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# Intelligence quotient changes over 10 years: Diversity of cognitive profiles in first episode of psychosis and healthy controls

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ABSTRACT

*Objective:* This study aimed to analyse whether intelligence quotient (IQ) improves, declines, or remains stable over 10 years among FEP patients and healthy subjects.
*Methods:* A group of FEP patients enrolled in a Program of First Episode Psychosis in Spain called PAFIP, and a sample of Healthy Controls (HC) completed the same neuropsychological battery at baseline and approximately 10 years later, which included the WAIS vocabulary subtest to estimate premorbid IQ and 10-year IQ. Cluster analysis was performed separately in the patient group and the HC group to determine their profiles of intellectual change.
*Results:* One hundred and thirty-seven FEP patients were grouped into five clusters: "Improved low IQ" (9.49 % of patients), "Improved average IQ" (14.6 %), "Preserved low IQ" (17.52 %), "Preserved average IQ" (43.06 %), and "Preserved high IQ" (15.33 %). Ninety HC were grouped into three clusters: "Preserved low IQ" (32.22 % of the HC), "Preserved average IQ" (44.44 %), and "Preserved high IQ" (23.33 %). The first two clusters of FEP patients, characterized by a low IQ, earlier age at illness onset, and lower educational attainment, showed a substantial cognitive improvement. The remaining clusters demonstrated cognitive stability.
*Conclusions:* The FEP patients showed intellectual improvement or stability, but no decline post-onset of psychosis. However, their profiles of intellectual change are more heterogeneous than that of HC over 10 years. Particularly, there is a subgroup of FEP patients with a significant potential for long-term cognitive enhancement.

## 1. Introduction

Extensive research has shown a generalized cognitive impairment in schizophrenia spectrum disorders (Ayesa-Arriola et al., 2018; Fioravanti et al., 2005; Sørensen et al., 2010). The identification of premorbid intelligence quotient (IQ) deficits in childhood and adolescence of affected individuals (Cosway et al., 2000; Dickson et al., 2012) supports the theory that schizophrenia is a neurodevelopmental disorder (Khandaker et al., 2011; Murray and Lewis, 1987). Agnew-Blais et al. (2015) reported that low IQ, along with behavioural problems during childhood, were specific markers of risk for schizophrenia. Furthermore, a meta-analysis found that the risk of schizophrenia had a dose-response effect on IQ, both in verbal and nonverbal abilities (Khandaker et al., 2011). However, although the literature shows evidence of IQ deficits prior to a first episode of psychosis (FEP), the subsequent long-term intellectual course is unclear.

To date, results on the trajectory of intellectual course post-FEP have varied. Several studies have found IQ stability in FEP patients after follow-up periods of 3-years (Leeson et al., 2011) and 5-years (Hedman et al., 2012). This stands in contrast to a meta-analysis that reported an

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increase of IQ by 0.33 points per year on average (Hedman et al., 2013). To put this into context, Jepsen et al. (2010) proposed that while patients can acquire new intellectual information and increase their IQ scores, they do so ultimately slower than healthy people. In contrast to evidence supporting either stability or increase, a third group of studies has indicated a trend toward IQ decline post-FEP (Fujino et al., 2017; Ohi et al., 2021), including Zanelli et al. (2019), who identified a decrease in IQ, verbal knowledge, and memory at 10-year follow-up. This heterogeneity of results suggests the existence of different intellectual trajectories among FEP patients, probably associated with other clinical, neurocognitive, and genetic characteristics. In fact, Panayiotou et al. (2020) proposed studying the intellectual course of schizophrenia patients taking into account whether their IQ is low or high.

It is important to recognize and describe the diversity of cognitive profiles among individuals who have experienced a FEP, as they are associated with different patterns of functional outcomes and treatment needs (Ayesa-Arriola et al., 2021). Recently, Dickinson et al. (2020) grouped individuals with schizophrenia into three clusters based on premorbid and current IQ, one of which showed preadolescent impairment, another adolescent decline, and the last one cognitive stability. Knowing the intellectual trajectory of FEP patients and comparing it with that of healthy people could be relevant to understand the role of premorbid factors in the evolution of the disorder. For instance, a trajectory of cognitive decline could indicate a post-FEP neurodegenerative process, requiring treatment strategies that slow deterioration. Otherwise, trajectories suggesting that the cognitive impairment in FEP remains stable or improves may indicate underlying neurodevelopmental alterations that require prevention and cognitive stimulation.

The main objective of this study was to analyse whether IQ improves, declines, or remains stable over 10 years in a sample of FEP patients and healthy controls (HC). Furthermore, we aimed to identify different intellectual profiles among FEP patients, and then compare their sociodemographic, clinical, and neurocognitive characteristics. Based on previous findings, we hypothesized that both FEP patients and HC would show IQ stability rather than improvement or decline.

## 2. Methods

### 2.1. Study design and setting

This is a retrospective observational study that analyses the cohort of first episode psychosis in Spain named PAFIP (Ayesa-Arriola et al., 2021), a longitudinal intervention program conducted at the University Hospital Marqués de Valdecilla where patients were referred from health-care services located in the region (Ayesa-Arriola et al., 2020). From February 2001 to July 2008, PAFIP patients completed a baseline evaluation, and approximately 10 years later (within a range between 8 and 12 years) they were invited to carry out a follow-up reassessment (Ayesa-Arriola et al., 2021).

The program was approved by the local institutional review board (ethics committee for research with medicine, CEIm Cantabria) according to international standards for research ethics (clinical trial numbers NCT0235832 and NCT02534363). All participants gave written informed consent.

### 2.2. Subjects

Out of the 307 patients assessed at baseline, 209 individuals completed the 10-year reassessment (Ayesa-Arriola et al., 2020, 2021). Baseline inclusion criteria were age between 15 and 60 years; living in the catchment area; experiencing a first episode of psychosis; and being antipsychotic medication naïve, or if previously treated, a total lifetime of adequate antipsychotic treatment of <6 weeks. Exclusion criteria were meeting the DSM-IV criteria for drug or alcohol dependence, having an intellectual disability, and/or having a history of neurological disease or head injury. The diagnoses were confirmed through the use of the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer et al., 1992) conducted by an experienced psychiatrist within 6 months of the baseline visit.

A group of 229 healthy controls (HC) underwent the same neurocognitive assessment as patients at baseline, while 91 of them completed the 10-year reassessment. They were recruited through advertisements from the local community and had no history of psychiatric disorders, mental disability, neurological or general medical illnesses, as established by the abbreviated version of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, 1987). HC were selected to have a similar distribution in age and sex to the patients.

