Subtyping based on premorbid profile: a strategy to personalize treatment in first episode affective psychosis?

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Running title: Premorbid subtyping in early affective psychosis

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Abstract

Aims: Premorbid history may have a major influence on the way patients cope with the onset of psychosis. This issue has been widely studied in the context of early intervention in schizophrenia but considerably less is known regarding affective psychosis. Our first goal was to investigate if sub-groups could be identified among affective psychosis patients based on premorbid factors. Our second goal was to compare these subtypes according to the evolution of mood symptoms and outcomes at the end of the program.

Methods: We conducted a three-year prospective study on a sample of 74 adults aged 18 to 35 with a first episode of affective psychosis. Latent class analysis was used to reveal distinct exploratory subgroups within affective psychosis patients.

Results: Three distinct sub-groups could be distinguished. One with later onset of psychosis mainly including women with more severe depressive symptoms in the first 6 months contrasting with two other sub-groups with more severe manic symptoms all along the follow-up and earlier onset of psychosis, with or without many serious antecedents. The sub-group with many serious antecedents was more likely to require several hospitalizations, less likely to achieve recovery, especially regarding professional integration and return to premorbid general functioning.

Conclusion: This study provides further evidence of poor functional recovery in the early phase of affective psychosis and shows that premorbid characteristics allow the identification of subgroups with distinct outcome which may require specification of treatment.

Key words: affective, early intervention, first-episode, premorbid, psychosis

1. Introduction

Psychotic disorders are often classified in clinical settings as affective or non-affective depending on clinical symptoms in the first episode (Torrent et al., 2018). Affective psychoses are characterized by the presence of psychotic features as well as depressive or manic episodes (Strakowski et al., 1998). These mood features impair functioning and complicate pathway to recovery (Paykel, 2008; Strakowski et al., 1998). While early non-affective psychoses have received extensive attention, less is known about affective psychoses although they represent an important proportion of psychotic disorders (Conus, Macneil, & McGorry, 2014; Salvadore, Drevets, Henter, Zarate, & Manji, 2008).

Premorbid factors in early psychosis patients could account for differences between patients with different diagnosis, which hence may be composed of subjects with similar clinical presentation related however to distinct illness processes. Indeed, some socio-demographic characteristics, such as gender (Bardenstein & McGlashan, 1990; Conus, Cotton, Schimmelmann, McGorry, & Lambert, 2007), marital status (Benabarre et al., 2001; Conus et al., 2007), socio-economic status (Byrne, Agerbo, Eaton, & Mortensen, 2004; Eid et al., 2013) and education level (MacCabe et al., 2010), seem to differ across diagnostic categories within psychotic disorders, and they correlate with differences regarding illness evolution and treatment response. In addition, and besides increasing the risk of psychosis (O'Donoghue et al., 2015), premorbid socio-economic and clinical conditions of individuals are correlated to outcome and risk of chronicity (van Os et al., 1995). Finally, past personal or familial psychiatric history, exposure to traumatic events, suicide attempts, history of substance abuse (Conus et al., 2007) and migration (Zolkowska, Cantor-Graae, & McNeil, 2001) are correlated to outcome. Studying premorbid factors in the initial course of psychotic disorders is therefore an opportunity to better understand how they are linked to clinical presentation and to provide clues for adjusting treatment.

This may be true for affective psychoses more specifically. Indeed, environment and life events impact mood stability in bipolar disorder (Aldinger & Schulze, 2017), suggesting that premorbid conditions may play a major role in the clinical course of affective psychoses. While sociodemographic and clinical distinctions have been made between diagnostic categories of psychoses, it remains unclear

how premorbid factors could differentially affect the course of early affective psychoses. Treatment response may also be affected by sociodemographic factors, a higher socioeconomic status in bipolar disorder being for example associated with better lithium response (Eid et al., 2013). Furthermore, affective psychoses have been associated with a shorter duration of untreated psychosis (DUP), an older age at onset (Benabarre et al., 2001; Conus et al., 2007; Large, Nielssen, Slade, & Harris, 2008), and a better social adjustment at adolescence (Cannon et al., 1997) than non–affective psychoses, which may influence evolution. Since premorbid factors play a role in mood evolution and treatment response in the early phase of affective psychosis, identifying subgroups of patients with different premorbid profiles may guide treatment choice.

