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Diagnostic shift in first episode psychosis: Results from the 2-year follow-up of the "Parma Early Psychosis" program

Lorenzo Pelizza [a,b,*], Emanuela Leuci [b], Anna Caterina Leucci [a], Emanuela Quattrone [b], Silvia Azzali [c], Simona Pupo [d], Enrico Plazzi [a], Giuseppina Paulillo [d], Pietro Pellegrini [b], Marco Menchetti [a]

[a] Department of Biomedical and Neuromotor Sciences, "Alma Mater Studiorum" Università di Bologna, Bologna, BO, Italy
[b] Department of Mental Health and Pathological Addiction, Azienda USL di Parma, Parma, PR, Italy
[c] Department of Mental Health and Pathological Addiction, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, RE, Italy
[d] Pain Therapy Service, Department of Medicine and Surgery, Azienda Ospedaliero-Universitaria di Parma, Parma, PR, Italy

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ABSTRACT

Purpose: Although the stability of current diagnostic criteria for people with First Episode Psychosis (FEP) is essential for treatment, it still remains poorly investigated. As its examination necessarily requires a prospective evaluation of diagnostic trajectories, the aims of the current longitudinal investigation were: (a) to assess diagnostic changes in an Italian FEP population treated within an "Early Intervention in Psychosis" service during a 2-year follow-up period, and (b) to identify potential sociodemographic and clinical moderators of diagnostic instability at entry.

Methods: All participants were FEP individuals, aged 12–35 years. Their primary diagnosis was formulated both at baseline and at the end of the follow-up. At entry, they also completed the Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) scale. As measure of diagnostic stability, the Kappa statistic was first calculated. The associations of diagnostic shift with baseline sociodemographic and clinical characteristics were then analyzed using a logistic model with the diagnostic change as dependent variable. Finally, a propensity score was calculated, based on logistic analysis results.

Results: 221 (50.1 %) FEP participants changed their initial diagnosis. The highest prospective diagnostic stability was found for initial diagnosis of schizophrenia (93.9 %) and affective spectrum psychoses (92.4 %). Diagnostic instability was high for initial diagnosis of brief psychotic disorder (100 %), schizophreniform disorder (100 %) and psychotic disorder not otherwise specified (92.1 %). The best predictors of diagnostic change were previous contact with neuropsychiatry services, shorter duration of untreated psychosis and higher baseline levels of disorganization.

Conclusions: Diagnostic stability is crucial for treatment and clinical decision making. Addressing instability in FEP diagnoses and detecting its moderators at entry are important challenges for future diagnostic development of early psychosis.

1. Introduction

Diagnostic shift/stability in young individuals with First Episode Psychosis (FEP) is relevant for clinical practice, especially in order to optimize early intervention (McGorry, 2013) and to evaluate the validity of the current diagnostic criteria for psychotic disorders (Coryell, 2011), already at the patient's first contact with mental healthcare services (Pelizza et al., 2023a) In this respect, evidence of diagnostic stability within the schizophrenia spectrum disorders or affective spectrum psychoses is crucial to select the most appropriate early treatment (Amin et al., 1999). Indeed, current international guidelines include different clinical recommendations for affective psychoses and schizophrenia, such as the use of specific psychosocial and psychopharmacological treatments, and differential strategies to favor recovery and manage risk and crisis (National Institute of health and Care Excellence (NICE), 2016).

* Corresponding author at: Istituto di Psichiatria "Paolo Ottonello", viale Pepoli, 5, 40126 Bologna, BO, Italy.
E-mail address: lorenzo.pelizza@unibo.it (L. Pelizza).

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Furthermore, the diagnosis of mental disorders is still now mainly operationalized on an expert clinical consensus about clusters of symptoms (American Psychiatric Association (APA), 2013, World Health Organization (WHO), 2019), without considering any more objective biological measures (Cegla-Schvartzman et al., 2019; Cano-Ruiz et al., 2020). Therefore, a continuous monitoring of the appropriateness of these diagnostic criteria for improving reliability across clinicians is needed, also at the onset of patients' psychopathological trajectories (Raballo et al., 2021).

However, studies on instability of FEP diagnoses reported highly heterogeneous findings (Fusar-Poli et al., 2016), especially in terms of predictive factors. Indeed, some investigators found that first episode schizophrenia had the highest 2-year diagnostic stability, while schizoaffective disorder the lowest (Schwartz et al., 2000). Other authors differently showed that first episode schizoaffective disorder had the highest 2-year diagnostic stability, followed by affective psychosis and schizophrenia (Salvatore et al., 2011). In this respect, a meta-analysis on diagnostic stability in FEP populations (Fusar-Poli et al., 2016) suggested that the publication year impacted on instability of psychotic disorder diagnoses, with higher instability over the most recent years. According to Fusar-Poli et al. (2016), as there are not enough studies examining on predictors of diagnostic instability in FEP samples, further prospective studies addressing this important topic within the "Early Intervention in Psychosis" (EIP) paradigm are needed, especially outside the well-known FEP research and datasets (Gale-Grant et al., 2021). This study may thus help shedding more light on predictive factors for diagnostic shift in young people with FEP and clarifying previous inconsistent findings. Moreover, to our knowledge, no Italian investigation on diagnostic instability in FEP samples has been previously reported. So, after >10 years of EIP intervention in Italy (Landi et al., 2021), our clinical experience is now ripe to offer an authoritative contribute on this relevant diagnostic topic, especially across a relative long (2-year) follow-up period including specialized treatments for FEP patients in a real-world clinical setting.

