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Long-term diagnostic stability, predictors of diagnostic change, and time until diagnostic change of first-episode psychosis: a 21-year follow-up study

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Original Article

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Abstract

Background. Although diagnostic instability in first-episode psychosis (FEP) is of major concern, little is known about its determinants. This very long-term follow-up study aimed to examine the diagnostic stability of FEP diagnoses, the baseline predictors of diagnostic change and the timing of diagnostic change.

Methods. This was a longitudinal and naturalistic study of 243 subjects with FEP who were assessed at baseline and reassessed after a mean follow-up of 21 years. The diagnostic stability of DSM-5 psychotic disorders was examined using prospective and retrospective consistencies, logistic regression was used to establish the predictors of diagnostic change, and survival analysis was used to compare time to diagnostic change across diagnostic categories.

Results. The overall diagnostic stability was 47.7%. Schizophrenia and bipolar disorder were the most stable diagnoses, with other categories having low stability. Predictors of diagnostic change to schizophrenia included a family history of schizophrenia, obstetric complications, developmental delay, poor premorbid functioning in several domains, long duration of untreated continuous psychosis, spontaneous dyskinesia, lack of psychosocial stressors, longer duration of index admission, and poor early treatment response. Most of these variables also predicted diagnostic change to bipolar disorder but in the opposite direction and with lesser effect sizes. There were no significant differences between specific diagnoses regarding time to diagnostic change. At 10-year follow-up, around 80% of the diagnoses had changed.

Conclusions. FEP diagnoses other than schizophrenia or bipolar disorder should be considered as provisional. Considering baseline predictors of diagnostic change may help to enhance diagnostic accuracy and guide therapeutic interventions.

Introduction

Psychotic disorders are highly heterogeneous conditions in terms of clinical presentation, response to treatment and course/outcome. Diagnostic stability has been highlighted as one of the most important validators of a diagnostic construct in psychiatry (Robins & Guze, 1970). This underscores the importance of long-term follow-up studies for the research of the temporal consistency of first-episode psychosis (FEP) diagnostic categories. Given the overall poor stability of specific diagnoses of psychotic disorders after a FEP (Fusar-Poli et al., 2016), establishing associations of early features of the illness with diagnostic stability or instability and specific diagnostic changes is of great importance because it can help to identify those patients who may be misdiagnosed at baseline, particularly those who need more vigorous interventions, which can help to guide therapeutic interventions and prevent disability (McGorry, 2015).

Prospective studies of diagnostic stability have a wide range of follow-up periods. However, most of the samples are followed-up for periods of less than 5 years, which shows an incomplete picture of real diagnostic stability (Salvatore et al., 2011; Schwartz et al., 2000). More recent studies with a sound methodology and longer follow-up periods (i.e. over 10 years) have confirmed low stability rates (Bromet et al., 2011; Heslin et al., 2015). Schizophrenia and bipolar disorder have consistently shown the highest prospective diagnostic stability over time, with figures ranging from 73% to 99% (Bromet et al., 2011; Heslin et al., 2015; Salvatore et al., 2011; Suárez-Pinilla et al., 2021). Other diagnoses – including schizoaffective disorder, major depressive disorder with psychotic features, brief psychotic disorder, delusional disorder, schizophreniform disorder, and psychosis not otherwise specified (PNOS) –

have shown much higher instability, generally less than 50%, and mainly convert to schizophrenia or mood disorders over the follow-up (Fusar-Poli et al., 2016; Heslin et al., 2015).

Prediction of change toward specific diagnostic categories has been mainly studied for schizophrenia. The variables that have been related with some consistency to later change to schizophrenia include longer duration of untreated psychosis (DUP) (Haahr et al., 2008; Heslin et al., 2015; Schwartz et al., 2000), severity of negative symptoms (Heslin et al., 2015; Ruggero et al., 2011; Schwartz et al., 2000), and poor premorbid adjustment (Haahr et al., 2008; Schwartz et al., 2000).

While there is general agreement that most diagnostic changes occur within a few years after a FEP, little is known about the temporal patterns of change toward specific diagnostic categories. Studies of acute and transient psychoses have shown that most changes occur within the first two years of illness (Castagnini, Bertelsen, & Berrios, 2008; Queirazza, Semple, & Lawrie, 2014). In addition, a recent study reported that the mean time for stabilization of a schizophrenia diagnosis was 53 months (Suárez-Pinilla et al., 2021).

To the best of our knowledge, no previous study has examined diagnostic stability and predictors of diagnostic change of FEP over a follow-up period longer than 10 years. Given that diagnostic change tends to increase over time, observing subjects across longer periods of time is necessary because it can depict a more accurate picture of diagnostic stability, timing of diagnostic change, and their predictors.

In this paper, we present a prospective cohort study of first-admission psychosis in a well-characterized sample covering the whole spectrum of functional psychotic disorders followed-up for a median time of 21 years. The study had three main objectives. First, to determine the prospective and retrospective consistencies of diagnostic categories of DSM-5 psychotic disorders. Second, to examine the background and first-episode predictors of specific diagnostic changes. Third, to analyze the temporal patterns of diagnostic change toward specific diagnostic categories. Furthermore, considering the high number of baseline cases that we expected to move to a diagnosis of schizophrenia over the illness course, a secondary aim of this study was to examine the degree to which subjects with a stable diagnosis of schizophrenia (i.e. diagnosis established at baseline and follow-up) differ from those who developed schizophrenia over the follow-up period.