The aims of this study are therefore, (1) to identify subgroups of patients within affective-psychoses based on premorbid factors, and (2), to compare their mood symptomatology and outcomes over a three-year follow-up.

2. Method

2.1 Sample and procedure

TIPP (Treatment and Early Intervention in Psychosis Program) is a specialized early psychosis program implemented in Lausanne (Switzerland) since 2004 at the Department of Psychiatry CHUV (Baumann et al., 2013; Conus & Bonsack, 2004). Patients entering the program are aged between 18 and 35, reside in the catchment area of Lausanne, and have crossed the psychosis threshold according to the "*Psychosis threshold*" subscale of the Comprehensive Assessment of At Risk Mental States scale (CAARMS; Yung et al., 2005). Patients who have more than 6 months of previous antipsychotic medication, an intoxication or an organic brain disease induced psychosis, or an intelligence quotient lower than 70, are addressed to other programs. In this program, a psychiatrist and a case manager are assigned to each patient. In a bio-psycho-social perspective, the treatment includes psychotherapy, psycho-education, family support, cognitive assessment and remediation, social support, assistance in finding employment, psychological interventions for cannabis use, and pharmacological treatment. In line with international guidelines, atypical antipsychotics are first-line pharmacological treatment with a prospective monitoring of any side effects (Baumann et al., 2013). Case managers, who have up to

one hundred instances of contact with patients during the program, complete a questionnaire specially designed for the TIPP. Detailed information about demographic characteristics, past medical history, exposure to life events, symptoms and functioning are collected for each patient. A psychologist and case managers carry out follow-up assessments at 2, 6, 12, 18, 24, 30, and 36 months, exploring various aspects of treatment and co-morbidities (e.g. level of insight; treatment adherence; presence or absence of forensic history and substance use; intermittent exposure to trauma; suicide attempts and forensic events), evolution of psychopathology and functional level. Every patient's file is revised by a psychologist at 18 and 36 months to collect data on hospital stays from discharge files.

This study was approved by the Human Research Ethics Committee of the Canton Vaud (protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if they provided consent. Of the first 386 patients enrolled in the program, all agreed for their clinical data to be used for research.

2.2 Diagnostic Assessment

Diagnosis results from an expert consensus discussed at 18 and 36 months, based on the DSM-IV criteria using the information from medical reports from treating psychiatrists, as well as from the TIPP-assigned psychiatrist and case manager. In this study, we used the latest consensus diagnostic available. We included bipolar disorder, major depression with psychotic features and schizoaffective disorder in affective psychoses.

2.3 Premorbid factors

Case managers collected premorbid information at entry. DUP was defined as the time between onset of psychosis defined by CAARMS and admission to TIPP. Socioeconomic status (SES) was subdivided into low, intermediate and high (Chandola & Jenkinson, 2000). Migration in adversity was defined as migration in adverse contexts (e.g. seeking protection for political reasons, threat of death, exposure to war or extreme poverty). Mapping of past psychiatric and substance abuse diagnoses was based on DSM-IV criteria (American Psychiatric Association, 1994), and past suicide attempts on the ICD-10 classification (Dilling & Dittmann, 1990). Early adolescent functional level was evaluated with the Premorbid Adjustment Scale [PAS] (Cannon-Spoor, Potkin, & Wyatt, 1982) using the early

adolescence sub-score (MacBeth & Gumley, 2008). Past history of trauma was rated by case managers (Alameda et al., 2015; Alameda et al., 2016), patients were considered to have a history of trauma if they had experienced at least one sexual or physical abuse prior the onset of psychosis.

2.4 Symptomatology and functioning at baseline

Manic and depressive symptoms were respectively measured with the Young Mania Rating scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). As data were not available at baseline, we used the two-month follow-up measures. We assessed general symptomatology with the Clinical Global Impression (CGI; Guy, 1976). The social and occupational level was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994). We used the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) to measure functioning regarding the impact of symptomatology.