The aims of this research were to assess the longitudinal diagnostic stability/instability of FEP diagnoses in a young Italian clinical population treated within an EIP program, and to investigate any potential baseline socio-demographic and clinical predictors of diagnostic change over time.

2. Material and methods

2.1. Setting and subjects

FEP participants were adolescents and young adults recruited and treated within the "Parma Early Psychosis" (Pr-EP) program between January 2013 and December 2020. The Pr-EP program is a specialized EIP protocol implemented as a diffuse infrastructure in all adult and adolescent mental healthcare services of the Parma Department of Mental Health, in Northern Italy (Pelizza et al., 2021).

Inclusion criteria of this research were: (a) age 12–35 years; (b) specialist help-seeking request; (c) enrollment in the Pr-EP program; (d) presence of FEP within one of the following DSM-5 diagnoses: schizophrenia, bipolar disorder with psychotic features, major depressive disorder with psychotic features, delusional disorder, brief psychotic disorder, schizophreniform disorder, and psychotic disorder not otherwise specified (American Psychiatric Association (APA), 2013); and (e) a Duration of Untreated Psychosis (DUP) of <2 years. The DUP was defined as the time interval between the onset of frank psychotic symptoms and the first antipsychotic intake (Zoghbi et al., 2023). A DUP of <2 years was specifically selected because it is the usual limit to provide effective treatments within the EIP paradigm (Sediqzadah et al., 2022). In all cases, the start of antipsychotic treatment was not longer than 4 weeks before the baseline assessment. Indeed, this is the time limit allowed for the initial evaluation in the Pr-EP protocol (Pelizza et al., 2021).

Exclusion criteria were: (a) past DSM-5 affective or non-affective psychotic episode; (b) past exposure to antipsychotic drug; (c) known intellectual disability (i.e., Intelligent Quotient <70); and (d) neurological disorder or any other medical condition presenting with psychiatric symptoms. In this examination, "past exposure to antipsychotic medication" (at any dosage and in previous illness episode before the Pr-EP recruitment) was considered a "functional equivalent" of past psychotic episode (Poletti et al., 2023). Indeed, the traditional EIP paradigm psychometrically defined the "psychosis threshold" as essentially that at which antipsychotic drug would probably be started in the common clinical practice (Poletti et al., 2020). Furthermore, "past psychotic episode" was intended as a previous illness episode manifesting with full-blown psychotic symptoms outside the current episode. In this sense, we included exclusively those patients for whom the onset of their frank psychotic symptoms was equal to the start of the current (first) episode of psychosis. Finally, given their widespread diffusion in the common clinical practice, substance use problems were not considered as part of any exclusion criteria, but recorded as part of our chart information collected at entry.

All patients and their parents (if minors) agreed to participate to the research and gave their written informed consent prior to their inclusion in the study. Local relevant ethical approval was obtained for the research (AVEN Ethics Committee protocol n. 36 102/2019). This investigation was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments including humans.

2.2. Assessment

For the specific goals of this research, a sociodemographic/clinical chart (including information on gender, age at entry, nationality, years of education, employment status, past specialist contact, current substance abuse and DUP) was completed at entry (for details see Pelizza et al., 2022a). The presence of FEP was detected at baseline using psychometric criteria of the "Comprehensive Assessment of At-Risk Mental States" (CAARMS), approved Italian version (Pelizza et al., 2019).

The clinical assessment included the Positive And Negative Syndrome Scale (Kay et al., 1987), the Global Assessment of Functioning (GAF) scale (American Psychiatric Association (APA), 2013) and the Health of the Nation Outcome Scale (HoNOS) (Wing et al., 1999). These instruments were completed by trained Pr-EP team members at baseline. Regular scoring workshops and supervision sessions ensured their inter-rater reliability (Pelizza et al., 2022b).

The PANSS is a clinical interview developed to measure psychosis psychopathology. It has been frequently used also in young Italian FEP populations (Pelizza et al., 2022c). As indicated by Shafer and Dazzi (2019), we considered 5 main psychopathological factors: "Negative Symptoms", "Affect" ("Depression/Anxiety"), "Positive Symptoms", "Disorganization" and "Resistance/Excitement-Activity".

The GAF is a widely used instrument to measure daily functioning in individuals with psychosis. It has been frequently used also in young Italian people with FEP (Pelizza et al., 2022d).

The HoNOS is a clinical interview specifically developed to assess social and clinical outcomes in people with severe mental illness. It has been frequently used also in young Italian FEP populations (Pelizza et al., 2022e). As proposed by Golay et al. (2016), we considered 4 main outcome domains: "Psychiatric Symptoms", "Impairment", "Social Problems" and "Behavioral Problems".