Methods

Study design and sample

This study was conducted as part of the Navarra First-Episode Psychosis study, which is a 21-year follow-up study of a cohort of subjects who were consecutively admitted to the psychiatric ward of the University Hospital of Navarra (Spain) for their first episode of a functional psychotic illness. The complete study protocol (e.g. detailed methodology and follow-up procedures) has been described elsewhere (Peralta et al., 2021). Briefly, the study cohort comprised subjects who met the following inclusion criteria: (a) admitted for a FEP fulfilling the DSM-III-R or DSM-IV criteria for a functional psychotic disorder; (b) between 15–65 years old; (c) residing in the catchment area of the hospital; (d) completing the inpatient treatment period and a 6-month assessment after discharge; and (e) available close relatives to provide broad background information. The exclusion criteria included: (a) previous antipsychotic treatment for more than 2 months; (b) a suspected or confirmed diagnosis of substance-induced psychosis; (c) history of serious medical or neurological disease; and (d) mental disability as defined by an IQ less than 70.

Of the 510 subjects who were assessed at baseline, 243 were successfully followed-up (57.3% of the survivors) and this group comprised the study sample. Followed and non-followed subjects did not differ in baseline sociodemographic, premorbid or FEP clinical variables, including DSM-5 diagnosis, except for age, which was higher in the non-followed subjects and related to subsequent mortality or severe medical comorbidity in this group (Peralta et al., 2022). All the participants gave written informed consent to participate and approval was granted by the local ethical committee. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2018.

Assessment methodology

The senior authors (V.P. and M.J.C.) assessed subjects at baseline. The follow-up interviewers (L.M.I. and E.G.J.) assessed the outcomes of each subject blindly to the baseline information. Assessments were performed using face-to-face interviews with each subject, interviews with significant others, such as extensive reviews of clinical and social records.

The Comprehensive Assessment of Symptoms and History (CASH) was the main assessment instrument in that study (Andreasen, Flaum, & Arndt, 1992). Specific assessment instruments were employed for some relevant variables that were not included in the CASH. The CASH is a structured interview and recording instrument that is designed to document a broad range of illness-related factors of subjects with psychotic or major mood disorders. Its main emphasis is to provide broad descriptive coverage to make diagnosis using a variety of criteria, which is especially important because of the changing diagnostic systems. Consequently, subjects were diagnosed at baseline using DSM-III-R or DSM-IV criteria and re-diagnosed with DSM-5 criteria using all information contained within the CASH. Final lifetime diagnoses, including time to diagnostic change, were made by consensus between the two senior authors using all available information.

We selected 34 candidate predictors of diagnostic change, which were grouped into sociodemographic, familial-genetic, antecedents, illness onset, first-episode characteristics and early treatment response variables. Most predictor variables were assessed in all the study's participants, excepting polygenic risk scores (PRS) that were assessed in 164 subjects consenting to DNA extraction, spontaneous movement disorders that were assessed in 194 drug-naïve subjects, and neurological soft signs that were assessed in 179 drug-naïve subjects and able to collaborate with the exploration. A complete description of the assessment instruments employed in this study is provided in the Supplementary Methods. The main sociodemographic and clinical characteristics of the subjects at final follow-up are presented in online Supplementary Table 1.

Statistical analysis

Following Schwartz et al. (2000), we calculated prospective consistency as the proportion of subjects who received a diagnosis at baseline and maintain that diagnosis at follow-up.

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Meanwhile, we calculated retrospective consistency as the proportion of subjects who receive a diagnosis at follow-up that they also had at baseline.

We examined the ability of baseline variables to predict diagnostic change over the follow-up using univariate logistic regressions, reporting odds ratios (OR) with their 95% confidence intervals (CI). Ordinal or continuous predictors were categorized using the median score, the 75th percentile in case of PRS, or preestablished cut-off scores of clinical significance. For each diagnostic change (coded 1), the comparator (coded 0) included all subjects not having the specific diagnostic change at baseline; i.e. subjects changing to a schizophrenia diagnosis at follow-up were compared with subjects having a diagnosis other than schizophrenia at baseline. We limited the analyses to the three main diagnostic changes, namely schizophrenia, schizoaffective disorder, and bipolar disorder (see below). With the goal of examining the independent contribution of baseline variables in predicting diagnostic change, we used hierarchical logistic regression where those independent variables significantly associated with diagnostic change in the univariate analyses (predictors) were entered stepwise following a chronological order.

We also examined the ability of baseline diagnosis to predict final follow-up diagnosis, but this analysis was made separately from the analyses predicting diagnostic change to avoid some circularity in reasoning because some of the predictor variables are to some degree enshrined within the diagnostic categories.

For comparing stable and newly developed schizophrenia across predictor and outcome variables we used chi-squared tests for categorical variables and the nonparametric Z-test for continuous variables since equal variance and sample size between the groups could not be assumed.

A comparison of temporal patterns of diagnostic change toward specific diagnostic categories was made using survival analysis. The log-rank (Mantel–Cox) test was used to compare the survival functions of the main diagnostic change groups.

All statistical tests were two-tailed and deemed to be significant at $p < 0.05$ level. The Benjamini–Hochberg procedure was applied to account for multiple testing. Statistical analysis was performed with IBM SPSS Statistics version 23.