### 2.3. Sociodemographic and clinical assessment

At baseline, sociodemographic data (sex, age, age of psychosis onset, years of education, cannabis consumption) were obtained from patients, their relatives and medical records on admission. Age at psychosis onset was defined as the age when the emergence of the first continuous (present most of the time) psychotic symptom occurred. Social premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), with ratings from 0 (indicating the "better") to 6 (denoting the "worse").

Clinical assessment was performed at baseline and after 6 weeks, 3 months, 12 months, 24 months and 36-month-follow-up by a trained psychiatrist (B.C.F.). Symptoms of psychosis were measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The duration of untreated illness (DUI, defined as the time from the first nonspecific symptom related to psychosis) and the duration of untreated psychosis (DUP, defined as the time from the first continuous psychotic symptom to initiation of adequate antipsychotic drug treatment) were estimated. At the 10-year follow-up, information on positive symptoms (using the SAPS), negative symptoms (using the SANS) and cannabis use was re-explored.

### 2.4. Estimation of premorbid IQ and 10-year IQ

We estimated premorbid IQ and 10-year IQ through the WAIS-III Vocabulary subtest. Previous research has demonstrated that Vocabulary is an appropriate measure of premorbid IQ (de Oliveira et al., 2014; Ringe et al., 2002; Wechsler, 1997), since it assess crystallized intelligence in both in the general population and in individuals with FEP (Lezak et al., 2004). Crystallized intelligence differs from fluid intelligence at the genetic level (Christoforou et al., 2014), is more stable allowing to estimate the cognitive ability previous to the onset of the disorder, and is related to the education attainment and the linguistic information of the native language (de Oliveira et al., 2014). Based on this evidence, our group has previously used Vocabulary as a proxy measure for premorbid intelligence, showing utility to study the IQ of FEP patients (Ayesa-Arriola et al., 2018).

Because the trajectory of crystallized intelligence is less age-dependent (Ardila, 2007; Beier and Ackerman, 2005), we used again Vocabulary to estimate IQ at the 10-year follow-up. This measure has a high test-retest reliability (Iverson, 2001), so we consider it provides a proxy measure of 10-year IQ that could detect non-age related cognitive change. Furthermore, by using the same test at both moments of the evaluation, we could avoid possible biases derived from comparing different measurement tools.

### 2.5. Neurocognitive assessment

At baseline, patients answered the neuropsychological battery on average 10.5 weeks (SD = 6.17) after entering the PAFIP program (once they were stable). Verbal memory was measured with the Rey Auditory Verbal Learning Test (RAVT) (Rey, 1964); visual memory with the Rey Complex Figure (RFC) (Osterrieth, 1944); processing speed with the

WAIS-III Digit Symbol subtest (Wechsler, 1997); working memory with the WAIS-III Digits Backward subtest (Wechsler, 1997); executive function with the Trail Making Test part B (TMTB) (Lezak et al., 2004); motor dexterity with the The Grooved Pegboard Test (Lezak et al., 2004); and attention with the Continuous Performance Test (CPT) (Cegalis and Bowlin, 1991). Raw scores were transformed into Z scores using a sample of 187 healthy volunteers described in previous studies (Setién-Suero et al., 2019).

Afterward, the Global Cognitive Functioning (GCF) score was estimated following Reichenberg et al. (2009). First, the T scores of each neuropsychological test were converted to deficit scores ranging from 0 to 5. The deficit score of 0 (T score > 40) indicates absence of impairment; a score of 1 (T score = 39 to 35) mild impairment, a score of 2 (T score = 34 to 30) mild to moderate impairment, a score of 3 (T score = 29 to 25) moderate impairment, 4 (T score < 20) moderate to severe impairment (T score = 24 to 20), and a score of 5 a severe impairment. Second, the GCF was calculated from the mean of the deficit scores of all the neuropsychological tests. Previous studies have established that a GCF greater than or equal to 0.5 indicates overall impairment (Reichenberg et al., 2009).

At the 10-year re-evaluation the same neuropsychological battery was carried out.

### 2.6. Statistical analysis

The data were analysed using the Statistical Package for Social Science (SPSS) 21.0. First, a hierarchical cluster analysis was performed to determine the patients' clusters by inputting their estimated premorbid IQ and their 10-year IQ. The hierarchical cluster analysis was based on Ward's linkage method and squared Euclidean distance. After visual inspection of the resulting dendrogram and the analysis of agglomeration coefficient changes, the definitive number of clusters was established. Next, a K-means cluster analysis was carried out and the final solution was confirmed by discriminant function analysis. Analysis of variance (ANOVA) or $\chi 2$ were used to compare sociodemographic, clinical, and neurocognitive variables between clusters. Neurocognitive comparisons were covariated with age, sex, and years of education. Post-hoc comparisons with Bonferroni correction were conducted to examine pairwise relationships.

Finally, the HC group was subjected to a hierarchical cluster and a K-means cluster analysis using their premorbid IQ and their 10-year IQ, following the same process.

## 3. Results

### 3.1. Clusters of FEP patients

Out of the 209 FEP patients that completed the 10-year follow-up evaluation, 137 (55.47 % males) had available information to estimate their premorbid IQ and their 10-year IQ (see Fig. 1). When comparing FEP patients completing and no completing the follow-up assessment (Supplementary material Table 1A), we observed that non-completers had a worse premorbid adjustment in childhood ($p$ = 0.007) and consumed cannabis at a higher rate in baseline ($p$ = 0.003).

After introducing these two variables in the hierarchical cluster analysis a five-cluster solution was suggested, and therefore introduced in the K-means analysis. This solution was confirmed by discriminant function analysis (see Fig. 2). From the five clusters of FEP patients, two showed an IQ improvement, while the other three showed IQ stability at the 10-year reassessment (see Table 1 and Fig. 3). No evidence of IQ decline was observed in our sample. The neurocognitive profile of each cluster is plotted in Supplementary material, Fig. 1A.

#### 3.1.1. Cluster 1 (improved low IQ)

Despite of the IQ improvement observed, these patients (9.49 % of the FEP patients) obtained a low IQ at both assessments. They had completed significantly less years of education and showed worse premorbid adjustment in childhood and early adolescence compared to other clusters. They had the lowest neurocognitive performance of all patients, particularly in attention and executive functions. At 10-year follow-up, they had more negative symptoms than other clusters (Table 2).

