the definition used for good or poor functioning in terms of occupational/vocational status, independent living and active social interactions. In our study, with a more than acceptable retention rate (70.4%), a good outcome was confirmed in 42.2% of the patients, those who 10 years later had attained their functional milestones in educational, residential, social and vocational domains, being really low the percentage of those with poor outcome, supporting that rates of good outcome may decrease in longer studies, while rates of poor outcome do not necessarily increase with time as would be expected in a progressive deteriorating illness

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Table 1. Cluster comparisons at baseline on sociodemographic, clinical, cognitive and functional characteristics

	Normal overall (1) *N* = 70		Interpersonal intermediate (2) *N* = 16		Instrumental intermediate (3) *N* = 21		Instrumental severe (4) *N* = 20		Instrumental and interpersonal severe (5) *N* = 23		Overall impaired (6) *N* = 16		Total *N* = 166					
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	*p*	Paired comparisons
Age	29.3	8.8	30.4	7.0	30.2	9.6	27.1	7.6	30.9	10.0	28.2	8.6	29.4	8.7	F	0.548	0.739	
Age of onset	28.6	8.8	28.0	6.6	29.5	9.3	25.9	7.3	29.7	9.3	26.4	8.0	28.3	8.5	F	0.693	0.630	
DUI (months)	19.8	21.3	38.1	50.5	24.1	26.6	25.9	44.9	35.1	36.8	21.7	28.5	25.2	32.1	F	1.405	0.226	
DUP (months)	9.1	11.5	28.5	51.2	8.8	11.6	13.8	42.4	14.1	22.6	10.8	16.2	12.4	25.4	F	1.699	0.138	
Education (years)	11.4	3.2	12.5	3.4	10.8	3.3	10.8	3.9	9.4	3.8	9.0	2.2	10.9	3.4	F	3.295	0.007	2 > 5, $p = 0.034$; 2 > 6 $p = 0.026$
Father age	31.6	6.1	31.4	5.4	33.2	7.6	31.6	10.1	32.3	7.7	29.5	3.9	31.7	6.8	F	0.537	0.748	
Mother age	28.5	5.9	28.8	5.1	30.0	6.6	28.3	9.3	28.4	8.0	26.9	6.7	28.6	6.7	F-w	0.364	0.870	
CGI	6.2	0.7	6.2	0.7	6.0	0.8	6.1	0.9	6.6	0.6	6.2	0.9	6.2	0.7	F	1.344	0.249	