Results

Distribution and shifts between diagnoses

Taking the diagnoses altogether, global stability was 47.7% (116/243); that is, the proportion of subjects of the sample that had the same baseline and lifetime DSM-5 diagnosis (Table 1). The following diagnoses had more cases at follow-up than at baseline: schizophrenia (+ 41, 36.3% increase), schizoaffective disorder (+ 27, 66.6% increase) and bipolar disorder (+ 22, 52.4% increase). All other diagnostic categories decreased in frequency over time, experiencing a whole shrinkage from 139 to 49 cases (64.7% decrease). The baseline diagnoses most frequently changing to schizophrenia included schizophreniform disorder (16/40, 40%), delusional disorder (8/17, 47%) and PNOS (7/12, 58%). The baseline diagnoses most frequently changing to schizoaffective disorder were schizophreniform disorder (9/40, 22%) and major depressive disorder (7/29, 24%). The baseline diagnoses most frequently changing to bipolar disorder included brief psychotic disorder (11/41, 26.8%) and major depressive disorder (9/29, 31.0%).

By considering the spectra concept instead of specific diagnoses and leaving out the schizoaffective disorder diagnosis, only 21 subjects (11.5%) from the schizophrenia spectrum moved into the affective spectrum (bipolar disorder and major depressive disorder) and only six subjects (12.2%) from the affective spectrum moved into the schizophrenia spectrum.

Prospective and retrospective consistencies

Schizophrenia and bipolar disorder had the greatest prospective diagnostic consistency (91.7% and 70%, respectively), followed by schizoaffective disorder (41.7%), with all other categories having much lower rates of prospective consistency (<34.1%) (Table 2). The retrospective consistency was very good for schizophreniform disorder (100%); good for major depressive disorder (80%), delusional disorder (75%) and brief psychotic disorder (70%); fair for schizophrenia (58.4%); poor for bipolar disorder (33.3%); and very poor for PNOS and schizoaffective disorder (0% and 12.8%, respectively). Notably, none of the subjects with a baseline diagnosis of PNOS maintained the diagnosis at follow-up and none of the patients with that diagnosis at follow-up had it at baseline.

Baseline diagnoses of schizophreniform disorder, delusional disorder and PNOS significantly predicted both any diagnostic change and change to schizophrenia (online Supplementary Table 2). The odds ratios (and 95% CI) of diagnostic change ranged between 3.69 (1.76–7.74) for change from schizophreniform disorder to schizophrenia and 13.1 (1.79–98.6) for change from PNOS to any other diagnosis.

Predictors of diagnostic change to schizophrenia, schizoaffective disorder, and bipolar disorder

As shown in Table 3, compared to subjects having a baseline diagnosis other than schizophrenia, those changing to a schizophrenia diagnosis over the follow-up had an increased odds of having a family history of schizophrenia spectrum disorders (SSD) (OR = 3.48), obstetric complications (OR = 4.38), developmental delay (OR = 5.52), childhood adversity (OR = 2.27), poor premorbid adjustment (OR = 3.00), low cognitive reserve (OR = 3.01), poor premorbid social networks (OR = 4.08), longer duration of untreated continuous psychosis (DUCP) (OR = 3.27), spontaneous dyskinesia (OR = 17.0), and longer duration of index admission (OR = 2.86). In addition, they had a decreased odds of having psychosocial stressors (OR = 0.30), marked symptom improvement at index admission (OR = 0.35) and symptomatic remission at 6 months after index admission (OR = 0.15). The odds ratios for lack of marked improvement at index admission and lack of symptomatic remission 6 months after were 2.87 (95% CI 1.35–5.88) and 6.46 (95% CI 2.68–15.52), respectively. Hierarchical regression analysis showed that a combination of 6 of these variables (family history of SSD, obstetric complications, developmental delay, psychosocial stressors, spontaneous dyskinesia, and 6-month symptomatic remission after index admission) independently predicted diagnostic change explaining 41.4% of model's variance (online Supplementary Table 3).

Compared to subjects having a baseline diagnosis other than schizoaffective disorder, those changing to a schizoaffective disorder diagnosis did not significantly differ in any of the predictor variables (online Supplementary Table 4).

Compared to subjects having a baseline diagnosis other than bipolar disorder, those changing to a bipolar disorder diagnosis had a decreased odds of having obstetric complications (OR = 0.23), childhood adversity (OR = 0.16), poor premorbid

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Table 1. Diagnostic changes from baseline to follow-up assessment

Follow-up diagnosis (n)									
Baseline diagnosis (n)	SZ	SF	BPD	DD	SAD	BD	MDD	PNOS	Total
Schizophrenia (SZ)	66	0	1	0	4	1	0	0	72
Schizophreniform disorder (SF)	16	6	2	0	9	3	1	3	40
Brief psychotic disorder (BPD)	7	0	14	0	5	11	1	3	41
Delusional disorder (DD)	8	0	0	3	3	2	0	1	17
Schizoaffective disorder (SAD)	5	0	1	0	5	0	0	1	12
Mania/Bipolar disorder (BD)	1	0	0	0	5	14	0	0	20
Major depression/ Major depressive disorder (MDD)	3	0	1	0	7	9	8	1	29
Psychosis not otherwise specified (PNOS)	7	0	1	1	1	2	0	0	12
Total	113	6	20	4	39	42	10	9	243

Note. Numbers for specific diagnosis changes from baseline to follow-up such as their percentage of variation are as follows: SZ = 72→113 (+41, ▲36.3%); SF = 40→6 (−34, ▼85%); BPD = 41→20 (−21, ▼51.2%); DD = 17→4 (−13, ▼76.5%); SAD = 12→39 (+27, ▲66.6%); BD = 20→42 (+22, ▲52.4%); MDD = 29→10 (−19, ▼65.5%); PNOS = 12→9 (−3, ▼25%).

