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Patients participating to neurobiological research in early psychosis: a selected subgroup?

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Conflict of interest with respect to the study and manuscript

The authors declare no conflict of interest in relation to the subject of the study.

Contributors

PG, PB and PC designed this study. PG analyzed and interpreted the data. PG, PB and RJ drafted the first version of the manuscript. PC and KD critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

ABSTRACT

Aim: Selection bias could be an important limiting factor in psychiatric neurobiological research. The study aim was to compare, within an early psychosis program, patients who agreed to participate to neurobiological research with patients who refused.

Methods: 284 patients with early psychosis were assessed at baseline on a large set of socio-demographic and clinical variables and were followed-up over 36 months.

Results: There were no differences between groups, except regarding forensic/psychiatric history, lifetime substance abuse and social-occupational level during follow-up.

Conclusions: While patients participating to neurobiological research seem representative of our clinical cohort, the few differences identified may deserve attention.

Key words: early psychosis, schizophrenia, neuroscience, selection bias, representativity.

1. INTRODUCTION

Exciting or demanding biomedical investigations may attract a specific subgroup of volunteers and conclusions derived from such research may present serious limitations (Gustavsson et al., 1997). Referral questions, motivation and ability to consent may induce selection bias of patients consenting to participate in psychiatric neurobiological research. Moreover many of such studies are based on relatively small number of participants. This might contribute to the lack of consensus between studies and affect findings' generalisation. Selection bias may thus fuel the so-called "*replicability crisis*" (Barch and Yarkoni, 2013; Gorgolewski and Poldrack, 2016; Tackett et al., 2016).

A study investigating the willingness to take part in research consecutively to psychiatric admission reported high (>70%) readiness to participate, and found that rather than remuneration or other factors, altruistic motivations such as the wish to help science to progress and to allow patients to benefit from better treatments were the most frequent (Zullino et al., 2003). Selection bias is difficult to investigate because data on patients who did not participate are typically not available. Data stemming from prospective clinical cohort studies can offer a context where such a limitation may be overcome. The goal of our study was to compare the characteristics, within a clinical cohort of patients with early psychosis treated at the Treatment and early Intervention in Psychosis Program (TIPP), of patients who consented to neurobiological research with those who didn't.

2. METHODS

2.1 Participants

TIPP is a specialized early psychosis program at the Department of Psychiatry in Lausanne University Hospital, Switzerland. Inclusion criteria are age between 18-35, living in catchment

area (population about 300'000) and meeting criteria for psychosis, as defined by the 'psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States scale (Yung et al., 2005). The program has been detailed elsewhere (Baumann et al., 2013). Patients with psychosis related to intoxication/organic brain disease, IQ<70 or that have been taking antipsychotic medication for more than six months are referred to other programs. All patients treated at TIPP are fully assessed at baseline on numerous premorbid characteristics and are then assessed regularly in order to monitor outcome and adapt treatment if improvement is insufficient. Access to the clinical data was granted by the Ethics Committee of Lausanne University and consequently all patients who received treatment within this program were automatically included in this study. This allowed us to have data on all patients whether or not they participated to neurobiological studies, which was based on an informed consent procedure. As such, and considering we are the only specialised program in our catchment area, this sample is highly representative of patients with early psychosis in our region.

2.2 Clinical assessments

Detailed evaluation of past medical history, demographic characteristics, exposure to adverse life events as well as symptoms and functioning was performed by case managers (CM) and a psychologist through interviews and a structured questionnaire. At baseline and after 2, 6, 12, 18, 24, 30 and 36 months of treatment, a series of assessments focusing on symptoms and functional level were conducted.

Functional characteristics at baseline were assessed with the Modified Vocational Status Index and Modified Location Code Index Independent living (MVSI & MLCI; Tohen et al., 2000). Premorbid functional level was evaluated with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982). Academic, social, childhood and early-adolescence sub-scores were computed (MacBeth and Gumley, 2008). Past history of trauma (sexual or physical abuse

before age 16) was evaluated by CM over the entire program (Alameda et al., 2016). Past diagnosis of substance abuse/dependence was rated according to DSM-IV. The Global Assessment of Functioning (GAF) and Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994) were used to assess the functional level at baseline. While GAF includes the intensity of symptoms, SOFAS only focus on social and occupational level. The lowest SOFAS and GAF scores before presentation were also estimated. Insight into illness was evaluated as complete, partial or absent (Conus et al., 2007). Severity of illness at baseline was assessed with the Clinical global impression scale (CGI; Guy, 1976).