YMRS	9.8	5.1	8.6	3.3	9.3	4.3	11.0	5.3	11.3	5.5	10.4	4.4	10.0	4.9	F	0.860	0.510	
CDSS	3.1	3.6	2.1	2.3	2.3	3.5	2.1	2.9	2.7	4.6	2.4	3.6	2.7	3.5	F	0.490	0.784	
BPR5	60.9	13.3	56.6	10.0	58.1	11.6	60.3	11.5	66.4	14.1	66.8	16.9	61.4	13.3	F	1.964	0.087	
SAPS	12.7	4.4	12.4	4.5	13.6	4.6	11.9	4.1	14.3	4.1	14.4	5.0	13.1	4.4	F	1.212	0.306	
SANS	7.4	6.0	5.9	4.9	7.7	7.0	6.0	4.8	10.1	7.1	11.2	8.6	7.9	6.5	F	2.208	0.056	
Positive dimension	7.1	2.4	7.2	2.2	7.4	2.4	7.1	2.4	8.2	2.1	8.3	2.3	7.4	2.4	F	1.246	0.290	
Disorganized dimension	5.5	3.5	5.3	3.4	6.2	3.7	4.8	3.1	6.1	3.5	6.2	4.2	5.6	3.5	F	0.545	0.742	
Negative dimension	5.4	5.3	4.6	4.6	5.9	6.5	5.0	4.7	8.1	6.5	9.0	7.6	6.0	5.8	F-w	1.540	0.194	
PAS childhood	1.8	1.3	2.2	1.3	2.0	0.9	2.5	1.4	2.1	1.2	3.2	1.7	2.1	1.3	F	3.205	0.009	1 < 6, $p = 0.005$
PAS early adolescence	1.9	1.1	2.5	1.0	2.2	0.9	2.7	1.3	2.9	1.3	4.0	1.5	2.4	1.3	F	8.732	<0.001	1 < 5 $p = 0.009$; 1 < 6, $p < 0.001$; 2 < 6, $p = 0.012$; 3 < 6, $p < 0.001$,; 4 < 6, $p = 0.044$
PAS late adolescence	2.1	1.4	2.6	1.5	2.5	1.1	3.0	1.9	3.1	1.6	4.2	2.0	2.7	1.6	F	5.046	<0.001	1 < 6, $p < 0.001$; 3 < 6, $p = 0.025$
PAS adulthood	1.6	1.7	2.5	2.4	1.5	1.8	2.4	2.5	2.4	2.5	4.3	2.7	2.1	2.2	F	3.694	0.004	1 < 6, $p = 0.002$; 3 < 6, $p = 0.010$
PAS general	2.5	1.7	3.1	1.9	2.8	1.8	3.8	19	3.8	2.1	4.7	2.1	3.1	1.9	F	4.194	0.001	1 < 6, $p = 0.004$
DAS premorbid	0.2	0.6	2.0	0.8	0.4	0.9	0.3	0.5	0.6	0.8	2.0	1.7	0.5	0.9	F	7.067	<0.001	1 < 2, $p < 0.001$; 1 < 6, $p = 0.002$; 2 > 3, $p = 0.026$; 2 > 4, $p = 0.012$; 2 > 5, $p = 0.023$; 4 < 6, $p = 0.030$
DAS baseline	1.0	1.2	0.8	1.3	0.9	1.2	1.4	1.6	1.9	1.7	1.4	1.5	1.1	1.4	F	1.924	0.094	
GAF premorbid	90.9	10.2	71.3	14.4	85.2	11.8	90.2	4.5	85.2	12.3	75.0	18.0	86.9	12.1	F	3.197	0.014	1 > 2, $p = 0.025$
GAF baseline	62.3	25.5	53.8	23.2	65.8	30.6	49.5	30.3	42.9	22.2	50.0	35.6	55.9	26.6	F	1.339	0.261	
Global Cognitive Functioning	1.3	0.9	1.2	1.0	1.2	1.0	1.3	0.9	1.7	1.2	2.0	1.0	1.4	1.0	F	1.353	0.247	