2.5 Level of depressive and manic symptoms

Depressive and manic symptoms were assessed at 2, 6, 12, 18, 24, 30, 36 months of follow-up. We measured the severity of depressive symptoms with the MADRS, and manic symptoms with the YMRS.

2.6 Outcomes at discharge

We classified hospital stays in three categories (none, unique, multiple) to compare the proportion of patients requiring none, one or several hospital stays. We assessed psychotic symptoms with the Positive and Negative Psychotic Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). Symptomatic recovery was defined following Andreasen's Criteria (score ≤ 3) on 8 items of the PANSS (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal, lack of spontaneity; Andreasen et al., 2005). Functional recovery was defined as a PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items (Strakowski et al., 1998). Independent living recovery (head of household/living alone, with partner, or with peers/living with family with minimal supervision) was measured with the Modified Vocational Status Index [MVSI] and working recovery (paid or unpaid full- or part-time employment/ being an

active student in school or university/head of household with employed partner (homemaker)/full or part-time volunteer) with the Modified Location Code Index Independent living [MLCI] (Tohen et al., 2000). Quality of life at discharge was assessed with the World Health Organization Quality Of Life assessment scale ("The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization," 1995) a 26-item self-rated scale measuring satisfaction with life and self-esteem the based on 5-point Likert scales ranging from 1 (low satisfaction) to 5 (high satisfaction). The case manager assessed insight (absence=0; partial=1; full=2). Insight recovery was defined as getting full insight at discharge, i.e. awareness of illness and necessity of treatment. We also included continuous outcome measures to consider change regarding depressive and manic symptoms, general symptomatology and functioning, respectively measured with the MADRS, the YMRS, the CGI, and the SOFAS/GAF. We we considered the difference between the baseline and the 36-month follow-up measures, except for the MADRS, and YMRS for which the first measure was available at 2 months.

2.7 Statistical analysis

We used latent class analysis (LCA) to identify sub-groups based on premorbid factors. To determine the number of latent classes we used the BIC coefficient, the Lo-Mendell-Rubin and the bootstrapped likelihood ratio tests. We used Pearson's Chi-square tests to test the repartition of diagnostic categories between classes. We used mixed effects models repeated measures analysis of variance (MMRM) to analyse differences between sub-groups over time on mood symptoms. In these models, the "within-group" factor was time and the "between-groups" factor was sub-groups. We selected the optimal within subject covariance matrix in each MMRM based on the AIC coefficient. We conducted one-way ANOVA to compare sub-groups regarding symptomatology and functioning at baseline. Outcome differences were assessed using logistic regression for categorical variables and one-way ANOVA or linear regression for continuous variables. We performed non-parametric Kruskal-Wallis tests to compare the number of hospital stays. We applied Bonferroni correction for post-hoc analyses. The analysis were performed with IBM SPSS statistics 25 and Mplus Version 7.4

3. Results

3.1 Patient sample

Our final sample consisted of 74 patients (Mean age = 25.16; 50.0% males) meeting diagnostic criteria for affective psychosis (24 with bipolar disorder, 17 with major depression with psychotic features, 33 with schizoaffective disorder).

3.2 *Sub-groups based on premorbid profile within affective psychosis*

Models including 1 to 5 class were estimated (*Table 1*). Estimation was problematic (model under-identification) for models with more than 3 classes. The Lo-Mendell Rubin test and the BIC pointed toward a one class model while the parametric bootstrapped likelihood ratio test, which is considered the most adequate test (Nylund, Asparouhov, & Muthén, 2008), suggested the three-class solution. Because of its theoretical interpretability, we selected this three-class model to identify sub-groups within affective psychosis (*Figure 1*).