#### 3.1.2. Cluster 2 (improved average IQ)

These patients (14.60 % of the patients) showed the greatest improvement in IQ, going from a low premorbid IQ to an average IQ at the 10-year re-assessment. They were younger at the psychosis onset and had completed less years of education than others. There were more

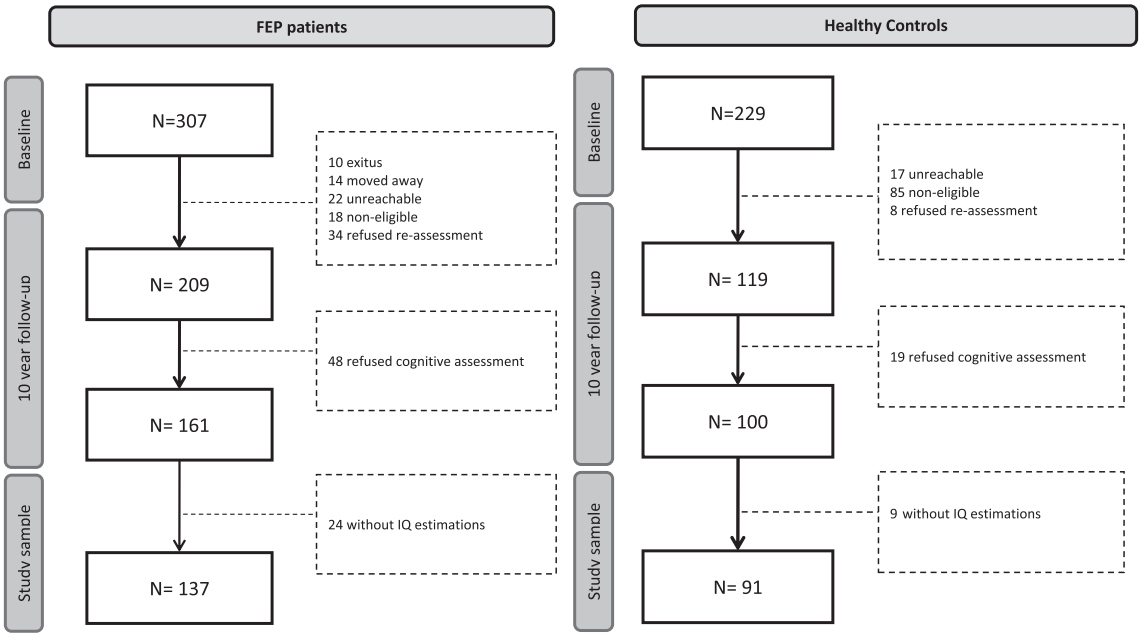


**Fig. 1.** Flow diagram for study participants. Representation of individuals recruited at baseline and reassessed at 10-year follow-up. The "non-elegible" label refers to people who, at the time of the follow-up evaluation, had passed <8 years since completing the baseline evaluation.

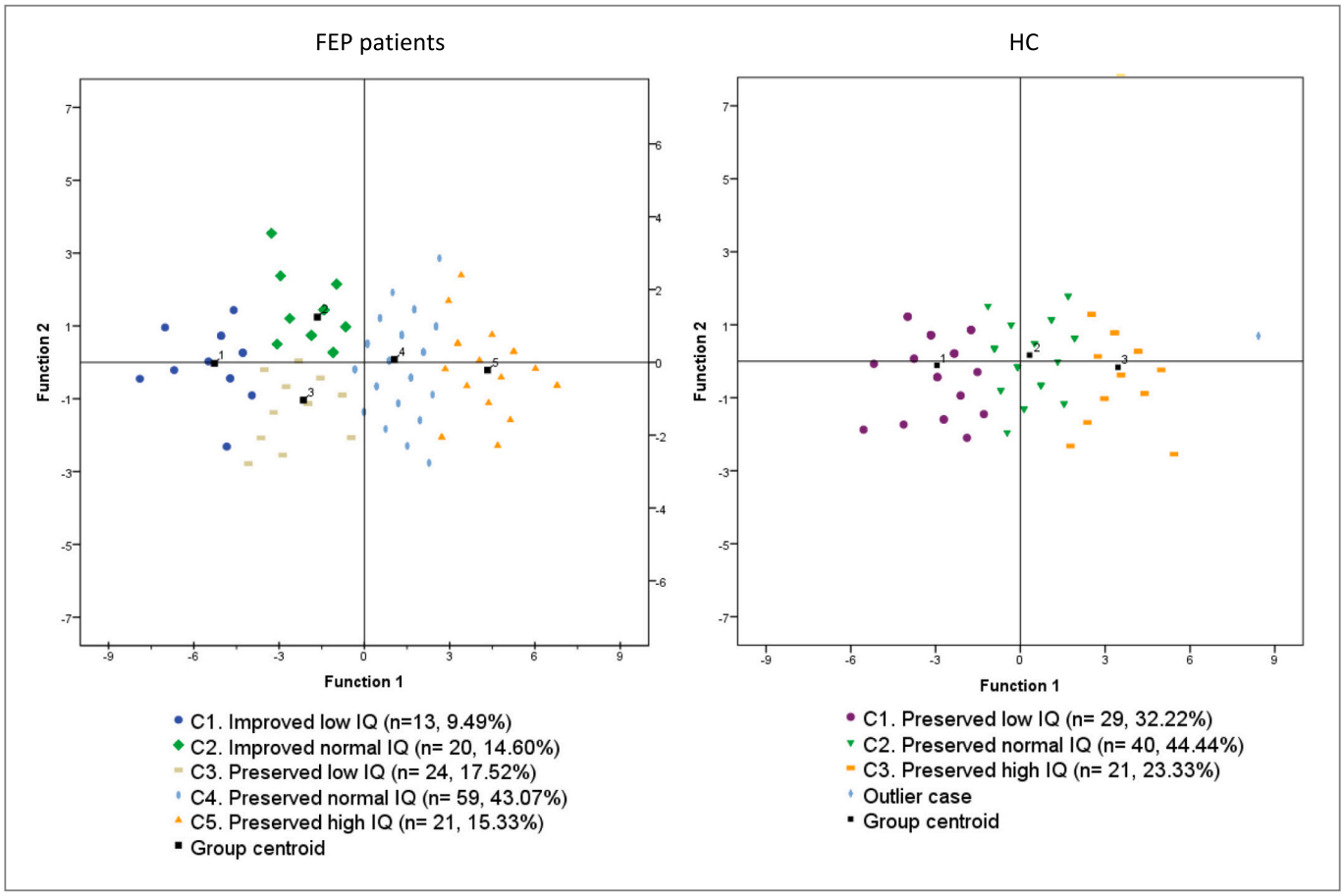


**Fig. 2.** Cluster membership of FEP patients and HC. Using discriminant analysis, standardized coefficients of two discriminant functions were estimated after setting premorbid IQ and 10-year IQ as predictor variables and cluster membership as grouping variable. This diagram represents the dispersion of the participants in the resulting functions. Wilks' lambda test showed that the mean of the discriminant functions was significantly different between the groups ($p < 0.001$), confirming that the clusters behave differently.

male patients and cannabis users at baseline in this cluster than in others. At baseline, they performed like patients with high IQ in working memory, and at 10-year follow-up, they outperformed those with low IQ (clusters 1 and 3) in several neurocognitive domains.