2.3. Procedures and statistical strategy

The DSM-5 diagnoses were formulated both at baseline and at the end of the 2-year follow-up period by at least two trained Pr-EP team members, using the "Structured Clinical Interview for DSM-5 mental disorder (First et al., 2017). The Pr-EP program provided a 2-year comprehensive treatment package including a psychopharmacological

therapy and a multi-element psychosocial intervention (combining individual psychotherapy based on cognitive-behavioral principles, psychoeducational sessions for family members and a recovery-oriented case management) in accordance with the current EIP guidelines (National Institute of health and Care Excellence (NICE), 2016).

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0 (SPSS Inc., 2010), and the R package (R Core Team, 2022). Statistical analyses were two-tailed with a significance level set at 0.05.

For an initial assessment of diagnostic stability, the kappa statistic was first calculated (Cegla-Schvartzman et al., 2021). This is a widely used method to measure the concordance between opening and final diagnoses. The k values ranged from −1 to +1. A score of 1 indicated perfect agreement. A value of −1 indicated perfect discordance.

A logistic regression model was then estimated using a "dummy" coding the diagnostic shift as dependent parameter and baseline sociodemographic and clinical characteristics as independent variables. Moreover, using the theoretical assumptions of the Propensity Score (PS) (Austin, 2011), a propensity measure was constructed on logistic regression analysis results. We defined PS as the estimated probability of developing a diagnostic shift. This score assigned to each participants a value ranged from 0 to 1 (where zero indicated no propensity for diagnostic change and 1 indicated a very high propensity for diagnostic shift). Specifically, being computed taking into account all the collected baseline sociodemographic and clinical features, the PS model was useful to identify those drivers influencing the likelihood of experiencing diagnostic shift. In other words, the PS allowed the risk of each FEP participant to be assessed, and, using its quartiles, allowed the total sample to be divided into bands of longitudinal propensity to diagnostic change (starting from the baseline characteristics introduced into the model). Based on the estimated PS, the total sample was then stratified into 4 main groups using median and quartile values as cut-offs (group I = PS ≤ first quartile; group II = first quartile < PS ≤ median; group III = median < PS ≤ third quartiles; group IV = PS > third quartile). For each group, diagnostic flows were described, clinical and sociodemographic parameters were computed, and kappa statistics were calculated.

3. Results

441 FEP participants were recruited within the Pr-EP program between January 2013 and December 2020 (283 [64.2 %] females; mean age = 25.38 ± 6.19 years). After 2 years of follow-up, 221 (50.1 %) FEP individuals changed their initial diagnosis and were included in the FEP/DS+ (Diagnostic Shift+) subgroup. The remaining 220 individuals were grouped in the FEP/DS- subgroup. Clinical and sociodemographic characteristics of the FEP total group and the two subsamples are shown in the Table 1.

Diagnostic workflows (from baseline diagnoses to any final diagnoses after the follow-up period) are shown in the Table 2. Specifically, brief psychotic disorder and schizophreniform disorder had the highest diagnostic shift rates (100 %), followed by psychotic disorder Not Otherwise Specified (NOS) (92.1 %) and substance-induced psychosis (78.6 %). Schizophrenia is the most stable diagnosis (diagnostic shift rate = 6.1 %), followed by affective psychosis (7.6 %). Overall, a kappa value of 0.34 indicated a medium to low concordance between opening and final diagnoses.

Table 3 showed that 93.9 % of FEP participants with initial schizophrenia confirmed their diagnosis at the end of follow-up. Similarly, 92.4 % of FEP individuals with affective psychosis at baseline confirmed their diagnosis in the final 2-year reformulation. Among subjects with brief psychotic disorder at entry, 35.9 % shifted to schizophrenia, 25.6 % to affective psychosis and 23.1 % to schizotypal personality disorder. Moreover, 52.6 % of psychotic disorder NOS at baseline shifted to schizophrenia at the end of our follow-up and 28.9 % changed their diagnosis in affective psychosis. Among FEP participants with schizophreniform disorder at presentation, 42.1 % shifted to schizophrenia and 31.6 % to affective psychosis. Furthermore, 35.7 % of substance-induced psychosis at entry shifted to affective psychosis at the end of follow-up and 21.4 % changed their diagnosis in schizophrenia. Finally, in patients with initial schizoaffective disorder, schizophrenia was the main diagnostic shift in the final 2-year reformulation.

Table 1 also showed the estimated odds ratios from our logistic regression analysis. Specifically, a significant predictive role of DUP for diagnostic change over time was found: i.e., as DUP increased, the likelihood of a shift in psychosis diagnosis decreased. Another robust predictor of diagnostic shift was the presence of previous specialist contact with Child and Adolescent Mental Healthcare Services

Table 1
Sociodemographic and clinical characteristics of the FEP total sample and the two subgroups, including results from the logistic regression model for PS estimate.