	N	%	N	%	N	%	N	%	N	%	N	%	Statistic	Value	p
Sex (male)	33	47.1	7	43.8	11	52.4	10	50.0	18	78.3	10	62.5	89	53.6	χ^2	8.049	0.154
Race (white)	68	97.1	16	100.0	21	100.0	20	100.0	22	95.7	16	100.0	163	98.2	Fisher		1.000
Family psychiatric history (yes)	16	22.9	4	25.0	3	14.3	7	35.0	6	26.1	2	13.3	38	23.0	Fisher		0.656
Hospitalization (yes)	37	52.9	9	56.3	14	66.7	15	75.0	18	78.3	10	62.5	103	62.0	χ^2	6.923	0.226
Socioeconomic status (low)	34	49.3	6	37.5	12	57.1	10	52.6	13	56.5	10	62.5	85	51.8	χ^2	2.671	0.751
Urban area (yes)	51	72.9	9	56.3	14	66.7	17	85.0	14	60.9	11	68.8	116	69.9	χ^2	4.879	0.431
Living with parents (yes)	40	57.1	10	62.5	9	42.9	7	35.0	12	52.2	11	68.8	89	53.6	χ^2	6.115	0.295
Living with family (yes)	54	77.1	12	75.0	15	71.4	10	50.0	17	73.9	14	87.5	122	73.5	χ^2	7.823	0.166
Single (yes)	51	72.9	12	75.0	15	71.4	17	85.0	16	69.6	13	81.3	124	74.7	χ^2	2.052	0.842
Couple (yes)	15	21.4	2	12.5	4	19.0	1	5.0	5	21.7	2	12.5	29	17.5	Fisher		0.608
Unemployed (yes)	18	25.7	6	37.5	7	33.3	6	30.0	13	56.5	10	62.5	60	36.1	χ^2	12.664	0.027	1 < 5, $p = 0.007$; 1 < 6, $p = 0.005$
Occupational status (yes)	47	67.1	9	56.3	14	66.7	12	60.0	9	39.1	5	31.3	96	57.8	χ^2	11.150	0.048	1 > 5, $p = 0.017$; 1 > 6, $p = 0.008$; 3 > 6, $p = 0.033$
Student (yes)	19	27.1	4	25.0	5	23.8	6	30.0	3	13.0	1	6.3	38	22.9	Fisher		0.393	
Diagnosis schizophrenia (yes)	38	54.3	13	81.3	13	61.9	11	55.0	16	69.6	13	81.3	104	62.7	χ^2	7.799	0.168	
Tobacco (yes)	34	48.6	7	43.8	10	47.6	14	70.0	18	78.3	7	43.8	90	54.2	χ^2	10.043	0.074	
Cannabis (yes)	20	28.6	5	31.3	8	38.1	10	50.0	11	47.8	6	37.5	60	36.1	χ^2	4.976	0.419	