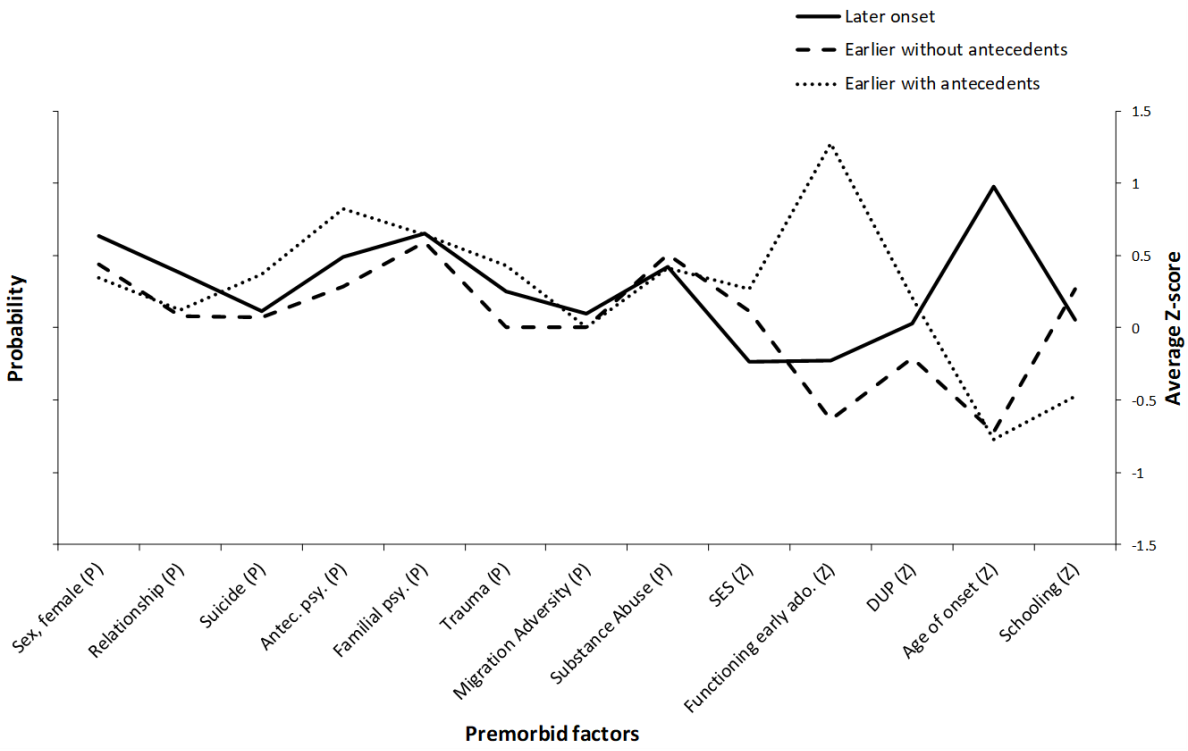
Table 1. Characteristics of the 1-5 latent class analysis solutions

Number of classes	Size of each class	BIC	Entropy	Model comparison n vs n-1 classes	
				Lo-Mendel-Rubin LRT p-value	Bootstrapped LRT p-value
1	74	1687.436	-		
2	15 (20.3%); 59 (79.7%)	1710.234	0.799	0.464	<.001
3	17 (23.0%); 25 (33.8%); 32 (43.2%)	1730.372	0.838	0.646	<.001
4	3 (4.1%); 19 (25.7%); 20 (27.0%); 32 (43.2%)	1759.956	0.888	0.282	.07
5	10 (13.5%); 12 (16.2%); 15 (20.3%); 16 (21.6%); 21 (28.4%)	1791.312	0.991	0.668	.10

Note. LRT: Likelihood Ratio Test

It is important to note that the distribution of bipolar disorder, major depression with psychotic features and schizoaffective disorder was similar across sub-groups ($\chi^2(4) = 2.852$, $p = .595$). The first

group included 32 people with later onset psychosis. This sub-group consisted mostly of women characterized by low socio-economic status, a good level of education, past relationships, and they were more likely to have a history of migration in adversity. In the two other sub-groups, patients had earlier onset of psychosis. One of these two sub-groups consisted of 17 people who cumulated many serious premorbid antecedents (suicide attempt, psychiatric antecedents, trauma, low premorbid adjustment at adolescence, low education level), the other one was composed of 25 people with few premorbid antecedents. There was no difference across sub-groups regarding prevalence of familial psychiatric history and history of premorbid substance abuse.



Note. P=Probability (dichotomous variable), Z=Average Z-score (continuous variable), Antec. psy. = personal psychiatric antecedents, Familial psy. = Familial psychiatric antecedents, SES = Socioeconomic status, DUP= Duration of Untreated Illness, Functioning early ado. = Functional adjustment in early adolescence.