adjustment (OR = 0.14), poor premorbid cognitive reserve (OR = 0.31), poor premorbid social networks (OR = 0.27), chronic onset (OR = 0.22), and long DUCP (OR = 0.27). Additionally, they had an increased probability of having psychosocial stressors (OR = 3.47), marked improvement at index admission (OR = 4.10), and symptomatic remission 6 months after (OR = 7.28) (online Supplementary Table 5). Hierarchical regression analysis showed that four of these variables (obstetric complications, poor premorbid adjustment, psychosocial stressors, and 6-month symptomatic remission after index admission) independently predicted diagnostic change explaining 28.2% of model's variance (online Supplementary Table 6).

Patterns of diagnostic change over time

No significant differences were found regarding time until diagnostic change toward schizophrenia, schizoaffective disorder, bipolar disorder, or other psychotic disorders: log-rank test = $1.35_{(df=3)}$, $p = 0.717$ (Fig. 1). The median time for diagnostic change was 5 years and the mean time was 6.47 years (S.D. = 5.24, range 1–29). At 5-year follow-up, approximately 50% of diagnoses had changed. At 10-year follow-up, around 80% of diagnoses had changed. Beyond year 10, the curve tends to stabilize, with around 85% of diagnoses having changed at year 15, and over 90% having changed at 20-year follow-up.

Table 2. Prospective and retrospective consistency of DSM-5 diagnoses of psychotic disorders

	Prospective consistency (%)	Retrospective consistency (%)
Schizophrenia	91.7	58.4
Schizophreniform disorder	15	100
Brief psychotic disorder	34.1	70
Delusional disorder	17.6	75
Schizoaffective disorder	41.7	12.8
Bipolar disorder	70	33.3
Major depressive disorder	27.6	80
Psychosis not otherwise specified	0	0

Differences between stable and newly developed schizophrenia

Whereas subjects with stable and newly developed schizophrenia did not differ in terms of major outcome domains at follow-up, they did differ across several baseline predictors (Table 4). Compared with stable schizophrenia subjects, those who developed the disorder over the follow-up exhibited less childhood adversity ($p < 0.001$), better premorbid adjustment ($p < 0.001$), more premorbid social networks ($p < 0.007$), a more acute onset ($p < 0.001$), shorter DUP and DUCP (both $p < 0.001$), less severe negative symptoms ($p = 0.003$), and better early treatment response at discharge from index admission ($p < 0.001$) and 6 months after ($p = 0.004$).

Discussion

Main findings

This study examined the diagnostic stability of FEP, baseline predictors of diagnostic change and timing of diagnostic change in a first-admission cohort of 243 subjects who were followed-up on average over a 21-year period. We also examined the baseline and outcome differences between stable schizophrenia diagnosis and newly diagnosed schizophrenia over the follow-up.

Our study has four major findings. First, only 47.7% of the cohort retained the same diagnosis throughout the follow-up period. Schizophrenia and bipolar disorder exhibited excellent and good prospective consistency, respectively, whereas the retrospective consistency of these diagnoses was fair. This indicates a tendency for other diagnoses to migrate to schizophrenia or bipolar disorder and that these disorders only rarely migrate to other categories of psychotic disorders. Notably, the largest proportion of diagnostic shifts was to schizoaffective disorder (66.6% increase), followed by bipolar disorder (52.4% increase) and schizophrenia (36.3% increase). The most unstable diagnoses were schizophreniform disorder, delusional disorder and PNOS, which significantly predicted both overall diagnostic change and change to schizophrenia.

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Table 3. Univariable logistic regression predicting the effect of baseline variables on diagnostic change to schizophrenia over the follow-up

