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Education and long-term outcomes in first episode psychosis: 10-year follow-up study of the PAFIP cohort

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Original Article

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Abstract

Background. Lower levels of education have been associated with the development of psychosis. Investigating educational achievement in the first episode of psychosis (FEP) patients may shed light on the origins of the alterations and on the variability of outcomes in psychotic disorders.

Methods. Education achievement was explored in a large sample ($n = 659$) of FEP patients enrolled in programa de atención a fases iniciales de psicosis (PAFIP), a research and assistance program conducted in Spain. Patients were stratified according to the Spanish educational system according to their attendance in primary (low), secondary (medium) or university studies (high). The three groups were compared on available premorbid, clinical and neuropsychological variables. A subgroup of patients ($n = 209$), comprising the 10-year follow-up PAFIP cohort, were again compared.

Results. Overall, 49% and 37% of FEP patients had low and medium levels of education, respectively. In total, 13% of the patients with a higher level of education were more frequently women (64%) and older at illness onset (36 years old), reported better premorbid adjustment, presented less severe positive symptoms and better functioning; and showed higher premorbid intelligence quotient and better performance on all the explored cognitive domains. Ten years later the FEP patients in the medium- and high-education groups had good global functioning and a neurocognitive performance within the normal limits.

Conclusions. Higher education is associated with better initial conditions and more favourable outcomes after an FEP. Sharing this information with the world's educational systems is essential to targeting resources and designing innovative programs or strategies to compensate for student difficulties.

Introduction

The low-level scholastic achievement has been associated with the risk of developing schizophrenia spectrum disorders (MacCabe et al., 2008). Subjects who developed schizophrenia were more likely to have had impairments in childhood educational scores (Rannikko et al., 2015). The link between education level and schizophrenia suggests that impairment in intellectual ability may exist from early in life, before the onset of illness. A pre-illness onset of impaired intellectual ability implies that the impairment seen among schizophrenia patients is not a consequence of the pathological process of the disease. This places abnormal neurodevelopment as a critical component in the pathogenesis of schizophrenia (Kobayashi et al., 2014) while also suggesting a genetic etiology (Dickinson et al., 2020). In this scenario, cognitive deficits could contribute to poor school performance. Investigating neurocognitive performance in relation to educational achievement at illness onset is thus important as it may shed light on the origins of cognitive deficits and on the variability of outcomes in psychotic disorders.

Several studies have found that higher education was associated with better clinical, cognitive and functional measures in the first episode of psychosis (FEP) patients (Amoretti et al., 2016; de la Serna et al., 2013). A similar association between better cognitive performance in higher education was found in later stages of illness (Holthausen et al., 2002). Specifically, schizophrenia patients who completed more years of education showed better scores on verbal memory tests than those with lower education achievements (Ward, Kraal, Flowers & Ellingrod, 2017). In this vein, Kanchanatawan et al. (2018) suggested that education, framed

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within the construct of cognitive reserve (CR), could be a protective factor in the development of psychosis and has, as well, a beneficial effect on outcomes. Regretfully, long-term studies examining the impact of baseline education on outcomes are scarce (Fusar-Poli, McGorry & Kane, 2017).

In this respect, education has been suggested as a proxy for measuring CR (Malek-Ahmadi et al., 2017). CR, as defined by Stern (2012), assumes that people develop a reserve of thinking abilities during their lives and that this protects them against losses that can occur through ageing and disease. It is applicable to almost any situation where brain function is disrupted such as cognitive changes associated with schizophrenia, dementia, depression, and traumatic brain injury (Stern, 2009). Opdebeeck, Martyr and Clare (2016) studied several methods in order to obtain reliable indicators for CR. Their results showed that education was the proxy more commonly used. In view of the foregoing, long-term research in FEP patients, assuming years of education achieved as a method to quantify CR, could provide evidence on the theory of CR.

The aims of the present study were as follows: (1) to explore the relationship between educational achievement and neurocognitive performance at illness onset in a large sample of FEP patients and (2) to analyse clinical, functional and cognitive outcomes of three education subgroups (low, medium and high) after an average time window of 10 years. Based on CR theory, we hypothesized that FEP patients with higher education would show cognitive performance within normal limits at baseline, and more favourable outcomes in the long term.

Materials and methods

Participants

The study sample comes from a large epidemiological, 3-year longitudinal intervention program on first-episode psychosis (PAFIP) at the University Hospital Marques de Valdecilla (Santander, Spain). A more detailed description of PAFIP has been previously given (Crespo-Facorro et al., 2006; Pelayo-Teran et al., 2008).

Educational achievement was explored in 659 FEP patients enrolled in PAFIP between February 2001 and December 2018. Patients were categorized according to their years of education, and their attendance in primary (low), secondary (medium) or university studies (high) as defined by the Spanish educational system. The three groups were compared on premorbid, clinical and neuropsychological available variables. A second analysis of the same educational achievement variables was conducted on a subgroup of patients ($n = 209$) who completed a 10-year follow-up reassessment (see Ayesa-Arriola et al., 2021). See flowchart in Fig. 1.

The study was approved by the Ethical Review Committee (CEIm de Cantabria) CEIC (Comité de Ética de Investigación Clínica).Written informed consent was obtained from all subjects after a complete description of the study.

The patients met the following criteria: (1) 15–60 years of age; (2) lived within the catchment area; (3) were experiencing a first episode of psychosis; (4) had no prior treatment with antipsychotic medication or, if previously treated, a total life-time of antipsychotic treatment of <6 weeks and (5) met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or not otherwise specified (NOS) psychosis. Patients varied in whether they received aripiprazole ($N = 214$; 32.5%), risperidone ($N = 196$; 29.7%), olanzapine ($N = 56$; 8.5%), quetiapine ($N = 70$; 10.6%), ziprasidone ($N = 66$; 10.0%) and haloperidol ($N = 57$; 8.6%), being the chlorpromazine equivalent initial dose of 205.6 ± 78.7 mg. The diagnoses, conducted by an experienced psychiatrist within six months from the baseline visit, were confirmed through the use of the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon & William, 2001). The diagnoses included in descending prevalence, schizophrenia ($N = 335$; 51.0%), brief psychotic disorder ($N = 78$; 11.9%), psychosis disorder NOS ($N = 56$; 8.5%), schizophreniform disorder ($N = 177$; 26.9%), schizoaffective disorder ($N = 8$; 1.2%) and delusional disorder ($N = 3$; 0.5%).

Measures

Definition of premorbid education subgroups

The education in Spain is divided into three levels: primary education, which includes three cycles of two years each for students primarily between 6 and 12 years of age; secondary education, which includes four school years for students primarily between 12 and 16 years of age, after which students choose to take baccalaureate or vocational training; and higher education, which includes university and higher levels of vocational training. Thus, according to the Spanish educational system, education is stratified into three levels: low (primary), medium (secondary) and high (university) studies.

Participants were asked to report their highest level of education, even if not completed. This strategy was chosen as subjects with psychotic disorders are less likely to complete their education because of the emergence of psychotic symptoms (Frissen et al., 2015).