Figure 1. Sub-groups in affective psychosis according to premorbid factors

Socio-demographic and premorbid characteristics of sub-groups are described in table 2.

Table 2. Sociodemographic and premorbid characteristics of sub-groups within affective psychosis

	Total	Later onset	Earlier onset without antecedents	Earlier onset with antecedents
	N =74	N=32	N=25	N=17
Gender, male % (N)	50.0 (37)	37.5 (12)	56.0 (14)	64.7 (11)
Age in year, M (SD)	25.16 (4.932)	29.94 (2.564)	21.56 (2.959)	21.47 (2.183)
Diagnosis, % (N)				
Schizoaffective disorder	44.6 (33)	43.8 (14)	48.0 (12)	41.2 (7)
Major depression with psychotic features	17.6 (3)	31.3 (10)	16.0 (4)	17.6(3)
Bipolar disorder	41.2 (7)	25.0 (8)	36.0 (9)	41.2 (7)
Education in year, M (SD)	10.48 (2.566)	10.44 (2.636)	11.33 (2.436)	9.15 (2.193)
Age of onset, M (SD)	24.19 (5.090)	29.19 (2.546)	20.52 (2.535)	20.18 (2.811)
Duration of untreated psychosis (days), Mdn (IQR)	50.00 (181.50)	59.50 (129.00)	19.00 (60.00)	190.00 (377.50)
Socio-economical level, % (N)				
Low	37.8 (28)	25.0 (8)	20.0 (5)	11.8 (2)
Intermediate	41.9 (31)	53.1 (17)	36.0 (9)	29.4 (5)
High	20.3 (15)	21.9 (7)	44.0 (11)	58.8 (10)
Marital status, % (N)				
Single	78.1 (57)	62.5 (20)	91.7 (22)	88.2 (15)
Married	12.3 (9)	21.9 (7)	4.2 (1)	5.9 (1)
Divorced	6.8 (5)	15.6 (5)	0.0 (0)	0.0 (0)
Cohabitation	2.7 (2)	0.0 (0)	4.2 (1)	5.9 (1)
Early adolescence adjustment, M (SD)	0.30 (0.183)	0.26 (0.114)	0.20 (0.114)	0.56 (0.140)
Past suicide attempt, % (N)	16.4 (12)	12.5 (4)	8.0 (2)	37.5 (6)
History of trauma[a], % (N)	26.8 (19)	35.5 (11)	0.0 (0)	47.1 (8)
Migration in adversity, % (N)	37.8(28)	50.0 (16)	16.0 (4)	29.4 (5)
Psychiatric history, % (N)	50.7 (37)	50.0 (16)	29.2 (7)	82.4 (14)
Familial psychiatric history, % (N)	62.9 (44)	64.3 (18)	60.0 (15)	64.7 (11)
Lifetime substance abuse (DSM), % (N)	44.6 (33)	40.6 (13)	52.0 (13)	21.2 (7)

Note. [a] physical or sexual abuse.

3.3 Symptomatology and functioning at baseline

We found no difference between sub-groups regarding symptomatology and functioning at baseline (*Table 3*).