DUI, duration untreated illness; DUP, duration untreated psychosis; CGI, clinical global impression; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SAPS, Scale Assessment Positive Symptoms; SANS, Scale Assessment Negative Symptoms; PAS, Premorbid Adjustment Scale; DAS, Disability Assessment Scale; GAF, Global Assessment of Functioning.

(Menezes *et al.*, 2006). Thus, using the words of Zipursky *et al.* (2018), 30 years of studying individuals with FEP has transformed our understanding of the outcomes of schizophrenia, once thought to be a progressive, deteriorating mental disorder and currently seen as a manageable condition for many people.

Overall, our results also highlighted the fact that it would be too naive to assume that the functional outcomes would simply group into good or poor outcomes. Menezes *et al.* (2006) reported that good and poor outcomes (grossly defined) were reported in 42% and 27% of FEP, respectively. If we had classified patients in this manner, we would not have taken into account almost 50% of the sample, i.e. those patients that show a wide diversity in functional outcomes. Indeed, in our study, the two clusters (clusters 2 and 3) close to normal function (cluster 1) encompassed 22.3% of patients, with cluster 2 being moderately impaired in interpersonal relationships and cluster 3 being moderately impaired in instrumental roles. Clusters 4 and 5 comprised patients who were more homogeneous on the GAF and DAS measures than the QLS domains and presented more severe deficits.

Negative symptomatology and premorbid adjustment as explanatory variables for outcome variability

The majority of individuals in the PAFIP cohort experienced a reduction and stabilization of positive symptoms, whereas negative symptoms showed less variation over 10 years. There is little doubt that the negative symptom dimension of psychotic disorders adversely influences functioning and outcomes (Galderisi *et al.*, 2018). As stated many times, people with sustained and persistent negative symptoms may experience significantly poorer functioning, worse psychological outcomes and lower rates of recovery compared to people who display reductions in negative symptoms over time (Austin *et al.*, 2013). Our results showed that all patients, except for those clustered as normal overall (cluster 1), failed to show a significant improvement in negative symptoms. However, clusters 2, 3, 4 and 5 displayed mild levels of negative symptoms, while only those clustered as overall impaired (cluster 6) displayed severe levels at the 10-year follow-up. Some studies of FEP patients have found that severe negative symptoms can be present at illness onset (Dominguez *et al.*, 2010) and can be predicted by being male, the particular schizophrenia diagnosis and a lengthy DUP (Austin *et al.*, 2015). Galderisi *et al.* (2013) found that persistent negative symptoms (not confounded by depression) were present in 6.7% of their FEP patients' sample, being blunted affect the symptom that more often persisted. These patients had a poorer psychopathological outcome, a worse global functioning and more frequent discontinuation after 1 year of treatment. It therefore comes as no surprise that these patients were less likely to achieve long-term optimal functioning. On the other hand, poor social functioning prior to and at illness onset could be an important marker for negative symptoms and eventually of poor functional outcomes (Santesteban-Echarri *et al.*, 2017). Thus, the combination of poor premorbid adjustment and enduring negative symptoms could potentially be present in those patients showing poor functional outcomes.

