Gender differences in first episode psychosis: Some arguments to develop gender specific treatment strategies

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ABSTRACT

Introduction: Some aspects of gender differences in patients with schizophrenia spectrum disorders (SSD) have been studied, especially in cross-sectional designs and with a short-term follow-up. However, only a few studies have considered the evolution during the follow-up of SSD patients according to their gender. In this study, we explore gender differences from the time of entry in an early intervention program for psychosis, up to three years follow-up.

Methods: We conducted a prospective study including a cohort of 474 patients treated at the Treatment and Early Intervention in Psychosis (TIPP) program, 319 men and 155 women, having presented a first episode of psychosis (FEP). Data regarding premorbid and baseline sociodemographic, psychopathological and patient functioning, were collected. These data were reassessed longitudinally after 2, 6, 12, 18, 24, 30 and 36 months after entry in TIPP.

Results: Regarding premorbid and baseline characteristics, woman developed threshold symptoms of a FEP 1 year later than men on average. Women were more likely to be married, men were more likely to live in pension or care home facility or to be homeless. Women displayed a higher rate of history of suicide attempts and exposure to childhood trauma, while men were more likely to have a forensic history, a history of abuse of alcohol and cannabis as well as a dependency to cannabis at the time of entry in TIPP. Regarding evolution, men were more prone to violent acts and were less likely to decrease their usage of substances. The longitudinal analysis highlighted that men displayed greater negative symptoms over the entire treatment period, lower functioning after 6 months and on all assessment points after. Both genders displayed similar rate of improvement in these 3 dimensions over time.

Conclusion: Our study confirms that there are some gender differences in the early phase of psychosis that may require differentiation of assessment and treatment to improve recovery.

1. Introduction

In the last years, a growing amount of research has focused on potential gender differences that may exist in the clinical profile and therapeutic needs in people living with a psychotic disorder (Carter et al., 2022; Ochoa et al., 2012). Despite the general awareness of gender differences, the most commonly used confounder in psychosis research (Riecher-Rössler and Häfner, 2020), little differentiation is made when it comes to psychosis treatment, calling for a more fine-grained understanding of therapeutical options. Many aspects of gender differences

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among patients with schizophrenia spectrum disorder, and more broadly with psychotic disorders, have been explored in the scientific literature with sometimes contradictory results.

The prevalence of these disorders between genders is not well established, some studies report an equal prevalence between genders (Ochoa et al., 2012; Saha et al., 2005; McGrath et al., 2008), while others state that psychosis occurs more frequently in men than in women, with a risk ratio being 1.4/1 (Kirkbride et al., 2012; Jongsma et al., 2019). The arguments supporting a difference in the age at the onset of symptoms is weaker. Indeed, although many studies report an earlier onset in men (Aleman et al., 2003; Bertani et al., 2012; Hui et al., 2014) with a mean difference of 1 to 5 years compared to women (Eranti et al., 2013), and an age at onset ranging from 18 to 25 years for men and 25 to 35 years for women (Ochoa et al., 2006), some studies do not confirm such a difference (Thorup et al., 2007; Chang et al., 2011). The same goes for duration of untreated psychosis (DUP) where initial findings of a longer DUP in males (Malla et al., 2002; Wunderink et al., 2006) is contradicted by more recent studies where such a difference is not found (Thorup et al., 2007; Tseliou et al., 2017; Cascio et al., 2012).

Regarding symptomatology, while prevalence of positive symptoms seems similar in both genders (Hui et al., 2014; Comacchio et al., 2020), some data suggest that women display more affective symptoms and men more negative symptoms (Thorup et al., 2007; Tseliou et al., 2017; Bertani et al., 2012; Hong et al., 2023; Bucci et al., 2023). This was also observed in the prodromal phase, female gender being a significant predictive factor for developing affective psychosis in individuals at high risk of psychosis (Barajas et al., 2015). If some studies did not find any significant difference in these regards (Ochoa et al., 2012), it should be noted that most of them were based on cross-sectional assessments conducted at entry to treatment and that longitudinal data in this domain is clearly missing. This is a strong limitation considering that, for example, affective symptoms within psychosis seem to play a modulating role in recovery when measured at follow-up (Alameda et al., 2017, 2020, 2022). Also, available studies converge to suggest a higher prevalence of suicide attempts during treatment in women (Bertani et al., 2012; Chang et al., 2011; Tseliou et al., 2017; Comacchio et al., 2020), with a possible link to the higher prevalence of affective symptoms mentioned above.

Violent behavior on the other hand seems more prevalent in males (Chang et al., 2011), as well as substance use, both before and after the onset of symptoms and mainly regarding use of alcohol, cannabis and cocaine (Crocker and Tibbo, 2018; Cotton et al., 2009; Chang et al., 2011).

There are very few longitudinal studies that have explored gender differences in the evolution of the disorder over time, and the few that do exist have been carried out over a very short period of time or without close follow-up. Available data suggest a higher rate of recovery in women, higher adherence to medication (Seeman, 2020), as well as fewer and shorter hospitalizations (Thorup et al., 2007; Tseliou et al., 2017). A few studies about the follow-up and evolution of patients with a first psychotic episode considered the gender effect, and showed that male gender, premorbid social functioning and negative symptoms may be risk factors for poor recovery (Bertelsen et al., 2009; Hall et al., 2019). Finally, gender differences have also been observed regarding functional levels. Most studies have shown that premorbid functioning, particularly vocational training, is better in women (Tseliou et al., 2017; Bertani et al., 2012; Hanlon et al., 2017; Thorup et al., 2007; Hui et al., 2014). This difference is observed in the prodromal phase (Barajas et al., 2015) and remains over time, with a higher rate of women maintaining a professional activity despite psychosis onset. Social functioning is also better in women, a higher proportion of them being married and having children (Tseliou et al., 2017; Bertani et al., 2012; Hanlon et al., 2017; Thorup et al., 2007; Hui et al., 2014). According to a recent study, mothers had better premorbid adjustment, and childless men presented a higher cannabis and tobacco consumption rate (Díaz-Pons et al., 2024).