#### 3.1.3. Cluster 3 (preserved low IQ)

Patients with a stable low IQ (17.52 % of the patients). They were younger at onset, had completed less years of education, and had worse childhood adjustment and worse general premorbid adjustment than others. They underperformed other patients in attention at baseline, and in motor dexterity at 10-year follow-up.

#### 3.1.4. Cluster 4 (preserved average IQ)

Patients with a stable average IQ (43.07 % of the patients). Their educational attainment and neurocognitive performance was intermediate between the previous clusters and the cluster with high IQ at both moments of assessment.

#### 3.1.5. Cluster 5 (preserved high IQ)

Patients with a stable high premorbid IQ (15.33 % of the patients). Compared to other patients, these were older at the psychosis onset, had completed more years of education, and showed a better adjustment during childhood and early adolescence. Overall, they had a better neurocognitive performance than others at both assessments.

### 3.2. Clusters of healthy controls (HC)

Ninety-one HC had estimations of premorbid IQ and 10-year IQ, but an outlier with scores of 130 and 135 respectively was eliminated from the analysis (see Fig. 1). When comparing completers and non-completers at baseline (Supplementary material, Table 2A), we observed that the first ones had completed fewer years of education ($p = 0.002$). The results of the hierarchical cluster analysis suggested a three-cluster solution, so a K-means analysis with this characteristic was run (see Table 3, Figs. 2, 3).

All three clusters of HC had a preserved IQ since their premorbid IQ remained similar after 10 years. Cluster 1 (32.22 % of the HC) had a low IQ, had completed less years of education and underperformed others in most neurocognitive domains. Cluster 2 (44.44 % of the HC) had an average premorbid IQ, and an intermediate neurocognitive performance between others. Cluster 3 (23.33 % of the HC) had a high premorbid IQ, had completed more years of education and performed better in most neurocognitive domains. The neurocognitive profile of each cluster is plotted in Supplementary material, Fig. 2A.

## 4. Discussion

In this study, we analysed whether IQ scores improve, decline, or remain stable over 10 years in FEP patients and HC, and identified different intellectual profiles through cluster analysis. We found that the intellectual course of FEP patients differs from that of unaffected individuals because they were grouped differently based on their IQ

**Table 1**
Sociodemographic and clinical characteristics of FEP patients according to their membership cluster.

| | Improved low IQ (C1) $N = 13$ | Improved average IQ (C2) $N = 20$ | Preserved low IQ (C3) $N = 24$ | Preserved average IQ (C4) $N = 59$ | Preserved high IQ (C5) $N = 21$ | F | P | Paired comparisons |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | | | |
| Premorbid IQ | 71.15 (6.50) | 84.50 (5.10) | 88.96 (5.31) | 100.76 (4.90) | 117.14 (7.34) | 180.87 | <0.001 | 1 < 2*, 1 < 3*, 1 < 4*, 1 < 5*, 2 < 4*, 2 < 5*, 3 < 4*, 3 < 5*, 4 < 5* |
| 10-Year IQ | 85.38 (5.94) | 103.25 (4.06) | 90.00 (5.32) | 105.76 (6.49) | 114.52 (6.87) | 77.47 | <0.001 | 1 < 2*, 1 < 4*, 1 < 5*, 2 > 3*, 2 < 5*, 3 < 4*, 3 < 5*, 4 < 5* |
| Points of IQ change | 14.23 (8.13) | 18.75 (7.23) | 1.04 (6.59) | 5.00 (8.51) | −2.62 (10.08) | 23.21 | <0.001 | 1 > 3*, 1 > 4**, 1 > 5*, 2 > 3*, 2 > 4*, 2 > 5*, 4 > 5** |
| Age | 26.44 (6.07) | 24.85 (4.08) | 25.99 (8.49) | 30.86 (9.54) | 33.20 (8.81) | 4.350 | 0.002 | 2 < 5**, 3 < 5*** |
| Age under 20 (yes %)[a] | 2 (15.4 %) | 2 (10 %) | 5 (20.8 %) | 6 (10.2 %) | 0 | $\chi2$ = 5.304 | 0.257 | – |
| Age of onset | 25.54 (5.81) | 24.11 (4.19) | 25.46 (8.41) | 29.68 (9.26) | 32.14 (8.48) | 3.993 | 0.004 | 2 < 5*** |
| Sex (male %) | 7 (53.8 %) | 15 (80 %) | 15 (62.5 %) | 29 (49.1 %) | 9 (42.8 %) | $\chi2$ = 7.672 | 0.104 | 2 > 4***; 2 > 5*** |
| Years of education | 8.31 (2.14) | 9.00 (2.10) | 9.00 (2.13) | 11.63 (3.39) | 14.38 (3.15) | 15.818 | <0.001 | 1 < 4**, 1 < 5*, 2 < 4**, 2 < 5*, 3 < 4**, 3 < 5*, 4 < 5** |
| PAS Childhood | 2.95 (1.10) | 2.48 (1.45) | 2.74 (1.48) | 1.90 (1.18) | 1.46 (0.98) | 4.889 | 0.001 | 1 > 5**, 3 > 5** |
| PAS Early adolescence | 3.27 (0.75) | 2.93 (1.36) | 2.95 (1.47) | 2.15 (1.17) | 1.95 (0.99) | 4.869 | 0.001 | 1 > 4***, 1 > 5*** |
| PAS Late adolescence | 2.71 (1.53) | 3.21 (1.68) | 3.33 (1.82) | 2.44 (1.47) | 2.31 (1.48) | 2.066 | 0.089 | – |
| PAS Adulthood | 2.83 (2.26) | 2.39 (2.36) | 3.04 (2.97) | 1.71 (1.89) | 2.06 (2.49) | 1.403 | 0.238 | – |
| PAS General | 3.62 (1.69) | 3.56 (2.00) | 3.99 (2.23) | 2.79 (1.72) | 2.21 (1.72) | 3.241 | 0.014 | 3 > 5*** |
| Cannabis at baseline (yes%) | 6 (46.15 %) | 12 (60 %) | 9 (37.50 %) | 15 (25.42 %) | 7 (33.33 %) | $\chi2$ = 8.556 | 0.073 | 2 > 4** |
| Cannabis at 10-years (yes%) | 2 (15.3 %) | 1 (5 %) | 3 (12.50 %) | 3 (5.08 %) | 0 | $\chi2$ = 4.790 | 0.310 | – |
| DUP (months) | 10.77 (16.50) | 8.94 (9.79) | 6.42 (9.47) | 14.08 (28.46) | 12.77 (20.02) | 0.628 | 0.643 | – |
| Schizophrenia diagnosis (yes%) | 7 (53.8 %) | 14 (70 %) | 17 (70.8 %) | 35 (59.3 %) | 12 (57.1 %) | 2.096 | 0.718 | – |
| SAPS at baseline | 12.69 (3.61) | 13.00 (4.09) | 12.79 (4.15) | 13.56 (4.76) | 12.19 (4.57) | 0.432 | 0.785 | – |
| SANS at baseline | 8.62 (5.90) | 7.75 (7.43) | 10.38 (6.6) | 7.63 (6.05) | 5.86 (5.42) | 1.563 | 0.188 | – |
| SAPS at 10-years | 2.77 (5.96) | 1.90 (4.16) | 2.50 (3.57) | 0.76 (1.41) | 0.10 (0.30) | 3.312 | 0.013 | – |
| SANS at 10-years | 7.23 (6.47) | 2.60 (4.68) | 6.17 (5.81) | 3.39 (3.63) | 2.95 (3.20) | 4.109 | 0.004 | 1 > 2*** |