	No diagnostic change ($n = 124$) †	Diagnostic change ($n = 47$)†	OR (95% CI)	p
Socio-demographics				
Age at follow-up, high (⩾47 years)	74 (59.7)	22 (46.8)	0.59 (0.30–1.16)	0.132
Male gender	63 (50.8)	33 (70.2)	2.28 (1.11–4.67)	0.024
Education, high school	65 (52.4)	16 (34.0)	0.46 (0.23–0.94)	0.033
Age at baseline assessment, high (⩾25 years)	72 (58.1)	21 (44.7)	0.58 (0.29–1.14)	0.118
Length of follow-up, high (⩾21 years)	63 (50.8)	27 (57.4)	1.30 (0.66–2.57)	0.438
Familial-genetic liability				
PRS for schizophrenia, high (⩾0.66)	23 (26.4)	10 (37.0)	1.63 (0.65–4.07)	0.291
PRS for bipolar disorder, high (⩾0.64)	27 (31.0)	7 (25.9)	0.77 (0.29–2.05)	0.613
PRS for major depression, high, (⩾0.68)	21 (24.1)	8 (29.6)	1.32 (0.50–3.45)	0.568
Family history of schizophrenia spectrum disorders	16 (12.9)	16 (34.0)	3.48 (1.56–7.75)	**0.002**
Family history of bipolar disorder	13 (10.5)	3 (6.4)	0.58 (0.15–2.14)	0.416
Family history of major depressive disorder	23 (18.5)	6 (12.8)	0.64 (0.24–1.69)	0.371
Antecedents				
Obstetric complications, any definite	9 (7.3)	12 (25.5)	4.38 (1.70–11.2)	**0.002**
Developmental delay at year 3, any	30 (24.2)	30 (63.8)	5.52 (2.68–11.3)	**<0.001**
Childhood adversity score, high (<77)	39 (31.5)	24 (55.1)	2.27 (1.14–4.51)	**0.019**
Premorbid adjustment score, poor (⩾4)	30 (24.2)	23 (48.9)	3.00 (1.48–7.07)	**0.002**
Premorbid cognitive reserve score, low (⩾41)	34 (27.4)	25 (53.2)	3.01 (1.50–6.03)	**0.002**
Premorbid social networks score, poor (<4)	27 (21.8)	25 (53.2)	4.08 (2.00–8.33)	**<0.001**
Drug abuse, any	41 (33.1)	15 (31.9)	0.94 (0.46–1.94)	0.886
Acute psychosocial stressors, any	62 (50.0)	11 (23.4)	0.30 (0.14–0.65)	**0.002**
Illness-onset variables				
Age at illness onset, early (≤22 years)	49 (39.5)	27 (57.4)	2.06 (1.04–4.08)	0.037
Chronicity of onset (>6months)	18 (14.5)	14 (29.8)	2.49 (1.12–5.56)	0.025
DUP, long (⩾2 months)	37 (29.8)	21 (44.7)	1.89 (0.95–3.79)	0.069
DUCP, long (⩾1 month)	34 (27.4)	26 (55.3)	3.27 (1.63–6.58)	**0.001**
First-episode characteristics				
Spontaneous dyskinesia, Schooler & Kane criteria	2 (1.9)	9 (24.3)	17.0 (3.48–83.3)	**<0.001**
Spontaneous parkinsonism score, high (⩾4)	11 (10.2)	7 (18.9)	2.05 (0.73–5.77)	0.171
Neurological soft signs score, high (⩾15)	37 (38.1)	18 (48.6)	1.53 (0.71–3.29)	0.271
Psychosis syndrome, global rating score >2	98 (79.0)	39 (83.0)	1.29 (0.53–3.10)	0.564
Disorganization syndrome, global rating score >2	51 (41.1)	20 (42.6)	1.06 (0.53–2.09)	0.866
Negative syndrome, global rating score >2	14 (11.3)	7 (14.9)	1.37 (0.51–3.65)	0.523
Catatonia syndrome, global rating score >2	15 (12.1)	7 (14.9)	1.27 (0.48–3.34)	0.626
Affective syndrome, global rating score >2	58 (46.8)	13 (27.7)	0.43 (0.21–0.90)	0.025
Duration of index admission, long (⩾3 weeks)	50 (40.3)	31 (66.0)	2.86 (1.42–5.78)	**0.003**
Early treatment response				
CGI-EI at index discharge, marked improvement	100 (80.6)	28 (59.6)	0.35 (0.17–0.73)	**0.005**
6-month symptomatic remission after index admission	69 (59.5)	102 (80.3)	0.15 (0.06–0.37)	**<0.001**

†Data are number (and percentages) of the stated features.
In bold are presented statistically significant associations after the Benjamini–Hochberg correction for multiple testing.
CGI-EI = Clinical global impression-Efficacy Index; DUP = Duration of Untreated Psychosis; DUCP = Duration of Untreated Continuous Psychosis; PRS = Polygenic Risk Score.

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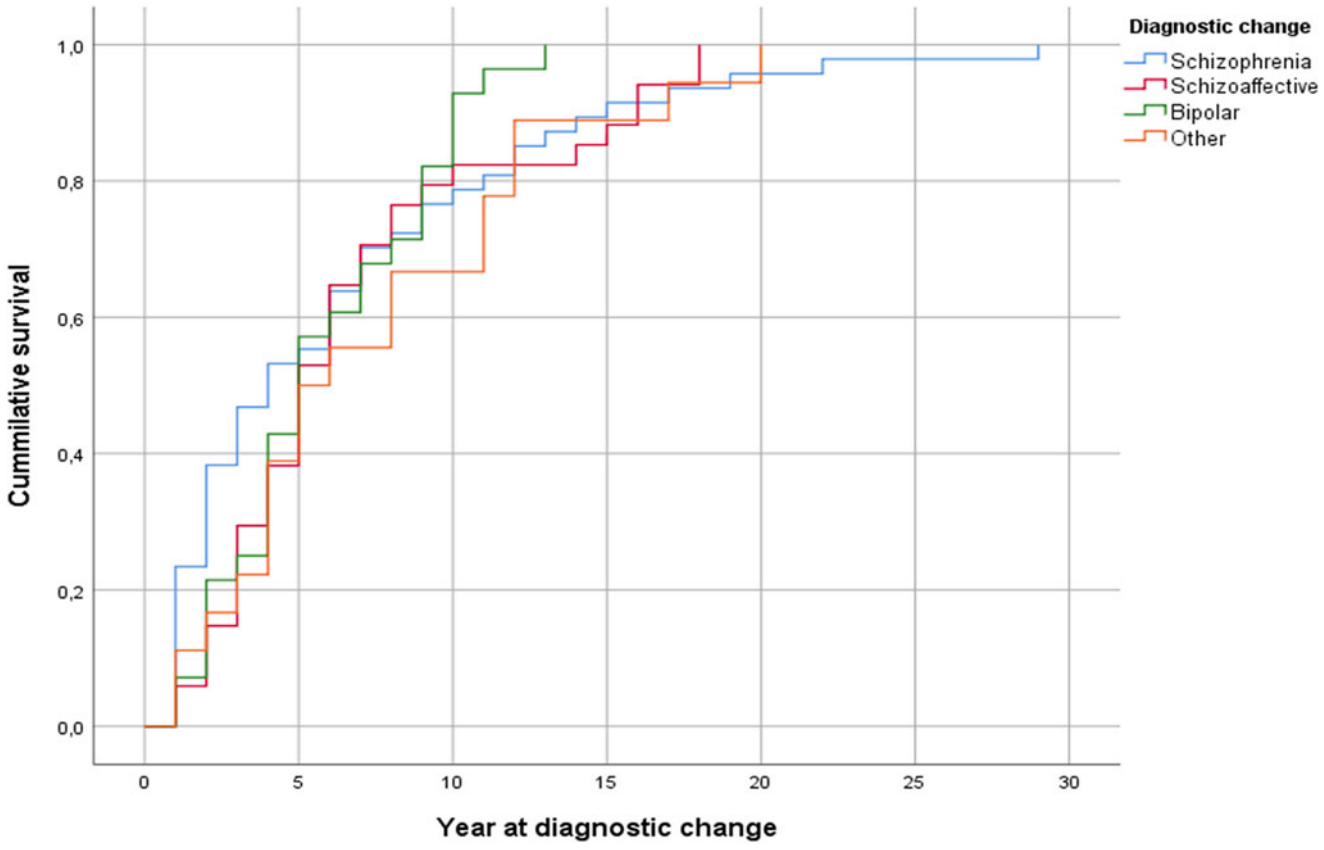