Considering the discrepancies regarding potential differences in age of onset, DUP and symptoms, the limitations linked to the cross-sectional nature of studies and the paucity of data regarding longer term outcome, we decided to explore the question of gender differences in a large and representative sample of early psychosis patients (EPP) who were closely followed-up prospectively over three years of their initial treatment for psychosis. A better knowledge of such potential differences in the early phase of psychosis is important considering it may pave the way to a better understanding of the mechanisms underpinning such differences, a specification of clinical and secondary prevention approaches as well as a better adaptation of treatment to the needs of patients.

2. Methods

2.1. Patients

This is a prospective study in a cohort of first-episode psychosis patients recruited from the TIPP program, specialized in the treatment and early intervention in psychosis, implemented at the Department of Psychiatry at the CHUV in Lausanne, Switzerland, in 2004 (Baumann et al., 2013). The admission criteria to the program are (1) to meet the criteria of psychosis according to psychosis threshold subscale of the CAARMS (comprehensive assessment of at-risk mental states) (Yung et al., 2005; Lejuste et al., 2021), (2) age between 18 and 35 years, and (3) to live in the Lausanne catchment area. Exclusion criteria are (1) antipsychotic treatment taken regularly for >6 months, (2) psychosis caused by intoxication or organic causes, and (3) an IQ < 70.

The patients included in the program are followed-up over 3 years by a psychiatrist and a case manager. The treatment is based on a bio-psycho-social approach including psychiatric follow-up, psycho-education and other forms of psychotherapy, social support, and pharmacological treatment. Case managers complete, at entry to the program, a questionnaire created specifically for the TIPP program to assess premorbid characteristics and presentation at baseline, including social and demographic characteristics, medical history, exposure to trauma, substance use, symptomatology, and functioning (Service of General Psychiatry, 2021). 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 2008. This study was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if the latter did not explicitly object to the use of their data for research purposes. Four patients of the cohort did not allow the use of their clinical data for this study.

2.2. Pre-morbid and baseline clinical and socio-demographic characteristics

Gender was assessed based on the biological sex, divided into two categories, male or female. DUP was defined as the time elapsing between symptom onset and first contact with the TIPP program (according to CAARMS psychosis threshold criteria). Socioeconomic status was separated into three categories: low, middle, high (Chandola and Jenkinson, 2000). Independent living location included patients living alone, with friends or family, in a private apartment, and without assistance from them. Employment status was separated into student, working life (part-time or full-time employment), or other. Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982). Trauma history was defined as exposure to physical, emotional, or sexual abuse prior to the onset of psychotic symptoms (Alameda et al., 2015; Alameda et al., 2016). Migration in adversity has been defined as migration linked to an adverse political context, threat of death or extreme poverty. History of substance abuse

or dependence was defined according to DSM-IV criteria (American Psychiatric Association, 1994), and history of suicide with the ICD-10 classification (Dilling and Dittmann, 1990). Forensic history included any type of offense that was linked to involvement with legal services. Insight was rated as absent, partial, or complete by case managers, based on awareness of the illness and of the need for treatment.

2.3. Symptoms and functional level

Baseline functioning was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994) and the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994). The SOFAS score includes the social and occupational level, whereas the GAF score includes the impact of the symptomatology on functioning. Positive, negative, and depressive symptoms were assessed at 2, 6, 12, 18, 24, 30, 36 months of follow-up. Functional recovery was defined as a GAF score >60 at follow-up. Psychotic symptoms were assessed using the Positive and Negative Psychotic Syndrome Scale (PANSS; Kay et al., 1987) and its subcategories to assess positive and negative symptomatology. Depressive symptoms were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Level of insight was rated by case managers as absent, partial or full regarding awareness of illness and necessity of treatment.

2.4. Diagnostic assessment

In the TIPP program, diagnosis is the result of an expert consensus (between a psychiatrist and a psychologist) and is based on the following elements: (1) Diagnosis reported by a treating psychiatrist in all medical documents and at the end of any hospitalization; (2) Longitudinal assessment by clinical case managers over the 3 years of treatment. They reviewed the entire file once after 18 months and again after 36 months or at the end of treatment and conduct a diagnostic process based on DSM-IV criteria (APA, 1994) discussing any unclear issue with the clinical case manager. Diagnosis was sub-divided into 5 classes: schizophrenia, schizophreniform disorder, schizoaffective disorder, major depression with psychotic features, bipolar disorder with psychotic features. Only the final diagnosis, defined at the end of the TIPP treatment period, is considered here.

