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**Premorbid Adjustment and IQ in Patients with First Episode Psychosis: a multisite Case-Control Study of their Relationship with Cannabis Use.**

**Running Title**

Premorbid Adjustment and Cannabis Use in Psychosis

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## Abstract

Psychotic patients with a lifetime history of cannabis use generally show better cognitive functioning than other psychotic patients. Some authors suggest that cannabis-using patients may have been less cognitively impaired and less socially withdrawn in their premorbid life.

Using a dataset comprising 948 patients with first-episode psychosis (FEP) and 1313 population controls across six countries, we examined the extent to which IQ and both early academic (AF) and social adjustment (SF) are related to the lifetime frequency of cannabis use in both patients and controls. We expected a higher IQ and a better premorbid social adjustment in psychotic patients who had ever used cannabis compared to patients without any history of use. We did not expect such differences in controls.

In both patients and controls, IQ was three points higher among occasional-users than in never-users [mean difference ( $M^{\text{diff}}$ )=2.9, 95% C.I.=(1.2, 4.7)]. Both cases and control daily-users had lower AF compared to occasional [ $M^{\text{diff}}$ =-0.3, 95% C.I.=(-0.5; -0.2)] and never-users [ $M^{\text{diff}}$ =-0.4, 95% C.I.=(-0.6; -0.2)]. Finally, patient occasional [ $M^{\text{diff}}$ =0.3, 95% C.I.=(0.1; 0.5)] and daily-users [ $M^{\text{diff}}$ =0.4, 95% C.I.=(0.2; 0.6)] had better SF than their never-using counterparts. This difference was not present in controls ( $F_{\text{group*frequency}}(2, 2\cdot 205)=4.995, p=0.007$ ).

Our findings suggest that the better premorbid social functioning of FEP with a history of cannabis use may have contributed to their likelihood to begin using cannabis, exposing them to its reported risk-increasing effects for Psychotic Disorders.

## 1. Introduction

Cannabis use is well established as a risk factor for psychosis<sup>1-3</sup>. While cannabis is known to have an acute adverse effect on cognition in healthy subjects<sup>4,5</sup>, paradoxically, patients with psychotic disorders who report lifetime cannabis use, but not current use<sup>6</sup>, appear to have better cognitive performance than patients who do not<sup>7-9</sup>.

Many, but not all, people with a diagnosis of psychosis show subtle cognitive and social impairments before the emergence of prodromal symptoms<sup>10-12</sup> and some authors suggest that cannabis-using patients may constitute a phenotypically distinct group, with different neurological, cognitive, clinical and prognostic characteristics<sup>13</sup>. One explanation of the counterintuitive cognitive findings concerning cannabis is that those psychotic patients who use cannabis had better premorbid cognitive function than those who have not.

In the GAP (Genetic and Psychotic Disorder) study<sup>14</sup>, we found that first episode psychotic patients (FEP) with a history of cannabis use at any time in their life, had a higher premorbid IQ compared to other FEP patients, a difference not witnessed among controls. We proposed that cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability to the disease<sup>7,14-19</sup>.

It has been suggested that good premorbid social functioning is crucial to develop and sustain an illegal drug habit<sup>20-22</sup>. However, there are few studies on the relationship between cannabis use and neurocognitive functioning in psychosis that controlled for premorbid functioning. One study on 104 FEP<sup>22</sup> reported higher premorbid sociability, but not differences in premorbid IQ, in those with cannabis use before the onset compared to those without any use. Two other studies<sup>23,24</sup> have shown that FEP with a history of cannabis use<sup>23</sup> or cannabis use disorder<sup>24</sup> have a better premorbid social adjustment but poorer premorbid academic adjustment and less educational attainment compared to other patients with no such history. Nonetheless, neither of these two studies had data on IQ.

Longitudinal studies on non-psychotic subjects consistently showed a relationship between higher IQ in childhood and occasional or discontinued cannabis-use (but not to habitual use which was

linked to lower or equal IQ, compared with non-use) probably due to the tendency of those with higher IQ to experiment with drugs<sup>25-31</sup>.