Figure 1. Kaplan–Meier time to diagnostic change over the follow-up.

Second, the shift to schizophrenia was more likely to occur when there was a family history of SSD, obstetric complications, developmental delay, poor premorbid functioning in several domains, long DUCP, lack of psychosocial stressors, spontaneous dyskinesia, longer duration of index admission and poor early treatment response. Remarkably, spontaneous dyskinesia was the strongest predictor of diagnostic change since it increased by 15 the odds of a diagnostic shift to schizophrenia. The shift to bipolar disorder was predicted by most of the variables predicting change to schizophrenia, but with lesser effect sizes and in the opposite direction (i.e. good premorbid functioning increased the odds of diagnostic shift to bipolar disorder). Notably, none of the baseline variables significantly predicted a diagnostic shift to schizoaffective disorder. This pattern of findings outlines the relevance of premorbid functioning indicators, illness onset features and early treatment response for predicting diagnostic change to schizophrenia or bipolar disorders, which are the extreme ends of the schizophrenia/ affective spectrum of psychotic disorders, while the lack of predictors of diagnostic shift to schizoaffective disorder may reflect the mixed nature of the disorder, since it is the lifetime co-occurrence of psychotic and mood symptoms that is diagnostic.

Third, the timing for diagnostic change was unrelated to specific diagnostic categories. Diagnostic changes occurred over the whole illness course, although approximately half of the changes had already occurred at 5-year follow-up. After 10-year follow-up, the change rate tends to stabilize and diagnostic changes continue to occur up to the final follow-up visit, although with decreasing frequency. These findings demonstrate that most diagnostic changes occur beyond the few years after a FEP.

Finally, we found that stable and newly diagnosed schizophrenia are essentially the same illness regarding familial-genetic risk factors and major outcome domains. However, the two conditions differed in several relevant clinical characteristics at baseline in that newly diagnosed subjects were less premorbidly impaired in several domains, had a more acute illness onset, shorter DUP and DUCP, less severe negative symptoms and better early response to treatment than subjects with stable schizophrenia. Although these differences may be quantitative rather than qualitative, they support the existence of two different underlying processes, one that it is already evident at the FEP and may be related to impaired neurodevelopment (stable schizophrenia) and another that develops after the FEP over the illness course and may be related to accelerated neurodegeneration that may underpin worsening negative symptoms (newly developed schizophrenia). These processes would have a gradient nature and should not be viewed as mutually exclusive but complementary (Owen & O'Donovan, 2017); the neurodevelopmental gradient predominating in stable schizophrenia and the neurodegenerative gradient predominating in newly developed schizophrenia.

Comparison with previous studies

The main limitation for comparing our findings with those from the literature arises from the different duration of the follow-up in the individual studies, since rates of diagnostic instability and predictors of diagnostic change are dependent on the duration of follow-up. Nevertheless, our results align with previous studies by showing that schizophrenia and bipolar disorder are the diagnostic categories that have the highest prospective consistency.

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Table 4. Baseline predictor variables and outcome domains at follow-up of individuals diagnosed of schizophrenia at intake and final follow-up (stable schizophrenia) and in those who developed schizophrenia over the follow-up (new-developed schizophrenia)