Psychopathology and functional level were scored at each assessment, with SOFAS, GAF, the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979).
This study is based on the prospective follow-up of the first 284 patients who were treated within TIPP.

2.3 Participants consenting to a biomarker study

In the frame of a discussion with the CM in charge of the patient, a biomarker study was proposed to each patient during the first months following their entry in TIPP. The delay for presenting the study was justified by the wish to prioritize clinical intervention and treatment during the acute phase of psychosis when patients typically present inability to provide informed consent. The biological assessments are part of a project focusing on the identification of neurobiological markers in the early phase of psychosis (hereafter, biomarker study; e.g. Fournier et al., 2014). Beyond psychopathology, these assessments include neuropsychological tests, genetic, biochemical and metabolomics analysis of blood and skin derived fibroblasts,

multimodal magnetic resonance imaging (structural MRI, fMRI and diffusion spectrum imaging, magnetic resonance spectroscopy) and EEG. Patients included in the biomarker study provided fully informed consent, and all procedures were approved by the Local Ethics Committee. Patients could also agree to participate to only a subset of tests of the full battery. As acknowledgment a symbolic financial compensation (from 30 to a maximum of 130 CHF for each visit depending on the number of tests) was proposed.

2.4 Statistical analysis

Comparisons between groups were performed with independent t-tests for continuous variables and Pearson's Chi-Square tests (or Fisher Exact tests) for categorical variables. Because of the longitudinal nature of some of the data, models were estimated in the multilevel framework. Mixed effects models repeated measures analysis of variance (MMRM) was used to determine group differences over time for the different measures. Time was introduced as a “within-group” factor and participation as a “between-groups” factor. From the model, the main effects for participation and time can be examined as well as their interaction. The selection of the optimal within subject covariance matrix in each MMRM model was determined with the AIC coefficient. Unstructured, autoregressive, compound symmetric and Toeplitz structures were tested. Because the homogeneity of variances across occasions may not hold, we also included heterogeneous versions of these structures.

3. RESULTS

Out of 284 patients, 95 (33.45%) consented to the biomarker study and 189 (66.55%) didn’t.

3.1 Sociodemographic and clinical data

Participants who were included in the biomarkers study differed from other patients on a small number of variables (Table 1): they had lower rate of history of offences (p=.043, OR=0.41) but higher rate of past psychiatric treatment (p=.009, OR =2.02). Patients who consented to the biomarker study were more likely to have a lifetime history of cannabis addiction (p=.012, OR=1.98) and other substances addiction (p=.006, OR=3.65) as well as lifetime history of other substances abuse (p=.005, OR=2.61).

3.2 Clinical and functional outcomes during the follow up

Results of the longitudinal analyses revealed that the groups did not differ regarding positive symptomatology ($F_{1,224.340}$=0.742, p=.390, mean difference = 0.43), negative symptomatology ($F_{1,194.718}$=0.088, p=.766, mean difference = -0.19) or depressive symptomatology ($F_{1,221.764}$=0.801, p=.372, mean difference = -0.86) during the follow-up. Similarly, for general functioning assessed with the GAF, no overall differences could be highlighted ($F_{1,273.444}$=3.281, p=.071, mean difference = -2.79). Patients included in the biomarkers study scored on average 2.96 points lower than other patients when general functioning was assessed by the SOFAS ($F_{1,276.888}$=3.894, p=.049). Post-hoc pairwise comparison of various assessment time points revealed no differences for the first half of the follow-up (baseline: p=.317, 2 months: p=.988, 6 months: p=.292, 12 months: p=.074) and also after 30 months (p=.464). Assessments during the second part of the follow-up (18 months: p=.027, mean difference = -4.48; 24 months: p=.006, mean difference = -5.68; 36 months: p=.041, mean difference = -4.39) revealed higher SOFAS scores in patients included in the biomarker study, contributing to the overall group difference (Figure 1). Comparison of the rate of improvement between baseline and all endpoints revealed no significant differences.

4. DISCUSSION

Globally, our results suggest that, in our cohort, patients included in a biomarker study were globally representative of all patients treated in our program and that our results can reasonably be generalized to other patients with early psychosis. While this need to be replicated in other samples, this observation is important when considering the important role translational research may play in advancing our understanding of the basic mechanisms linked to severe mental disorders. However, the few differences identified may deserve attention and should be systematically evaluated in future studies.