Using data from the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI) study, we set out to examine the association between current IQ, premorbid social and academic adjustment and lifetime frequency of cannabis use in patients with a first episode psychotic disorder (FEP) and a sample of population controls.

We expected a higher IQ and a better social premorbid adjustment in psychotic patients who had ever used cannabis compared to patients without any history of use. We did not expect such differences in controls.

## **2. Methods**

### **2.1. Study Design**

Data were derived from *The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions* (EU-GEI) study (<http://www.eu-gei.eu>)<sup>32,33</sup>. Subjects were identified between 01/05/2010 and 01/04/2015 across centres in five different European countries and Brazil to examine incidence rates of psychotic disorders. We performed an extensive assessment of approximately 1000 FEP patients and 1000 population-based controls during the same period to investigate risk factors for psychosis.

### **2.2. Subjects**

**Patients:** Screening was run by skilled researchers on all potential FEP patients at their first contact with the mental health services and residents in each catchment area, who were aged 18-64 years and received a diagnosis of psychoses (ICD-10: F20-F33)<sup>34</sup> in the study period. We excluded those with psychotic symptoms precipitated by acute intoxication (ICD10: F1X.5), or psychosis due to another medical condition (ICD10: F09), and those who had previously received antipsychotic medication.



Controls: Population-based volunteers aged 18 to 64 years, who had never received treatment for psychosis, representative of each local population, were recruited through a mixture of random and quota sampling (population stratification by age, gender and ethnicity)<sup>33,35</sup>. All the study sites received approval from their local ethical committees. All subjects signed a written consent form and data was stored anonymously<sup>32</sup>.

### 2.3. Measures

We used the modified version of the Medical Research Council (MRC) socio-demographic scale<sup>36</sup>. Diagnoses, first ascertained by clinical interview, were operationalised through the 90-item computerised OPCRIT system for psychosis<sup>37,38</sup>. The Cannabis Experience Questionnaire, further modified for the EUGEI study (CEQ<sub>EU-GEI</sub>)<sup>35</sup>, included a section from Composite International Diagnostic Interview (CIDI) on other substances of abuse, and tobacco use in the last 12 months<sup>39</sup>.

An abbreviated version of the WAIS was used in patients and controls in order to estimate full scale-IQ scores<sup>40</sup>. Given the multi-site design, we could not use a psychometric test to assess premorbid IQ, but only performed an exploratory supplementary analysis on the WAIS subtests, to examine the relation with cannabis use of the “hold” intellectual capacities<sup>41</sup>. To assess premorbid adjustment, we used nine scales from the Premorbid Adjustment Scale (PAS)<sup>42,43</sup> to examine in patients and controls “the degree of achievement of developmental goals”<sup>44-46</sup>, in two distinct developmental age-periods: childhood to age 11 and early adolescence (i.e. 12 to age 16), so that all patients could score the same scales, regardless of their age-of-onset<sup>47,48</sup> (further details on measures are in the Supplementary Material).

### 2.4. Statistical Analysis

In the patient/control comparisons, we used either t-test or ANCOVA and Welch test for continuous variables and the Chi-square tests, for categorical variables, with adjusted ORs and 95% C.I.s for cannabis variables. Confounders were selected if they resulted associated with both

patient/control status and the outcomes. Cannabis and premorbid variables were adjusted for gender, age, ethnicity and country. IQ was further corrected by education.

The frequency of cannabis-use in the lifetime was reduced to three categories by adjusted logistic regression and codified as never use=0; occasional use=1; daily use=2. Daily use was conservatively chosen as the highest category. Never use was separated a priori as the baseline category, for theoretical reasons. Occasional-users were people who used cannabis up to “more than once a week” (Supplementary Material, Supplementary-Table 1).

We calculated a reverse-score and extracted two factors from the Premorbid Adjustment Scale (PAS), namely the Social Factor (SF) and the Academic Factor (AF), obtained by a principal-component analysis (PCA), which explained the 64.4% of the variance (Supplementary Material).