DUP: duration of untreated psychosis; FEP: First Episode Psychosis; IQ: Intelligence Quotient; PAS: Premorbid Adjustment Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms. Note: all paired comparisons were conducted with Bonferroni correction.

*** $p < 0.050$.

** $p < 0.010$.

* $p \leq 0.001$.

[a] Age ranges: C1 = 17.92–34.33; C2 = 18.95–30.55; C3 = 17.18–49.07; C4 = 15.91–57.84; C5 = 20.47–51.66.

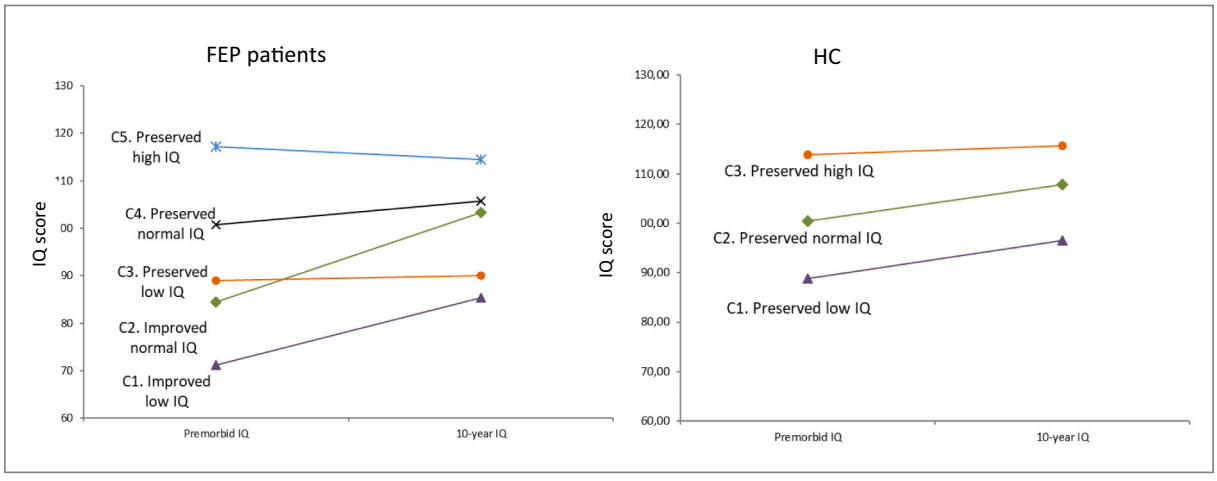


**Fig. 3.** IQ change of FEP patients and HC from baseline to 10-year follow-up. The graphs show the mean points of IQ change among the obtained clusters, where steep slopes indicate improvement.

estimations. While HC were classified into three clusters, FEP patients were subdivided into five groups with different neurocognitive profiles. This result replicates previous findings on the heterogeneity of cognitive course after the psychosis onset (Fett et al., 2020; Hedman et al., 2013; Ohi et al., 2021; Zanelli et al., 2019). But contrasts with others showing three instead of five different patterns of cognitive change among FEP patients (Badcock et al., 2005; Dickinson et al., 2020).