Variable	FEP total sample (n = 441)	FEP/DS- (n = 220)	FEP/DS+ (n = 221)	OR	p
Gender (female)	64.2 %	65.0 %	63.3 %	0.94	0.610
Age at entry	25.38 (6.19)	26.23 (6.21)	24.53 (6.06)	0.99	0.690
Unemployed	52.6 %	52.7 %	52.5 %	1.13	0.400
Nationality (Italian)	76.4 %	76.8 %	76.0 %	0.92	0.480
Education (in years)	11.35 (2.82)	11.09 (2.78)	11.62 (2.87)	1.03	0.460
Previous specialist contact	44.2 %	47.7 %	41.2 %	0.82	0.250
Previous contact with CAMHS	15.81 %	11.82 %	19.91 %	1.62	0.010
DUP (in months)	9.90 (9.94)	12.57 (10.11)	7.24 (9.04)	0.94	0.0001
Substance abuse (at entry)	39.5 %	34.5 %	44.3 %	1.13	0.320
Baseline antipsychotic prescription	86.8 %	90.4 %	83.3 %	0.84	0.240
Baseline antidepressant prescription	19.1 %	21.4 %	16.7 %	0.89	0.390
Baseline benzodiazepine prescription	36.1 %	39.1 %	33.0 %	0.87	0.360
Baseline mood stabilizer prescription	13.8 %	17.7 %	9.9 %	0.84	0.060
HoNOS total score	30.54 (11.47)	29.44 (11.62)	30.66 (9.95)	1.05	0.180
HoNOS "Psychiatric Symptoms" domain score	10.09 (3.28)	9.82 (3.48)	10.36 (3.06)	1.08	0.420
HoNOS "Social Problems" domain score	7.74 (3.84)	7.62 (3.78)	7.87 (3.90)	1.00	0.920
HoNOS "Behavioral Problems" domain score	3.85 (2.45)	3.73 (2.48)	3.97 (2.42)	1.02	0.730
HoNOS "Impairment" domain score	3.21 (2.09)	3.21 (2.02)	3.20 (2.17)	0.99	0.910
PANSS total score	46.65 (12.84)	46.27 (13.26)	47.08 (12.38)	1.00	0.810
PANSS "Affect" factor score	15.98 (5.48)	15.95 (5.85)	16.02 (5.06)	0.95	0.190
PANSS "Disorganization" factor score	20.92 (7.79)	20.68 (7.29)	21.19 (8.35)	1.09	0.030
PANSS "Resistance/ Excitement- Activity" factor score	9.93 (5.01)	10.02 (4.70)	9.83 (5.36)	1.07	0.160
PANSS "Negative Symptoms" factor score	24.03 (9.80)	23.97 (9.08)	24.09 (10.60)	0.96	0.140
PANSS "Positive Symptoms" factor score	21.14 (7.39)	21.60 (7.46)	20.62 (7.30)	0.93	0.060
GAF**	44.62 (10.28)	44.09 (10.84)	45.18 (9.67)	1.01	0.700

Note. FEP = First Episode Psychosis; DS = Diagnostic Shift; FEP/DS- = FEP participants without DS; FEP/DS+ = FEP participants with DS; PS = Propensity Score; OR = Odds Ratio; p = statistical significance; CAMHS = Child/Adolescent Mental Health Services; DUP = Duration of Untreted Psychosis; HoNOS = Health of the Nation Outcome Scale; PANSS = Positive And Negative Syndrome Scale; GAF = Global Assessment of Functioning. Percentages and mean (standard deviation) values are reported.

Table 2
Distribution of FEP patients with DS by diagnostic categories at baseline and after the 2 years of follow-up (n = 441).

Final diagnosis	Baseline diagnosis								
	Schizophrenia	Affective psychosis	Substance-induced psychosis	Brief psychotic disorder	Psychosis NOS	Schizoaffective disorder	Schizophreniform disorder	Delusional disorder	Total
Schizophrenia	138	4	3	14	40	5	32	1	237
Affective Psychosis	5	61	5	10	22	2	24	3	132
Substance-Induced Psychosis			3	1	1				5
Psychosis NOS				1	6				7
Schizoaffective Disorder	2	1		1	1	5	2		12
Delusional Disorder							1	7	8
Schizotypal Personality Disorder	2			9	5		9		25
Borderline Personality Disorder			3	3	1		8		15
Total	147	66	14	39	76	12	76	11	441
% in the total sample	33.33 %	14.97 %	3.17 %	8.84 %	17.23 %	2.72 %	17.23 %	2.49 %	
DS (%)	6.12 %	7.58 %	78.57 %	100.00 %	92.11 %	58.33 %	100.00 %	36.36 %	
OP	0.49								
EP	0.24								
Kappa	0.34								

Note. FEP = First Episode Psychosis; DS = Diagnostic Shift; NOS = Not Otherwise Specified; OP = Proportion of Observed concordance between initial and final diagnoses; EP = Expected Proportion of concordance between initial and final diagnoses; DS (%) was calculated as "xd/nd" (where "d" indicated the initial diagnosis, "x" the number of FEP patients with diagnostic shift, and "n" the number of FEP patients with initial "d" diagnosis). Frequencies, percentages and kappa values are reported.

(CAMHS): i.e., a previous referral to CAMHS increased the likelihood of a shift in psychosis diagnosis. Moreover, we observed that the likelihood of change in diagnosis increased together with increasing baseline PANSS "Disorganization" factor score. Finally, statistical trends for the prediction of longitudinal diagnostic stability were also found in terms of higher baseline prescription rate in mood stabilizer medication and higher PANSS "Positive Symptoms" factor score at entry.