In order to establish differences in SF, AF and IQ (i.e. the outcomes) related to frequency of cannabis use and patient/control group as fixed factors, we performed a MANCOVA which allowed us to take into account the correlation among these dependent variables. In the case of asymmetric distributions of the outcomes, bias-corrected and accelerated (BCa) 95% confidence intervals (C.I.s) were calculated, using 1000 Bootstrap samples<sup>49</sup>. Box’s M was used to test the covariance matrix. Pillai’s trace statistics tested statistical significance. Bonferroni multiplicity correction for multiple comparisons was applied. Interactions were explored in a follow-up ANCOVA for each dependent variable.

One hypothesised mechanism involving cannabis in risk of psychosis implicates dopaminergic dysregulation<sup>50</sup>, similarly to other drugs’, such as stimulants<sup>51</sup> and tobacco<sup>52</sup>. Additionally, current cannabis use<sup>53</sup> is associated with worse cognitive performance, and the effect of nicotine on neurocognition is still controversial in schizophrenia<sup>54,55</sup>. Therefore, to ensure that the results were not biased, we ran sensitivity analyses by eliminating from the sample, alternatively and then simultaneously in any combination, all subjects (i) who used cannabis in the last twelve months (i.e. current cannabis users), (ii) who used tobacco in the last twelve months (i.e. current tobacco users), and (iii) who abused at least one illegal drug, other than cannabis, in their lifetime (i.e. lifetime other

drug-abusers). Figures were obtained by transforming the outcome variables into standardised scores. To account for symptomatology, which could confound results in IQ, we wanted to exploratory correct the primary analysis, by including the patients' group only, for the negative symptoms dimension score extracted from the OPRCIT<sup>56</sup>.

We used an inverse probability weight, calculated on key demographics such as age, gender and ethnicity, to account for controls' under- or oversampling<sup>35</sup> and this weight was applied to all the analyses (Supplementary Material). All statistical analyses were conducted using SPSS 25.

### 3. Results

#### 3.1. Descriptive Characteristics

The sample studied comprised those 2261 subjects (948 patients and 1313 controls) from the original sample who completed at least the CEQ<sub>EU-GEI</sub> and the PAS instrument (Supplementary-Figure 1; Supplementary-Table 2). Patients were more often men [61.9% (587) vs 47.6% (625);  $\chi^2(1)=45.3$ ] and younger than controls [mean age= 30 (10.4) vs 36.1 (13);  $t(2257)=-10.9$ ]. Controls were more likely to be of white ethnicity [77.3% (1015) vs 63.2% (599);  $\chi^2(2)=54.8$ ] and to have achieved a university degree [38.8% (508) vs 16% (151);  $\chi^2(3)=222.7$ ] than patients. Patients were more often unemployed at the time of the interview [73.8% (962) vs 42.4% (394);  $\chi^2(1)=225.2$ ]; they were also more likely to be single [64.1% (605) vs 30.5% (399);  $\chi^2(2)=272.6$ ] or living with their parents [57.5% (539) vs 27.1% (353);  $\chi^2(2)=252.9$ ] (all  $p<0.001$ ) (Supplementary-Table 3).

#### 3.2. Cannabis Use

Patients were almost twice as likely to have used cannabis in their lifetime [OR=1.71 95% C.I.=(1.41; 2.07)], to have chosen high potency cannabis [OR=1.73, 95% C.I.=(1.31; 2.27)] (i.e. total levels of THC $\geq$ 10%) and to currently use cannabis [OR=1.61, 95% C.I.=(1.26; 2.06)]; patients were also five times more likely to have used cannabis on a daily basis [OR=5.0, 95% C.I.=(3.75; 6.69)], compared to controls. 77.3% (464) of patients and 84.9% (535) of controls [ $\chi^2(1)=11.5$ ,  $p=0.001$ ]

who had ever used cannabis declared they started smoking cannabis socially, i.e. because their friends were using it. However, patients mostly used cannabis in solitude at the time of the interview compared to controls [OR=3.78, 95% C.I.=(2.69; 5.32)]. Finally, patients were more than three times more likely to be current tobacco-users (OR=3.47, 95% C.I.=[2.88; 4.19]) and to have abused other drugs in their lifetime (OR=3.43, 95% C.I.=[2.35; 4.99]) (Supplementary-Table 4).