Generally, we found that all participants, both patients and HC, can

**Table 2**
Neurocognitive performance of FEP patients according to their membership cluster.

| | Improved low IQ (C1) N = 13 | Improved average IQ (C2) *N* = 20 | Preserved low IQ (C3) N = 24 | Preserved average IQ (C4) *N* = 59 | Preserved high IQ (C5) N = 21 | F | P | Paired comparisons |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | | | |
| Baseline | | | | | | | | |
| Verbal memory | −3.09 (1.42) | −2.97 (0.95) | −2.38 (1.31) | −2.18 (1.21) | −1.41 (1.55) | 3.93 | 0.005 | 1 < 4*** 1 < 5* 2 < 4*** 2 < 5* 3 < 5*** 4 < 5*** |
| Visual memory | −1.22 (1.12) | −0.56 (0.88) | −0.58 (0.98) | −0.43 (1.00) | 0.03 (0.91) | 2.76 | 0.030 | 1 < 4*** 1 < 5* |
| Processing speed | −1.77 (0.98) | −2.13 (0.89) | −1.65 (0.95) | −1.46 (0.99) | −0.73 (0.95) | 4.36 | 0.002 | 1 < 5** 2 < 4** 2 < 5* 3 < 5** 4 < 5** |
| Working memory | −0.82 (0.52) | −0.10 (0.70) | −0.68 (0.64) | −0.54 (0.77) | 0.03 (1.11) | 4.07 | 0.004 | 1 < 2** 1 < 5** 3 < 2*** 3 < 5** 4 < 2*** 4 < 5** |
| Executive function | −2.87 (2.69) | −1.14 (1.54) | −0.51 (1.87) | −1.00 (1.70) | −0.23 (0.57) | 4.97 | 0.001 | 1 < 2** 1 < 3*1 < 4* 1 < 5* |
| Motor dexterity | −1.85 (2.54) | −0.99 (1.52) | −2.38 (6.05) | −0.95 (1.22) | −0.68 (1.04) | 1.17 | 0.326 | ns |
| Attention | −3.14 (3.24) | −3.97 (5.97) | −4.93 (6.07) | −1.59 (3.33) | −1.41 (3.89) | 2.20 | 0.073 | 3 < 4** 3 < 5*** |
| GCF | 2.15 (0.90) | 1.71 (0.95) | 1.65 (1.13) | 1.24 (0.84) | 0.76 (0.63) | 3.92 | 0.005 | 4 < 1** 5 < 1* 5 < 2** 5 < 3** |
| 10 years | | | | | | | | |
| Verbal memory | −2.59 (1.46) | −2.29 (0.96) | −2.64 (1.35) | −1.67 (1.23) | −0.75 (1.26) | 6.09 | <0.001 | 1 < 4***1 < 5*2 < 5* 3 < 4** 3 < 5* 4 < 5** |
| Visual memory | −1.40 (0.59) | −0.51 (0.74) | −0.81 (0.82) | −0.42 (0.72) | −0.09 (0.73) | 6.18 | <0.001 | 1 < 2* 1 < 3*** 1 < 4* 1 < 5* 3 < 4*** 3 < 5** |
| Processing speed | −1.34 (0.92) | −0.56 (1.04) | −1.16 (0.69) | −0.49 (0.91) | −0.48 (0.90) | 4.38 | 0.002 | 1 < 2** 1 < 4** 1 < 5**3 < 2*** 3 < 5*** |
| Working memory | −1.19 (0.54) | −0.22 (0.84) | −0.78 (0.72) | −0.42 (0.73) | 0.17 (0.73) | 7.25 | <0.001 | 1 < 2* 1 < 4* 1 < 5* 3 < 2*** 3 < 5* 4 < 5** |
| Executive function | −1.67 (1.71) | −0.25 (1.40) | −1.55 (1.85) | −0.51 (1.35) | −0.59 (1.48) | 3.49 | 0.010 | 1 < 2*** 1 < 4*** 3 < 2** 3 < 4** |
| Motor dexterity | −1.46 (1.10) | −1.41 (3.33) | −2.53 (3.91) | −0.63 (1.43) | −0.39 (1.40) | 2.85 | 0.027 | 3 < 4* 3 < 5** |
| Attention | −4.98 (6.60) | −1.57 (2.71) | −3.94 (6.38) | −0.76 (2.65) | −1.23 (4.55) | 3.75 | 0.006 | 1 < 2*** 1 < 4** 1 < 5*** 3 < 4** |
| GCF | 1.84 (0.84) | 0.99 (0.78) | 1.54 (0.83) | 0.79 (0.77) | 0.59 (0.67) | 6.50 | <0.001 | 2 < 1** 2 < 3*** 4 < 1* 4 < 3* 5 < 1* 5 < 3* |
| Z-score change | | | | | | Time effect | | |
| Verbal memory | 0.50 | 0.68 | 0.19 | −0.50 | −0.68 | 0.64 | 0.424 | – |
| Visual memory | −0.18 | 0.06 | 0.23 | 0.18 | −0.06 | 4.07 | 0.046 | – |
| Processing speed | 0.42 | 1.57 | 1.15 | −0.42 | −1.57 | 0.85 | 0.358 | – |
| Working memory | −0.37 | −0.12 | 0.24 | 0.37 | 0.12 | 2.61 | 0.108 | – |
| Executive function | 1.20 | 0.89 | −0.32 | −1.20 | −0.89 | 0.73 | 0.392 | – |
| Motor dexterity | 0.39 | −0.43 | −0.81 | −0.39 | 0.43 | 7.01 | 0.009 | – |
| Attention | −1.84 | 2.39 | 4.24 | 1.84 | −2.39 | 1.77 | 0.185 | – |
| GCF | −0.31 | −0.73 | −0.41 | 0.31 | 0.73 | 0.73 | 0.394 | – |

GCF: Global Cognitive Functioning; FEP: First Episode Psychosis. Notes: neurocognitive comparisons are covariated by sex, age and years of education. All paired comparisons were conducted with Bonferroni correction.

*** $p < 0.050$.

** $p \leq 0.010$.

* $p \leq 0.001$.

improve their IQ scores in the long term. According to Hartshorne and Germine (2015), crystallized intelligence peaks around age 50 in the general population, therefore, the HC's slight improvement in the vocabulary subtest can be considered normal. However, the greater increase of FEP patients might suggest that at baseline they performed below their cognitive abilities, thus having a bigger window for improvement in the long term, probably due to a neurodevelopmental alteration. A similar intellectual rise over time post-FEP has been previously reported and linked to the practice effect (Van Haren et al., 2019), which allows to improve the cognitive performance after repeated exposures (Albus et al., 2006; Hedman et al., 2013). Our finding demonstrates that FEP patients can manage new information despite their underlying intellectual deficit. Since age influences this effect (Granholm et al., 2010), the great increase of patients in the clusters "Improved low IQ" and "Improved average IQ" could be explained in part by the fact that they were younger than HC. However, after comparing the proportion of individuals under age 20 in each cluster, we observed no significant differences. Therefore, we can rule out that these patients had an underestimation of their premorbid IQ due to a young age at baseline, and their IQ gain would be related to other features. Although our results differ from others indicating a lack of cognitive improvement post-FEP (Albus et al., 2006; Fujino et al., 2017; Zanelli et al., 2019), the discrepancies may be related to the data analysis strategy. The cluster analyses used in this study might have identified two subgroups of FEP patients with an outstanding potential for cognitive improvement. They were characterized by an earlier age at onset of psychosis and lower educational attainment. Consequently, these results could justify the early treatment of psychosis, both in its clinical and cognitive dimensions.

In total 49 patients from our sample were cannabis users at baseline, of whom 9 continued to use at 10 years of follow-up. Although our sample size lacks the statistical power to draw conclusions in this regard, it is relevant to further study the possible effects of cannabis withdraw on the intellectual course. A pattern of cognitive improvement was described in a previous study of our group (Setién-Suero et al., 2019), and agrees with Weibell et al. (2019) who observed that early substance discontinuation among FEP patients was related to cognitive, clinical, and functional improvements. Hence, stopping cannabis use could