The relatively high rate of consent to the biomarker study (close to 35%) is probably linked to the role played by case managers who establish a trusting relationship with patients, considering that, according to Zullino et al. (2003), patients rely greatly on their treating team to make a decision in this regard.

While baseline and premorbid characteristics were similar in both groups, they differed in two domains. First, patients who refused the biomarker study were more likely to have had a history of offences. This is in line with Keks et al. (1991) who reported that patients refusing a neuro-endocrine study were more likely to display hostility. It is likely that young patients who had to deal with the judiciary system would be less trusting of any form of institution and hence less likely to trust clinicians and researchers. This is in line with the observation that patients with early psychosis who have a forensic history are more likely to disengage from treatment (Conus et al., 2010). Second, patients who consented to the biomarker study were more likely to have a lifetime history and/or current substance abuse comorbidity. This finding raises the ethical issue of the role played by the financial compensation that we provided and the possibility it contributed to the perpetuation of substance abuse and this needs to be further explored.

However, the observation by Zullino et al. (2003) that financial compensation was rarely mentioned by patients as an argument neither to agree (23%) nor to refuse (7%) participation to research may temper this concern. Considering the impact of cannabis and other substances on neuro-biological processes (for example see Rigucci et al., 2017) as well as the impact of substance abuse discontinuation on outcome (Lambert et al., 2005; Schoeler et al., 2016) , it is very important to assess this variable in such studies.

The analysis of clinical data revealed there were no differences between groups regarding symptoms and GAF scores at baseline and during the study, showing that patients who consented to the biomarker research were not less ill than those who refused. Although the difference we observed on the SOFAS rating during the second half of the treatment phase was statistically significant, its effect size was negligible, and rate of change between both groups were not different.

Conclusion

Our study showed that, although it implied an important number of assessments, patients of our cohort who participated to our biomarker study were globally representative of patients in the entire cohort. While this needs to be replicated in other samples and the few differences identified should be systematically evaluated in future studies, this suggests that findings from neurobiological studies are likely to have a good validity and can be generalised to other patients with early psychosis.

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Figure caption.

Figure 1. **Social and Occupational Functioning Assessment Scale (SOFAS) scores over 36 months.** * = p<.05. Overall group difference across all measurements: $F_{1,276.888} = 3.894$, p = .049. No significant differences between groups in the rate of improvement between baseline and all endpoints.