Premorbid and sociodemographic information

Premorbid and sociodemographic information was collected from patients, relatives and from medical record at admission. These variables included sex, age, age of psychosis onset [defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred], duration of untreated illness [DUI, defined as the time from the first non-specific symptom related to psychosis (i.e. with no return to the previous level of functioning) to antipsychotic treatment onset], and duration of untreated psychosis [DUP, defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment]. Premorbid social adjustment was measured by the Premorbid Adjustment Scale (PAS) with ratings from 0 (indicating the 'healthiest') to 6 (denoting the 'least healthy') (Cannon-Spoor, Potkin & Wyatt, 1982).

The FEP patients were screened for the following sociodemographic characteristics: sex, age, years of education, ethnicity ('caucasian' *v.* 'others'), living area ('urban' *v.* 'rural,' in which urban is defined as a settlement of at least 10 000 inhabitants), living status ('living with family' *v.* 'other'), socioeconomic status derived from the parents' occupation ('low-qualification worker' *v.* 'other') relationship status ('married/cohabiting' *v.* 'single/divorced/separate or widowed'), occupational status ('studying' *v.* 'others').

Clinical and functional assessment

Clinical symptoms of psychosis were assessed by means of the Scale for the Assessment of Negative symptoms (SANSs) (Andreasen, 1983) and the Scale for the Assessment of Positive

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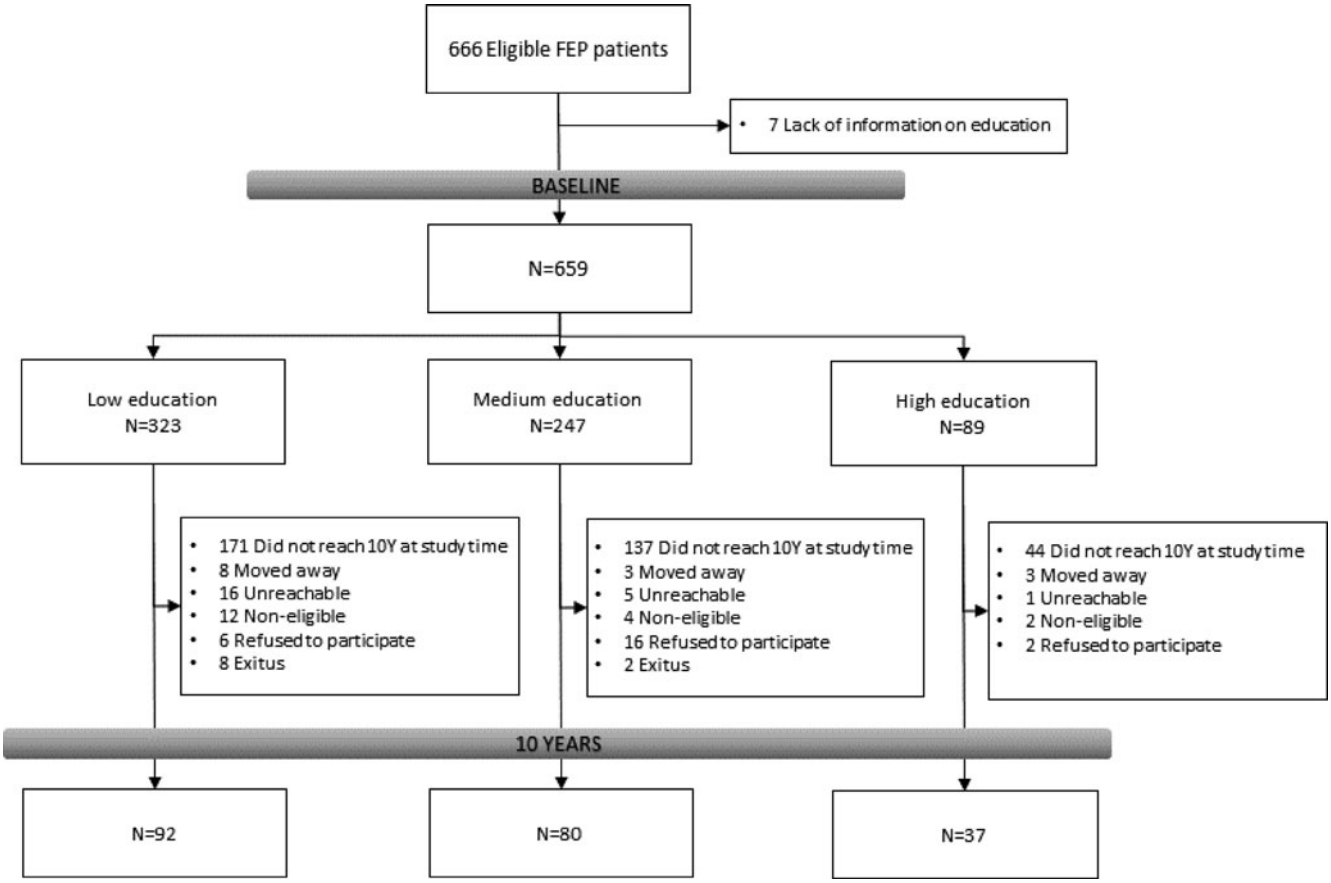

Fig. 1. Flow chart.

symptoms (SAPSs) (Andreasen, 1984). The SANS and SAPS scores were used in generating dimensions of positive (scores for hallucinations and delusions), disorganized (scores for formal thought disorder, bizarre behaviour and inappropriate affect) and negative (scores for alogia, affective fattening, apathy and anhedonia) symptoms (Grube, Bilder & Goldman, 1998). General psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) (Flemenbaum & Zimmermann, 1973), and depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington & Maticka-Tyndale, 1993). Functional assessment was conducted with the Disability Assessment Scale (DAS) Spanish version (Mañá, Ivorra & Girón, 1998). The Clinical Global Impressions were administered to track changes in symptoms over time.

Neuropsychological assessment

Trained neuropsychologists carried out the neuropsychological assessments. In order to maximize cooperation, assessments occurred when the patients' clinical status permitted, which resulted in assessments occurring an average of 10.5 weeks after admission. A detailed description has been reported elsewhere (Gonzalez-Blanch et al., 2007). The following cognitive domains, which have consistently been shown to be impaired in schizophrenia (Nuechterlein et al., 2004), were tested: (1) verbal memory: the Rey Auditory Verbal Learning test (Rey, 1964) (list recall score); (2) visual memory: Rey Complex Figure (Osterrieth, 1944) (delayed recall); (3) working memory: Wechsler Adult Intelligence Scale (WAIS-III) digits forward and backward subtests (Wechsler, 1997) (standard total score); (4) executive function: Trail Making test (Reitan & Wolfson, 1985) (trail, B-A score); (5) processing speed: WAIS-III digit symbol subtest (Wechsler, 1997) (standard total score); (6) motor dexterity: Grooved Pegboard test (Lezak, 1995) (time to complete with dominant hand); (7) attention: Continuous Performance test (CPT) (Cegalis, 1991) (correct responses). The WAIS-III vocabulary subtest (Wechsler, 1997) was used to estimate premorbid intelligence quotient (IQ).