2.5. Statistical analysis

To allow all comparisons to be included on the same metric a series of logistic regression analyses were conducted with female gender (yes/no) as the dependent variable, and the individual premorbid and service entry variables as predictors. From these analyses, odds ratios (OR) and the 95 % confidence intervals (CI) of the ORs were derived. Because age and diagnostic differed in the baseline comparison, all further models were adjusted for these variables. The course of symptoms (positive, negative, depressive) and functioning (GAF, SOFAS) over time were compared between groups using mixed effects models repeated measures analysis of variance (MMRM). MMRM is advantageous because it includes all existing data in the model, without imputation or substitution of missing data. All existing data comprise the model.

In these models, the "within-group" factor was time, and the "between-groups" factor was gender. Age and diagnostic were entered as covariates. From the model, the main effects of gender and time can be examined as well as their interaction. We selected the optimal within-subject covariance matrix in each MMRM with the Akaike Information Criterion (AIC) coefficient.

3. Results

Statistical analysis is based on all patients included in the program for whom data was available at the time of data extraction on October 2021. Among the 582 patients involved in the program at that date, 474 TIPP patients had sufficient data for analysis, among which 319 were males (67.3 %) and 155 were females (32.7 %)." In this paper, we conducted the comparison considering only two genders, male or female. Nevertheless, none of the patients identified themselves to any other non-binary gender.

3.1. Premorbid and baseline characteristics

Regarding premorbid and baseline characteristics we found some significant differences between genders, regarding the age of onset of psychosis, women passing the CAARMS threshold for psychosis onset 1 year later than men on average (men = 24.17 (4.48) vs women = 25.58 (5.11); $p = 0.023$); however, we didn't observe any significant difference regarding DUP. While women were more likely to be married (men = 5.1 (16) vs women = 16.8 (25); $p < 0.001$), men were more likely to live in pension or care home facility (men = 6.5 (20) vs women = 1.3 (2); $p = 0.012$) or to be homeless (men = 7.1 (22) vs women = 2.0 (3); $p = 0.017$). There was no difference concerning number of years of education, even if men displayed a significantly higher degree of impairment in the academic domain of the PAS (men = 0.37 (0.20) vs women = 0.31 (0.21); $p = 0.022$), but not in the social domain. Women displayed a higher rate of history of suicide attempts (men = 11.6 (35) vs women = 18.9 (28); $p = 0.033$) and were more likely to report exposure to childhood trauma (men = 27.3 (86) vs women = 40.9 (63); $p = 0.004$), while men were more likely to have a forensic history (men = 21.5 (58) vs women = 4.7 (6); $p < 0.001$), a history of abuse of alcohol (men = 23.6 (73) vs women = 10.7 (16); $p = 0.004$) and cannabis (men = 40.8 (127) vs women = 12.8 (19); <0.001) as well as a dependency to cannabis (men = 33.0 (103) vs women = 10.2 (15); $p < 0.001$) (See Table 1).

3.2. Evolution over the treatment period and outcome

Regarding evolution over the treatment period and outcome at the end, there were very few differences between genders. Men displayed significantly more violent acts than women (men = 14.1 (29) vs women = 4.3 (4); $p = 0.026$) over the three years of treatment period and they were less likely to decrease their usage of substances at the end (men = 21.6 (60) vs women = 8.5 (11); $p < 0.001$). The rate of recovery based on GAF score at the end of the treatment period and return to premorbid functional level were similar in both genders, as well as the rate of symptom remission. Distribution of final main diagnosis was similar in both genders, except for depression with psychotic features which was more prevalent among women (men = 2.2 (7) vs women = 5.8 (9); $p = 0.029$) (See Table 2).

3.3. Longitudinal assessment of symptoms and functional levels

In addition to cross sectional assessment of symptomatic and functional outcomes, we conducted a longitudinal analysis of the potential impact of gender on these three-year trajectories. While we did not find any differences neither for depressive symptoms assessed with the MADRS scale, nor for positive symptoms assessed with the PANSS positive scale, we observed that male patients displayed significantly greater negative symptoms scores on the PANSS over the entire treatment period (see Fig. 1). Similarly, we observed a gender effect on the GAF (see Fig. 2) and SOFAS (see Fig. 3) scores. Both genders displayed a similar score at baseline, and then we observed a significantly better improvement on both scales in women after 6 months of treatment that persisted throughout on all assessment points. The improvement curves are then parallel, with women always scoring significantly better.

4. Discussion

To our knowledge, this study is the first to explore gender differences

Table 1
Pre-morbid and baseline sociodemographic and clinical characteristics according to gender.