### 3.3. Clinical Characteristics

Compared to controls, patients had lower IQ [mean difference ( $M^{\text{diff}}$ )=-17.3, 95% C.I.=(-18.6; -15.40)], lower SF [ $M^{\text{diff}}$  -0.4, 95% C.I.=(-0.5; -0.3)], and AF scores [ $M^{\text{diff}}$ =-0.5, 95% C.I.=(-0.6; -0.4)] (Table 1).

The outcomes (SF, AF and IQ) were weakly skewed (SF=-0.68; AF=-0.97; IQ=0.13). SF and AF were related to IQ (Spearman's Rho: IQ\*AF=0.439,  $p<0.001$ ; IQ\*SF=0.049,  $p<0.026$ ).

### 3.4. IQ and Premorbid Adjustment by Frequency of Cannabis Use in Patients and Controls

There was a significant effect of patient/control status [Pillai=0.15,  $F(1, 2\cdot040)=122.8$ ;  $p<0.001$ ], frequency of cannabis use [Pillai=0.03  $F(2, 2\cdot040)=13.6$ ,  $p<0.001$ ], country [Pillai=0.16,  $F(5, 2\cdot040)=23$ ,  $p<0.001$ ], gender [Pillai=0.04,  $F(1, 2\cdot040)=30.8$ ,  $p<0.001$ ], age [Pillai=0.008,  $F(1, 2\cdot040)=5.5$ ,  $p=0.001$ ], and ethnicity [Pillai=0.11;  $F(2, 2\cdot040)=42.8$ ,  $p<0.001$ ] on IQ, SF and AF scores (Table 2). The association between the three outcomes and frequency of cannabis use was different in patients and controls [Pillai $^{\text{group*frequency}}$ =0.006,  $F(2, 2\cdot040)=2.17$ ,  $p=0.042$ ]. Follow up analysis revealed that frequency of use had a similar effect on the IQ of patients and controls [ $F^{\text{group*frequency}}$ (2, 2·062)=0.45,  $p=0.635$ ]. Overall, occasional-users had three points higher IQ, compared to never-users [ $M^{\text{diff}}$ =2.9, 95% C.I.=(1.2, 4.7)], but there were no differences between daily-users and both occasional [ $M^{\text{diff}}$ =-2.1, 95% C.I.=(-4.6, 0.3)] and never-users [ $M^{\text{diff}}$ =0.8, 95% C.I.=(-1.7, 3.3)].

On the other hand, patients and controls who were daily cannabis-users were very similar to each other regarding AF [ $M^{\text{diff}}$ =-0.2, 95% C.I.=(-0.6; 0.003)] and they both had lower scores, as compared

to their respective occasional [ $M^{\text{diff}}=-0.3$ , 95% C.I.=( $-0.5$ ;  $-0.2$ )] and never-using counterparts [ $M^{\text{diff}}=-0.4$ , 95% C.I.=( $-0.6$ ;  $-0.2$ )] [ $F^{\text{group*frequency}}(2, 2\cdot205)=1.22$ ,  $p=0.295$ ].

Regarding SF, we found a significant interaction effect [ $F^{\text{group*frequency}}(2, 2\cdot205)=4.99$ ,  $p=0.007$ ]: SF was better in patients who were occasional [ $M^{\text{diff}}=0.3$ , 95% C.I.=( $0.1$ ;  $0.5$ )] or daily-users [ $M^{\text{diff}}=0.4$ , 95% C.I.=( $0.2$ ;  $0.6$ )], compared to never-user patients, while there was no effect of cannabis use on SF in controls (Table 2, Figure 1).

The results concerning the patient group stayed consistent once corrected for negative symptoms (Pillai<sup>frequency</sup>=0.052,  $F(6, 1\cdot542)=6.84$ ,  $p<0.001$ ) (Supplementary-Table 5).