The mean of the PS obtained from the model estimated on the FEP total sample was 0.50 ± 0.19 (maximum value = 0.84, minimum value = 0.06). The median of the PS was 0.53 with an interquartile range between 0.36 (first quartile) and 0.65 (third quartile). These quartiles allowed us to identify 4 main FEP subgroups characterized by an increasing longitudinal propensity to diagnostic shift (Table 4). The first was the most stable subgroup and consisted of 107 FEP participants with a prevalent diagnosis of schizophrenia (43.9 %) and affective psychosis (28.9 %). In the second subgroup (n = 115), schizophrenia was also the modal opening diagnosis (40.0 %). However, compared to the subgroup I, a significantly higher percentage of schizophreniform disorder was observed (19.1 %). The proportion of FEP participants affected by initial diagnosis of schizophrenia (28.6 %) was even lower in the subgroup III (n = 105), although it remained the modal diagnosis. In this subgroup, the diagnosis of schizophreniform disorder was also high (26.7 %) and the proportions of FEP patients with brief psychotic disorder or psychosis NOS increased (when compared to the first two subgroups). Finally, the subgroup IV (n = 113) had the highest propensity score, and the proportions of psychosis NOS (23.1 %) and brief psychotic disorder (23.1 %) grew further, so becoming the modal diagnoses. Kappa coefficients calculated for each subgroup confirmed that the group I was the one with the highest diagnostic concordance (k = 0.44) and the group IV was the one with the lowest concordance (k = 0.18).

Sociodemographic and clinical comparisons among the 4 FEP subgroups identified through the PS are shown in the Table 5. Compared to the subgroup I, the subgroup IV had younger age at entry, shorter DUP, higher baseline rates of substance abuse and previous specialist contact with CAMHS, and lower baseline prescription rates of antidepressant and mood stabilizer medications. Moreover, the subgroup IV showed higher baseline severity levels in PANSS "Disorganization" and "Affect" factor scores, as well as in HONOS "Psychiatric Symptoms" and "Behavioral Problems" domain subscores.

4. Discussion

The results of this investigation confirm a high diagnostic stability of schizophrenia (93.9 %) and affective spectrum psychosis (92.4 %), similarly to findings reported in other comparable international FEP populations (Chang et al., 2009; Kingston et al., 2013; Fusar-Poli et al., 2016). This prospective stability can help clinicians in following the current ("on-label") prescribing recommendations proposed by agencies licensing the use of antipsychotic medications in psychosis (Pelizza et al., 2022f). In this respect, the European Medicines Agency (EMA) approved the use of paliperidone exclusively for the treatment of schizophrenia and schizoaffective disorder, risperidone for schizophrenia and manic episode in bipolar disorder, and haloperidol for psychotic disorders in general (European Medicines Agency (EMA), 2012).

Although diagnostic stability is a key criterion for the "nosological" validity of most FEP categories, some unstable diagnoses could be formulated "a priori" on expected diagnostic uncertainty at the psychosis onset (e.g., brief psychotic disorder), or on inadequate information available for a specific psychotic disorder at entry (e.g., psychosis NOS) (Rahm and Cullberg, 2007; Fusar-Poli et al., 2016). Therefore, diagnostic shifts in these specific disorders are to be expected. In this examination, we found that all initial cases of brief psychotic disorder and schizophreniform disorder, and 92.1 % of psychosis NOS changed their diagnostic status during the 2-year follow-up period. Only about 8 % of FEP patients with psychosis NOS retained their opening diagnosis, suggesting few prospective clinical uncertainty and poor clinician reluctance to longitudinally specify other (more defined) psychotic categories (Belvederi Murri et al., 2023). In our opinion, the in-depth diagnostic assessment of initial unstable and/or clinically undefined FEP categories could allow a better knowledge of the patient's subjective suffering, a stronger adherence to current guidelines indicating specific (evidence-based) treatments for different psychotic disorders, and a greater strength in therapeutic alliance and motivation to care (Pelizza

Table 3
Proportion of FEP patients with diagnostic shift by baseline diagnosis (n = 441).