	Men	Women	Odds ratio	95 % CI of OR		p-Value
	N = 319 (67.3 %)	N = 155 (32.7 %)		LCI	UCI	
Age in year, M (SD)	24.17 (4.48)	25.58 (5.11)	1.049	1.006	1.093	**0.023**
Duration of untreated psychosis in days, Mdn (IQR)[a]	95.00 (477.00)	66.00 (253.00)	0.928	0.720	1.195	0.561
Socio-economical level, % (N)			0.877	0.676	1.137	0.321
Low	22.3 (71)	26.5 (41)				
Intermediate	41.7 (133)	40.6 (63)				
High	36.1 (115)	32.9 (51)				
Age of onset in year, M (SD)	22.91 (4.70)	23.91 (5.55)	1.000	0.922	1.058	0.557
Education in year, M (SD)	10.09 (2.61)	10.24 (2.88)	1.001	0.922	1.084	0.993
Marital status, % (N)						
Single	91.1 (286)	71.1 (106)	Ref. cat.			
Married	5.1 (16)	16.8 (25)	3.886	1.873	8.065	**<0.001**
Divorced	0.6 (2)	7.4 (11)	14.060	2.971	66.546	**0.001**
Cohabitation	3.2 (10)	4.7 (7)	1.890	0.680	5.251	0.222
Professional activity, % (N)						
Unemployed	48.9 (152)	42.5 (65)	Ref. cat.			
Full time job	7.7 (24)	12.4 (19)	1.744	0.870	3.494	0.117
Student/Traineeship	16.1 (50)	18.3 (28)	1.424	0.779	2.602	0.251
Part time job	3.2 (10)	3.3 (5)	0.948	0.301	2.981	0.927
Disability annuity	1.9 (6)	3.9 (6)	2.153	0.647	7.169	0.211
On Sickness leave	22.2 (69)	19.6 (30)	0.954	0.561	1.625	0.864
Living situation, % (N)						
Family	18.4 (57)	27.8 (42)	Re. cat.			
Independent household	22.3 (69)	23.8 (36)	0.725	0.403	1.307	0.285
With friends	45.6 (141)	45.0 (68)	0.792	0.453	1.386	0.414
Pension/care home	6.5 (20)	1.3 (2)	0.138	0.030	0.642	**0.012**
Unsettled (hotel, shelter homeless)	7.1 (22)	2.0 (3)	0.199	0.053	0.745	**0.017**
Premorbid Adj. (PAS) M (SD)						
Childhood	0.31 (0.17)	0.28 (0.20)	0.459	0.135	1.565	0.214
Early adolescence	0.33 (0.17)	0.30 (0.18)	0.561	0.152	2.065	0.385
Social	0.28 (0.20)	0.28 (0.22)	1.249	0.431	3.622	0.683
Academic	0.37 (0.20)	0.31 (0.21)	0.283	0.093	0.856	**0.025**
Total	0.32 (0.16)	0.29 (0.19)	0.517	0.128	2.090	0.354
Past suicide attempt, % (N)	11.6 (35)	18.9 (28)	1.828	1.048	3.189	**0.034**
History of trauma[b], % (N)	27.3 (86)	40.9 (63)	1.828	1.201	2.782	**0.005**
Migration in adversity, % (N)	26.0 (83)	29.0 (45)	1.146	0.738	1.780	0.544
Forensic history, % (N)	21.5 (58)	4.7 (6)	0.182	0.075	0.441	**<0.001**
Psychiatric history, % (N)	56.3 (170)	62.5 (95)	1.387	0.919	2.094	0.119
Familial psychiatric history, % (N)	54.7 (156)	57.9 (81)	1.129	0.742	1.718	0.571
Familial schizophrenia history, % (N)	18.6 (52)	16.8 (22)	0.933	0.533	1.633	0.807
Lifetime substance abuse (DSM), % (N)						
Alcohol	23.6 (73)	10.7 (16)	0.422	0.233	0.764	**0.004**
Cannabis	40.8 (127)	12.8 (19)	0.216	0.125	0.374	**<0.001**
Other substances	10.5 (33)	9.2 (14)	0.906	0.461	1.779	0.774
Lifetime substance addiction (DSM), % (N)						
Alcohol	7.4 (23)	3.3 (5)	0.436	0.159	1.191	0.105
Cannabis	33.0 (103)	10.2 (15)	0.235	0.129	0.429	**<0.001**
Other substances	5.4 (17)	5.2 (8)	0.982	0.407	2.370	0.968
Insight at presentation, % (N)			1.084	0.813	1.444	0.583
Absent	32.2 (98)	28.7 (43)				
Partial	47.7 (145)	48.7 (73)				
Complete	20.1 (61)	22.7 (34)				
GAF, M (SD)						
Program entry	41.51 (15.33)	42.32 (18.93)	1.001	0.988	1.014	0.888
	27.08 (10.54)	28.53 (11.97)				
Worst during psychosis			1.013	0.994	1.033	0.189
SOFAS, M (SD)						
Program entry	42.74 (14.00)	43.09 (18.53)	1.000	0.987	1.014	0.985
	29.41 (10.64)	30.11 (12.71)				
Worst during psychosis			1.006	0.988	1.025	0.519
CGI, M (SD)						
Program entry	4.50 (1.33)	4.63 (1.47)	1.121	0.944	1.331	0.194
Higher during psychosis	5.70 (0.77)	5.76 (0.77)	1.150	0.849	1.559	0.367

Note. Significant results (p < 0.05) were highlighted in bold. CI = confidence interval. OR = odds ratio. LCI = lower confidence interval. UCI = upper confidence interval. Mdn = Median. IQR = Interquartile range. Ref.cat = reference category. GAF = global assessment of functioning. SOFAS = social and occupational functioning assessment scale. CGI = clinical global impression.

[a] Raw data are presented, however the test statistics were based on log10 (+constant) transformed data because of extreme positive skewness.

[b] Physical, emotional or sexual abuse.

Table 2

Outcome characteristics according to gender.

