Daily use of high potency cannabis is associated with more positive symptoms in first episode psychosis patients: the EU-GEI case-control study

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Abstract

Background: Daily use of high potency cannabis has been reported to carry a high risk for psychotic disorder. However, the evidence is mixed on whether any pattern of cannabis use is associated with a particular symptomatology in first episode psychosis (FEP) patients.

Method: We analysed data from 901 patients and 1235 controls recruited across six countries, as part of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study. We used item response modelling to estimate two bifactor models, which included general and specific dimensions of psychotic symptoms in patients and psychotic experiences in controls. The associations between these dimensions and cannabis use were evaluated using linear mixed effects models analyses.

Results: In patients, there was a linear relationship between the positive symptom dimension and the extent of lifetime exposure to cannabis, with daily users of high potency cannabis having the highest score (B=0.35; 95%CI 0.14 to 0.56). Moreover, negative symptoms were more common among patients who never used cannabis compared with those with any pattern of use (B=-0.22; 95%CI -0.37 to -0.07). In controls, psychotic experiences were associated with current use of cannabis but not with the extent of lifetime use. Neither patients nor controls presented differences in depressive dimension related to cannabis use.

Conclusions: Our findings provide the first large scale evidence that first episode psychotic patients with a history of daily use of high potency cannabis present with more positive and less negative symptoms than those who never used cannabis or used low potency types.

Keywords

Cannabis use; symptom dimensions; psychopathology; psychotic experiences; cannabis-associated psychosis

Introduction

There is compelling evidence suggesting that cannabis use is associated with psychotic disorders (Marconi *et al.*, 2016). However, it is unclear whether cannabis use is a 'modifier' factor for psychotic disorders, which affects symptom presentation. The existence of a pattern of psychotic symptomatology particularly associated with cannabis has been described in several case series (Walter Bromberg, 1934, Talbott and Teague, 1969, Spencer, 1971, Bernhardson and Gunne, 1972, Chopra and Smith, 1974). Nevertheless, case and cohort studies have found mixed results as to whether (Negrete *et al.*, 1986, Peralta and Cuesta, 1992, Bersani *et al.*, 2002, Green *et al.*, 2004, Grech *et al.*, 2005, Addington and Addington, 2007, Foti *et al.*, 2010, Ringen *et al.*, 2016, Seddon *et al.*, 2016) or not (Thornicroft *et al.*, 1992, Stirling *et al.*, 2005, Dubertret *et al.*, 2006, Boydell *et al.*, 2007, van Dijk *et al.*, 2012, Tosato *et al.*, 2013, Barrowclough *et al.*, 2015) psychotic patients using cannabis present with more positive symptoms than those not using cannabis. Moreover, there is mixed evidence of any relationship between cannabis use and negative symptoms in psychosis. Some reports suggest fewer negative symptoms in psychotic patients that use cannabis (Peralta and Cuesta, 1992, Bersani *et al.*, 2002, Green *et al.*, 2004), which is consistent with having enough social skills to obtain the substance (Murray *et al.*, 2017). However, this association has not been confirmed in other studies (Grech *et al.*, 2005, Seddon *et al.*, 2016) and others even reported a positive association (Ringen *et al.*, 2016).

These inconsistencies might be explained by differences in study design and methods. For example, only a few findings were based on first episode psychosis (FEP) patients (Grech *et al.*, 2005, Addington and Addington, 2007, Tosato *et al.*, 2013, Seddon *et al.*, 2016), which minimize selection and recall bias, and the confounding effect of antipsychotic drugs on symptoms. In addition, a metanalysis of longitudinal studies concluded that most results lacked sufficient power to detect an effect of cannabis on symptoms, or inadequately controlled for potential confounders (Zammit *et al.*, 2008). Furthermore, although a few studies included information on frequency of use, all failed to obtain detailed information on the lifetime pattern of cannabis use, especially on the type and strength of cannabis used. Of note, potent cannabis varieties, with high concentrations of Delta-9-Tetrahydrocannabinol (Δ9-THC), have been associated with the most harm to mental health (Di Forti *et al.*, 2015, Freeman *et al.*, 2018) and, in recent years, these potent types have become more available worldwide (ElSohly *et al.*, 2016, Potter *et al.*, 2018, Freeman *et al.*, 2019). Finally, no studies have used factor analysis of observed symptoms to evaluate to what extent cannabis use is a factor influencing the clinical heterogeneity of psychosis.

On the other hand, in the general population there are consistent findings regarding the association between cannabis use and psychotic experiences (Ragazzi *et al.*, 2018). However, most studies had limited geographical coverage and the examined population was scarcely representative of the population at risk of psychosis (Ragazzi *et al.*, 2018).

In this study, we set out to clarify the association between detailed patterns of cannabis use and transdiagnostic symptom dimensions in a large multinational FEP sample. In addition, we examine the association between detailed patterns of cannabis use and

subclinical symptom dimensions in a large sample of controls representative of the population at risk in each catchment area.

Specifically, we sought to test the hypotheses that: (1) positive psychotic symptoms are more common among FEP patients with more frequent lifetime use of cannabis and greater exposure to use of high potency varieties; (2) positive psychotic experiences are more common in population controls with a recent use of cannabis, who would be more resilient to the long-term effects of cannabis; (3) negative symptoms are more common among those patients who have never used cannabis.

Methods

Study design and participants

This analysis is based on the incidence and case-control study work package of the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI).

FEP individuals were identified between 2010 and 2015 across six countries to examine incidence rates of schizophrenia and other psychotic disorders (Jongsma *et al.*, 2018), and symptomatology at psychosis onset (Quattrone *et al.*, 2019). For examining risk factors, we sought to perform an extensive assessment on approximately 1,000 FEP patients and 1,000 population-based controls during the same time period.

Patients were included in the case-control study if they met the following criteria during the recruitment period: (a) aged between 18 and 64 years; (b) presentation with a clinical diagnosis for an untreated FEP, even if longstanding [International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes F20-F33]; (c) resident within the catchment area. Exclusion criteria were: (a)

previous contact with psychiatric services for psychosis; (b) psychotic symptoms originating from an identified organic condition; and (c) transient psychotic symptoms resulting from acute intoxication (ICD-10: F1x.5).

The recruitment of controls followed a mixture of random and quota sampling methods, in order to achieve the best possible representativeness in age, sex, and ethnicity of the population living in each catchment area. The identification process varied by site and was based on locally available sampling frames, including mostly the use of lists of all postal addresses and general practitioners' lists from randomly selected surgeries. When these resources were not fully available, internet and newspapers advertising were used to fill quotas. Exclusion criteria for controls were: (a) diagnosis of a psychotic disorder; (b) ever having been treated for psychotic symptoms.

We analysed data from eleven catchment areas, including urban and less urban populations (i.e. Southeast London, Cambridgeshire and Peterborough (England); central Amsterdam, Gouda and Voorhout (the Netherlands); Bologna municipality, city of Palermo (Italy); Paris [Val-de-Marne], Puy-de-Dôme (France); Madrid [Vallecas], Barcelona (Spain); and Ribeirão Preto (Brazil). Further information on the case-control sample and the recruitment strategies is included in the supplementary material.