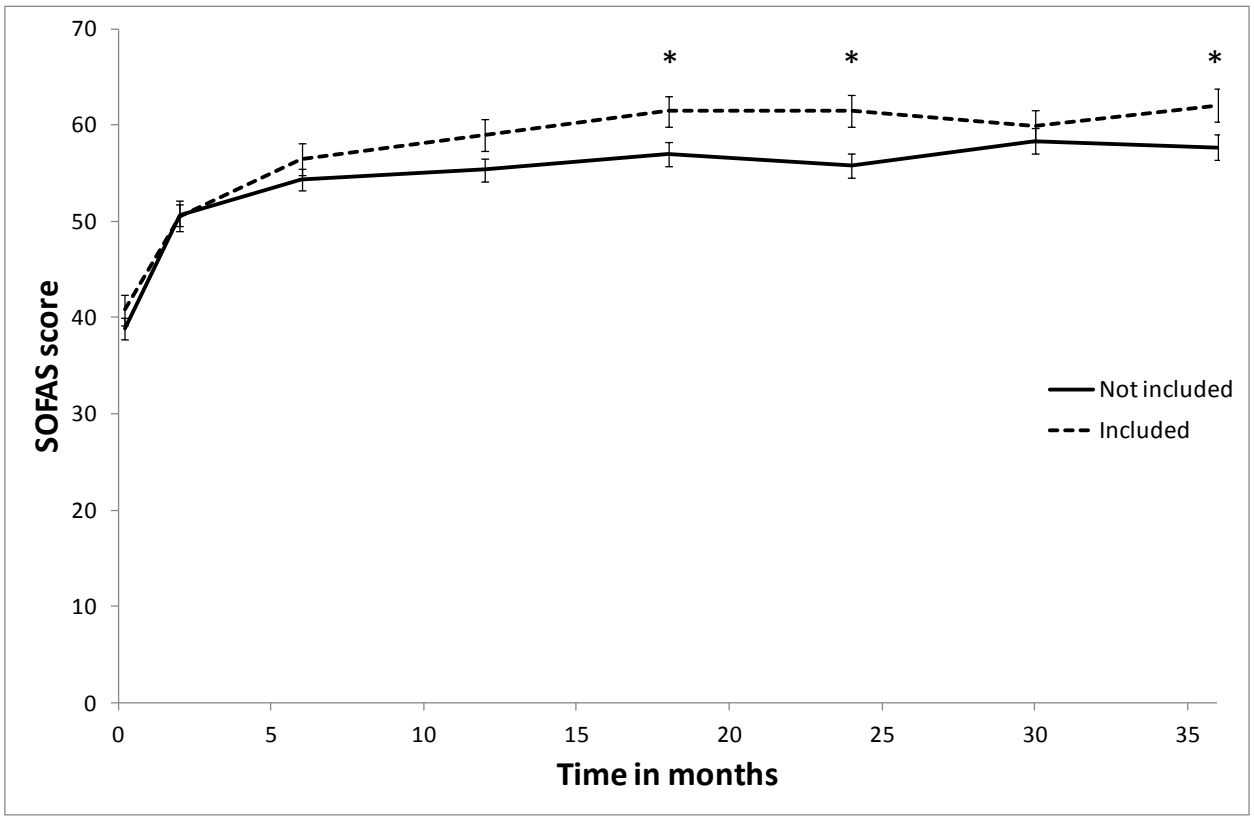

Table 1. Sociodemographic and clinical data according to inclusion in neuroscience studies.

	Total N = 284	Not included N = 189	Included N = 95	statistic	p-value	Effect size
Gender, male, % (N)	64.4 (183)	60.8 (115)	71.6 (68)	$\chi^2(1) = 3.178$	.075	OR = 1.63
Age in year, M (SD)	24.65 (4.77)	24.83 (4.89)	24.31 (4.54)	t(282) = 0.866	.387	d = -0.11
Duration of untreated psychosis in days, Mdn (IQR)[a]	90.5 (474.0)	89.0 (437.0)	98.0 (489.0)	U = 8758.5	.737	Z = -0.34
Socio-economical level, % (N)						
Low	19.0 (54)	22.8 (43)	11.6 (11)	$\chi^2(2) = 5.276$	.072	$\varphi = 0.14$
Intermediate	44.7 (127)	43.4 (82)	47.4 (45)			
High	36.3 (103)	33.9 (64)	41.1 (39)			
Education in year, M (SD)	9.80 (2.74)	9.66 (2.91)	10.04 (2.42)	t(247) = -1.077	.283	d = 0.14
Marital status, % (N)						
Single	83.1 (231)	81.5 (150)	86.2 (81)	F.E.T	.399	$\varphi = 0.10$
Maried	9.4 (26)	11.4 (21)	5.3 (5)			
Divorced	2.9 (8)	25.7 (5)	3.2 (3)			
Cohabitation	4.7 (13)	4.3 (8)	5.3 (5)			
Born in Switzerland, % (N)	53.5 (152)	51.3 (97)	57.9 (55)	$\chi^2(1) = 1.098$	.295	OR = 1.31
Professional activity, % (N)						
Full time job	12.2 (34)	12.4 (23)	11.8 (11)	F.E.T	.983	$\varphi = 0.06$
Student/Traineeship	16.5 (46)	15.7 (29)	18.3 (17)			
Part time job	2.5 (7)	2.7 (5)	2.2 (2)			
Disability annuity	3.2 (9)	3.8 (7)	2.2 (2)			
On Sickness leave	17.6 (49)	17.3 (32)	18.3 (17)			
Unemployed	47.8 (133)	48.1 (89)	47.3 (44)			
Lifestyle, % (N)						
Family	40.1 (110)	37.2 (68)	46.2 (42)	F.E.T	.496	$\varphi = 0.11$
Independent household	26.6 (73)	26.8 (49)	26.4 (24)			
With friends	23.4 (64)	25.7 (47)	18.7 (17)			
Pension / care home	3.6 (10)	3.3 (6)	4.4 (4)			
Unsettled (hotel, shelter homeless)	6.2 (17)	7.1 (13)	4.4 (4)			
Premorbid Adj. (PAS) M (SD)						
Childhood	0.30 (0.19)	0.30 (0.19)	0.31 (0.18)	t(216) = -0.568	.571	d = 0.05
Early adolescence	0.32 (0.17)	0.32 (0.18)	0.31 (0.16)	t(220) = 0.223	.824	d = -0.06
Social	0.28 (0.20)	0.29 (0.21)	0.28 (0.19)	t(214) = 0.206	.837	d = -0.05
Academic	0.35 (0.20)	0.35 (0.21)	0.36 (0.19)	t(219) = -0.436	.664	d = 0.05
Total	0.31 (0.17)	0.30 (0.17)	0.32 (0.16)	t(198) = -0.468	.641	d = 0.12
Past suicide attempt, % (N)	13.5 (36)	11.5 (20)	17.2 (16)	$\chi^2(1) = 1.694$	.193	OR = 1.60
History of trauma[b], % (N)	28.8 (81)	29.0 (54)	28.4 (27)	$\chi^2(1) = 0.011$	.915	OR = 0.97
Forensic history, % (N)	14.3 (35)	17.6 (28)	8.1 (7)	$\chi^2(1) = 4.088$	.043	OR = 0.41
Offences during program, % (N)	11.9 (16)	13.3 (11)	9.8 (5)	$\chi^2(1) = 0.357$	.550	OR = 0.71
Psychiatric history, % (N)	61.0 (169)	55.5 (101)	71.6 (68)	$\chi^2(1) = 6.789$	.009	OR = 2.02
Familial psychiatric history, % (N)	62.1 (159)	61.6 (101)	63.0 (58)	$\chi^2(1) = 0.053$	.818	OR = 1.06
Familial schizophrenia history, % (N)	22.8 (49)	22.4 (30)	23.5 (19)	$\chi^2(1) = 0.033$	.856	OR = 1.06
Lifetime substance abuse (DSM), % (N)						