	Men	Women	Odd ratio	95 % CI of OR		p-Value
	N = 319 (67.3 %)	N = 155 (32.7 %)		LCI	UCI	
Program commitment, % (N)						
Lost from sight	9.0 (22)	10.3 (13)	1.131	0.530	2.414	0.750
Follow-up after program, % (N)						
Specialized ambulatory care						
Other ambulatory care	42.4 (87)	36.9 (38)	Ref. cat.			
Private practice psychiatrist/psychologist	19.5 (40)	10.7 (11)	0.525	0.236	1.166	0.114
General practitioner	23.4 (48)	35.0 (36)	1.518	0.831	2.774	0.174
No follow-up needed						
Other	6.8 (14)	6.8 (7)	0.944	0.326	2.733	0.916
	2.9 (6)	4.9 (5)	1.417	0.377	5.322	0.606
	4.9 (10)	5.8 (6)	1.294	0.425	3.940	0.650
Suicide attempt during program, % (N)	6.1 (17)	4.8 (6)	0.796	0.293	2.158	0.653
Offences during program, % (N)	14.1 (29)	4.3 (4)	0.288	0.096	0.860	**0.026**
Substance use remitted, % (N)						
No SUD	51.1 (142)	78.5 (102)	Ref. cat.			
Decreased	21.6 (60)	8.5 (11)	0.248	0.122	0.506	**<0.001**
Persistent	27.3 (76)	13.1 (17)	0.290	0.157	0.533	**<0.001**
Functional recovery (GAF ≥ 60), % (N)	50.5 (112)	60.2 (62)	1.379	0.841	2.263	0.203
Functional recovery – independent work, % (N)	30.7 (70)	35.5 (39)	1.190	0.712	1.989	0.506
Functional recovery – independent living, % (N)	60.1 (137)	67.3 (74)	1.102	0.660	1.840	0.709
Combined functional recovery (indep. work & living), % (N)	24.7 (56)	30.0 (33)	1.229	0.714	2.114	0.457
Hospitalizations during program, % (N)			1.063	0.795	1.422	0.679
None	22.9 (64)	23.2 (29)				
One	34.8 (97)	32.8 (41)				
Several	42.3 (118)	44.0 (55)				
Final diagnosis, % (N)						
Schizophrenia	59.9 (191)	47.7 (74)	Ref. cat.			
Schizophreniform/brief	14.7 (47)	13.5 (21)	1.194	0.666	2.141	0.552
Schizo-affective	7.8 (25)	11.6 (18)	1.811	0.930	3.528	0.081
Major depression[c]	2.2 (7)	5.8 (9)	3.231	1.153	9.055	**0.026**
Bipolar disorder	6.3 (20)	10.3 (16)	2.037	0.997	4.161	0.051
Other	9.1 (29)	11.0 (17)	1.524	0.787	2.949	0.211

Note. Significant results (p < 0.05) were highlighted in bold. CI = confidence interval. OR = odds ratio. LCI = lower confidence interval. UCI = upper confidence interval. Ref.cat = reference category. All model were adjusted for age and diagnosis.

[c] With psychotic features. All model were adjusted for age and diagnosis.

in the early phase of psychosis over a long period of time (3 years) and based on such a high number of prospective assessments of symptomatic and functional outcome variables over time.

In this cohort, gender prevalence was very uneven, with 67.3 % of males and 32.7 % of females. Some studies stated that psychosis occurs more frequently in men than in women, with a risk ratio being of 1.4/1 (Kirkbride et al., 2012; Jongsma et al., 2019), which is less than what we observe here. As the onset of the disease is slightly later in women, some may have been excluded from the TIPP program, as the age limit is 35. Another explanation could be that late-onset schizophrenia is much more frequent in women and peaks between age 45 to 55 (Riecher-Rössler et al., 1997; Van Der Werf et al., 2014; Brzezinski-Sinai and Seeman, 2017). This is believed to be related with the decline of oestrogen level after menopause, suggesting a protective role of this hormone (Kulkarni et al., 2012; Mu et al., 2024). This subgroup of patient was not included since they were older than 35, which could at least partially contribute to explain this prevalence result. There are five main domains of results stemming from our study which may justify specification of treatment approaches according to patient's gender. First, male patients seem to be more impacted socially in the pre-morbid phase and during the time elapsing until start of treatment. Second, at baseline, males display significantly more history of violent behavior and substance use disorder than females. Third, women are significantly more likely to have been exposed to childhood abuse (sexual, physical and emotional) and to have displayed suicidal behavior. Fourth, while rates of recovery from psychosis and return to a GAF of at least 60 % is similar in both genders, the longitudinal assessment reveals that male patients display more negative symptoms and lower functional levels throughout the entire treatment period. Finally, age at onset is later in female patients, which is in line with several studies (Aleman et al., 2003; Bertani

et al., 2012; Hui et al., 2014), and could to a certain extent be explained by the protective role of estrogens (Kulkarni et al., 2012; Brzezinski-Sinai and Seeman, 2017; Mu et al., 2024). DUP is similar in both genders, as well as diagnostic distribution, except for a higher prevalence of major depression in women, which is in line with a lot of studies (Thorup et al., 2007; Tseliou et al., 2017; Bertani et al., 2012; Hong et al., 2023; Bucci et al., 2023).

Although our data does not allow to infer causality between the later diagnosis of psychosis and levels of functioning during childhood and at baseline, male patients seem more impaired than female patients in these domains. Indeed, based on the scores of PAS scale, male patients displayed more impairment during childhood in the academic dimensions of the scale, although the number of school years achieved and rate of unemployment at baseline were similar in both groups which is at odds with several other studies (Tseliou et al., 2017; Bertani et al., 2012; Hanlon et al., 2017; Thorup et al., 2007; Hui et al., 2014). Moreover, and in line with other studies (Hui et al., 2014; Bertani et al., 2012; Thorup et al., 2007; Tseliou et al., 2017; Hanlon et al., 2017), women were more likely to be married than men, which can be considered as a marker of a certain degree of stability and capacity to build long-term relationships and social interactions. Finally, male patients were more likely to live in sheltered accommodation or to be homeless, while women were more likely to live independently or with friends. Taken together, these elements suggest that at the time of entry to the program, male patients may need additional social support and more help to rebuild a social network that is more often deficient than in female patients.