**Table 3**
Sociodemographic characteristics and neurocognitive performance of HC according to their membership cluster.

| | Preserved low IQ ($N = 29$) | Preserved average IQ ($N = 40$) | Preserved high IQ ($N = 21$) | F | P | Paired comparisons |
|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | | | |
| IQ at baseline | 88.79 (5.61) | 100.50 (4.64) | 113.81 (5.90) | 137.71 | <0.001 | 1 < 2*. 1 < 3*. 2 < 3* |
| 10-Year IQ | 96.55 (5.84) | 107.88 (5.76) | 115.71 (5.76) | 70.33 | <0.001 | 1 < 2*. 1 < 3*. 2 < 3* |
| Points of IQ change | 7.76 (8.82) | 7.38 (7.59) | 1.90 (9.81) | 3.513 | 0.034 | – |
| Age | 30.58 (8.28) | 29.63 (9.66) | 28.40 (6.03) | 0.40 | 0.670 | – |
| Age under 20 (yes %)[a] | 5 (17.2 %) | 7 (17.5 %) | 3 (14.3 %) | $\chi2 = 0.113$ | 0.945 | |
| Sex (male %) | 13 (44.82 %) | 23 (57.50 %) | 11 (52.3 %) | 1.08 | 0.582 | – |
| Years of education | 10.34 (1.52) | 10.68 (2.80) | 13.89 (2.56) | 14.82 | <0.001 | 1 < 3*. 2 < 3* |
| Neurocognitive performance at baseline | | | | | | |
| Verbal memory | −1.45(1.17) | −1.14 (1.32) | −0.81 (1.06) | 1.51 | 0.227 | – |
| Visual memory | −0.44(1.23) | 0.15 (0.90) | 0.05 (0.71) | 3.83 | 0.026 | 1 < 2** |
| Processing speed | −0.17(1.04) | 0.10 (0.86) | 0.65 (0.88) | 3.33 | 0.041 | 1 < 3*** |
| Working memory | −0.25(0.97) | 0.15 (0.99) | 0.25 (0.97) | 1.74 | 0.182 | – |
| Executive function | −0.40(1.24) | 0.16 (0.73) | 0.26 (0.87) | 3.27 | 0.043 | 1 < 2*** 1 < 3*** |
| Motor dexterity | 0.15(0.78) | −0.04 (0.93) | 0.26 (0.56) | 0.86 | 0.429 | – |
| Attention | −0.55(1.38) | 0.04 (1.02) | 0.22 (0.54) | 2.82 | 0.066 | 1 < 2*** 1 < 3 ($p = 0.051$) |
| GCF | 0.70(0.61) | 0.36 (0.43) | 0.29 (0.28) | 5.43 | 0.006 | 2 < 1** 3 < 1** |
| Neurocognitive performance at 10-year follow-up | | | | | | |
| Verbal memory | −1.00 (1.12) | −0.56 (1.13) | −0.52 (1.04) | 1.73 | 0.184 | – |
| Visual memory | 0.13 (0.81) | 0.34 (0.65) | 0.47 (0.69) | 1.44 | 0.243 | – |
| Processing speed | 0.36 (0.85) | 0.65 (0.69) | 1.03 (0.72) | 3.76 | 0.028 | 1 < 3** |
| Working memory | −0.27 (0.94) | 0.33 (1.04) | 0.38 (0.91) | 3.93 | 0.024 | 1 < 2** 1 < 3*** |
| Executive function | −0.05 (0.77) | 0.01 (0.71) | 0.12 (0.59) | 0.25 | 0.781 | – |
| Motor dexterity | 0.59 (0.63) | 0.41 (0.99) | 0.64 (0.45) | 0.70 | 0.500 | – |
| Attention | −0.66 (2.66) | −0.05 (0.89) | 0.68 (0.27) | 2.81 | 0.066 | 1 < 3*** |
| GCF | 0.39 (0.45) | 0.21 (0.37) | 0.15 (0.21) | 2.81 | 0.066 | 2 < 1*** 3 < 1 ($p = 0.054$) |
| Z-score change | | | | Time effect | | |
| Verbal memory | 0.45 | 0.58 | 0.29 | 2.46 | 0.121 | – |
| Visual memory | 0.57 | 0.19 | 0.43 | 0.18 | 0.674 | – |
| Processing speed | 0.53 | 0.55 | 0.39 | 1.31 | 0.256 | – |
| Working memory | −0.02 | 0.18 | 0.13 | 1.23 | 0.271 | – |
| Executive function | 0.34 | −0.15 | −0.15 | 0.24 | 0.624 | – |
| Motor dexterity | 0.43 | 0.45 | 0.38 | 4.24 | 0.043 | – |
| Attention | −0.11 | −0.09 | 0.45 | 2.83 | 0.067 | – |
| GCF | −0.30 | −0.15 | −0.14 | 1.71 | 0.195 | – |

GCF: Global Cognitive Functioning; IQ: Intelligence Quotient; FEP: First Episode Psychosis. Notes: neurocognitive comparisons are covariated by sex, age, and years of education. All paired comparisons were conducted with Bonferroni correction.

*** $p < 0.050$.

** $p < 0.010$.

* $p \leq 0.001$.

[a] Age ranges: C1 = 18.18–50.16; C2 = 15.15–51.48; C3 = 18.84–39.69.

reverse its potential negative effects on cognition (Setién-Suero et al., 2019), but it is important to consider moderating variables such as the amount and pattern of consumption (Schoeler et al., 2016), sex (Ayesa-Arriola et al., 2020; Setién-Suero et al., 2017), age (Barnes et al., 2006), and genetic factors (Van Winkel et al., 2011). However, there is literature reporting better cognitive functioning associated with cannabis use in FEP (Hájková et al., 2021; Kayir et al., 2022), so current evidence is inconclusive (Ahmed et al., 2021).

The specific neurocognitive profile among clusters of FEP patients may also contribute to their intellectual course. The cluster with the greatest IQ increase showed a relative spare performance in working memory ("Improved average IQ"), while the cluster with the lowest IQ ("Improved low IQ") had the poorer performance in working memory at both assessments. Previous research has described that adolescents at familial high-risk for psychosis have impaired working memory function and altered brain activity during this task (van Gool et al., 2022). Therefore, FEP patients with a noticeable deficit in this domain may represent a subgroup of individuals at higher liability for psychosis from early ages. Other cognitive domains potentially related to this differential profile are attention and executive functioning, since patients in the "Improved low IQ" cluster showed a marked executive dysfunction at baseline and a marked attentional deficit at 10-year follow-up. A recent study of our group found that these same domains were especially affected in first-degree relatives of FEP patients, which make them suitable endophenotypes for psychotic disorders (Murillo-García et al., 2022).

Our findings corresponds with evidence on low premorbid IQ and cognitive impairment as potential endophenotypes of schizophrenia spectrum disorders (Burdick et al., 2006; Lemvigh et al., 2020; McCarthy et al., 2018). Despite the long-term cognitive improvement of FEP patients, they had a significant higher rate of low premorbid IQ than HC (27.7 % and 13.3 % respectively, $\chi2 = 6.609$, $p = 0.037$), and obtained worse neurocognitive outcomes at 10-year follow-up. This finding agrees with a previous study from our research group describing that low IQ was more frequent in FEP patients than in controls (Ayesa-Arriola et al., 2018). Even patients in the "preserved" clusters with average and high IQ showed significant impairments in most cognitive domains, contrary to HC with equivalent IQ scores. Which suggests cognitive deficits as markers of the disorder and could be a result of a neurodevelopmental alteration (Bertisch et al., 2009; Gur et al., 2015). Moreover, the substantial processing speed deficit in the FEP patients from our sample could have affect their performance in the rest of domains (Bechi et al., 2019) despite having an average or high IQ. In addition, HC could have a higher cognitive reserve contributing to a

better performance in different cognitive functions (Magdaleno Herrero et al., 2021).