Measures

Data on age, sex, and ethnicity were collected using a modified version of the Medical Research Council Sociodemographic Schedule (Mallett, 1997). The OPerational CRITeria (OPCRIT) system (McGuffin *et al.*, 1991) was used by centrally trained investigators, whose reliability was assessed before and throughout the study (k=0.7), to assess psychopathology in the first four weeks after the onset and generate research-based diagnoses based on different diagnostic classification systems. The Community Assessment of Psychic Experiences (CAPE) (Stefanis *et al.*, 2002) was

administered to controls to self-report their psychotic experiences. The reliability of the CAPE is good for all the languages spoken in the countries forming part of the EU-GEI study (http://cape42.homestead.com).

A modified version of the Cannabis Experience Questionnaire ($CEQ_{EU\text{-}GEI}$) (Di Forti *et al.*, 2009) was used by investigators to collect extensive information on the patterns of use of cannabis and other drugs. We used six measures of cannabis use (Supplementary Table S2), including a variable measuring specific patterns of cannabis exposure by combining the frequency of use with the potency of cannabis. As illustrated in the supplementary material, the cannabis potency variable was based on the data published in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2013, Di Forti *et al.*, 2019).

We selected confounders based on their possible association with cannabis use and/or symptom dimensions. These included: sex; age; ethnicity; use of stimulants, hallucinogens, ketamine, cocaine, crack, and novel psychoactive substances; current use of cigarettes (smoking 10 cigarettes or more per day=1), and current use of alcohol (drinking 10 alcohol units or more per week=1).

Statistical analysis

Dimensions of psychotic symptoms in patients and psychotic experiences in controls

Data from OPCRIT and CAPE were analysed using multidimensional item response modelling in M*plus*, version 7.4 (Muthén and Muthén, 2012), to estimate two bifactor models, based on the associations among observer ratings of psychotic symptoms in patients and self-ratings of psychotic experiences in controls. This methodology is described in full in our EU-GEI paper on symptom dimensions in FEP patients

(Quattrone *et al.*, 2019), and it was likewise applied to psychotic experiences in population controls. Briefly, CAPE items were dichotomized as 0 'absent' or 1 'present'. In order to ensure sufficient covariance coverage for item response modelling, we used items with a valid frequency of 'present' ≥10% in our sample, and we excluded items with low correlation values (<.3) based on the examination of the item correlation matrix. As in the previous analysis in patients, the bifactor solution was compared with other solutions (i.e., unidimensional, multidimensional, and hierarchical models) using Log-Likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC) as model fit statistics. Path diagrams that illustrate these models are presented in Supplementary Figure S1. Reliability and strength indices such as McDonald's omega (ω) (Rodriguez *et al.*, 2016), omega hierarchical (ω_H) (Rodriguez *et al.*, 2016), and index *H* (Hancock and Mueller, 2001), were computed to determine: 1) the proportion of common variance accounted by general and specific symptom dimensions; 2) the proportion of reliable variance accounted by the general dimension not unduly affected by the specific dimensions; 3) the proportion of reliable variance accounted for by each specific dimension not unduly affected by the general and all the other specific dimensions; 4) the overall reliability and replicability of the bifactor construct of psychosis-like experiences. Finally, we generated factor scores for one general psychotic experience dimension and three specific dimensions of positive, negative, and depressive psychotic experiences.

For patients, we used the previously generated factor scores for one general psychosis dimension and five specific dimensions of positive, negative, disorganised, manic, and depressive symptoms (Quattrone *et al.*, 2019).

Symptom dimensions and cannabis use

We evaluated the relationship between psychotic symptom dimensions in patients, or psychotic experience dimensions in controls, and cannabis use using linear mixed effects models in STATA14 (StataCorp, 2015). We specifically modelled symptom dimension scores as a function of each of the six measures of cannabis use. We then evaluated the combined effect of frequency of use and potency of cannabis. To account for the non-independence of symptom profiles of subjects assessed within the same country (for example, due to cultural similarities), and for the potential within-site correlation (for example, due to context factors), we fitted a three-level mixed model, where the random effect encompassed two levels of random intercepts: one due to the countries, and another due to the sites within the countries. Finally, we used the Benjamini-Hochberg (B-H) procedure to reduce the false discovery rate, which we set at 5%.

Results

Sample characteristics

We analysed data from 901 FEP patients and 1,235 controls. The main socio-demographic characteristics and history of substance misuse of patients and controls are presented in Supplementary Table S1. Supplementary Tables S3 and S5 show the sample prevalence of psychotic experiences in controls and of psychotic symptoms in patients.

Bifactor model of psychotic experiences in controls

Supplementary Table S4 shows that, as in our previous analysis of the OPCRIT items (Quattrone *et al.*, 2019), the bifactor model provided the best fit for the CAPE items, as illustrated by AIC, BIC and SABIC substantially lower compared with competing models. This solution explained 60% of the unique variance. In addition, Figure 1

shows that, within the bifactor model, the explained variance was due to individual differences mostly on the general psychotic experience dimension. This is illustrated by the relative omega coefficient, which, for example, showed that 85% of the reliable variance was due to the general dimension when partitioning out the variability in scores due to the specific dimensions. Moreover, factor loadings of moderate to high magnitude were observed for most items on the general psychotic experience dimension, whereas factor loadings of a smaller magnitude were observed for the specific dimensions (Figure 1). Consistently, the index *H*, which is a measure of the construct reliability and replicability across studies (Hancock and Mueller, 2001), was very high for the general dimension (0.92), moderate for positive (0.78) and negative (0.71) dimensions and lower for the depressive dimension (0.41).

Symptom dimensions in patients by pattern of cannabis use

Models' results are presented in Table 1.1 which shows that:

1) There were no differences in the distribution of positive symptoms according to early age at first use (=<15 years old), nor, after B-H correction, according to ever or current use of cannabis. However, positive symptoms were more common among patients who spent more than 20 euros per week on cannabis (B=0.3; 95%CI 0.11 to 0.48; p=0.001).

2) Fewer negative symptoms were observed among those patients who used cannabis at least once compared with those who never tried (B=-0.22; 95%CI -0.37 to -0.07; p=0.004). Early age at first use and current use of cannabis was not associated with negative symptomatology.

3) Manic symptoms were more frequent among patients who had ever used cannabis (B=0.22; 95%CI 0.08 to 0.36; p=0.002).

4) There were no differences in the distribution of the scores on the depressive, disorganization and general psychosis dimensions according to any measure of cannabis use.

Psychotic experience dimensions in population controls by patterns of cannabis use

Models' results are presented in Table 1.2, which shows that:

1) There were no differences in the distribution of positive psychotic experiences according to ever use of cannabis or early age at first use (=<15 years old). However, positive psychotic experiences were more commonly reported by subjects who currently used cannabis (B=0.33; 95%CI 0.15 to 0.51; p<0.001) and who spent more than 20 euros per week on cannabis (B=0.39; 95%CI 0.09 to 0.69; p=0.011).

2) There were no differences in the distribution of the depressive and negative experiences in population controls according to cannabis use.