This disruption of social network and functioning in male patients may also be related to the higher rate of forensic issues, violent behavior and substance use they display, elements which can be interconnected and that have been observed by others. Indeed, our finding of a higher
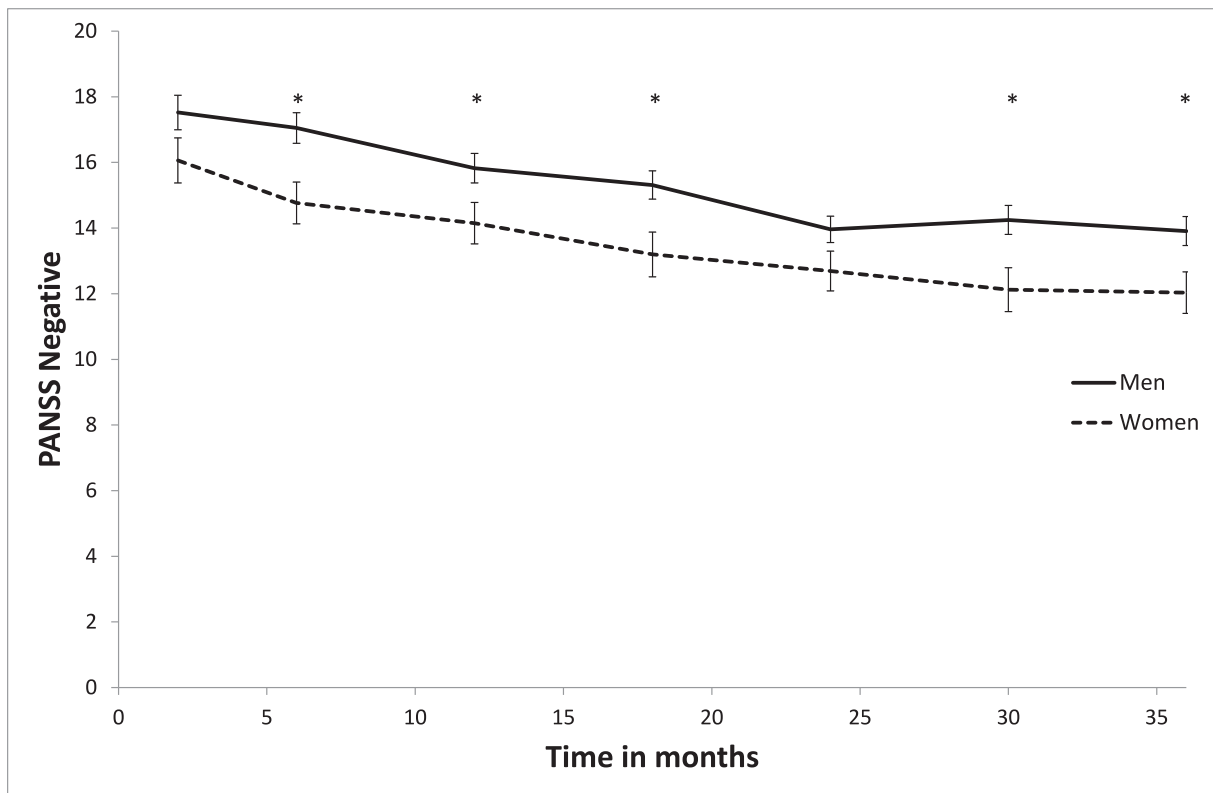
Fig. 1. PANSS Negative – Course of negative symptoms across the 36 months follow-up. * refers to visit-wise group differences $p < 0.05$.
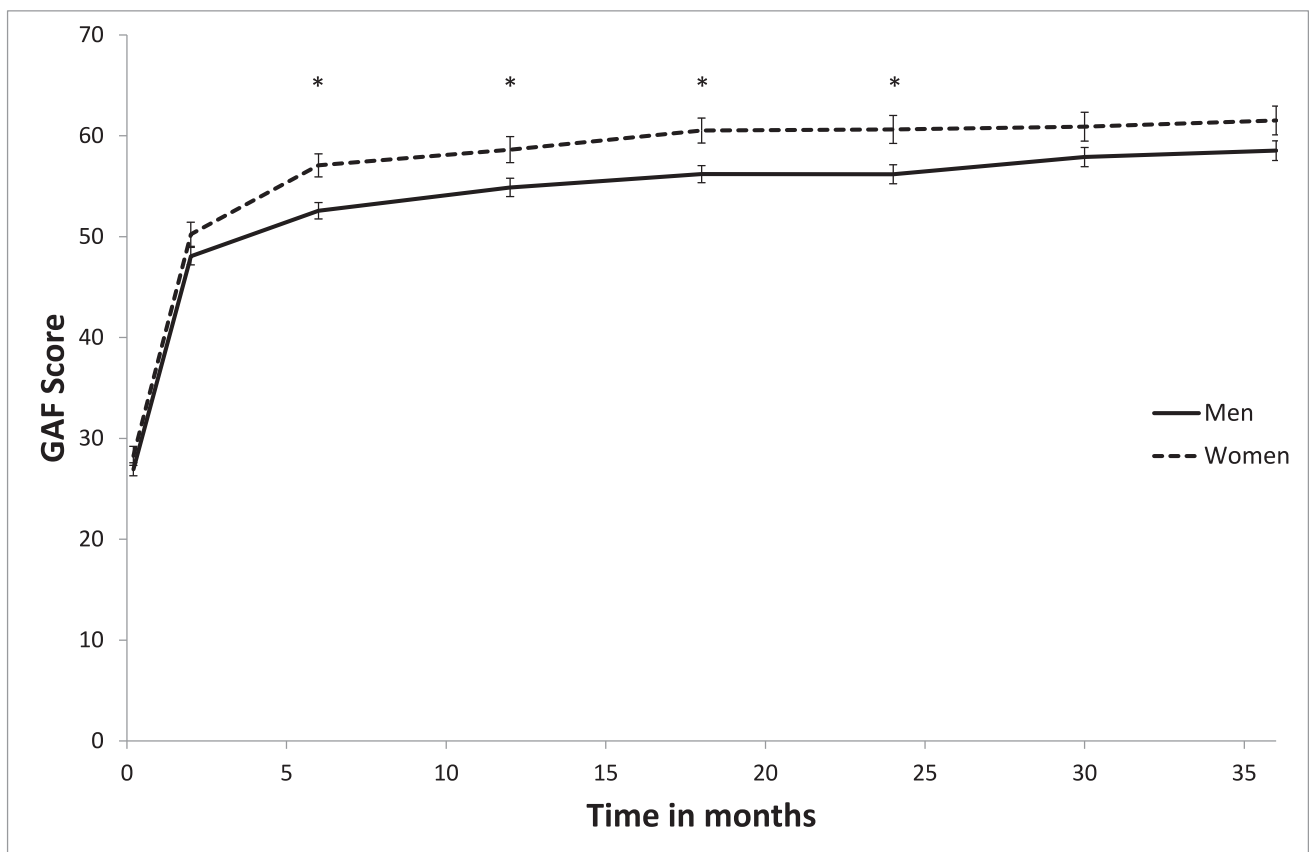