### 3.5 Sensitivity-analysis

We identified (i) 209 FEP and 146 controls who were current cannabis-users; (ii) 515 FEP and 311 controls who were current tobacco-users; (iii) 120 FEP and 37 controls who were lifetime other drug-abusers (Supplementary-Table 2). When these subjects were removed, in any combination, the results were consistent with the primary analysis. The most interesting result was revealed when all previous categories were simultaneously removed. This final sample comprised 382 patients and 921 controls. We found a significant interaction effect on IQ [ $F^{\text{group*frequency}}(2, 1\cdot208)=4.42$ ,  $p=0.012$ ]. Patients who were occasional-users (N=97; mean IQ=87.6, SE=1.8) had eight points higher IQ [ $M^{\text{diff}}=8.3$ , 95% C.I.=( $4.2$ ;  $12.7$ )] than never-user patients (N=249; mean IQ=79.3, SE=1.1), while in controls we only found a three points difference [ $M^{\text{diff}}=2.8$ , 95% C.I.=( $0.07$ ;  $5.6$ )] between occasional (N=302, mean IQ=98.7, SD=1.1) and never-users (N=584; mean= 95.8, SE=0.8).

In line with the original analysis, AF was similarly related to cannabis use in patients and in controls [ $F^{\text{group*frequency}}(2, 1\cdot272)=0.93$ ,  $p=0.392$ ]. Both patients and control daily-users had lower scores than never- [ $M^{\text{diff}}=-0.5$ , 95% C.I.=( $-0.8$ ;  $-0.2$ )] and occasional-users [ $M^{\text{diff}}=-0.5$ , 95% C.I.=( $-0.8$ ;  $-0.1$ )], but difference with occasional-users was more significant for controls (Table 3).

Regarding SF, we replicated the interaction effect of frequency of cannabis use in patients, but not in controls [ $F^{\text{group*frequency}}(2, 1\cdot272)=6.75$ ,  $p=0.001$ ]: patients who were occasional [ $M^{\text{diff}}=0.2$ , 95%

C.I.=(0.006; 0.5)] or daily-users [ $M^{\text{diff}}=0.7$ , 95% C.I.=(0.3; 1.1)] had higher scores than never-user patients, and daily-users scored better than occasional-users [ $M^{\text{diff}}=0.4$ , 95% C.I.=(0.05; 0.8)]. Furthermore, patients who were daily-users had 1) similar IQ ( $M^{\text{diff}}=-5.5$ , 95% C.I.=[-17.1, 4.2]) and AF ( $M^{\text{diff}}=-0.07$ , 95% C.I.=[-0.6; 0.4]) compared to daily-user controls; and 2) they had very similar or even better mean scores of SF (mean=0.2, 95% C.I.=[-0.1; 0.5]) than control daily- (mean=0.3, 95% C.I.=[0.03; 0.5]), occasional (mean=0.2, 95% C.I.=[0.1; 0.3]), and never-users (mean=0.1, 95% C.I.=[0.07; 0.2]) (Table 3, Figure 2).

## 4. Discussion

### 4.1 Summary of main results

Our first main finding indicated higher IQ in the cannabis occasional-using subgroup of patients compared with their never-user counterparts, and a similar effect in controls. Early academic adjustment (AF) was lower when the frequency of cannabis use increased in both patients and controls. Finally, patients with a history of occasional or daily cannabis use had been less socially withdrawn (i.e. had higher SF scores) compared to those psychotic patients who never used cannabis, a difference that was not seen within controls.

### 4.2 Comparison with previous literature

All differences between patients and controls, in terms of socio-demographics<sup>57-59</sup>, IQ<sup>60-62</sup> and premorbid conditions<sup>63,64</sup> were expected as the control group was selected to be representative of the general population of each area and not to be matched with the case group. We also confirmed the expected differences between patients and controls in patterns of cannabis use<sup>24,35,65-67</sup>.