Symptom dimensions by frequency of use and potency of cannabis

The independent effects of frequency of use and potency of cannabis is reported in Supplementary Tables S6.1 and S6.2, and Supplementary Figure S2, showing that, only in patients, positive symptoms were more common in those who used cannabis on a daily basis and exposed to high potency varieties

Testing the combined 'type-frequency' variable in patients, we found evidence of a linear relationship between the positive symptom dimension and the extent of exposure to cannabis, with daily users of high potency cannabis showing the highest score (B=0.35; 95%CI 0.14 to 0.56; p=0.001). Therefore, we introduced a contrast operator and plotted the exposure-response relationship for positive symptoms

(Figure 2), by comparing the predictive margins of the adjusted mean of each group against the grand adjusted mean of all groups. Figure 2 shows that the adjusted mean for daily users of high potency cannabis was 0.2 units greater than the grand adjusted mean. Moreover, the adjusted means for the groups who never or rarely used cannabis were respectively 0.16 or 0.18 units lower than the grand adjusted mean.

A negative relationship between the negative symptom dimension score and patterns of cannabis use was also observed in patients. Figure 3 shows that patients with psychosis who never used cannabis had more negative symptoms either compared with the grand adjusted mean or with any pattern of cannabis use.

Discussion

Principal findings

This is the first multinational study analysing data on the potency of the cannabis used by FEP patients to investigate a dose effect relationship between cannabis use and dimensions of symptoms, and also its effect on dimensions of psychotic experiences in population controls. We provide the first evidence that: 1) in patients, a positive correlation exists between the extent of premorbid cannabis use and the score on the positive symptom dimension, with daily users of high potency cannabis showing the most positive symptoms at FEP; 2) psychotic experiences in non-clinical populations are associated with current use of cannabis but are independent of the extent of lifetime exposure to cannabis; 3) negative symptoms at FEP are more common in patients who have never tried cannabis; 4) depressive symptoms are independent of any pattern of use of cannabis.

Limitations

Our findings must be considered in the context of two main limitations. First, individual data on patterns of cannabis use are not validated with biological samples. However,

biological tests are not considered the gold standard method for such a validation (Large *et al.*, 2012) and would not allow one to ascertain the extent of cannabis use over the years (Taylor *et al.*, 2017). Moreover, studies combining self-report and laboratory data support the reliability of subjects in reporting the type of cannabis they use (Wolford *et al.*, 1999, Freeman *et al.*, 2014). Second, we did not take into account the cannabidiol (CBD) contribution to the potency variable, as official data on its content in the different cannabis varieties were not available in most study sites; CBD might counterbalance Δ9-THC effects and minimise both psychotic experiences (Schubart *et al.*, 2011) and symptoms (McGuire *et al.*, 2018).

Comparison with previous research

We extend previous research on cannabis and psychotic symptoms to a multinational sample confirming the association between cannabis use and positive symptoms of FEP (Ringen *et al.*, 2016, Seddon *et al.*, 2016). Our results are in line with Schoeler et al. (2016), who carefully scrutinised the literature on the effect of continuation of cannabis use after FEP, concluding that this would be associated with a more severe positive symptomatology (Schoeler *et al.*, 2016). That said, any comparison with previous research is limited by the lack of information on frequency and potency in all the previous studies along with subjects' exposure to more potent varieties of cannabis in recent years (Potter *et al.*, 2018). In this respect, we firstly provide some evidence that cannabis affects positive symptoms in a dose response manner, further supporting the converging epidemiological and experimental evidence that the use of cannabis with high content of Δ9-THC has a more detrimental effect than other varieties (Di Forti *et al.*, 2009, Morrison *et al.*, 2009, Freeman *et al.*, 2018).

We also report evidence in a multinational FEP sample of an association between lifetime cannabis use and fewer negative symptoms, the latter often considered as a

marker of greater neurodevelopmental impairment in psychotic subjects. Two opposite interpretations should be discussed.

First, some authors have suggested that people with a psychotic disorder might use cannabis as an attempt to self-medicate negative symptoms, and thus the observed reduction in negative symptomatology would be an epiphenomenon due to the cannabis intake itself (Peralta and Cuesta, 1992).

Second, psychotic disorders may be characterized by less neurodevelopmental features when associated with cannabis use (Ruiz-Veguilla *et al.*, 2012, Ferraro *et al.*, 2013, Murray *et al.*, 2017, Ferraro *et al.*, 2019), hence FEP patients who do not initiate to use cannabis would have more negative symptoms.

The lack of a dose dependency in our study appears to speak against the first and in favour of the second possibility, as the difference holds between those who never obtained cannabis and those who may have used it only once. Moreover, negative symptoms would reduce the social and instrumental skills that were necessary to obtain illegally cannabis and sustain its use in all the countries included in the study, except Holland.

Last, we report that the cumulative exposure to cannabis does not impact on psychotic experiences in controls. One could of course argue that the largest proportion of subjects with the harmful pattern of cannabis use were patients. However, further research is needed to look into plausible mechanisms of resilience to the psychotogenic effect of cannabis as observed in our controls, who report psychotic experiences if current users but do not seem to accumulate a risk over life time cannabis use and develop psychotic disorders. Indeed, future studies should aim to: 1) investigate if and how genetic factors, plausibly regulating the endocannabinoid and dopamine systems, pose a small subset of cannabis users at high risk of developing

a psychotic disorders with particular symptomatology; 2) clarify over the course of the disorder whether or not differences in symptomatology between current and former cannabis users may be related to residual cannabis effects.

Implications

The novelty of our study is based on our examination of data on lifetime frequency of cannabis use and on the type of the cannabis used; high potency types are increasing worldwide. For instance, a recent potency study revealed that in London, the high potency type of cannabis called skunk has now taken up 96% of the street market (Potter *et al.*, 2018). The EMCDDA has described a European cannabis market characterised by potent varieties (European Monitoring Centre for Drugs and Drug Addiction, 2013) like those present in Amsterdam coffee shops that can reach up to 39% of THC. Indeed, as daily use, and use of high potency cannabis, have been associated both with greatest risk to develop psychotic disorders and to high rates of psychotic disorders across Europe (Di Forti *et al.*, 2019), here we show that in FEP patients daily use of high potency cannabis drives a high score on the positive symptom dimension. Further research should aim to determine biological mechanisms underlying how cannabis impacts on different clinical manifestations of psychosis. Meanwhile, translating current findings into clinical practice, symptom dimension scores can be used to stratify patients and develop secondary prevention schemes for cannabis-associated psychosis.

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Conflicts of interest

None.