In order to calculate the *Z*-scores for each cognitive domain, direct scores obtained in a group of 221 healthy volunteers, which had carried out the same neuropsychological battery, were used (Ayesa-Arriola et al., 2018). Prior to standardization, raw cognitive scores were reversed when appropriate so they were all in the same direction (i.e. the higher the score, the better the performance). In addition, in line with previous methodology (Reichenberg et al., 2009), a measure of global cognitive functioning (GCF) was calculated as *T*-scores ($M = 50$, S.D. = 10) derived from the healthy comparison sample. *T*-scores were converted to deficit scores that reflected the presence and severity of cognitive deficit on each cognitive domain. Deficit scores were then averaged to create the GCF measure.

Data availability

The data that support the findings of this study are available on request from the corresponding author R.A.A. The data are not publicly available due to the presence of information that could compromise research participant privacy/consent.

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Statistical analysis

Statistical analyses were performed with SPSS, version 19.0. Univariate analyses of variance (ANOVA) and chi-square (χ^2) were used to compare three groups (i.e. low, medium and high education in patients) on baseline sociodemographic, clinical and neuropsychological variables. When ANOVA was significant, pairwise comparisons were performed.

In order to address longitudinal comparisons, repeated measures ANOVA, adjusted for the covariates of sex, age and premorbid IQ were used to investigate the main effects of the education group. Post hoc multiple comparisons (pairwise t test) were corrected by Bonferroni. All statistical tests were two-tailed, and significance was determined at the 0.05 level.

Results

A total of 659 FEP patients were classified into three levels: low education ($N = 323$, 49% of cases), medium education ($N = 247$, 37.48% of cases) and high education ($N = 89$, 13.5% of cases). In the low-education group, 152 subjects met the time criteria to participate in PAFIP-10 reassessment, however, 92 agreed to participate, resulting in a retention rate of 60.5%. In the medium-education group, 110 subjects met the criteria and 80 agreed to participate, resulting in a retention rate of 72.7%. In the higher-education group, 45 subjects met the time criteria and 37 agreed to participate, resulting in a retention rate of 82.2%. Significant differences in attrition were found between low- and high-education groups ($p = 0.022$).

Baseline clinical and neuropsychological information in terms of baseline education achievement

As presented in Table 1, the high-education group significantly consisted of women (63%), individuals of high-socioeconomic status that lived independently, and those that showed later age at illness onset, better premorbid adjustment, higher premorbid IQ (mean = 106), less frequent consumption of both legal and illegal substances and less severe psychotic symptoms. The low-education patients presented more severe symptoms (psychotic dimension and BPRS) than those in the high-education group. Concerning cognitive domains, the high-education group showed better performance than the low- and medium-education groups in all domains. In addition, high-education patients significantly outperformed those in the medium-education group in processing speed and motor dexterity domains and in their GCF (all $p < 0.01$) (see Fig. 2).

Follow-up clinical and neuropsychological information in terms of baseline education achievement

Information about long-term follow-up was available for 209 patients (see Table 2). The percentages of patients in the PAFIP-10 cohort for each education level were as follows: 44% ($N = 92$) for the low-education group, 38.3% ($N = 80$) for the medium-education group and 17.7% ($N = 37$) for the high-education group. Out of these 209 patients, a subgroup of 147 subjects completed a 10-year follow-up clinical reassessment and 137 subjects completed the follow-up neurocognitive reassessment. The groups were again evaluated.

As observed in Table 3, repeated measures ANOVAs confirmed significant between-group effects for processing speed ($F_{1,130} = 5.29$; $p = 0.006$), working memory ($F_{1,131} = 4.49$; $p = 0.013$) and executive functions ($F_{1,127} = 3.34$; $p = 0.039$). Significant within-group effects were observed for processing speed ($F_{1,130} = 6.5$; $p = 0.012$). Group-by-time effects were found for verbal memory ($F_{1,131} = 4.27$; $p = 0.016$). Post hoc analyses of verbal memory revealed a significant increase in scores over time (0.84 S.D.) in the medium-education group that improved significantly well compared with the low and high groups ($p < 0.001$). This increase was specifically significant for females (men, $p = 0.038$; women, $p \leq 0.001$). Post hoc analyses of processing speed revealed that over time the scores increased significantly less in the low-education group (0.56 S.D.) than in the medium (1.02 S.D.) and high (1.03 S.D.) groups ($p = 0.001$ and $p = 0.003$, respectively). Post hoc analyses of executive functions revealed an increase in scores over time (0.84 S.D.) in the high-education group ($p = 0.041$). In sum, 10 years later, patients in the medium- and high-education groups showed a global neurocognitive performance similar to healthy controls, exhibiting significant improvements in processing speed and executive function domains (see Figs 3 and 4).

In terms of clinical and functional variables, group-by-time effects were found for SANS ($F_{1,141} = 3.32$; $p = 0.039$) and negative dimension ($F_{1,141} = 3.18$; $p = 0.044$). Post hoc analyses revealed significant improvements in negative symptoms in the medium-education group with regard to low and high groups ($p < 0.001$) (see Fig. 5).

Concerning the disproportion between subjects in the three education groups, additional analyses were conducted to detect differences at follow-up. Using the median value (10 years of education) as a cutoff, two groups, low and high education, were compared. At a 10-year follow-up, the two groups consisted of 100 low education and 109 high education FEP patients who significantly differed in all but a premorbid adjustment in adulthood, DUP, DUI, BPRS, symptoms in psychotic dimension and the visual memory cognitive domain. All of the differences showed disadvantages for those FEP patients who presented at a low-education level, who were more frequently young men with low premorbid IQ and low-socioeconomic status, were living with family, and more frequently consuming cannabis, alcohol and/or cocaine at illness onset. In repeated measures ANOVA, group-by-time significant differences were found in the processing speed domain ($F_{1,131} = 4.13$; $p = 0.044$), showing that patients in the high-education group made more significant improvements. All of these comparisons can be consulted in online Supplementary Tables S1 and S2.

Discussion

The present study explored the relationship between education achievement at illness onset, and baseline and long-term clinical and neurocognitive outcomes among FEP patients. As hypothesized, higher education was associated with better global baseline neurocognitive performance, remarkable in processing speed and motor dexterity domains, and improvements in memory and processing speed at follow-up. Interestingly, the medium-education group, particularly females, showed significant improvements in verbal memory and better outcomes for negative symptoms than the patients in the low- and high-education groups. At an average period of 10 years after the FEP, the patients in both medium- and high-education groups presented a GCF similar to that of healthy controls.