	Schizophrenia				Affective Psychosis				Substance-Induced Psychosis		
	Percentage	Jefferey CI (lower).	Jefferey CI (upper)		Percentage	Jefferey CI (lower)	Jefferey CI (upper)		Percentage	Jefferey CI (lower)	Jefferey CI (upper)
Schizophrenia	93.87	89.12	96.93	Schizophrenia	6.06	2.08	1.37	Schizophrenia	21.42	6.43	46.9
Affective Psychosis	3.4	1.31	7.29	Affective Psychosis	92.42	84.19	97.05	Affective Psychosis	35.71	15.14	61.54
Schizoaffective Disorder	1.36	0.28	4.29	Schizoaffective Disorder	1.51	0.02	6.8	Substance-Induced Psychosis	21.42	6.43	46.9
Schizotypal Personality Disorder	1.36	0.28	4.29								
	Brief Psychotic Disorder				Psychosis NOS				Schizoaffective Disorder		
	Percentage	Jefferey CI (lower)	Jefferey CI (upper)		Percentage	Jefferey CI (lower)	Jefferey CI (upper)		Percentage	Jefferey CI (lower)	Jefferey CI (upper)
Schizophrenia	35.89	22.28	51.52	Schizophrenia	52.63	41.48	63.58	Schizophrenia	41.66	18.04	68.8
Affective Psychosis	25.64	14.01	40.73	Affective Psychosis	28.94	19.67	39.78	Affective Psychosis	16.66	3.63	43.62
Substance-Induced Psychosis	2.56	0.33	11.36	Substance-Induced Psychosis	1.31	0.11	5.98	Schizoaffective Disorder	41.66	18.04	68.8
Psychosis NOS	2.56	0.33	11.36	Psychosis NOS	7.89	3.36	1.55				
Schizoaffective Disorder	2.56	0.33	11.36	Schizoaffective Disorder	1.31	0.21	5.98				
Schizotypal Personality Disorder	23.07	12.07	37.91	Schizotypal Personality Disorder	6.58	2.55	1.38				
Borderline Personality Disorder	7.7	0.02	19.12	Borderline Personality Disorder	1.31	0.12	5.98				
	Schizophreniform Disorder				Delusional Disorder						
	Percentage	Jefferey CI (lower)	Jefferey CI (upper)		Percentage	Jefferey CI (lower)	Jefferey CI (upper)				
Schizophrenia	42.10	31.47	53.32	Schizophrenia	9.09	0.91	35.29				
Affective Psychosis	31.58	21.96	42.56	Affective Psychosis	27.27	83.48	56.5				
Schizoaffective Disorder	2.63	0.5	8.18	Delusional Disorder	63.63	34.69	86.26				
Delusional Disorder	1.31	0.12	5.98								
Schizotypal Personality Disorder	11.84	6.02	20.49								
Borderline Personality Disorder	10.52	5.1	18.88								

Note. FEP = First Episode Psychosis; NOS = Not Otherwise Specified; CI = Confidence Intervals. Percentages are reported. Due to the very small numbers of FEP patients stratified by initial and final diagnosis in some psychosis categories, the non-parametric approach to calculate confidence intervals obtained very large (and consequently uninformative) values.

Table 4
Baseline diagnosis distribution in the 4 subgroups identified through the propensity score in the FEP total sample (n = 441).

	Group I (n = 107)	Group II (n = 115)	Group III (n = 105)	Group IV (n = 113)	I vs II	I vs III	I vs IV	II vs III	II vs IV	III vs IV
Kappa	0.44	0.39	0.23	0.18	p					
Schizophrenia	43.93 %	40.00 %	28.57 %	21.24 %		***	***	***	*	*
Affective psychosis	28.97 %	17.39 %	6.67 %	7.08 %	*	***	***	***	**	
Substance-induced psychosis	3.74 %	1.74 %	4.76 %	2.65 %	*		*	**	**	
Brief psychosis	0.0 %	1.74 %	10.48 %	23.01 %	–	–	–	***	**	
NAS psychosis	14.02 %	13.04 %	19.05 %	23.01 %		*	**		**	
Schizoaffective disorder	1.87 %	4.35 %	0.95 %	2.65 %						
Schizophreniform disorder	3.74 %	19.13 %	26.67 %	19.47 %	**	***	***			
Delusional disorder	3.74 %	2.61 %	2.86 %	0.88 %						

Note. FEP = First Episode Psychosis. Kappa values and percentages are reported. ***p < 0.001, ** p < 0.01; *p < 0.05.

et al., 2023b).

Diagnostic shift from schizophrenia spectrum disorders to affective spectrum psychoses was uncommon in our sample. Only 4 (6.1 %) out of 66 FEP patients with initial affective psychosis shifted towards schizophrenia and 5 (3.4 %) of 138 FEP patients with initial schizophrenia shifted towards affective spectrum psychoses (Table 3). These findings

Table 5
Distribution of sociodemographic and clinical characteristics at baseline among the 4 FEP subgroups identified through the propensity score in the FEP total sample (n = 441).