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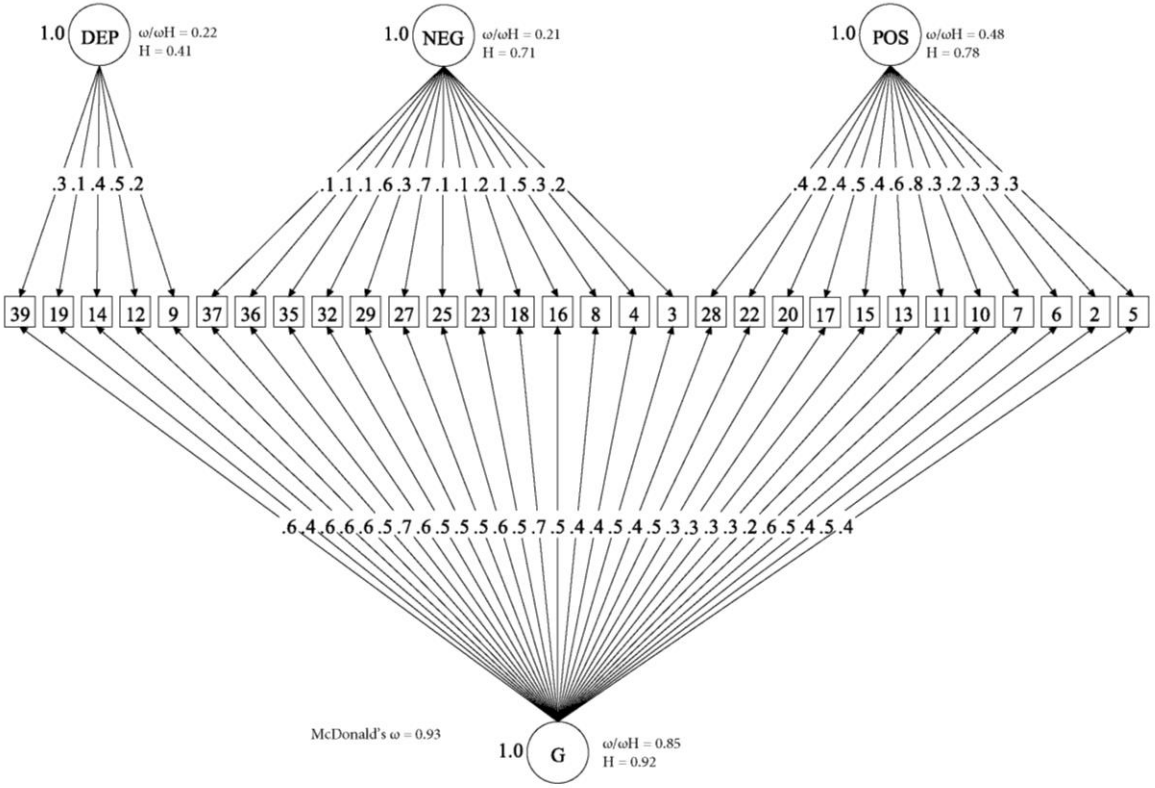
Figure 1. Bifactor model of psychotic experiences in controls



(☐) Observed variables (No. of CAPE items); (○) Unobserved variables (latent factors); (→) standardized item loading estimation onto latent factors; G, general psychosis-like factor; Specific psychotic experiences factors: DEP, Depression; NEG, Negative; POS, Positive. Reliability and strenght estimates: H=construct reliability index; ω= McDonald omega; ω_H=hierarchical omega; ω/ω_H= Relative omega.

Explanatory note: McDonald's ω is an estimate of the proportion of the common variance accounted by general and specific symptom dimensions.(Rodriguez *et al.*, 2016). Relative omega (ω/ω_h) is the amount of reliable variance explained in the observed scores attributable to a) the general factor independently from the specific symptom dimensions, and 2) each specific symptom dimension independently from the general factor.

H is an index of the quality of the measurement model based on the set of CAPE items for each dimension.(Hancock and Mueller, 2001) Indices can range from 0 to 1, with values closer to 1 indicating a better construct reliability and replicability across studies.

Figure 2. Positive symptom dimension in cases by patterns of cannabis use.

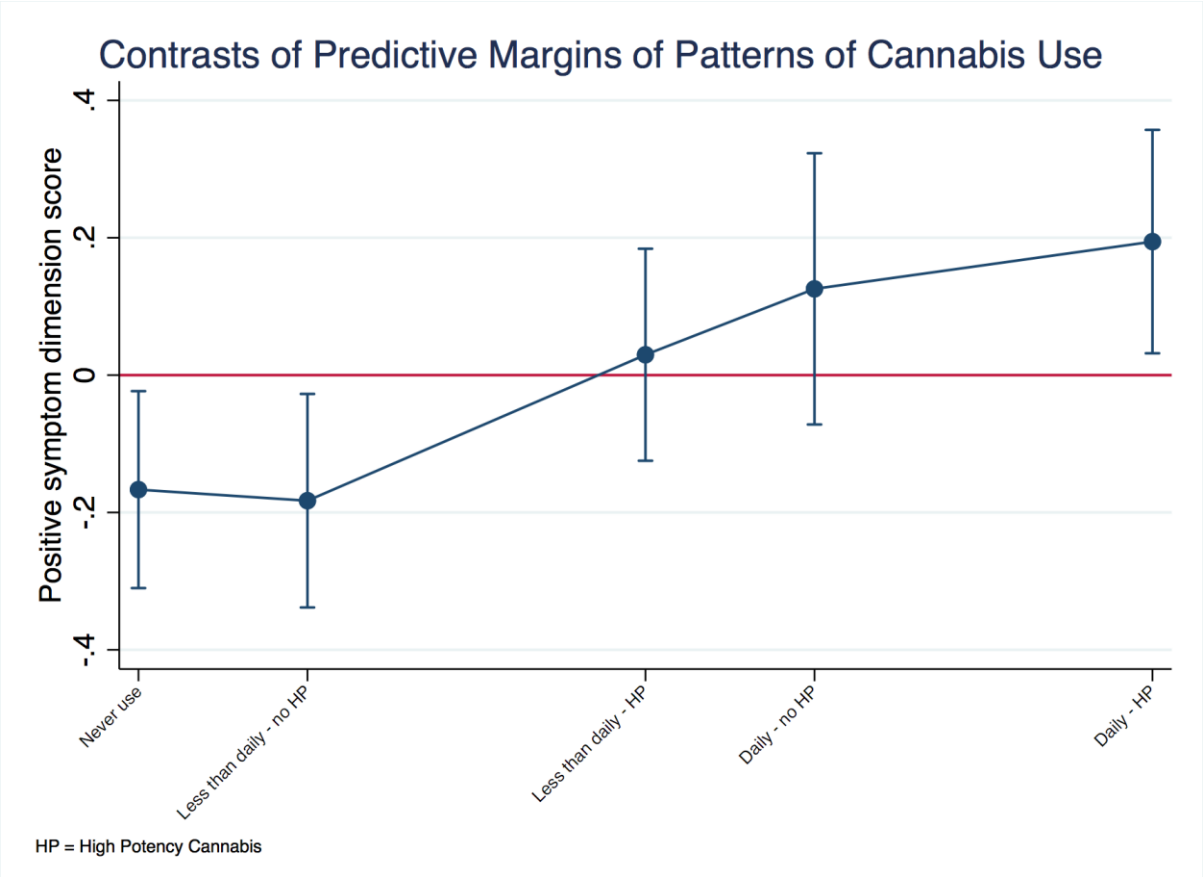


Figure 2 shows the contrasts of the positive symptom dimension predicted mean of each group of patterns of use of cannabis against the predicted grand mean of all groups (represented by the red line). The positive value for the contrast of the daily use of high potency cannabis indicates more positive symptomatology in this group. On the other hand, negative values for the contrasts of the first two groups indicates less positive symptomatology when there is less exposure to cannabis. These differences are statistically significant, as indicated by 95% confidence intervals that do not overlap with zero. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect. Values were adjusted for age, sex, ethnicity, diagnosis, and use of other recreational/illicit substances.