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Table 1. Baseline sociodemographic, neuropsychological and clinical comparisons between FEP patients from the three education subgroup

	Low education		Medium education		High education				
N = 659	*N* = 323		*N* = 247		*N* = 89				
Sociodemographic variables	*N*	%	*N*	%	*N*	%	Statistic	Value	Post hoc
Males	210	65.0	128	51.8	32	36.0	χ^2	26.931**	1 > 2; 1 > 3; 2 > 3
Diagnosis (schizophrenia)	182	56.5	115	46.7	38	42.7	χ^2	8.164*	
Caucasian	290	90.1	231	93.5	89	100.0	χ^2	10.573*	1 < 3; 2 < 3
Urban area	221	69.1	177	71.7	73	82.0	χ^2	5.78	
Living with family	251	78.2	173	70.0	56	62.9	χ^2	10.089*	1 > 3
Low-socioeconomic status	226	71.3	108	43.9	24	27.6	χ^2	72.681**	1 > 2; 1 > 3; 2 > 3
Single	231	71.7	192	77.7	54	60.7	χ^2	9.727*	2 > 3
Student	46	14.3	65	26.3	25	28.1	χ^2	15.794**	1 < 2; 1 < 3
Tobacco	187	59.6	135	56.0	31	34.8	χ^2	17.337**	1 > 3; 2 > 3
Cannabis	162	50.5	99	40.4	16	18.0	χ^2	30.706**	1 > 3; 2 > 3
Cocaine	70	21.9	36	14.8	5	5.6	χ^2	14.552*	1 > 3
Alcohol	170	53.8	112	46.3	26	29.2	χ^2	17.098**	1 > 3; 2 > 3
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
Age	29.7	10.8	30.3	8.8	36.4	8.1	*F*-w	22.716**	1 < 3; 2 < 3
Age of onset	28.7	10.4	29.0	8.7	35.1	8.1	*F*-w	21.771**	1 < 3; 2 < 3
Years of education	7.4	0.9	11.5	0.9	16.2	1.0	*F*	3525.530**	1 < 2; 1 < 3; 2 < 3
DUI (months)	21.2	38.0	23.1	41.1	24.2	42.9	χ^2	1.293	
DUP (months)	12.9	33.5	14.6	33.9	14.9	29.6	χ^2	1.654	
PAS: general	4.2	2.2	3.0	2.0	1.9	1.8	*F*-w	48.909**	1 > 2; 1 > 3; 2 > 3
Premorbid IQ	90.0	12.7	97.8	11.6	106.8	10.3	*F*	55.964**	1 < 2; 1 < 3; 2 < 3
Clinical variables	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
SAPS	14.6	4.5	14.0	4.8	13.6	4.5	*F*	2.13	
SANS	6.7	6.3	6.4	6.3	5.4	5.5	χ^2	2.864	
Psychotic dimension	7.8	2.4	7.5	2.5	6.9	2.4	*F*	5.583*	1 > 3
Negative dimension	4.8	5.8	4.6	5.6	3.9	4.7	χ^2	0.564	
Disorganized dimension	6.7	3.6	6.6	3.7	6.7	3.6	*F*	0.194	
BPRS	67.1	14.7	64.5	15.0	61.7	15.4	*F*	5.319*	1 > 3
CDSS	2.1	3.2	2.2	3.0	2.0	2.8	χ^2	2.384	
DAS	1.5	1.6	1.4	1.5	1.4	1.6	*F*	0.808	
CPZ equivalent initial dose	208.1	86.6	204.8	69.1	199.0	74.0	χ^2	0.701	
Cognitive domains	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
Verbal memory	−2.7	1.3	−2.1	1.4	−1.8	1.3	*F*	16.085**	1 < 2; 1 < 3
Visual memory	−0.8	1.0	−0.5	1.0	−0.3	0.9	*F*	10.960**	1 < 2; 1 < 3
Processing speed	−1.8	0.9	−1.2	1.1	−0.7	1.0	*F*-w	40.108**	1 < 2; 1 < 3; 2 < 3
Working memory	−0.7	0.9	−0.4	0.8	−0.2	0.8	χ^2	28.155**	1 < 2; 1 < 3;
Executive function	−1.9	2.3	−0.9	2.1	−0.8	1.6	χ^2	31.815**	1 < 2; 1 < 3
Motor dexterity	−1.7	2.8	−1.0	1.8	−0.3	1.0	χ^2	33.694**	1 < 2; 1 < 3; 2 < 3
Attention	−3.2	4.4	−2.1	4.1	−2.1	4.3	χ^2	16.399**	1 < 2; 1 < 3
Global cognitive functioning	1.8	1.0	1.3	0.8	0.9	0.8	*F*-w	25.017**	1 > 2; 1 > 3; 2 > 3

DUI, duration of untreated illness; DUP, duration of untreated psychosis; PAS, Premorbid Adjustment Scale; IQ, intelligence quotient; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; DAS, Disability Assessment Scale; CPZ, Chlorpromazine.

*Group differences significant at $p < 0.05$.

**Group differences significant at $p < 0.01$.

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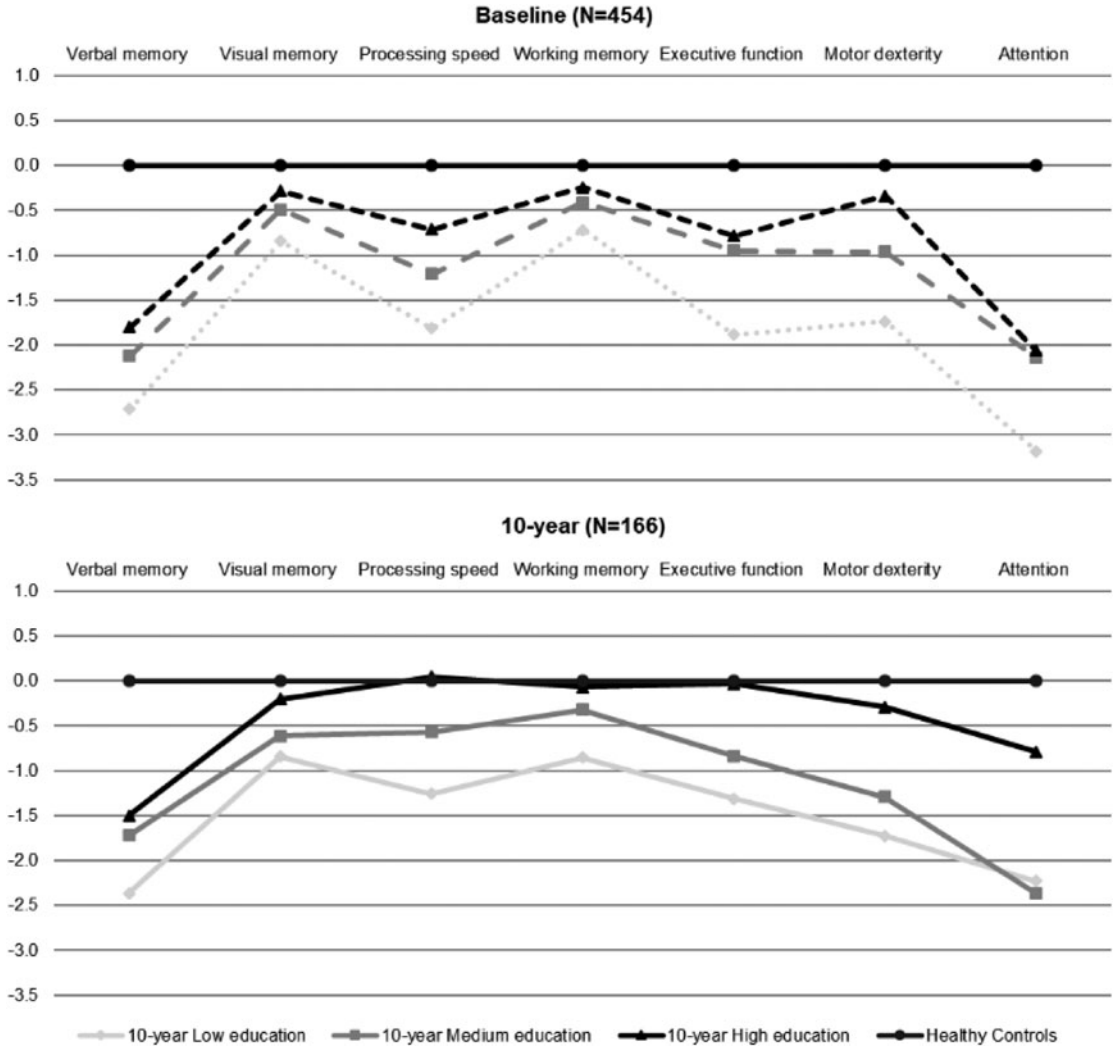