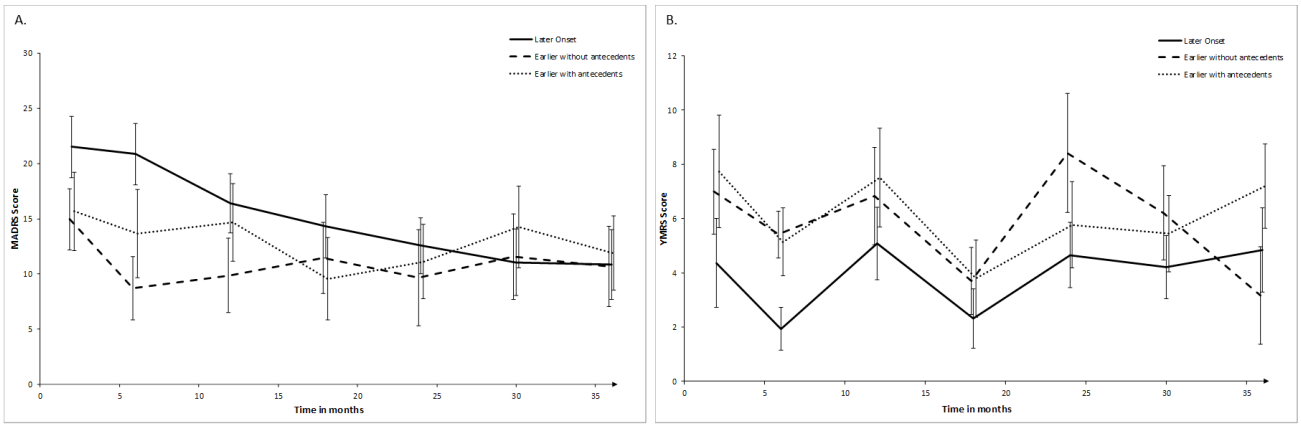
Table 3. Analysis of variance (ANOVA) between sub-groups of symptomatic and functioning profiles at baseline

	Mean (SD)	Sum of square	df	Mean Square	F	p-value
MADRS*		290.761	2	145.381	1.128	.339
Later onset	21.27 (13.33)					
Earlier onset without antecedents	14.17 (9.47)					
Earlier onset with antecedents	17.14 (10.93)					
YMRS*		49.811	2	24.905	.846	.440
Later onset	4.45 (5.03)					
Earlier onset without antecedents	6.50 (5.54)					
Earlier onset with antecedents	7.71 (5.85)					
CGI		8.371	2,61	4.185	1.565	.217
Later onset	4.48 (1.78)					
Earlier onset without antecedents	4.68 (1.64)					
Earlier onset with antecedents	5.40 (1.30)					
SOFAS		847.571	2,66	423.785	1.534	.223
Later onset	42.14 (16.56)					
Earlier onset without antecedents	45.83 (13.71)					
Earlier onset with antecedents	36.44 (20.38)					
GAF		870.043	2,64	435.022	1.330	.272
Later onset	41.36 (17.50)					
Earlier onset without antecedents	45.83 (15.83)					
Earlier onset with antecedents	36.25 (21.84)					

Note. df = degrees of freedom; *data for the YMRS, and the MADRS were only available at 2 months.

3.4 *Evolution of depressive and manic symptoms over the program*

Depressive symptoms were higher in the sub-group with later onset than in the sub-group with earlier onset and few antecedents during the first 6 months (*Figure 2 A.*; mean difference at 6 months = 12.127, df = 138.405, p = .003, 95% IC = [4.227;20.027]). The sub-group with later onset had significantly less manic symptoms over the 36 months period than the sub-group with earlier onset and few antecedents (*Figure 2 B.;* mean difference = -1.903, df = 61.343, p = .044, 95% IC = [-3.756;-.049]), as well as than the sub-group with earlier onset and many serious antecedents (*Figure 2 B.;* mean difference = -2.170, df = 53.000, p = .024, 95% IC = [-4.041;-.300]).



Note. The error-bars indicate +/- one standard error.

Figure 2. Course of depressive (A.) and manic (B.) symptoms over the TIPP according to the sub-groups of affective psychosis defined with premorbid factors

3.5 Outcomes at discharge

Results of the outcomes at discharge *(Table 4)* revealed that sub-groups with earlier onset and few antecedents had significantly better general functional recovery (p = .038) and work-related recovery (p = .030) than the sub-group with earlier onset and many serious antecedents. Subgroups differed regarding quality of physical health (F(2,20) = 3.992, p = .35). The sub-group earlier onset without antecedents (M = 30.33, SD = 2.94) had a significantly better physical health (mean difference = 6.167, p = .040) than the sub-group with later onset (M = 24.17, SD = 4.86). No differences were found between sub-groups regarding quality of psychological aspects, environment, and relationships at discharge. Analyses regarding hospitalization revealed a significant difference between sub-groups regarding the number of hospitalizations along the program (H(2) = 9.091, p = .011). The sub-group earlier onset with antecedents had more multiple hospitalizations (75%) compared to the sub-group earlier onset without antecedents. We did not find any difference regarding symptomatic or functional changes assessed with the 3-year difference scores.