We found that the overall normal group (cluster 1) differed significantly from the patients who presented more severe functional impairments in their premorbid adjustment. Several studies have shown that the differences in functioning prior to disease onset may contribute to the heterogeneity of schizophrenia outcome (Larsen *et al.*, 2004; Cole *et al.*, 2012; Quee *et al.*, 2014). Using a similar cluster analysis to that in our study, Quee *et al.*

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Table 2. Cluster comparisons at 10-year follow-up on sociodemographic, clinical, cognitive and functional characteristics

	Normal overall (1) *N* = 70		Interpersonal intermediate (2) *N* = 16		Instrumental intermediate (3) *N* = 21		Instrumental severe (4) *N* = 20		Instrumental and interpersonal severe (5) *N* = 23		Overall impaired (6) *N* = 16		Total *N* = 166					
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	*p*	Paired comparisons
CGI – 10Y	1.5	0.8	2.5	0.9	2.2	1.2	3.5	1.3	3.6	1.2	5.2	1.1	2.6	1.6	F	45.251	0.000	1<2, $p = 0.006$; 1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 5, $p = 0.025$; 2 < 6, $p < 0.001$; 3 < 4, $p = 0.001$; 3 < 5, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
YMRS – 10Y	0.7	2.4	1.0	1.7	0.9	2.2	2.6	4.0	1.7	2.9	6.3	4.0	1.6	3.2	F-w	6.224	<0.001	1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p = 0.002$; 5 < 6, $p < 0.001$
CDSS – 10Y	0.2	0.7	1.9	3.5	0.6	1.2	1.0	2.1	0.6	1.5	1.6	4.1	0.7	2.1	F-w	1.782	0.136	
BPRS – 10Y	25.9	3.6	30.0	5.2	28.8	4.4	33.8	7.8	34.4	7.7	45.9	11.1	31.2	8.3	F-w	14.502	<0.001	1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 5, $p = 0.038$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
SAPS – 10Y	0.4	1.0	0.9	1.6	0.7	1.2	2.0	3.1	1.5	2.4	6.6	6.5	1.4	3.1	F-w	4.792	0.001	1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
SANS – 10Y	1.2	2.3	3.6	2.6	3.1	2.9	5.6	3.6	7.4	4.1	13.4	3.3	4.2	4.7	F-w	44.384	<0.001	1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 5, $p = 0.002$; 2 < 6, $p < 0.001$; 3 < 5, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
Positive dimension – 10Y	0.3	0.7	0.8	1.6	0.5	1.1	1.3	2.2	1.0	1.8	4.0	3.4	0.9	1.9	F-w	5.119	0.001	1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
Disorganized dimension – 10Y	0.1	0.5	0.1	0.3	0.2	0.6	0.7	1.7	0.5	1.1	2.6	3.4	0.5	1.5	F-w	2.975	0.020	1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
Negative dimension – 10Y	1.0	2.1	3.4	2.1	2.9	2.4	4.9	3.7	7.1	3.8	11.8	3.5	3.8	4.3	F-w	36.294	<0.001	1 < 2, $p = 0.038$; 1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 5, $p = 0.001$; 2 < 6, $p < 0.001$; 3 < 5, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p < 0.001$; 5 < 6, $p < 0.001$
Global Cognitive Functioning – 10Y	0.8	0.8	0.9	1.0	1.2	0.8	1.1	0.8	1.4	0.9	2.1	0.7	1.1	0.9	F	4.587	0.001	1 < 6, $p < 0.001$; 2 < 6, $p = 0.023$
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	Statistic	Value	*p*	
Treatment – 10Y (yes)	51	72.9	13	81.3	20	95.2	20	100.0	22	95.7	14	87.5	140	84.3	Fisher		0.008	1 < 3, $p = 0.035$; 1 < 4, $p = 0.005$; 1 < 5, $p = 0.020$
Student – 10Y (yes)	13	18.6	6	37.5	3	14.3	2	10.0	1	4.3	0	0.0	25	15.1	Fisher		0.036	2 > 5, $p = 0.013$; 2 > 6, $p = 0.018$
Urban area 10Y (yes)	46	65.7	9	56.3	12	57.1	15	75.0	16	69.6	8	500	106	63.9	χ^2	3.648	0.601	
Living with parents – 10Y (yes)	23	32.9	8	50.0	10	47.6	9	45.0	11	47.8	12	75.0	73	44.0	χ^2	10.259	0.068	
Living with family – 10Y (yes)	54	77.1	14	87.5	15	71.4	14	70.0	16	69.6	14	87.5	127	76.5	Fisher		0.633	
Single – 10Y (yes)	32	45.7	10	62.5	14	66.7	14	70.0	15	65.2	13	81.3	98	59.0	χ^2	10.344	0.066	
Couple – 10Y (yes)	33	47.1	6	37.5	5	23.8	4	20.0	6	26.1	2	12.5	56	33.7	χ^2	12.173	0.032	1 > 4, $p = 0.030$; 1 > 6, $p = 0.011$
Unemployed – 10Y (yes)	12	17.1	6	37.5	9	42.9	10	50.0	11	47.8	5	31.3	53	31.9	χ^2	14.107	0.015	1 < 3, $p = 0.020$; 1 < 4, $p = 0.006$; 1 < 5, $p = 0.003$