Fig. 2. Baseline and 10-year neuropsychological profiles of education subgroups.

A remarkable finding of this study is that higher education was reached by only 13.5% of FEP patients (8% male and 19% female). The percentage of our FEP patients who completed just primary education was similar to the general population, according to the Spanish National Institute for Statistics (Estadística, 2020) for the year 2019. However, medium and higher education were not completed by FEP patients in the same percentages as those of their peers, for either males or females. Further exploration of the data showed that 20 (8 females, 12 males), 9 (4 females, 5 males) and 1 (female) FEP patients went back to school in the low-, medium- and high-education groups, respectively. Furthermore, 17 (18.5%) patients passed low- to medium-education level and 8 (10%) medium- to high-education level. In total, 33% (one in three) continued their education in the following years after an FEP. Considering that Spain is one of the countries with the highest rates of academic failure and attrition within the European Union (Rodriguez, Tinajero and Paramo, 2017), those are very encouraging findings for FEP programs.

In this study, we aimed to take into account the nuances of cognitive deficits in lieu of educational achievements. It is not contentious to note that the cognitive deficits that have been consistently reported (Addington, Brooks & Addington, 2003; Bilder et al., 2000) lead to global cognitive deficits. Interestingly, gradient facilitation in processing speed, motor dexterity and GCF was seen on the effect of education. This, together with the significant improvement in verbal memory in the medium-education group, positions FEP patients from the medium- and high-education groups within a similar range of cognitive performance to that of healthy controls. These results support the deficit and nondeficit theory of schizophrenia (Carpenter, Heinrichs & Wagman, 1988). Certain individuals with schizophrenia, in this case, those with medium and higher education, presented in general good baseline conditions and more favourable outcomes. On the contrary, those in the low-education group could be considered as deficit schizophrenia, characterized by features such as low GCF and negative symptoms. Although the current study did not provide data in this regard, the results are suggestive of a neurodevelopmental basis to schizophrenia. For instance, Rowland et al. (2009) found alterations, best explained to have occurred during development, in the integrity of frontal and parietal regions in deficit-schizophrenia patients who would explain their specific cognitive impairments. In addition, and in line with the findings of younger age at illness onset among low-education individuals, Dickinson et al. (2020) identified a

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Table 2. Sociodemographic, neuropsychological and clinical comparisons between patients from the three education subgroup who completed 10-year follow-up

	Low education		Medium education		High education				
N = 209	*N* = 92		*N* = 80		*N* = 37				
Sociodemographic variables	*N*	%	*N*	%	*N*	%	Statistic	Value	Post hoc
Males	65	70.7	37	46.3	12	32.4	χ^2	19.144**	1 > 2; 1 > 3;
Diagnosis (schizophrenia): 10 y	67	80.7	47	72.3	23	65.7	χ^2	3.297	
Same diagnosis	59	71.1	51	78.5	21	60.0	χ^2	3.831	
Caucasian	90	97.8	79	98.8	37	100.0	χ^2	0.913	
Urban area	60	65.2	55	68.8	29	78.4	χ^2	2.134	
Living with family	73	79.3	55	68.8	22	59.5	χ^2	5.735	
Low-socioeconomic status	65	70.7	39	48.8	9	25.7	χ^2	22.448**	1 > 2; 1 > 3
Single	68	73.9	65	81.3	25	67.6	χ^2	2.82	
Keep studying	20	26.0	9	13.6	1	3.0	χ^2	9.468**	1 > 3
Tobacco	54	58.7	49	61.3	15	40.5	χ^2	4.748	
Cannabis	44	47.8	27	33.8	8	21.6	χ^2	8.611*	1 > 3
Cocaine	21	22.8	12	15.0	2	5.4	χ^2	6.027*	
Alcohol	56	60.9	39	48.8	13	35.1	χ^2	7.442*	1 > 3
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
Age	27.9	10.0	29.0	7.2	33.9	7.0	*F*	6.679*	1 < 3; 2 < 3
Age of onset	26.8	9.3	27.8	7.0	32.4	7.1	*F*	6.411*	1 < 3; 2 < 3
Years of education	7.5	0.8	11.8	0.6	16.5	1.3	*F*-w	1117.301**	1 < ; 1 < 3; 2 < 3
DUI (months)	28.9	41.6	24.4	30.5	23.7	32.9	χ^2	1.274	
DUP (months)	13.2	32.5	12.1	25.3	18.0	31.6	χ^2	0.052	
PAS: General	4.1	2.0	2.8	1.8	2.0	1.7	*F*	16.984**	1 > 2; 1 > 3
Premorbid IQ	88.3	12.1	96.4	12.7	109.5	10.7	*F*	32.027**	1 < 2; 1 < 3; 2 < 3
Clinical variables	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
SAPS	13.8	4.1	12.9	5.0	12.9	4.8	*F*	1.019	
SANS	8.5	6.8	8.1	6.3	5.4	4.9	*F*-w	4.743*	1 > 3
Psychotic dimension	7.9	2.4	7.3	2.4	6.6	2.2	*F*	4.618*	1 > 3
Negative dimension	6.6	6.3	6.2	5.7	4.0	4.3	*F*-w	3.951	
Disorganized dimension	5.9	3.3	5.6	3.9	6.4	3.9	*F*	0.647	
BPRS	64.0	12.6	60.2	12.5	60.6	15.6	*F*	2.071	
CDSS	2.6	3.7	2.7	3.2	2.5	3.3	χ^2	0.771	
DAS	1.4	1.5	0.9	1.2	1.1	1.6	*F*	2.171	
CPZ equivalent dose	233.9	79.8	239.9	84.5	219.1	79.4	*F*	0.826	
Cognitive domains	Mean	S.D.	Mean	S.D.	Mean	S.D.	Statistic	Value	Post hoc
Verbal memory	−2.7	1.3	−2.2	1.4	−1.6	1.3	*F*	7.077**	1 < 3
Visual memory	−0.7	1.1	−0.5	1.0	−0.3	1.1	*F*	1.941	
Processing speed	−1.9	0.9	−1.3	1.1	−0.8	1.2	*F*	13.552**	1 < 2;1 < 3
Working memory	−0.8	0.8	−0.4	0.9	0.0	0.9	*F*	10.095**	1 < 2; 1 < 3
Executive function	−1.9	2.4	−0.8	1.9	−0.6	1.1	χ^2	13.503**	1 < 2; 1 < 3
Motor dexterity	−2.1	3.9	−0.8	1.2	−0.3	1.1	χ^2	15.061**	1 < 2; 1 < 3
Attention	−3.7	5.0	−2.5	4.7	−1.2	2.5	χ^2	9.561**	1 < 3
Global cognitive functioning	1.8	1.1	1.3	0.9	0.9	0.8	*F*-w	9.028**	1 > 2; 1 > 3