Figure 3. Negative symptom dimension in cases by patterns of cannabis use.

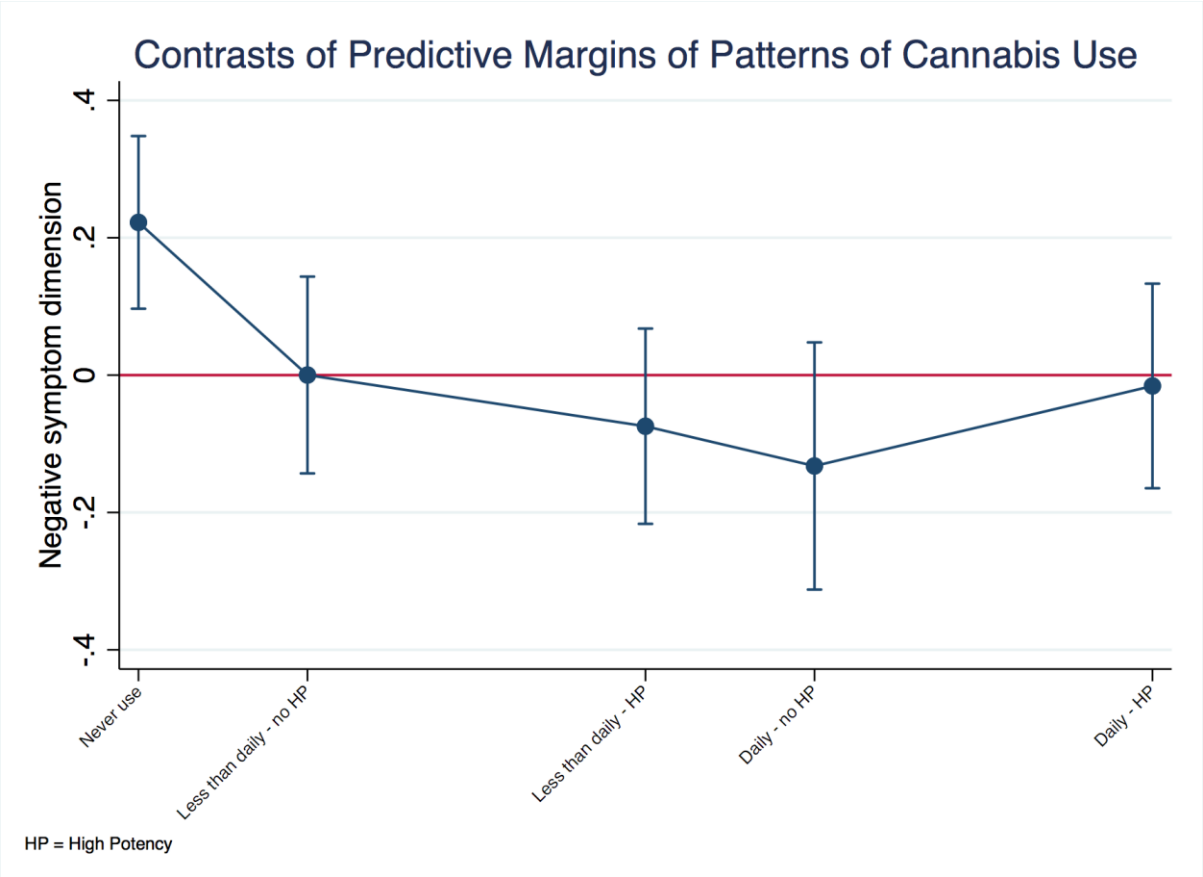
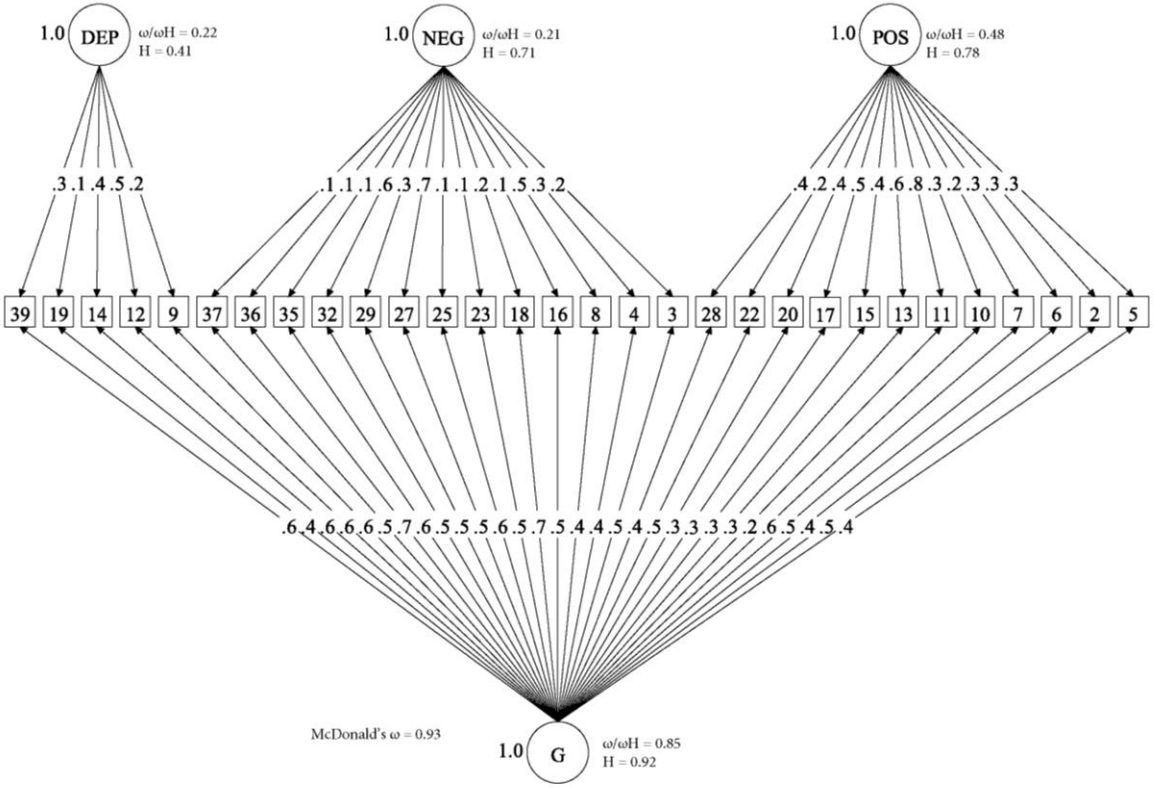


Figure 3 shows the contrasts of the negative symptom dimension predicted mean of each group of patterns of use of cannabis against the grand adjusted predicted mean (represented by the red line). Subjects who had never used cannabis presented with more negative symptoms compared to the whole sample. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect.