	Group I (n = 107	Group II (n = 115)	Group III (n = 105)	Group IV (n = 113)	I vs II	I vs III	I vs IV	II vs III	II vs IV	III vs IV
					p					
Woman	63.55 %	66.09 %	66.67 %	61.06 %						
Nationality (Italian)	82.24 %	69.57 %	76.19 %	77.88 %	*					
Substance abuse at entry	24.30 %	28.70 %	42.86 %	61.95 %		*	***	**	***	*
Baseline antidepressant prescription	25.23 %	25.22 %	7.62 %	16.81 %		***	***	**		*
Baseline mood stabilizer prescription	24.30 %	18.26 %	10.48 %	2.65 %		**	***	*	***	*
Baseline benzodiazepine prescription	41.12 %	40.00 %	40.00 %	23.01 %					**	*
Previous contact with CAMHS	10.28 %	6.09 %	16.19 %	30.09 %	*		***	*	***	*
Propensity score	0.23 (0.08)	0.44 (0.05)	0.59 (0.03)	0.72 (0.05)	**	***	***			
Age at entry	27.39 (6.24)	26.93 (6.16)	24.56 (5.94)	22.65 (5.28)		**	**	**	***	**
HoNOS "Psychiatric Symptoms" domain score	9.08 (3.49)	9.69 (3.23)	10.55 (3.06)	11.04 (3.04)		*	***	*	**	
HoNOS "Social Problems" domain score	6.93 (3.95)	8.01 (3.60)	8.17 (4.02)	7.85 (3.74)	**					
HoNOS "Behavioral Problems" domain score	3.46 (2.43)	3.38 (2.33)	4.32 (2.40)	4.26 (2.52)		**	*	**	**	
HoNOS "Impairment" domain score	3.18 (2.09)	3.02 (2.14)	3.5 (2.08)	3.15 (2.05)						
Education (in years)	11.35 (3.05)	11.58 (3.03)	11.68 (2.94)	11.56 (2.40)		*				
DUP (in months)	19.98 (11.82)	9.39 (7.59)	6.10 (5.04)	4.15 (4.71)	***	***	***	***	***	**
PANSS "Affect" factor score	14.93 (5.34)	15.44 (5.01)	15.98 (5.07)	17.37 (6.10)			*			
PANSS "Disorganization" factor score	19.97 (7.32)	20.76 (7.92)	21.51 (8.88)	21.32 (7.14)			*			
PANSS "Resistance-Excitement-Activity" factor score	10.25 (4.71)	9.13 (4.72)	10.70 (5.42)	9.62 (5.10)						
PANSS "Negative Symptoms" factor score	23.81 (9.18)	23.84 (9.44)	24.14 (10.98)	24.28 (9.74)						
PANSS "Positive Symptoms" factor score	20.81 (6.82)	20.02 (7.65)	21.26 (7.60)	22.25 (7.47)						
GAF	44.53 (10.75)	45.27 (10.70)	44.12 (10.05)	44.65 (9.91)						

Note. FEP = First Episode Psychosis; CAMHS = Child and Adolescent Mental Health Services; HoNOS = Health of the Nation Outcome Scale; PANSS = Positive And Negative Syndrome Scale; GAF = Global Assessment of Functioning. Percentages and means (standard deviation) are reported. ***p < 0.001, **p < 0.01, *p < 0.05.

are slightly lower than those reported in the meta-analysis by Fusar-Poli et al. (2016), and support clinicians who have to follow the differential guidelines for early affective spectrum psychoses vs. schizophrenia (Amini et al., 2005).

Furthermore, we found that diagnostic shift was frequently to schizophrenia (52.6 % of initial psychotic disorder NOS, 42.1 % of initial schizophreniform disorder, 35.9 % of initial brief psychotic disorder and 21.4 % of initial substance-induced psychotic disorder), affective spectrum psychosis (35.7 % of initial substance-induced psychotic disorder, 31.6 % of initial schizophreniform disorder, 28.9 % of initial psychotic disorder NOS and 25.6 % of initial brief psychotic disorder) and (schizotypal or borderline) personality disorders (30.8 % of initial brief psychotic disorder, 22.4 % of initial schizophreniform disorder, 21.4 % of initial substance-induced psychotic disorder and 7.9 % of initial psychotic disorder NOS) (Table 3). These results are slightly higher than those reported in the meta-analysis by Fusar-Poli et al. (2016) and further support that a relevant number of FEP subjects may be misdiagnosed at baseline (Menezes and Milovan, 2000; Rufino et al., 2005). Careful reassessment and monitoring of FEP patients (especially those with initial remitting and unstable psychotic disorder diagnosis) are thus crucial (Carr et al., 2023).

As for initial diagnosis of schizoaffective disorder, previous empirical findings are conflicting, with some studies showing the lowest diagnostic stability (Schwartz et al., 2000), while others reporting the highest one (Salvatore et al., 2011). In this research, we found a relatively high (58.3 %) diagnostic shift rate for initial diagnosis of schizoaffective disorder across the follow-up, especially to schizophrenia and affective psychosis. In our opinion, a relatively long (2-year) longitudinal observation could help disambiguating and disentangling schizoaffective psychopathology towards more define psychosis categories (i.e., affective psychosis vs. schizophrenia).

An additional aim of this investigation was to examine any baseline predictors of diagnostic instability in order to identify specific characteristics of FEP patients who may be misdiagnosed at entry. In this respect, previous contact with CAMHS, a shorter DUP and higher severity levels of disorganization were relevant predictive factors of prospective diagnostic shift in our sample (especially from undefined and/or unstable psychotic categories towards more stable FEP diagnoses [i.e, schizophrenia, affective spectrum psychosis and personality disorders]), thus playing a role as important indicators of greater clinical and diagnostic severity. In this respect, the presence of shorter DUP and past contact with CAMHS (commonly associated with categorical diagnoses outside the psychosis spectrum) could make mental health professionals cautious during the diagnostic process. At the same time, high levels of disorganization at entry may often be considered as a psychopathological feature of more stable and defined FEP diagnoses overtime, given its crucial role in the psychopathology of major affective and nonaffective psychoses (especially in schizophrenia spectrum disorders) (Pelizza et al., 2022b).