DUI, duration of untreated illness; DUP, duration of untreated psychosis; PAS, Premorbid Adjustment Scale; IQ, intelligence quotient; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; DAS, Disability Assessment Scale; CPZ, Chlorpromazine.
*Group differences significant at $p < 0.05$.
**Group differences significant at $p < 0.01$.

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Table 3. Repeated measures ANOVAs for cognitive domains and clinical variables

		Low education						Medium education						High education							
		Baseline		10 year				Baseline		10 year				Baseline		10 year		Effects size	Group	Time	Time × Group
N = 137	*N*	Mean	S.D.	Mean	S.D.	Effects size	*N*	Mean	S.D.	Mean	S.D.	Effects size	*N*	Mean	S.D.	Mean	S.D.		*F* values		
		−2.52	1.31	−2.29	1.35			−2.42	1.34	−1.58	1.31			−1.59	1.28	−1.52	1.26	0.056	0.51	0.01	4.27*
Visual memory	59	−0.56	1.07	−0.76	0.85	−0.259	50	−0.56	0.96	−0.48	0.75	0.116	27	−0.13	0.92	−0.20	0.75	−0.104	1.79	1.47	1.56
Processing speed	60	−1.91	0.86	−1.26	1.03	0.706	49	−1.45	1.08	−0.45	0.82	1.075	27	−0.75	1.19	0.10	0.64	0.917	5.29*	6.50*	2.60
Working memory	60	−0.73	0.69	−0.74	0.78	−0.015	50	−0.39	0.89	−0.26	0.80	0.164	27	0.10	0.90	−0.09	0.81	−0.237	4.49*	1.13	1.74
Executive function	56	−1.42	2.03	−1.20	1.83	0.103	50	−0.56	1.58	−0.70	1.41	−0.084	27	−0.59	1.02	0.00	0.97	0.535	3.34*	2.56	2.09
Motor dexterity	58	−1.96	4.06	−1.60	2.88	0.127	48	−0.93	1.22	−1.00	2.29	−0.048	26	−0.22	1.01	−0.37	1.28	−0.162	1.67	0.62	0.29
Attention	48	−3.13	4.54	−1.92	4.69	0.293	45	−2.89	5.16	−2.10	4.99	0.174	25	−1.08	2.46	−0.63	1.83	0.232	1.35	0.52	0.05
Global cognitive functioning	46	1.64	1.06	1.37	0.86	−0.311	43	1.44	0.86	0.90	0.88	−0.690	24	0.83	0.65	0.59	0.56	−0.440	1.93	1.17	1.45
N = 147	*N*	Mean	S.D.	Mean	S.D.	Effects Size	*N*	Mean	S.D.	Mean	S.D.	Effects size	*N*	Mean	S.D.	Mean	S.D.		*F*-values		
SAPS	67	13.13	3.81	2.09	3.61	−2.220	52	13.29	4.98	1.54	4.05	−1.932	28	12.96	5.09	0.46	1.04	−2.539	0.03	1.01	0.02
SANS	67	8.94	6.90	6.10	6.16	−0.373	52	8.08	6.16	2.65	3.67	−0.920	28	5.68	5.22	4.29	4.45	−0.246	1.38	0.13	3.32*
Psychotic dimesion	67	7.57	2.37	1.33	2.31	−1.989	52	7.48	2.29	0.96	2.39	−2.077	28	6.50	2.19	0.36	0.91	−2.731	0.70	0.11	1.94
Negative dimension	67	7.07	6.34	5.49	5.44	−0.234	52	6.02	5.69	2.21	2.97	−0.735	28	4.46	4.56	4.07	4.25	−0.077	2.11	0.04	3.18*
Disorganized dimension	67	5.57	3.16	0.76	1.67	−1.436	52	5.81	3.88	0.58	1.90	−1.292	28	6.46	4.00	0.11	0.57	−1.677	0.63	2.89	0.80
BPRS	67	62.64	11.50	34.16	11.20	−1.986	52	61.04	12.58	29.77	8.89	−2.272	28	60.71	17.47	30.04	5.49	−1.875	1.17	1.60	0.29
CDSS	66	3.02	3.97	0.65	2.25	−0.552	51	2.37	3.24	0.45	1.22	−0.589	28	2.29	2.98	1.21	3.01	−0.271	0.79	0.12	0.76
DAS	58	1.33	1.42	1.45	1.23	0.072	48	1.00	1.24	0.62	0.94	−0.275	24	1.08	1.67	0.58	0.83	−0.302	3.07*	0.53	0.73

SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; DAS, Disability Assessment Scale.
Using sex, age and premorbid IQ as covariates, and Bonferroni adjusted.
*Group differences significant at $p < 0.05$.
**Group differences significant at $p < 0.01$.