Figure 1. Bifactor model of psychotic experiences in controls



(☐) Observed variables (No. of CAPE items); (○) Unobserved variables (latent factors); (→) standardized item loading estimation onto latent factors; G, general psychosis-like factor; Specific psychotic experiences factors: DEP, Depression; NEG, Negative; POS, Positive. Reliability and strenght estimates: H=construct reliability index; ω= McDonald omega; ω_H=hierarchical omega; ω/ω_H= Relative omega.

Explanatory note: McDonald's ω is an estimate of the proportion of the common variance accounted by general and specific symptom dimensions.(Rodriguez *et al.*, 2016). Relative omega (ω/ω_h) is the amount of reliable variance explained in the observed scores attributable to a) the general factor independently from the specific symptom dimensions, and 2) each specific symptom dimension independently from the general factor.

H is an index of the quality of the measurement model based on the set of CAPE items for each dimension.(Hancock and Mueller, 2001) Indices can range from 0 to 1, with values closer to 1 indicating a better construct reliability and replicability across studies.

Figure 2. Positive symptom dimension in cases by patterns of cannabis use.

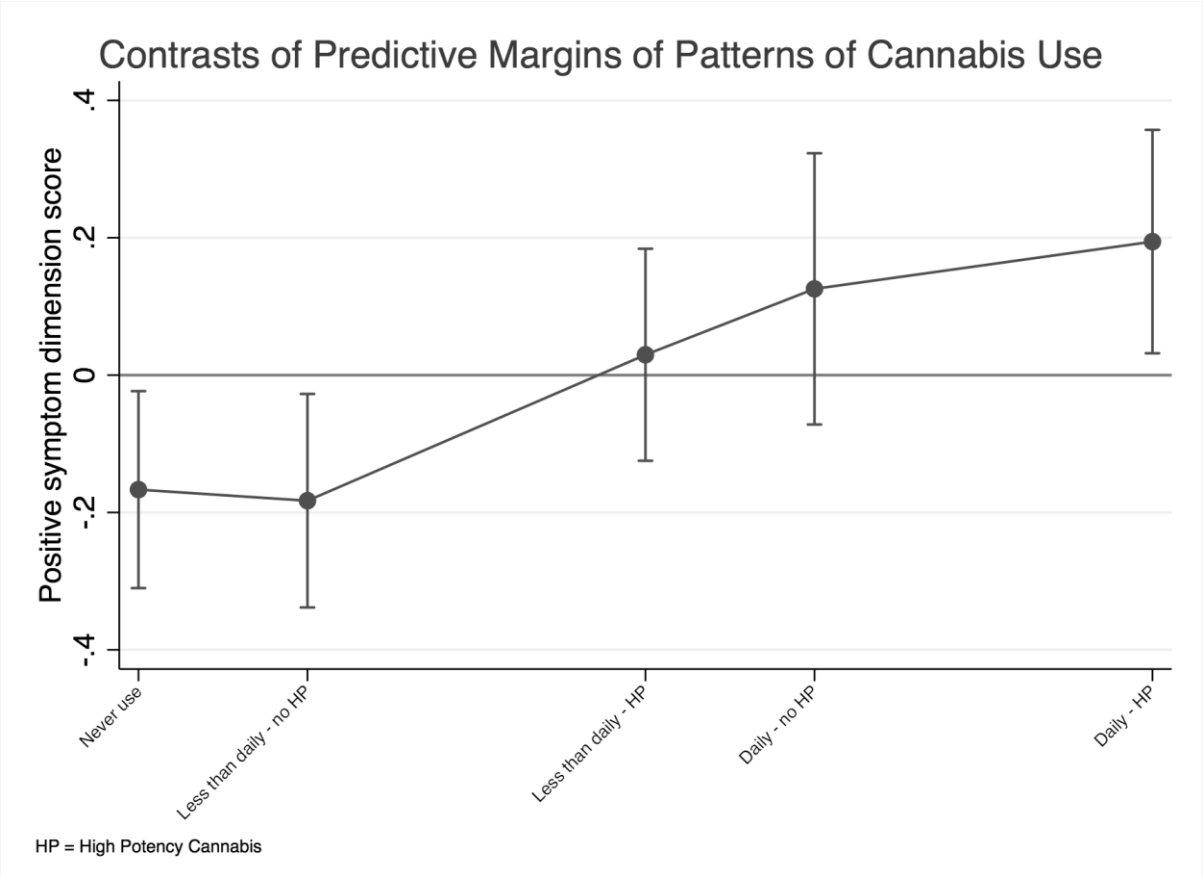


Figure 2 shows the contrasts of the positive symptom dimension predicted mean of each group of patterns of use of cannabis against the predicted grand mean of all groups (represented by the red line). The positive value for the contrast of the daily use of high potency cannabis indicates more positive symptomatology in this group. On the other hand, negative values for the contrasts of the first two groups indicates less positive symptomatology when there is less exposure to cannabis. These differences are statistically significant, as indicated by 95% confidence intervals that do not overlap with zero. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect. Values were adjusted for age, sex, ethnicity, diagnosis, and use of other recreational/illicit substances.

Figure 3. Negative symptom dimension in cases by patterns of cannabis use.