Fig. 2. GAF – Course of GAF score across the 36 months follow-up. * refers to visit-wise group differences $p < 0.05$.
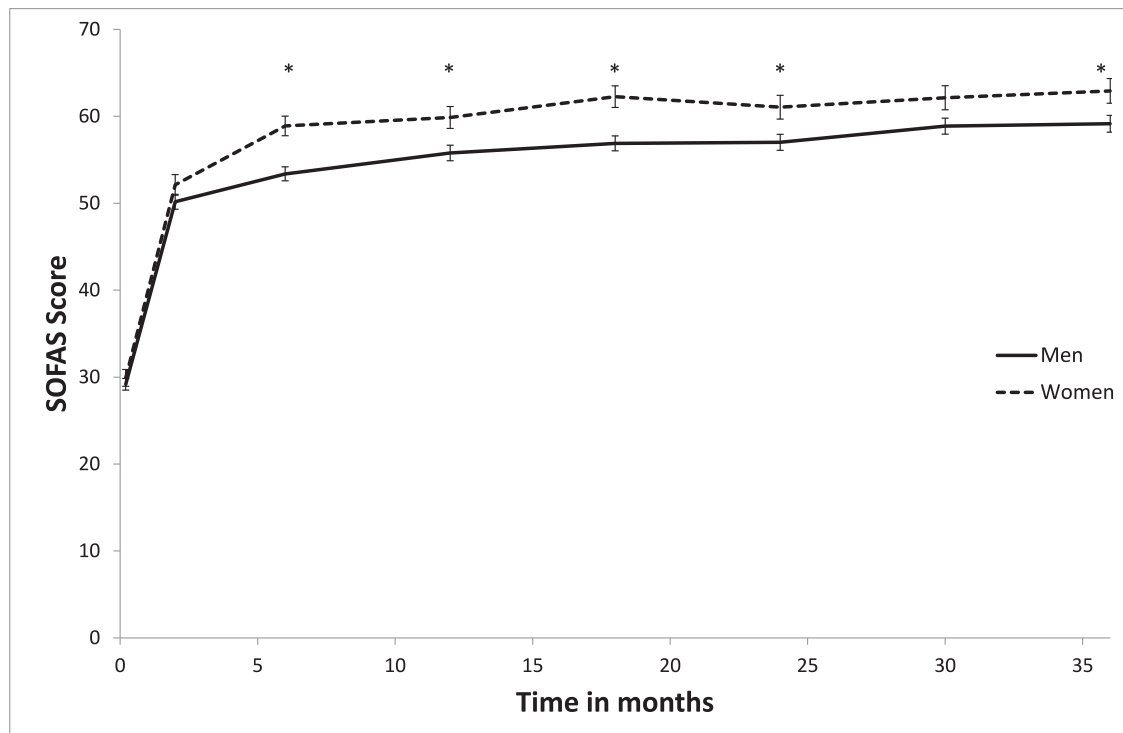
Fig. 3. SOFAS – Course of SOFAS score across the 36 months follow-up. * refers to visit-wise group differences p < 0.05.

prevalence of substance use in males, particularly alcohol and cannabis, is in line with previous papers (Crocker and Tibbo, 2018; Cotton et al., 2009; Chang et al., 2011; Irving et al., 2021; Crosas et al., 2018; Talamo et al., 2006; Moulin et al., 2020) as well as that of more frequent occurrences of violent behaviors in males (Witt et al., 2013; Taylor, 2008; Taylor and Bragado-Jimenez, 2009). However, a recent paper showed that gender differences regarding manifestations of violence disappeared when substance use was considered (Irving et al., 2021). These elements suggest that male patients may require more careful attention regarding treatment of substance abuse early in the treatment, in order to reduce risks of disruptive behavior, which in turn may aggravate social isolation, and to minimize the well identified negative impact of substance abuse on outcome (Archie et al., 2007; Lambert et al., 2005).