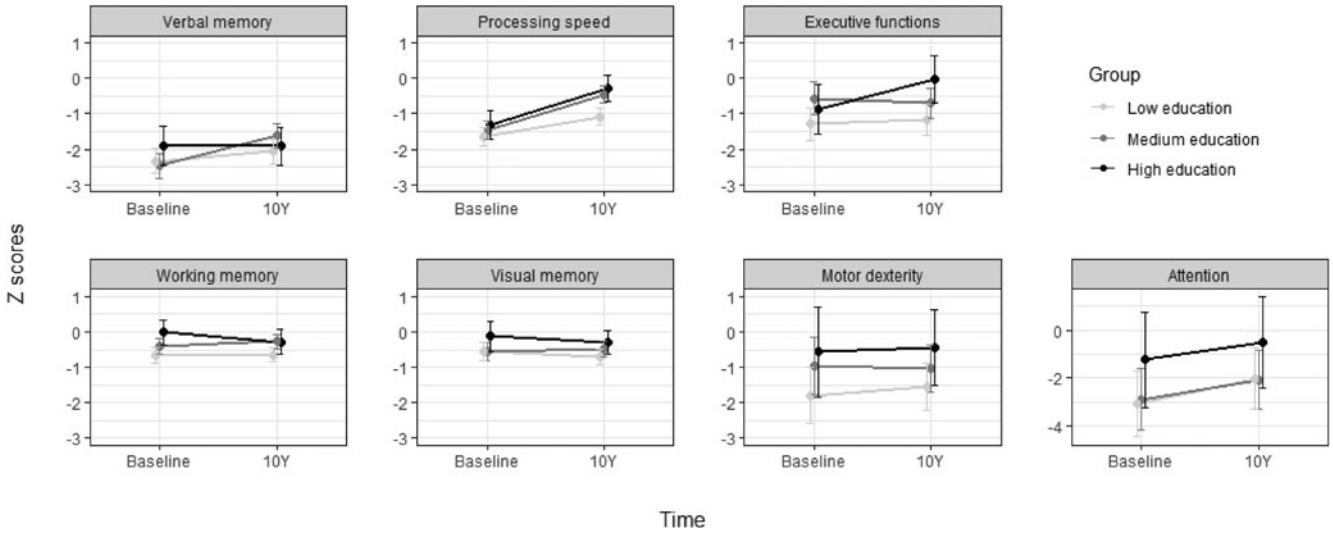

Fig. 3. Repeated measures: ANOVA of cognitive domains.

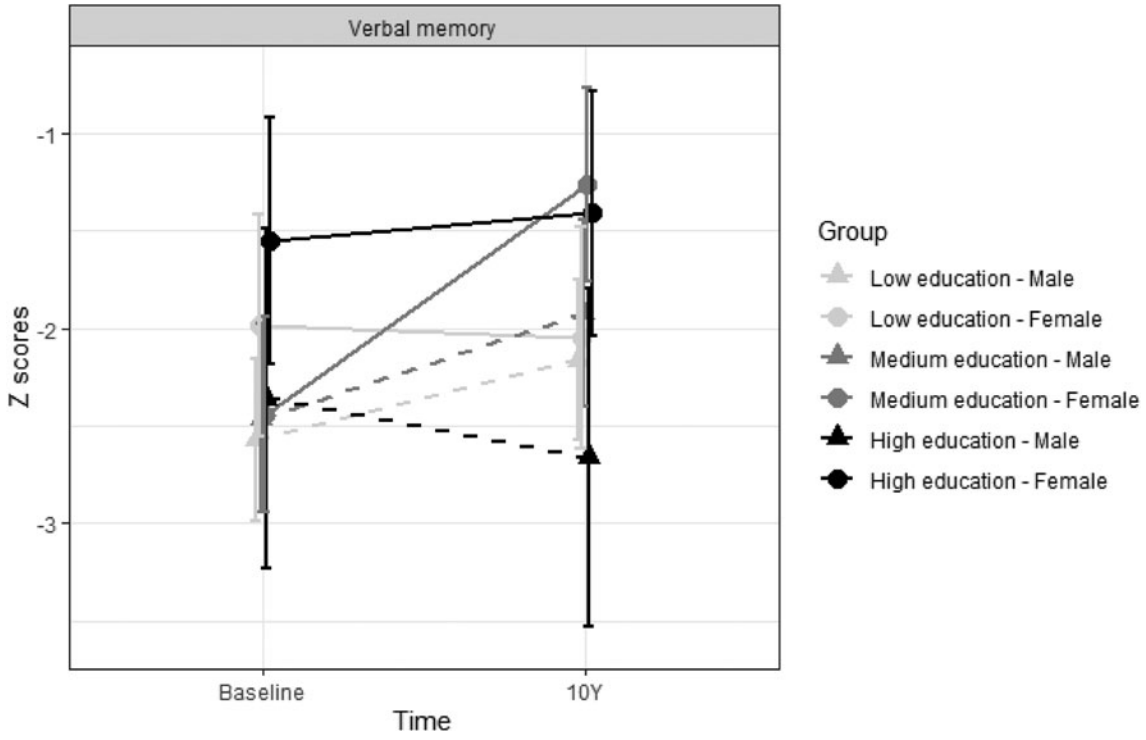

Fig. 4. Repeated measures: ANOVA of verbal memory for education groups in male and female FEP patients.

subgroup of schizophrenia patients that showed preadolescent impairment associated with reduced educational attainment polygenic scores. Their results suggest that early-life cognitive abnormalities are a consequence of a distinct genetic aetiology. Meanwhile, the longitudinal birth cohort study by Mollon, David, Zammit, Lewis and Reichenberg, (2018) confirmed that abnormalities in verbal learning and motor development, among individuals who later developed psychotic disorders, affected verbal and non-verbal abilities throughout the first two decades of life and led to increased dysfunction. Finally, Bilder et al. (2000) found deficits across most cognitive domains detectable at the time of the first episode, showing memory deficits among even those patients with less severe generalized deficits, and executive and attention deficits among the more severely disabled patients. In sum, cognitive deficits, specifically in verbal memory, are a core feature of psychotic disorders that provide a window into understanding developmental risk for psychosis and lifespan perspectives (Sheffield, Karcher & Barch, 2018).

The three education groups differed in some sociodemographic aspects such as sex, family socioeconomic status, substances use, and as previously mentioned, age at illness onset.