	N	%	N	%	N	%	N	%	N	%	N	%	N	%	Statistic	Value	p	
Occupational status – 10Y (yes)	48	68.6	7	43.8	3	14.3	0	0.0	0	0.0	0	0.0	58	34.9	χ^2	71.003	<0.001	1 > 3, $p < 0.001$; 1 > 4, $p < 0.001$; 1 > 5, $p < 0.001$; 1 > 6, $p < 0.001$; 2 > 4, $p = 0.001$; 2 > 5, $p < 0.001$; 2 > 6, $p = 0.007$
Employment time (⩾7Y)	43	61.4	9	56.3	4	19.0	0	0.0	2	8.7	3	18.8	61	36.7	χ^2	45.430	<0.001	1 > 3, $p < 0.001$; 1 > 4, $p < 0.001$; 1 > 5, $p < 0.001$; 1 > 6, $p = 0.002$; 2 > 3, $p = 0.019$; 2 > 4, $p < 0.001$; 2 > 5, $p = 0.003$; 2 > 6, $p = 0.028$
Achieved stability – 10Y (yes)	65	92.9	14	87.5	18	85.7	15	75.0	19	82.6	8	50.0	139	83.7	Fisher		0.003	1 > 4, $p = 0.040$; 1 > 6, $p < 0.001$; 2 > 6, $p = 0.022$; 3 > 6, $p = 0.030$; 5 > 6, $p = 0.041$
Remission – 10Y (yes)	64	91.4	14	87.5	18	85.7	15	75.0	17	73.9	3	18.8	131	78.9	Fisher		<0.001	1 > 6, $p < 0.001$; 2 > 6, $p < 0.001$; 3 > 6, $p < 0.001$; 4 > 6, $p < 0.001$; 5 > 6, $p < 0.001$
Functional recovery – 10Y (yes)	67	95.7	14	87.5	15	71.4	7	35.0	10	43.5	0	00	113	68.1	χ^2	78.076	<0.001	1 > 3, $p = 0.004$; 1 > 4, $p < 0.001$; 1 > 5, $p < 0.001$; 1 > 6, $p < 0.001$; 2 > 4, $p = 0.001$; 2 > 5, $p = 0.005$; 2 > 6, $p < 0.001$; 3 > 4, $p = 0.019$; 3 > 6, $p < 0.001$; 4 > 6, $p = 0.011$; 5 > 6, $p = 0.002$
Suicidal attempt – 10Y (yes)	0	0.0	0	0.0	1	4.8	3	15.0	0	0.0	1	6.3	5	3.0	Fisher		0.012	1 < 4, $p = 0.010$
Diagnosis schizophrenia – 10Y (yes)	46	65.7	12	75.0	14	66.7	17	85.0	18	78.3	15	93.8	122	73.5	χ^2	7.693	0.174	
Same diagnosis (yes)	49	70.0	12	75.0	16	76.2	10	50.0	18	78.3	12	75.0	117	70.5	χ^2	5.352	0.374	
Tobacco – 10Y (yes)	32	45.7	7	43.8	11	52.4	13	65.0	13	56.5	9	56.3	85	51.2	χ^2	3.159	0.676	
Cannabis – 10Y (yes)	3	4.3	1	6.3	0	0.0	4	20.0	3	13.0	2	12.5	13	7.8	Fisher		0.081	
Children (yes)	22	31.4	4	25.0	5	23.8	3	15.0	5	21.7	3	18.8	42	25.3	χ^2	3.057	0.691	
Children after FEP (yes)	8	11.4	2	12.5	3	14.3	2	10.0	2	8.7	1	6.3	18	10 8	Fisher		0.984	
Social support-10Y (yes)	10	14.3	1	6.3	17	81.0	20	100.0	17	73.9	16	100.0	81	48.8	χ^2	97.233	<0.001	1 < 3, $p < 0.001$; 1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 3, $p < 0.001$; 2 < 4, $p < 0.001$; 2 < 5, $p < 0.001$; 2 < 6, $p < 0.001$; 4 > 5, $p = 0.023$
Depression – 10Y (yes)	10	20.8	3	25.0	1	6.7	5	35.7	2	12.5	0	0.0	21	18.1	Fisher		0.185	
Disability – 10Y (yes)	24	34.3	5	31.3	15	71.4	18	90.0	16	69.6	12	75.0	90	54.2	χ^2	32.393	<0.001	1 < 3, $p = 0.003$; 1 < 4, $p < 0.001$; 1 < 5, $p = 0.003$; 1 < 6, $p = 0.003$; 2 < 3, $p = 0.015$; 2 < 4, $p < 0.001$; 2 < 5, $p = 0.018$; 2 < 6, $p = 0.013$
Dependency – 10Y (yes)	0	0.0	0	0.0	2	9.5	3	15.0	1	4.3	7	43.8	13	7.8	Fisher		<0.001	1 < 4, $p = 0.010$; 1 < 6, $p < 0.001$; 2 < 6, $p = 0.007$; 3 < 6, $p = 0.024$; 5 < 6, $p = 0.004$
Disabled – 10Y (yes)	0	0.0	0	0.0	0	0.0	3	15.0	2	8.7	4	25.0	9	5.4	Fisher		<0.001	1 < 4, $p = 0.010$; 1 < 6, $p < 0.001$; 3 < 6, $p = 0.028$
Financial support – 10Y (yes)	2	2.9	0	0.0	2	9.5	6	30.0	5	21.7	5	31.3	20	12.0	Fisher		<0.001	1 < 4, $p = 0.001$; 1 < 5, $p = 0.009$; 1 < 6, $p = 0.002$; 2 < 4, $p = 0.024$; 2 < 6, $p = 0.043$