The observation of a higher rate of exposure to childhood trauma (in this study restricted to experiences of abuse) in women is also in line with previous publications on this topic (Fisher et al., 2009; Conus et al., 2010; Alameda et al., 2015; McCabe et al., 2012), and justify accounting for gender when studying this issue. This may explain our observation of a higher incidence of suicide attempts in female patients, a link that has already been suggested by others (Thonney et al., 2021; Vila-Badia et al., 2021) and which seems stronger in women (Comacchio et al., 2019; Garcia et al., 2016). The well identified negative impact of trauma exposure on outcome (Conus et al., 2010; Fisher et al., 2009), even more so if it happens at a younger age (Alameda et al., 2015) or if patients display depressive symptoms (Alameda et al., 2017; Alameda et al., 2022), suggest first that the occurrence of such events must be explored in all patients and especially in women, and second that trauma focused and specific treatment in this regard should be proposed, including the depressive dimension but also dissociation which have shown to be strong mediating factors linking abuse with psychosis and treatment outcome (Alameda et al., 2020).

Our detailed longitudinal assessment of this cohort allowed an acute exploration of the evolution of symptoms and functioning over time. While rates of recovery from positive psychotic symptoms and return to a GAF score of at least 60 at the end of treatment was similar in both genders, we found two main differences. First, male patients displayed

more negative symptoms levels throughout the entire treatment period. This confirms and extends results from studies reporting higher prevalence of negative symptoms at baseline in male patients (Tseliou et al., 2017; Bertani et al., 2012; Hui et al., 2014; Comacchio et al., 2020; Chang et al., 2011). Although negative symptoms should be detected and treated in all patients, particular attention should be paid to male patients, especially considering the direct correlation between the importance of negative symptoms and social functioning (Thorup et al., 2007), and on wellbeing as a whole (Galderisi et al., 2018). Second, we found that while both genders displayed similarly low levels of functioning at baseline, women displayed significantly higher scores at 6 months on both GAF and SOFAS scales and that they kept a higher functional level throughout the treatment, which is in line with previous studies (Bertelsen et al., 2009; Pang et al., 2016, Hall et al., 2019). As mentioned above, negative symptoms might impair functional recovery through social isolation and avoidance of social interactions which may aggravate the loss of social network already observed at baseline. Negative symptoms could also affect the therapeutic relationship, and therefore reduce the effectiveness of the treatment. Previous studies from our group showed in particular that patients who have gone through a first episode of psychosis reduce their interactions and develop an avoidance of cities (Conus et al., 2019) and suggest that there is a need for the development of new approaches to promote access of patients to the socially enriching aspects of the urban milieu (Baumann et al., 2020).

These results must be interpreted with some limitations in mind. First, some characteristics such as exposure to abuse were assessed retrospectively and may be under reported in people with a psychotic disorder (Howard, 1993). Second, the naturalistic nature of the cohort prevented us from including all sample individuals at each assessment considering some patients either refused or did not attend assessment at various time points. Nevertheless, the multi-level framework as used in our longitudinal analysis included all existing data with requirement of imputation or substitution of missing data with estimated or hypothetical values. Moreover, our measure of gender, restricted to biological sex, did not allow us to consider gender diversity (Barr et al., 2021), and

it may have missed some clinical implications for patients for whom gender identification is more of a complex issue. Additionally, we did not test complex mediations with other important variables like trauma or substance use but this should be investigated in further studies. Lastly, the number of statistical tests carried out was significant and our results were not corrected for multiple testing as our outcomes were separate hypothesis that did not refer to a universal null hypothesis predicting no difference across all the domains of the different tests performed. As a result, the risk of type I error has to be borne in mind when interpreting the associations identified".

5. Conclusion

Although all the elements we have discussed need to be assessed in each individual patient, our results provide pointers for individualizing management.

In the case of men, more attention needs to be paid to the manifestation of negative symptoms and their consequences, particularly on daily functioning. We should also be aware that men are more prone to violent behavior and substance abuse. These factors are self-perpetuating and should be part of the overall treatment to reduce symptoms and improve quality of life. If necessary, social and/or addictive follow-up should be provided.

In the case of women, depressive symptoms and their consequences, including suicidal ideation, should be explored in particular, as should any trauma they may have suffered. Specific treatment should then be proposed. If patients have children, the functioning of family life should be assessed, and support provided if necessary.

Our study confirms that there are some gender differences in the early phase of psychosis that may require differentiation of assessment and treatment in order to improve recovery.

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CRediT authorship contribution statement

Aude Salvadé: Conceptualization, Writing – original draft, Writing – review & editing. **Philippe Golay:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **Lilith Abrahamyan:** Supervision. **Vincent Bonnarel:** Supervision. **Alessandra Solida:** Supervision. **Luis Alameda:** Supervision. **Julie Ramain:** Supervision, Writing – original draft. **Philippe Conus:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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