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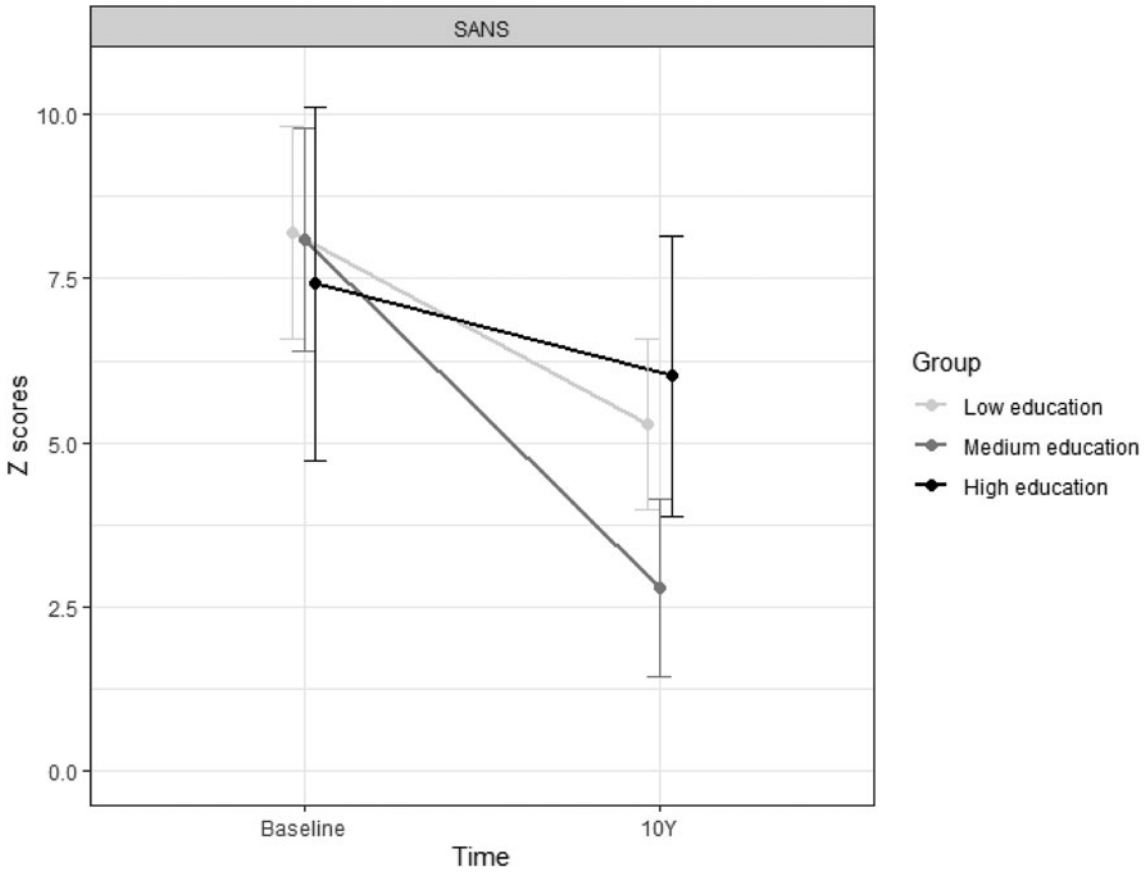

Fig. 5. Repeated measures: ANOVA of negative symptoms.

In terms of clinical variables, only slight differences in psychotic dimension and BPRS were observed between low- and high-education groups. This is an important finding that does not support the contention that those individuals who by the time of their FEP had achieved higher education were also those who presented milder symptoms. The heterogeneity of psychosis spectrum disorders impedes the identification of patients by stratification methods based on symptoms severity (Martinuzzi et al., 2019). As a brief note about substances uses, our results showed higher use of tobacco, alcohol and cannabis in the low-education group. This confirms previous literature in the field that has found that low-academic achievement and disengagement are related to greater substance use suggesting that academic failure may promote substance use as a coping mechanism (Bergen, Martin, Roeger & Allison, 2005).

After an average period of 10 years, the patients in the low-education group showed moderate and stable (confirmed at both baseline and 10-year reassessment) deficits in processing speed, executive functions and motor dexterity; and severe deficits in verbal memory and attention. In general, more years of education have been linked to better initial performance in each cognitive domain while a higher level of education has been linked to a higher tendency towards better outcomes (Alley, Suthers & Crimmins, 2007). Interestingly, each group has its specific features in cognitive function. The FEP patients in the medium-education group showed a severe and stable deficit in attention, and moderate deficits in verbal memory and motor dexterity. However, it should be noted that there was significant improvement (from severe to moderate deficit) in verbal memory, particularly among females, and in processing speed (from moderate deficit to normal range) in this group. In the case of the FEP patients in the high-education group, they showed cognitive performance within the normal limits in all but verbal memory. A possible explanation for these intriguing results could be the known ceiling effects of the measures, which are commonly used that do not allow for greater sensitivity among FEP patients with higher levels of education (Tucker-Drob, Johnson & Jones, 2009). Hoff, Svetina, Shields, Stewart and DeLisi, (2005) found similarity among FEP patients in neurocognitive deficits between illness onset and 10-year follow-up. Previous studies in our group, conducted at a similar follow-up period as Hoff and co-authors, support the argument that while cognitive functions are stable, their inter-variations point towards subgroup characterization (Rodriguez-Sanchez et al., 2020). On the other hand, the percentage of females who achieve medium and higher education was significantly higher than in males and more females than males in the low-education group continued studying in some point between baseline and 10-year follow-up. This could be explained in terms of later age at illness onset in females (Ayesa-Arriola et al., 2020). Early compared to later onset often arises in a context of good socioemotional functioning and the presence of a beneficial coping style (Kohler et al., 2007). These conditions suggest, as well, that differences in aetiology, the availability of opportunities and achievements in professional and personal life brought on by longer exposure to educational, occupational and leisure activities, may result in more efficient cognitive networks and CR (Scarmeas & Stern, 2003). The obtained results may strengthen the knowledge about education's contribution to CR

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(Kanchanatawan et al., 2018). Previously Amoretti et al. (2016) found that CR could prevent functional and cognitive decline in FEP patients at two-year follow-up. Future studies are needed that explore sub-group variation in terms of the association between CR and FEP at illness onset and long-term outcomes.

Strengths and limitations

Studies that take education achievements as their principal focus in schizophrenia are scarce. This is particularly true of studies that not only consist of a large sample ($N = 659$) of FEP patients, but also provide long-term information (average period of 10 years). There are, however, several limitations. First, the observed differences in attrition, significantly lower in the high-education group, seem be related to social factors (gender, family background), premorbid IQ and to previous educational achievements. This last relationship is somewhat circular. Second, cognitive performance could reflect other social learning experiences that provide the skills, knowledge, and interest to pursue intellectual challenges across the life span (Costa & Faria, 2018). In accordance with Sousa, Teixeira and Paul (2020), and with the exception of verbal memory tasks, findings suggest that education-related benefits are partially explained by frequent participation in intellectual activities. Therefore, formal education and cognition could be affected by other factors in the field of informal education that are difficult to balance. Third, stability in cognitive performance observed in some tests (e.g. working memory and visual memory) could be explained by their ceiling effects, and thus the inability to distinguish patients from controls among the upper levels of performance. Fourth, it is neither possible to confirm nor disconfirm the deficit schizophrenia theory or the presence of neurodevelopmental alterations that lead to difficulties in educational attainment, but the higher percentages of schizophrenia diagnosis in the low-education group and of brief psychotic disorder in high education patients could be due to diversity in underlying pathways. It is possible that, in certain FEP patients, neurodevelopmental cognitive alterations may lead to difficulties that make it not possible to reach higher education. Yet, it is also possible that social maladjustment contributes to school drop-outs at an early age (Goulding, Chien & Compton, 2010).

Conclusion

Our results purport that education level is related to a delay in illness onset and a better illness course for those individuals who develop psychotic disorders. A challenge is thus to identify those individuals at risk for psychosis and the consideration of educational achievements together with other known risk factors such as male sex, cannabis use and poor social functioning deserve attention whiting preventive programs. Meanwhile, the question of the role of CR in FEP patients is an ongoing debate.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721001112.

Data. The data that support the findings of this study are available on request from the corresponding author, RAA.

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Conflict of interest. The authors have no conflict of interest to declare.

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