Alcohol	25.2 (68)	22.7 (41)	30.3 (27)	$\chi^2(1) = 1.870$	.171	OR = 1.48
Cannabis	38.5 (104)	35.2 (63)	45.1 (41)	$\chi^2(1) = 2.476$	.116	OR = 1.51
Other substances	14.0 (39)	9.8 (18)	22.1 (21)	$\chi^2(1) = 7.805$	.005	OR = 2.61
Lifetime substance addiction (DSM), % (N)						
Alcohol	8.9 (24)	7.2 (13)	12.2 (11)	$\chi^2(1) = 1.892$	.169	OR = 1.79
Cannabis	30.7 (83)	25.7 (46)	40.7 (37)	$\chi^2(1) = 6.343$	.012	OR = 1.98
Other substances	6.8 (19)	3.8 (7)	12.6 (12)	$\chi^2(1) = 7.617$	.006	OR = 3.65
Insight at presentation, % (N)						
Absent	35.6 (96)	35.9 (65)	34.8 (31)	U = 7416.5	.250	$\varphi = 0.14$
Partial	47.0 (127)	50.3 (91)	40.4 (36)			
Complete	17.4 (47)	13.8 (25)	24.7 (22)			
GAF, M (SD)						
Baseline	37.91 (16.23)	37.24 (16.66)	39.17 (15.41)	t(257) = -0.908	.365	d = 0.12
Worst during psychosis	26.08 (10.90)	25.45 (11.23)	27.16 (10.30)	t(248) = -1.204	.230	d = 0.16
SOFAS, M (SD)						
Baseline	39.80 (15.35)	39.19 (15.83)	40.98 (14.41)	t(267) = -0.908	.365	d = 0.12
Worst during psychosis	29.10 (11.77)	28.51 (12.08)	30.14 (11.20)	t(251) = -1.061	.290	d = 0.14
CGI, M (SD)						
Baseline	4.81 (1.38)	4.86 (1.39)	4.72 (1.36)	t(240) = 0.764	.445	d = -0.10
Higher during psychosis	5.81 (0.76)	5.83 (0.80)	5.78 (0.70)	t(240) = 0.460	.646	d = -0.07
Diagnostic, % (N)						
Schizophrenia	59.5 (169)	57.1 (108)	64.2 (61)	F.E.T	.184	$\varphi = 0.16$
Schizophreniform/brief	11.6 (33)	13.8 (26)	7.4 (7)			
Schizo-affective	9.5 (27)	7.9 (15)	12.6 (12)			
Major depression[c]	3.5 (10)	4.8 (9)	1.1 (1)			
Bipolar disorder	7.4 (21)	6.9 (13)	8.4 (8)			
Other	8.5 (24)	9.5 (18)	6.3(6)			

Note. Analyses between groups were performed with t-tests for continuous variables and Chi-Square test (or Fisher's exact test when appropriate) for categorical variables. Mdn = Median. IQR = Interquartile range. F.E.T. = Fisher's exact test. a = Because DUP values were highly skewed comparisons were performed using Mann-Whitney U tests; [b] physical or sexual abuse [c] with psychotic features. OR = odd ratio.