Table 4. Comparison of outcomes between sub-groups at the end of the program

	% (N)	Odds ratio	95% CI of OR		p-value
			LCI	UCI	
Symptomatic recovery					
Earlier onset with antecedents	50.0 (5)	Ref cat.	-	-	
Later onset	44.4 (4)	.800	.131	4.874	.809
Earlier onset without antecedents	62.5 (5)	1.667	.251	11.071	.597
General functional recovery					
Earlier onset with antecedents	28.6 (4)	Ref cat.	-	-	
Later onset	57.7 (15)	3.409	.844	13.774	.085
Earlier onset without antecedents	66.7 (12)	5.000	1.096	22.820	**.038***
Premorbid adjustment recovery					
Earlier onset with antecedents	66.7 (6)	Ref cat.	-	-	
Later onset	33.3 (6)	.250	.046	1.365	.109
Earlier onset without antecedents	69.2 (9)	1.125	.183	6.935	.899
Working recovery					
Earlier onset with antecedents	7.1 (1)	Ref cat.	-	-	
Later onset	24.0 (6)	4.105	.441	38.234	.215
Earlier onset without antecedents	47.4 (9)	11.700	1.265	108.200	**.030***
Independent living recovery					
Earlier onset with antecedents	64.3 (9)	Ref cat.	-	-	
Later onset	84.0 (21)	2.917	.632	13.459	.170
Earlier onset without antecedents	68.4 (13)	1.204	.280	5.182	.803
Insight recovery					
Earlier onset with antecedents	69.2 (9)	Ref cat.	-	-	
Later onset	76.0 (19)	1.407	.316	6.265	.654
Earlier onset without antecedents	66.7 (12)	.889	.192	4.114	.880
	M (SD)	*B*	95% CI of OR		p-value
			LCI	UCI	
ΔMADRS					
Earlier onset with antecedents	3.00 (2.828)	Ref cat.	-	-	
Later onset	-8.00 (20.347)	-11.000	-38.648	16.648	.378
Earlier onset without antecedents	-2.00 (2.944)	-5.000	-32.648	22.648	.682
ΔYMRS					
Earlier onset with antecedents	-5.00 (7.071)	Ref cat.	-	-	
Later onset	-1.50 (7.047)	3.500	-9.990	16.990	.559

Earlier onset without antecedents	-4.25 (5.909)	.750	-12.740	14.240	.899
ΔCGI					
Earlier onset with antecedents	-1.75 (.957)	Ref cat.	-	-	
Later onset	-.43 (2.070)	1.321	-.983	3.626	.237
Earlier onset without antecedents	-1.60 (1.517)	.150	-2.317	2.617	.897
ΔSOFAS					
Earlier onset with antecedents	24.85 (24.344)	Ref cat.	-	-	
Later onset	20.83 (12.984)	-4.020	-16.182	8.142	.510
Earlier onset without antecedents	21.50 (16.671)	-3.346	-16.104	9.411	.601
ΔGAF					
Earlier onset with antecedents	22.67 (28.308)	Ref cat.	-	-	
Later onset	21.52 (13.853)	-1.145	-14.895	12.605	.868
Earlier onset without antecedents	18.00 (17.773)	-4.667	-19.225	9.892	.522

**p<.05*

4. Discussion

The purpose of this study was to identify potential sub-groups within affective psychosis based on premorbid characteristics, and if these subgroups would have distinct outcomes. Our results showed that, over and above diagnostic categories, the analysis of premorbid profile allows the detection of sub-groups of patients with different course of mood symptoms and distinct functional outcome over the early phase of affective psychosis. If replicated, these results may pave the way to the specification of intervention based on characteristics that clinicians could identify in the very early phase of treatment.