CGI, clinical global impression; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SAPS, Scale Assessment Positive Symptoms; SANS, Scale Assessment Negative Symptoms; DAS, Disability Assessment Scale; GAF, Global Assessment of Functioning; FEP, First Episode Psychosis.

Table 3. Cluster comparisons at 3-year follow-up on sociodemographic, clinical, cognitive and functional characteristics

	Normal overall (1) *N* = 70		Interpersonal intermediate (2) *N* = 16		Instrumental intermediate (3) *N* = 21		Instrumental severe (4) *N* = 20		Instrumental and interpersonal severe (5) *N* = 23		Overall impaired (6) *N* = 16		Total *N* = 166					
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	*p*	Paired comparisons
CGI – 3Y	1.9	1.3	2.6	1.2	3.2	1.3	3.8	1.7	3.2	1.5	4.3	1.4	2.8	1.6	F	10.321	0.000	1 < 3, $p = 0.008$; 1 < 4, $p < 0.001$; 1 < 5, $p = 0.003$; 1 < 6, $p < 0.001$; 2 < 6, $p = 0.028$
YMRS – 3Y	0.9	2.5	1.7	2.9	1.9	3.3	3.3	5.5	2.8	3.7	2.8	3.5	1.8	3.4	F	2.141	0.064	
CDSS – 3Y	0.4	1.4	0.8	1.4	0.6	1.1	1.5	2.4	0.4	1.3	1.2	2.6	0.7	1.6	F	1.523	0.186	
BPRS – 3Y	28.2	8.2	29.8	5.6	32.0	10.8	38.4	14.4	34.5	9.5	41.3	11.7	32.0	10.5	F	6.268	<0.001	1 < 4, $p = 0.001$; 1 < 6, $p < 0.001$; 2 < 6, $p = 0.038$
SAPS – 3Y	1.1	2.7	1.5	2.5	2.3	4.1	3.9	6.0	2.0	3.1	3.3	2.9	1.9	3.6	F-w	1.890	0.115	
SANS – 3Y	1.8	3.4	3.1	4.3	4.0	3.7	6.4	5.7	6.9	5.8	10.8	5.6	4.2	5.2	F-w	9.439	<0.001	1 < 4 $p = 0.002$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 6, $p < 0.001$; 3 < 6 $p < 0.001$
Positive dimension – 3Y	0.6	1.6	1.0	1.3	1.5	2.8	2.2	2.9	1.5	2.2	1.9	2.1	1.2	2.1	F-w	2.119	0.081	
Disorganized dimension – 3Y	0.5	1.3	0.5	1.5	0.8	1.4	1.8	3.8	0.5	1.5	1.3	1.7	0.7	1.9	F	1.811	0.114	
Negative dimension – 3Y	1.4	2.9	2.4	3.4	3.4	3.3	5.2	4.9	6.6	5.6	9.7	5.3	3.6	4.7	F-w	9.730	<0.001	1 < 4, $p = 0.004$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 5, $p = 0.022$; 2 < 6, $p < 0.001$; 3 < 6, $p < 0.001$; 4 < 6, $p = 0.039$
DAS – 3Y	0.5	1.0	0.7	0.9	1.3	1.3	2.0	1.3	2.0	1.2	2.6	1.2	1.2	1.3	F-w	12.724	<0.001	1 < 4, $p < 0.001$; 1 < 5, $p < 0.001$; 1 < 6, $p < 0.001$; 2 < 4, $p = 0.010$; 2 < 5, $p = 0.004$; 2 < 6, $p < 0.001$; 3 < 6, $p = 0.019$
GAF – 3Y	91.0	5.7	75.3	21.5	81.0	10.2	70.2	22.9	67.9	19.6	51.7	11.5	79.9	17.9	F-w	9.210	0.002	1 > 4, $p = 0.022$; 1 > 5, $p < 0.001$; 1 > 6, $p < 0.001$
Global Cognitive Functioning – 3Y	0.8	0.8	0.9	0.9	0.9	0.5	1.1	0.8	0.9	0.7	1.3	0.7	0.9	0.8	F	0.674	0.644	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	Statistic	Value	*p*	
Drop before – 3Y (yes)	4	5.7	0	0.0	1	4.8	1	5.0	0	0.0	4	25.0	10	6.0	Fisher		0.064	
Student – 3Y (yes)	15	31.9	3	21.4	3	18.8	2	15.4	1	9.1	1	11.1	25	22.7	Fisher		0.583	
Living with parents – 3Y (yes)	40	60.6	10	62.5	13	65.0	12	63.2	13	56.5	11	91.7	99	63.5	χ^2	4.854	0.434	
Living with family – 3Y (yes)	54	81.8	13	81.3	18	90.0	16	84.2	16	69.6	12	100.0	129	82.7	Fisher		0.322	
Unemployed 3Y (yes)	17	25.8	2	12.5	5	25.0	4	21.1	6	26.1	4	33.3	38	24.4	Fisher		0.857	
Occupational status – 3Y (yes)	44	66.7	13	81.3	10	50.0	9	47.4	8	34.8	3	25.0	87	55.8	χ^2	16.915	0.005	1 > 5, $p = 0.008$; 1 > 6, $p = 0.010$; 2 > 4, $p = 0.039$; 2 > 5, $p = 0.004$; 2 > 6, $p = 0.003$
Financial support – 3Y (yes)	8	16.3	2	25.0	6	40.0	8	50.0	8	40.0	9	81.8	41	34.5	χ^2	20.563	0.001	1 < 4, $p = 0.016$; 1 < 6, $p < 0.001$; 2 < 6, $p = 0.024$

CGI, Clinical Global Impression; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SAPS, Scale Assessment Positive Symptoms; SANS, Scale Assessment Negative Symptoms; DAS, Disability Assessment Scale; GAF, Global Assessment of Functioning.