In particular, the FEP cluster "Improved low IQ" allows us to make substantial interpretations. First, they showed more unfavourable premorbid characteristics than other patients during childhood and early adolescence, which suggest neurodevelopmental disruption (Dickinson et al., 2020). Second, their cognitive trajectory was associated with more severe negative symptomatology at 10-year follow-up, replicating previous findings (Leeson et al., 2011). Based on a family approach, Zhang et al. (2018) confirmed the same relationship in first-degree relatives of individuals with schizophrenia, proposing that negative symptoms together with cognitive impairment could indicate a higher genetic risk burden for the disorder. This body of evidence supports the notion of the psychosis spectrum as a continuum over limited diagnostic categories, with patients cognitively impaired and substantial negative symptoms at one end, and patients with high premorbid IQ, better global functioning, and greater insight at the other (Černis et al., 2015).

In this study, no evidence of cognitive decline at 10 years was observed in FEP patients or HC, which is consistent with a recent finding from our group on general cognitive stability across the entire group of patients and healthy subjects (Rodríguez-Sánchez et al., 2020). This result agrees with a systematic review comprised of 26 studies (Bozikas and Andreou, 2011) that described cognitive stability after a FEP and indicated that the cognitive impairment preceded the psychosis onset. Interestingly, our findings suggest that FEP patients cognitively stable (the three clusters of preserved IQ) improved to a lesser degree than HC. This result corresponds with Jepsen et al. (2010), who described a diminished capacity of FEP patients to acquire intellectual information, probably due to a neurodevelopmental alteration. Patients in the "Preserved high IQ" cluster diminished their 10-year IQ, but their intellectual trajectory could be considered stable because the decrease was minimal. Members of this cluster evidenced protective variables including high premorbid IQ, older age at onset, more years of education, and better premorbid social adjustment, all related to a cognitive reserve that allows coping better with brain pathology (Amoretti et al., 2016; Leeson et al., 2011). In addition, FEP patients with average and high IQ were more frequently women, which replicates previous results of our group (Ayesa-Arriola et al., 2018; Rodríguez-Sánchez et al., 2020) and others reporting better cognitive functioning among female patients, and a better course a few years after commencing the treatment of psychosis (Seeman, 2019). In fact, a recent work by our group showed that a higher educational attainment was more frequent among female patients, which was associated with better long-term outcomes (Ayesa-Arriola et al., 2021). Other advantageous situations more frequently found in women than in men with a FEP are older age at onset, lower rates of cannabis use (Ochoa et al., 2012), having employment, marrying, and having children (Ayesa-Arriola et al., 2020; Seeman, 2019), as well as better coping strategies (Li et al., 2014).

Our evidence on cognitive improvement and stability among FEP patients contradicts several findings that reported an IQ decline (Fett et al., 2020; Fujino et al., 2017; Ohi et al., 2021; Zanelli et al., 2019). The heterogeneity of results might be due to methodological differences such as the characteristics of the participants. For instance, some studies included patients with affective and non-affective psychosis (Agnew-Blais et al., 2015; Jepsen et al., 2010; Leeson et al., 2011), while others (Dickinson et al., 2020; Heaton et al., 2001; Hoff et al., 2005), like ours, exclusively selected non-affective psychosis patients. Likewise, the inclusion of outpatients with probable better cognitive functioning might cause a loss of data about inpatients with lower functionality (Fett et al., 2020). Furthermore, the follow-up periods of the studies must be considered because they can inform on cognition at different stages of the disease. However, it would not be appropriate to directly compare their results. Therefore, the cognitive profile described a few years post-FEP (Jepsen et al., 2010; Leeson et al., 2011) could change over the long term (Fett et al., 2020; Hoff et al., 2005; Zanelli et al., 2019). The evaluation procedure could also explain the variability of the findings, as some authors estimated premorbid and current IQ using different neuropsychological tests in a cross-sectional assessment (Fujino et al., 2017), while others administered the same measure at baseline and follow-up (Jepsen et al., 2010). Finally, the inclusion of HC is relevant due to the need to know the cognitive course in unaffected individuals to properly interpret the results (Albus et al., 2006; Hedman et al., 2013; Hoff et al., 2005; Ohi et al., 2021).

### 4.1. Strengths and limitations

The main strength of this study was the long-term design that allows the evaluation of neuropsychological performance at 10-year follow-up. In addition, having the same longitudinal data from a group of HC was valuable as comparisons between outcomes of patients and healthy individuals. However, some limitations were identified. When performing cluster analysis and subdividing the total sample, some groups included few members, hindering the generalizations of the findings. Another limitation refers to the retrospective estimation of the premorbid IQ. The patients in our sample were assessed after the FEP; hence this estimation could be less precise than prospective measures in subjects at risk before psychosis onset. Regarding the HC sample, subjects were volunteers not randomly chosen from the population, which could represent a recruitment bias. In addition, both for the sample of FEP patients and HC there were dropouts at the 10-year follow-up, and group comparisons (Supplementary material) showed that patients' non-completers had a worse premorbid adjustment and higher rates of cannabis consumption, while HC non-completers had accomplished fewer years of education. Thus, we could have lost information on participants with possible worse cognitive outcomes.

## 5. Conclusions

This study has identified more heterogeneity of intellectual change among FEP patients than in HC at 10-year follow-up, showing stability and different degrees of improvement. Affected individuals with worse premorbid characteristics and low IQ had significant potential for long-term cognitive enhancement, so this subgroup should be a primary target for early drug treatment and cognitive remediation. Our results on the cognitive course of FEP patients suggest a more gradual intellectual rise than healthy people rather than a post-FEP decline. This is consistent with the neurodevelopmental hypothesis of schizophrenia that states that neurocognitive deficits of patients precede the onset of psychosis.

## CRediT authorship contribution statement

NMG and RAA formulated the research question and carried out the design of this study. MMC, JVB and ESS participated in the recruitment and evaluation of the subjects. BCF led the PAFIP cohort and assessed the included patients. VOG participated in data management and analysis. KN and JMH participated in the writing of the article.

## Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.02.025.

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