The latent class analysis we conducted on premorbid characteristics allowed the identification of three exploratory sub-groups. The first one, composed of patients with a relatively late onset of psychosis, around age 30, included a majority of females who were married or in de-facto relationship and had a good educational level. They however had a low socio-economic status and the majority reported previous exposure to adverse events such as migration in adversity. The second group was composed of patients with onset of psychosis around age 20, who had hardly any exposure to adverse events, and no past-history of psychiatric disorder. The third group was also composed of patients with an onset of psychosis around age 20, but who had low educational level, low premorbid adjustment,

exposure to serious childhood trauma, and psychiatric problems such as suicide attempts before onset of psychosis. Interestingly, these three subgroups displayed distinct patterns of symptomatic evolution and significant differences in functional outcome.

Regarding symptoms, while all three groups reached symptomatic remission at the end of the program, they differed regarding the pattern followed by mood symptoms over the three-year follow-up. The subgroup with later onset displayed higher levels of depressive symptoms compared to the two other subgroups, mainly within the first six months. These symptoms should be considered when designing the treatment since previous research has shown that their presence, especially in patients previously exposed to trauma, mediates poorer functional outcome (Alameda et al., 2017). The rapid decrease of depressive symptoms in this subgroup, including a majority of females, suggests a good resilience capacity. This is in line with previous research showing a tendency of women to express more depressive symptoms (Bardenstein & McGlashan, 1990), but with good resilience capacity and ability to cope with stressful events (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). The two other sub-groups displayed higher scores of manic symptoms than the subgroup with later onset overall but with substantial variability, it would therefore require further investigation to explore to which extent they need specific mood stabilizer treatment adaptation. In addition, the sub-group with earlier onset and many serious antecedents was more likely to undergo multiple hospitalizations. Clinicians should therefore identify them early in order to provide more intensive relapse prevention and probably more support.

The three subgroups differed significantly regarding functional outcome at discharge despite similar symptomatic outcome. Many studies have shown that in affective psychoses, while symptomatic outcome is favourable in the vast majority of patients, functional recovery remains challenging (Conus et al., 2010; Conus et al., 2006; Conus & McGorry, 2002). Our data suggest that subtyping premorbid profiles might allow the identification of a subgroup at high risk of poor functional outcome. Indeed, patients with early onset and many serious antecedents showed significantly more difficulty to recover premorbid functioning, and less than 10% of them had employment at discharge. This is in line with previous studies showing that premorbid history with comorbidities, poor adjustment, and traumatic

events are associated with poor functional outcome (Conus et al., 2007), an earlier age of onset, and risk of chronicity (Aldinger & Schulze, 2017; van Os et al., 1995). Future research should explore if the early implementation of strategies aiming at promoting functional recovery, like cognitive remediation, supported employment, would help these patients to improve their functional recovery. Despite displaying a better functional outcome, both other subgroups did not do well either. Indeed, only 56% of patients in the group with later onset returned to their pre-morbid functioning, and only 24% returned to work at discharge. This is in line with previous findings (Golay et al., 2017) showing that bringing patients back to work is challenging despite employment before psychosis onset, suggesting specific strategies are needed to protect competencies patients acquired before the disorder emerges.

Although this study provides useful insights for early intervention in affective psychoses, it has limitations. First, the TIPP program only includes patients aged between 18-35, excluding patients with very early and late onset of psychosis. Second, patients were including in affective psychoses according to their diagnosis over the entire treatment period. Diagnosis could sometimes change across follow-up making the use of these premorbid subtypes challenging in clinical settings. Fourth, our sample size was relatively limited. Different class structures may emerge with other larger, or more heterogeneous samples. Selected premorbid variables were considered in the LCA based on previous literature, thus different class structures may also emerge with the use of other data (e.g., neurocognition).,

In conclusion, our data confirm that functional outcome is relatively poor in affective psychosis patients, and suggest it is possible to identify subgroups with distinct outcome profiles among these patients. Considering the clinical relevance of this way of identifying subgroups of patients, it would be interesting to investigate premorbid subtyping in non-affective psychosis in further study. More research is also required to see if specification of treatment according to these profiles could improve outcome.

Acknowledgements

This study was supported by the Swiss National Science Foundation (320030_122419 to PC and Kim Q. Do), National Center of Competence in Research (NCCR) "SYNAPSY—The Synaptic Bases of Mental Diseases" financed by the Swiss National Science Foundation (n° 51AU40_185897). We would like to thank the case-managers of the TIPP program for collecting data over years.

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