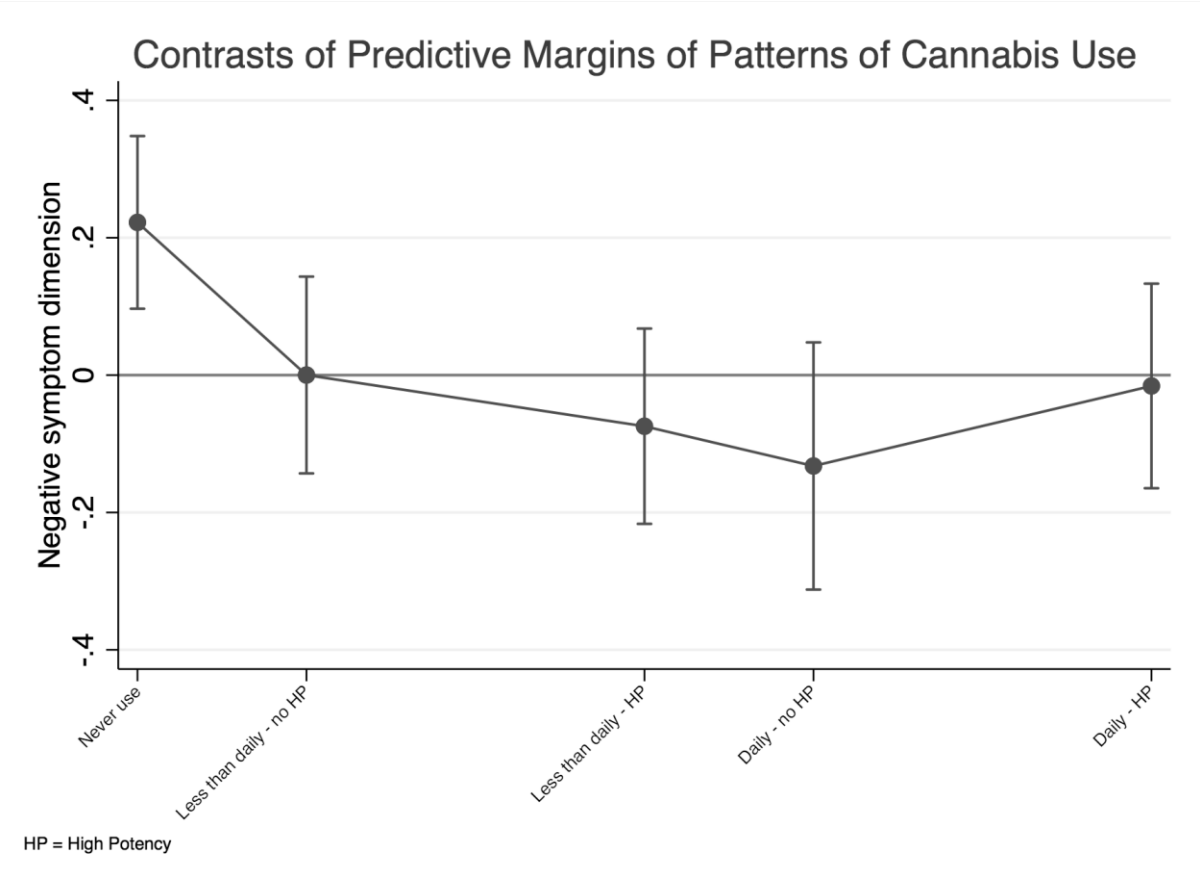


Figure 3 shows the contrasts of the negative symptom dimension predicted mean of each group of patterns of use of cannabis against the grand adjusted predicted mean (represented by the red line). Subjects who had never used cannabis presented with more negative symptoms compared to the whole sample. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect.

Table 1.1 Symptom dimensions in FEP patients by measures of cannabis use[a]

Symptom dimension	Ever used cannabis B (95% CI)	Current use of cannabis B (95% CI)	Age at first use of cannabis B (95% CI)	Money used for cannabis B (95% CI)
Positive	0.16* (0 to 0.31)	0.21* (0.04 to 0.37)	0.05 (-0.13 to 0.22)	**0.3**** (0.11 to 0.48)
Negative	**-0.22**** (-0.37 to -0.07)	-0.09 (-0.26 to 0.07)	0.07 (-0.09 to 0.22)	0.07 (-0.12 to 0.25)
Depressive	-0.08 (-0.24 to 0.08)	-0.08 (-0.22 to 0.06)	-0.09 (-0.23 to 0.05)	-0.11 (-0.29 to 0.06)
Disorganization	-0.01 (-0.24 to 0.03)	0.01 (-0.05 to 0.26)	0.11 (-0.06 to 0.28)	0.1 (-0.17 to 0.19)
Manic	**0.22**** (0.08 to 0.36)	0.12 (-0.02 to 0.27)	-0.09 (-0.25 to 0.07)	0.05 (-0.11 to 0.22)
General factor	0.05 (-0.06 to 0.17)	0.02 (-0.1 to 0.14)	-0.06 (-0.09 to 0.22)	0.03 (-0.11 to 0.17)

[a]All models were adjusted for age, sex, ethnicity, use of other recreational/illicit substances, and diagnosis. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * p < 0.05, ** p < 0.01, *** p < 0.001; associations that survived after Benjamini-Hochberg correction are showed in bold.

Table 1.2 Psychotic experience dimensions in controls by cannabis use[a]

Psychotic experience dimension	Ever used cannabis B (95% CI)	Current use of cannabis B (95% CI)	Age at first use of cannabis B (95% CI)	Money used for cannabis B (95% CI)
Positive	0.05 (-0.06 to 0.17)	**0.33***** (0.15 to 0.51)	0.08 (-0.11 to 0.25)	**0.39*** (0.09 to 0.69)
Negative	0.11 (-0.01 to 0.24)	0.16 (-0.03 to 0.36)	-0.11 (-0.29 to 0.07)	-0.12 (-0.2 to 0.44)
Depressive	0.09 (-0.03 to 0.21)	0.01 (-0.19 to 0.20)	-0.02 (-0.21 to 0.16)	-0.02 (-0.3 to 0.35)
General factor	0.04 (-0.08 to 0.17)	0.13 (-0.07 to 0.33)	0.08 (-0.11 to 0.22)	0.15 (-0.18 to 0.48)

[a]All models were adjusted for age, sex, ethnicity, and use of other recreational/illicit substances. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * p < 0.05, ** p < 0.01, *** p < 0.001; associations that survived after Benjamini-Hochberg correction are showed in bold.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Socio-demographic characteristics and history of substance misuse of the analysed sample

	FEP N=901	**Controls N=1235**
Age (mean; SD)	30.8 (10.5)	36.1 (13.3)
Sex (male %; N)	61.9 (558)	47 (581)
Self-reported Ethnicity		
White (%; N)	59.05 (532)	75.22 (929)
Black	18.65 (168)	9.55 (118)
Mixed	11.54 (104)	9.15 (113)
Asian	3.55 (32)	2.67 (33)
North African	4.66 (42)	1.86 (23)
Others	2.55 (23)	1.54 (19)
Ever used cannabis		
Yes (%;N)	64.93 (585)	46.48 (574)
Missing	1.44 (13)	1.05 (13)
Current use of cannabis		
Yes (%;N)	21.64 (195)	10.61 (131)
Missing	1.78 (16)	1.05 (13)
Age at first use of cannabis		
Never Used (%; N)	33.63 (303)	52.47 (648)
<=15 year old	27.75 (250)	13.52 (167)
16 year old and older	35.74 (322)	32.96 (407)
Missing	2.89 (26)	1.05 (13)
Money used for cannabis (weekly)		
From 0 to 20 euro	76.47 (689)	92.3 (1,140)
More than 20 euro	16.1 (145)	3.16 (39)
Missing	7.44 (67)	4.53 (56)
Lifetime frequency of use		
Never use	56.83 (512)	52.47 (648)
Less than daily	11.54 (104)	39.68 (490)
Daily	28.86 (260)	6.72 (83)
Missing	2.77 (25)	1.13 (14)
Type of cannabis		
Never used	33.63 (303)	55.57 (648)
Less than 10% THC	26.64 (240)	23.89 (295)
More than 10% THC	32.63 (294)	18.06 (223)
Missing	7.1 (64)	5.59 (69)
Current tobacco use		

>10 cigarettes x day (%;N)	28.71 (262)	10.85 (134)
Missing	3.77 (34)	1.94 (24)
Current use of other drugs		
Stimulants (%;N) Missing	8.62 (82) 1.6 (15)	4.53 (56) 1.05 (13)
Hallucinogens Missing	5.23 (49) 1.92 (18)	2.02 (25) 1.21 (15)
Ketamine Missing	2.13 (20) 1.92 (18)	1.05 (13) 1.21(15)
Novel Psychoactive Substances Missing	1.39 (13) 1.71 (16)	0.65 (8) 1.05 (13)
Crack Missing	2.67 (25) 1.6 (15)	2 (0.16) 1.05 (13)
Cocaine Missing	14.94 (140) 1.81 (17)	5.83 (72) 1.13 (14)
Current alcohol overuse		
Drinks =>10 units per week (%;N) Missing	10.88 (98) 11.4(103)	12.47 (154) 3.24(40)
Diagnosis		
Schizophrenia (%;N)	13.2 (282)	
Schizoaffective disorders	17.84 (381)	
Bipolar Disorders	2.48 (53)	
Psychotic Depression	1.92 (41)	
Unspecified Psychosis	6.74 (144)	