Focusing on the new insights that our research can provide, it is first necessary to underline that empirical evidence on predictive factors of longitudinal diagnostic change in young people with FEP is mixed and inconsistent. Schimmelmann et al. (2005) reported that the best predictors of a shift from schizophreniform disorder to schizophrenia or schizoaffective disorder in a sample of 786 FEP subjects recruited within the "Early Psychosis Prevention and Intervention Centre" (EPPIC) in Australia were lower premorbid functioning and greater baseline "Clinical Global Impression" (CGI) score. In a population of 301 FEP patients from four national health care sectors in Denmark and Norway, Haahr et al. (2008) differently found that features discriminating schizophreniform individuals developing schizophrenia at 1 year were male gender, poor premorbid functioning, longer DUP and less severe

general psychotic symptoms. In 83 FEP adolescents, Castro-Fornieles et al. (2011) observed that independent predictors of change to schizophrenia spectrum disorders were a poorer baseline functioning and lower depression severity scores. Moreover, in a group of 150 FEP individuals in the South Korea, Kim et al. (2011) reported that female gender, higher levels of premorbid functioning, a shorter DUP and greater baseline severity levels in positive and manic symptoms are good predictors of diagnostic change from non-affective psychosis to bipolar disorder. Finally, the meta-analytic results by Fusar-Poli et al. (2016) suggested that there was greater diagnostic stability when the initial diagnosis was formulated in an inpatient unit as compared to mixed medical setting.

However, the meta-analytic findings by Fusar-Poli et al. (2016) did not identify significant variance in terms of sociodemographic (i.e., gender and age) and clinical (i.e., comorbid substance abuse, DUP, GAF score and duration of follow-up) features. In this respect, the authors stated that there were not enough studies reporting on predictors of diagnostic stability in FEP patients and meta-analyses carried over limitations of these original investigations. Moreover, conflicting results on predictive factors may also suggest that FEP samples were not large enough, or a lack of clarity about some predictors, or some problems with the diagnostic classification. Anyway, the lack of prediction related to age seems to support the guidelines recommendation suggesting that early intervention services should be accessible to all people with FEP, irrespective of age (National Institute of health and Care Excellence (NICE), 2016). In our research, compared to FEP individuals at greater risk of diagnostic stability (group I), participants with higher risk of diagnostic instability (group IV) also showed younger age at entry, higher baseline prevalence of substance abuse, lower baseline prescription rates of antidepressants and mood stabilizers, and higher baseline severity levels in PANSS "Affect" factor score. These PS-based findings partially differ from our logistic regression ones. This might be because in the multivariate model, controlling for some of the risk factors overshadowed the isolated effects of others.

4.1. Limitations

Several limitations of the current investigation are also to be acknowledged. A first weakness was the relatively small sample size of our FEP subgroups. This may have limited the strength and accuracy of our statistical analysis results. Thus, larger studies to replicate our results and clarify statistical trends are needed.

Second, our follow-up period was limited to 2 years. Longer perspective studies to confirm and clarify our findings are thus needed, especially those specifically investigating any relevant predictors of longitudinal diagnostic change.

Third, compared to previous results of other international investigations, some of our statistically significant predictors of diagnostic shift are similar, while others are different. This could suggest that our FEP sample was nor larger enough, or some problems with the diagnostic classification. Therefore, future studies on larger FEP populations and with more clarity about predictors' definition are needed.

Finally, in the present research we used the DSM-5 diagnostic criteria for mental disorders also for FEP adolescents, following a common practice in mixed adolescent and young adult FEP populations (Schandrin et al., 2023). This may be of concern when formulating a diagnosis of personality disorders, which would require the age of >18 years. Therefore, future studies specifically examining adolescent FEP samples with more indicated clinical interviews (such as the Kiddie schedule for mental disorders) are needed.

5. Conclusions

The results of this research support a high prospective diagnostic stability for FEP patients with initial diagnosis of schizophrenia and affective spectrum psychoses. However, diagnostic stability was overall low, especially for an opening diagnosis of brief psychotic disorder, schizophreniform disorder, psychotic disorder NOS and substance-induced psychotic disorder. In this study, most of diagnostic shift were towards schizophrenia, affective psychosis and personality disorders.

Moreover, the best predictors of diagnostic change over time were previous contact with CAMHS, a shorter DUP and higher baseline severity levels in disorganization. As diagnostic stability is important for caretakers and patients and offers general guidance for clinical decision making and for the development of treatment guidelines (Heslin et al., 2015), addressing instability in FEP diagnosis and its potential predictors at baseline is an important challenge for future diagnostic evolution of early psychosis.

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CRediT authorship contribution statement

Lorenzo Pelizza: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Anna Caterina Leucci:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Emanuela Quattrone:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Silvia Azzali:** Data curation. **Simona Pupo:** Data curation, Writing – review & editing. **Enrico Plazzi:** Formal analysis, Writing – original draft, Writing – review & editing. **Giuseppina Paulillo:** Writing – review & editing. **Pietro Pellegrini:** Writing – review & editing. **Marco Menchetti:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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