	Stable schizophrenia ($n = 66$)	New-developed schizophrenia ($n = 47$)	χ^2 or Z	p
Socio-demographics				
Age at follow-up, years	46.2 (9.58)	47.6 (10.0)	−0.62	0.535
Male gender, n (%)	37 (56.1)	33 (70.2)	2.33	0.127
Years of education	10.6 (3.04)	10.5 (3.03)	−0.51	0.703
Age at baseline assessment, years	25.8 (9.24)	25.6 (8.73)	−0.24	0.856
Length of follow-up, years	20.4 (5.87)	21.9 (5.62)	−1.47	0.241
Familial-genetic liability				
Polygenic risk score for schizophrenia	−0.12 (0.89)	0.22 (1.00)	−1.43	0.158
Polygenic risk score for bipolar disorder	−0.14 (0.71)	0.01 (1.09)	−0.57	0.565
Polygenic risk score for major depressive disorder	−0.03 (1.04)	0.11 (0.82)	−0.56	0.573
Family history of SSD, n (%)	15 (22.7)	16 (34.0)	1.76	0.184
Family history of bipolar disorder, n (%)	5 (7.6)	3 (6.4)	0.59	0.807
Family history of major depressive disorder, n (%)	9 (13.6)	6 (12.8)	0.18	0.893
Antecedents				
Obstetric complications	0.42 (0.68)	0.34 (0.63)	−0.71	0.477
Developmental delay at year 3	1.94 (1.84)	1.28 (1.28)	−1.66	0.096
Childhood adversity	51.2 (23.2)	69.9 (19.7)	−4.17	**<0.001**
Premorbid adjustment	8.73 (4.32)	5.85 (3.82)	−3.54	**<0.001**
Premorbid cognitive reserve	35.5 (12.2)	39.4 (10.5)	−1.82	0.207
Premorbid social networks	7.20 (2.91)	5.38 (3.01)	−3.19	**0.003**
Drug abuse	1.21 (1.86)	1.57 (2.50)	−0.26	0.830
Acute psychosocial stressors	1.32 (0.88)	1.68 (1.30)	−1.64	0.180
Illness onset variables				
Age at illness onset	22.8 (8.38)	24.6 (7.99)	−1.40	0.260
Chronicity of onset	3.65 (0.81)	2.45 (1.23)	−5.54	**<0.001**
Duration of untreated psychosis	30.5 (46.1)	12.2 (33.3)	−4.96	**<0.0001**
Duration of untreated continuous psychosis	25.3 (44.5)	7.04 (20.3)	−5.12	**<0.001**
First-episode characteristics				
Duration of index admission, weeks	3.69 (1.74)	3.46 (2.37)	−1.69	0.220
Spontaneous dyskinesia	1.74 (2.53)	1.78 (3.11)	−0.40	0.735
Spontaneous parkinsonism	2.74 (3.02)	2.03 (2.63)	−1,57	0.215
Neurological soft signs	19.0 (8.80)	19.4 (12.4)	−0.42	0.719
Psychosis syndrome	4.02 (1.33)	3.74 (1.40)	−1.42	0.255
Disorganization syndrome	2.79 (1.60)	2.23 (1.68)	−1,76	0.210
Negative syndrome	2.03 (1.47)	1.15 (1.31)	−3,19	**0.003**
Catatonia syndrome	0.83 (1.18)	0.91 (1.41)	−0.06	0.954
Affective syndrome	0.94 (1.14)	1.45 (1.57)	−1.59	0.210
Early response to treatment				
Clinical Global Impression Efficacy Index	2.18 (0.84)	1.53 (0.47)	−4.13	**<0.001**
Six-month symptomatic remission, (n (%)	24 (36.4)	30 (63.8)	8.30	**0.004**
Outcome domains at follow-up				

(*Continued*)

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Table 4. (*Continued.*)

	Stable schizophrenia ($n = 66$)	New-developed schizophrenia ($n = 47$)	χ^2 or Z	p
Symptomatic remission, n (%)	19 (28.8)	10 (21.3)	0.81	0.368
Functional recovery, n (%)	18 (27.3)	13 (27.7)	0.00	0.964
Personal recovery, n (%)	27 (40.9)	16 (34.0)	0.54	0.459
Psychosis syndrome	1.39 (1.49)	1.76 (1.49)	−1,39	0.163
Disorganization syndrome	1.57 (1.37)	1.51 (1.61)	−0.53	0.593
Negative syndrome	2.68 (1.29)	2.65 (1.40)	−0.06	0.945
Catatonia syndrome	0.42 (0.80)	0.62 (1.07)	−0.69	0.487
Affective syndrome	1.11 (0.76)	1.19 (0.73)	−0.43	0.664

Note: Unless otherwise indicated values are means (s.d.). Higher scores indicate more impairment except for childhood adversity, premorbid cognitive reserve, and premorbid social networks.
In bold are presented the statistically significant associations after the Benjamini–Hochberg correction for multiple comparisons.

Our prospective consistency for schizophrenia (91.7%) is one of the highest reported in the literature, which may be because we specifically reassessed baseline diagnoses 6 months after index admission in order to maximize diagnostic reliability at the FEP. Certainly, the high prospective consistency of that diagnosis may be in part the result of some circularity of diagnostic criteria requiring a symptom duration of at least 6 months. Overall, our prospective and retrospective stability figures of psychotic disorders are more similar to those reported in a 10-year follow-up study (Heslin et al., 2015) than those derived from a meta-analysis of 42 studies with an average follow-up of 4.5 years (Fusar-Poli et al., 2016). This probably reflects the fact that most diagnostic changes have already occurred at 10-year follow-up. In the same line of reasoning, we found a 47.7% of overall diagnostic stability, which is slightly lower than that the 59.6% reported by Heslin et al. (2015) and probably reflects the higher follow-up length of our study.