(2014) identified six clusters in premorbid adjustment profiles, labeled normal, social intermediate, academic decline, overall decline, overall intermediate and overall impaired adjustment, with each differing from the others on cognitive, clinical and functional characteristics after disease onset. Cole *et al.* (2012) identified three latent trajectory classes (poor-deteriorating, insidious-onset, good-stable) from premorbid adjustment to functioning after onset, suggesting that subtyping schizophrenia patients in terms of premorbid history may be useful for untangling the heterogeneity of schizophrenia outcomes. These studies are in line with the theories that propose different etiologies in the development of psychosis, suggesting patterns of premorbid maladjustment may reflect a neurodevelopmental pathway to psychosis (Larsen *et al.*, 2004). It is not clear where the boundaries are, but the confluence of poor premorbid adjustment, lower premorbid IQ, fewer years of education and worse GCF at baseline in those patients who presented an overall impairment in long-term function may support more severe forms of the disease (Cuesta *et al.*, 2015). It will be difficult for researchers to establish whether these premorbid and neurocognitive characteristics, repeatedly found representative of the more deteriorating courses, are a cause or consequence of illness. However, there is no doubt that negative symptoms are a key, and hopefully modifiable, factor in the long-term functional outcomes.

Social factors that contribute to the variability in cluster outcome

Patients within the more dysfunctional clusters, cluster 4 (instrumental severe) and cluster 6 (overall impaired), used more community-based rehabilitation resources, designed to interface with the existing outreach mental health teams, and focused on psychosocial interventions. Dependency was particularly significant in cluster 6 (43.8%) compared to the rest of the clusters, as well as in cluster 4 (15%) when compared with cluster 1 (0%). Disability was more significant in clusters 3–6 (71.4, 90, 69.6 and 75%, respectively) than in clusters 1 and 2 (34.3% and 31.3%), and it was particularly remarkable in cluster 4 (90%). Similar results were observed for financial state support, but in this case, the percentage of patients in cluster 3 (instrumental intermediate) who received some kind of public government financial state support (81%) showed that the patients in this cluster spent more time studying than patients in cluster 6. Worldwide, the most common method of financing mental health care is taxation (60%), followed by social insurance (19%), out-of-pocket payments (16%), external grants (3%) and voluntary insurance (2%) (Saxena *et al.*, 2007). Research evidence suggests that disability applicants with a valid diagnosis of schizophrenia have significant impairment across multiple dimensions of functioning and will typically remain impaired for the duration of the normal working ages or until new interventions are developed (Harvey *et al.*, 2012). It was observed that only the patients in clusters 1 and 2 were more frequently employed during the 10 years of follow-up (61.4% and 56.3%, respectively). This suggests the importance of early employment for long-term functional outcomes and supports the effort of implementing specific EI services to address vocational and educational challenges after an FEP as part of the treatment.

Strengths and limitations

The major contribution of this study was differentiating the heterogeneity of functional outcomes in FEP patients using an objective evaluation in the determination of clusters. This kind of analysis enhanced the speed and sensitivity of identifying similarities and improved the consistency of annotation within clusters. Moreover, very few studies have followed a cohort of FEP patients over such a long period of time and examined functional outcomes accurately with a very low attrition rate. Some limitations should also be considered. First, the assessment points during the 10 years were not equally spaced over this period. The follow-up in the PAFIP cohort was scheduled for 3 years, at which point, the patients were discharged from EI to traditional community mental health services. For the purpose of the current study, they were contacted at 10 years, and we cannot rule out other information that was not recorded but could have affected outcomes. Second, the analyses were not focused on trajectories of changes over time, which would have been made possible only with more elaborate profiles. However, those analyses exceeded the aims of the current study. Third, the current study did not address the question of whether outcomes following treatment as usual might have been similar to the outcomes in these patients at the 10-year follow-up period.

Future research and suggestions

Our findings indicated that psychotic disorders are still mental illnesses with a rather unfavorable prognosis but with favorable rates clearly increasing. Studies using longitudinal data can contribute to a better understanding of the course of the illness and help clinicians identify critical periods that merit specific interventions and adjust the timing, length and intensity of the interventions to optimize primary outcomes (symptoms and functioning) for people who have experienced an FEP. Finally, cluster analysis methods can be leveraged to develop tailored care management interventions designed to improve specific functional outcomes.

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