Regarding IQ, we confirmed that cannabis-using patients have higher IQ than never-users and showed that this effect is attributable to occasional cannabis-users, who represent the biggest

proportion of users<sup>68</sup>. In contrast to previous research with a similar design<sup>69</sup>, our results remained consistent after controlling for several confounders and the sensitivity analysis revealed an IQ more than eight points higher in occasional-using patients than in never-users, a much greater effect than the three-points difference detected among controls (see also<sup>70,71</sup>). To date, this is the first study that a) included a control group in exploring this effect and b) found a higher IQ in cannabis occasional-using population controls. These findings differ from the Dunedin study, which identified an IQ decline in cannabis-users but this latter was over several decades of adult life<sup>72</sup>. Nevertheless, in the Dunedin study, those who reported lifetime use of cannabis, but not dependence, were cognitively spared, while in currently dependent people cognition declined<sup>72</sup>. The descriptive differences we found between daily- and occasional-user controls indicate a higher academic achievement and a later contact with the substance in the latter, which could have prevented them from dependence and related academic failure, thus influencing future IQ. However, education was not sufficient to account for the differences in IQ according to frequency of cannabis use in our analysis, when it was inserted to adjust comparisons. This is not surprising, as we know that IQ scores are multi-determined and partially hereditary<sup>73</sup>, and therefore probably differently related to premorbid IQ accordingly to patterns of cannabis use, as suggested in longitudinal studies of non-psychotic subjects<sup>25-31</sup>. Additionally, there are recent suggestions that IQ in psychosis is associated with the polygenic risk score (PRS) that indexes cognition in the general population and is partly independent from PRS predisposing to schizophrenia<sup>74</sup>; this could corroborate our finding of a similar relationship of IQ with cannabis use in patients and controls.

Those patients and controls who used cannabis, especially daily-users, had shown lower AF. A recent longitudinal study conducted in the UK on a representative cohort of pupils showed that high childhood academic adjustment at age 11 increased the risk of both occasional and persistent cannabis use in late adolescence (19-20 years)<sup>75</sup>. Our study embraces different countries, and the results are in line with those from other studies with non-psychotic people, which indicated that poor school performance was a common antecedent of cannabis and other substance use, regardless of IQ, with

the odds of dropping out from school increasing with the frequency of use<sup>76-79</sup>. Similar mechanisms are probably implicated in determining AF in patients.

Finally, we found that patients, but not controls who were cannabis users, particularly daily-users had shown better SF than their non-using counterparts. This was even more evident when lifetime abusers of other drugs, current cannabis-users, and current tobacco-users were removed from the model, and daily-users scored similarly or even better than controls in SF scores.

In this sensitivity analysis, the confidence intervals in IQ, SF and AF scores increased in patients who used cannabis occasionally or daily, compared to never-users; this higher variability is present also in control daily users, compared to the other two groups. This may suggest a higher intragroup variability in cognition and premorbid functioning or it could, of course, be due to the small numbers, which can additionally mask the differences between patients and control daily-users, at least regarding the five-point mean-difference in IQ.

The majority of studies that explored premorbid functioning in psychotic patients selected current or recent daily-users and compared them with non-users, revealing worse academic functioning in the former<sup>23,24,53</sup>, conceptually in line with our results on lifetime daily-users. Other studies found no association between premorbid function and drug or cannabis abuse<sup>80-82</sup>, probably because they used total PAS mean scores; therefore, inverse results in social and academic factors, related to cannabis-use, could have nullified each-other. Some authors used a different methodology, focusing on recent cannabis-use, and did not find any relationships with premorbid sociability<sup>83,84</sup>, but better current social cognition in recent cannabis-abusers<sup>83</sup>. This last result was not replicated in a recent study, which looked at lifetime cannabis use in relation to current social cognition. . However, as the authors state, it is possible that subjects with psychosis and cannabis use, had higher levels of premorbid social cognition, responsible for the contact with the substance, which then decreased after the diagnosis<sup>85</sup>.



#### 4.3 What can we speculate about premorbid predisposition to psychosis related to cannabis use?

Cannabis use is probably first self-selected, depending on predisposing factors, such as higher early sociability, and later reinforced, in some patients, in a pattern of abuse; this involves the subject in a less challenging world (e.g. dropping out from school<sup>86-89</sup>), that contributes to lower the future IQ. This latter does not happen in occasional-users whose IQ is more representative of their premorbid cognition<sup>14</sup> (see also exploratory analysis on the WAIS subtest – Supplementary Material).