In contrast with most of the literature indicating that the largest proportion of diagnostic shifts is to schizophrenia, we found that it was to schizoaffective disorder. This is likely because previous studies use DSM-IV or ICD-10 criteria, which essentially characterize the disorder from a cross-sectional perspective. In contrast, the DSM-5 takes a longitudinal approach to that diagnosis; an approach that may be more in line with the clinical reality of the frequent co-occurrence of psychosis and mood syndromes over the illness course, which results in a substantial increase of that diagnosis over longer follow-ups (Marneros, Deister, & Rohde, 1991).

Many potential predictors of diagnostic change after a FEP have been reported, as reviewed in (Palomar-Ciria et al., 2019). However, many of these findings are either inconsistent or have remained poorly replicated, which may be due to differences in the methodology of studies and the paucity and variability of the potential predictors examined. Indeed, meta-analytical evidence did not reveal meaningful predictors of change (Fusar-Poli et al., 2016; Murrie, Lappin, Large, & Sara, 2020). Notwithstanding that, poor premorbid psychosocial functioning is probably the most replicated finding that predicts change to a schizophrenia diagnosis (Palomar-Ciria et al., 2019). In addition to this variable, we also described for the first time several predictors of diagnostic shift to schizophrenia or bipolar disorder, including familial-genetic factors, a broad range of premorbid antecedents, illness-onset factors, and FEP characteristics. However, these findings need to be confirmed by other authors.

We are aware of only one previous study that examined the outcome characteristics of subjects with stable and newly diagnosed schizophrenia (Gale-Grant et al., 2021). In line with that study, we found no differences between the two schizophrenia categories regarding the outcome measures; however, the study did not examine putative differences in baseline variables.

Implications

Given that more than a half of FEP subjects change their diagnosis at follow-up, FEP diagnoses need to be considered as provisional. It is important to distinguish diagnoses with good prospective consistency (i.e. schizophrenia and bipolar disorder) from the other diagnoses that (at best) pose moderate or fair consistencies, which may be of direct relevance to clinicians who are required to follow the differential treatment guidelines for early schizophrenia and bipolar disorders.

The differential predictive value of a wide range of background and first-episode variables concerning subsequent diagnostic change also has important clinical and therapeutic implications. In this regard, and to enhance diagnostic specificity and accuracy, we recommend a comprehensive assessment of background variables and FEP characteristics (Maj et al., 2021), in order to monitor closely those individuals with risk factors of diagnostic change during the first few years after a FEP. More specifically, a positive family history of SSD together with premorbid and first-episode indicators of poor outcome in patients with a FEP diagnosis other than schizophrenia should alert the clinician about the possibility of a subsequent diagnostic change to schizophrenia. Furthermore, subjects with a FEP diagnosis of schizophreniform disorder, brief psychotic disorder or PNOS should warn the clinician about the high risk of subsequent diagnostic change that deserves careful monitoring and reassessment.

On the basis of a systematic review of symptomatic changes of FEP over time, McGorry (1994) proposed the hypothesis that a process of differentiation may occur in functional psychosis such that atypicality and syndromic change reduce and prototypical Kraepelinian diagnostic forms are easier to discern with increasing duration of illness. McGorry thought that this process was particularly evident for schizophrenia, and less so for affective and schizoaffective psychoses. Overall, our findings support this hypothesis, with the major difference that the process of differentiation may be of more relevance for bipolar and schizoaffective

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disorders than schizophrenia, as indicated by the corresponding retrospective consistence figures. The high rate of diagnostic changes toward schizoaffective disorder clearly challenges the Kraepelinian dichotomy and requires further study.

Strengths and limitations

As far as we are aware, this study has the longest period of follow-up examining diagnostic stability, early predictors of diagnostic change and timing of diagnostic change. We examined a broad array of potential early predictors of diagnostic change and we extended the predictors of diagnostic change to schizoaffective and bipolar disorders, for which the literature is scanty, Moreover, we examined the early predictors of newly developed schizophrenia relative to stable schizophrenia for the first time.

Our findings must be viewed within the context of some study's limitations. First, the sample included subjects who were hospitalized with psychotic symptoms. Therefore, the results may not be generalized to community patients, which likely favors a selection bias toward the most severely ill subjects. Indeed, given that hospital samples tend to produce more stable diagnosis (Fusar-Poli et al., 2016), our data may have overestimated diagnostic stability. Furthermore, patients still in contact with health services may have been over-represented in our followed sample.

Second, the small sample sizes of subjects in several of the diagnostic categories may have limited statistical power in predicting changes to specific diagnoses, which particularly applies to PRS analyses. Furthermore, the low sample sizes did not allow for analysis of the predictors of each baseline diagnosis changing to each lifetime diagnosis. In this regard, larger powered samples are clearly needed.

Third, substance-induced psychosis was an exclusionary criterion in our study. Subjects with drug-induced FEP have a substantial risk of transition to schizophrenia (Fusar-Poli et al., 2016; Murrie et al., 2020; Starzer, Nordentoft, & Hjorthøj, 2018) and bipolar disorder (Starzer et al., 2018). Thus, the lack of inclusion of substance-induced psychosis may have influenced our retrospective stability estimates, particularly that of schizophrenia and bipolar disorder.

Finally, we used a follow-back design to assess diagnostic change. Although this is a valid procedure for some purposes (van Os, Schaub, & Carpenter, 2021), it precluded us from accurately examining the timing of transition rates and their precise predictors. Therefore, further analyses are needed to explore whether there is a regular movement from one diagnosis to another over time, which will require a longitudinal study with very frequent follow-up contacts to closely track clinical changes.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003173.

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