The early neuropsychological and social deficits (i.e. lower IQ and SF) of non-using patients evoke a more ‘classical’ profile of people at-risk to develop psychosis<sup>90</sup>, in line with the neurodevelopmental hypothesis<sup>10,91,92</sup>. Non-using patients and controls had higher AF before their 16<sup>th</sup> year, compared with cannabis users. While this result is intuitive in controls, it apparently contradicts the expectation of a greater impairment in this group of neurodevelopmentally impaired psychotic individuals. Previous results showed that premorbid academic adjustment in psychosis is impaired and further declines from childhood to late adolescence<sup>93,94</sup>. These studies reported the most significant deterioration between 16 and 18 years (late adolescence), while our PAS measures stop at age 16 (early adolescence). Interestingly, one of them<sup>93</sup> reported a greater premorbid academic decline in those with less premorbid social impairment, whom they defined “non-deficit” schizophrenic patients, similarly to our results; however, they did not account for cannabis-use.

#### 4.4 Strengths and Limitations

The EU-GEI study has strengths, such as the large sample size and the use of samples from several countries. Even if a prospective cohort study would be able to provide the most robust design for establishing causal connections, such a design is problematic, because psychosis is a rare disorder, with a large time lag between the occurrence of environmental adversities and the onset.

The quota sampling strategy to obtain controls with characteristics of each of the study catchment areas’ population at risk<sup>38</sup> allowed us to have a more representative control sample, as compared to previous studies, and suggests that the prevalence of patterns of cannabis use in our controls represent

those of the local population<sup>35</sup>. Sensitivity supplementary analysis revealed the appropriateness of this strategy for the outcomes measured, because selection bias was unlikely to explain our findings (Supplementary Material).

The higher IQ in occasional cannabis using controls could be identified thanks to the large sample across different countries. People with psychotic disorders might be more likely to recall risk factors<sup>95</sup> and, for example, could recall greater disadvantages in their early life in PAS or to have used drugs in CEQ interview. However, the interviews were completed by at least one corroborative source of information (e.g. family, clinical notes, other clinicians), and the validity of self-report at the PAS has been supported in persons with schizophrenia<sup>96</sup>. Unlike present use, a history of lifetime use of cannabis cannot be assessed by a biological test. Results from our previous study suggest that the accuracy of self-reported data on cannabis use is high<sup>67</sup>.

Finally, family history for psychosis could be associated with the relationship between cognition and cannabis use in patients<sup>97</sup>. However, no substantial difference in PRS for schizophrenia was found in the GAP study between FEP cannabis users and non-users<sup>98</sup>.

#### 4.5 Implications

Those patients who use cannabis daily, and only cannabis, in their lifetime were very similar to daily-using controls regarding IQ, early sociability and academic adjustment. Thus we can speculate that cannabis could have had a role in their psychosis onset, acting as a crucial risk factor<sup>35</sup>.

This evidence, coupled with recent confirmations about the strong link between cannabis daily use and increased risk for psychosis<sup>35</sup>, further supports the need to improve primary prevention in the general population, and suggests that future studies should look at those factors that make the difference between cannabis daily-using subjects that develop psychosis and those who do not.

## 4.6 Conclusions

The study confirms that patients with first-episode psychosis who used cannabis occasionally have higher IQ than never using patients. The findings also demonstrate that both occasional and daily cannabis-using patients have better premorbid sociability than non-using patients and that this difference is not present among controls. Our findings are compatible with the view that the better premorbid social adjustment of cannabis-using patients may have contributed to their early contact with the substance, and that cannabis use increases the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability for psychosis.

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**Figure 1.** Standardised scores (estimated marginal means and standard errors) of IQ, Academic Factor (AF) and Social Factor (SF) by frequency of cannabis use in patients and controls.

**Figure 2.** Sensitivity analysis. Standardised scores (estimated marginal means and standard errors) of IQ, Academic Factor (AF) and Social Factor (SF) by frequency of cannabis use in patients and controls.