Supplementary table S2. Cannabis measures in the EU-GEI study

Lifetime cannabis use	0=*never used*	1=*Yes*	
Currently using cannabis	0=*no use at the time of recruitment in the study and over the previous 4 weeks*	1=Yes	
Age at first use of cannabis	0=*started at age 16 years or older*	*1=started at age 15 years or younger*	
Lifetime frequency of use	*0=never used*	*1=used less than daily*	*2=used daily*
Money spent weekly on cannabis	*0=never used or spent 20 EURO or less per week*	*1= spent more than 20 EURO per week*	
Type of cannabis used[1]	*0= never used*	*1= types with THC<10%*	*2= types with THC=>10%*

[1]Explanatory note: The potency variable was defined by a cut off of 10% of the THC concentration expected in the different varieties of cannabis in each catchment area, based on government and national data examined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2013, Di Forti et al., 2019).

Cannabis varieties classified as low-potency (THC<10%) were: hash/resin from UK and Italy, imported herbal cannabis from UK, Italy, Spain and France, Brazilian marijuana and hash and the Dutch Geimporteerde Wiet.

Cannabis varieties classified as high-potency (THC>10%) were: UK home-grown skunk/sensimilla UK Super Skunk, Italian home-grown skunk/sensimilla, Italian Super Skunk, the Dutch Nederwiet,

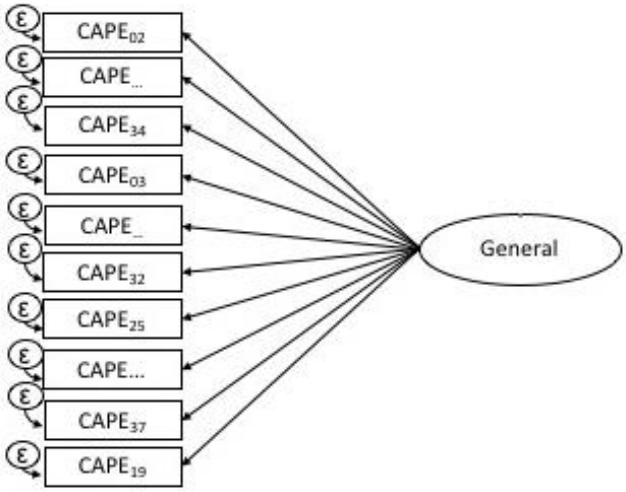
Nederhasj and geimporteerde hasj, the Spanish and French Hashish (from Morocco), Spanish home-grown sensimilla, French home-grown skunk/sensimilla/super-skunk and Brazilian skunk.

Supplementary table S3. Prevalence of CAPE psychotic experiences in population controls

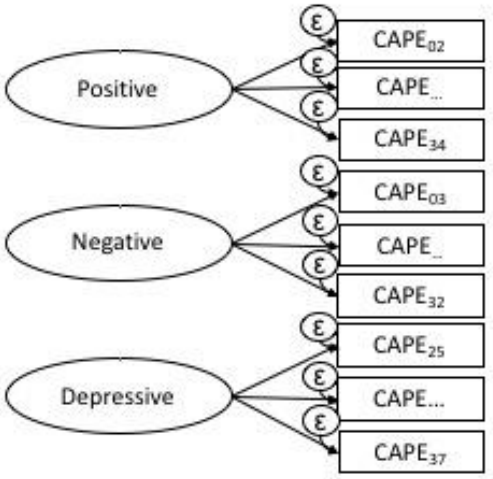
CAPE ITEM	*Item no.*	*Factor*	*Valid frequency Total sample*
Do you ever feel as if people seem to drop hints about you or say things with a double meaning?	*2*	*POS*	*50.9% (629)*
Do you ever feel as if things in magazines or on TV were written especially for you?	*5*	*POS*	*17.6% (217)*
Do you ever feel as if some people are not what they seem to be?	*6*	*POS*	*74.7% (923)*
Do you ever feel as if you are being persecuted in some way?	*7*	*POS*	*18.9% (233)*
Do you ever feel as if there is a conspiracy against you?	*10*	*POS*	*12.4% (153)*
Do you ever feel as if you are destined to be someone very important?	*11*	*POS*	*30.6% (378)*
Do you ever feel that you are a very special or unusual person?	*13*	*POS*	*35.5% (438)*
Do you ever think that people can communicate telepathically?	*15*	*POS*	*25.6% (316)*
Do you ever feel as if electrical devices such as computers can influence the way you think?	*17*	*POS*	*11.2% (138)*
Do you belief in the power of witchcraft, voodoo or the occult?	*20*	*POS*	*27.3% (337)*
Do you ever feel that people look at you oddly because of your appearance?	*22*	*POS*	*34.2% (422)*
Do you ever feel as if the thoughts in your head are being taken away from you?	*24*	*POS*	*3.9% (48)*
Do you ever feel as if the thoughts in your head are not your own?	*26*	*POS*	*7.3% (90)*
Have your thoughts ever been so vivid that you were worried other people would hear them?	*28*	*POS*	*10.6% (131)*
Do you ever hear your own thoughts being echoed back to you?	*30*	*POS*	*9.1% (112)*
Do you ever feel as if you are under the control of some force or power other than yourself?	*31*	*POS*	*5.3% (66)*
Do you ever hear voices when you are alone?	*33*	*POS*	*6.8% (84)*
Do you ever hear voices talking to each other when you are alone?	*34*	*POS*	*1.9% (23)*
Do you ever feel that you are not a very animated person?	*3*	*NEG*	*44.8% (553)*
Do you ever feel that you are not much of a talker when you are conversing with other people?	*4*	*NEG*	*51.8% (640)*
Do you ever feel that you experience few or no emotions at important events?	*8*	*NEG*	*38.1% (470)*
Do you ever feel that you have no interest to be with other people?	*16*	*NEG*	*50.2% (620)*
Do you ever feel that you are lacking in motivation to do things?	*18*	*NEG*	*67.2% (830)*
Do you ever feel that you are lacking in energy?	*21*	*NEG*	*70.9% (876)*
Do you ever feel that your mind is empty?	*23*	*NEG*	*24.6% (304)*
Do you ever feel that you are spending all your days doing nothing?	*25*	*NEG*	*42.6% (526)*
Do you ever feel that your feelings are lacking in intensity?	*27*	*NEG*	*26.2% (323)*
Do you ever feel that you are lacking in spontaneity?	*29*	*NEG*	*39.6% (489)*
Do you ever feel that your emotions are blunted?	*32*	*NEG*	*31% (383)*
Do you ever feel that you are neglecting your appearance or personal hygiene?	*35*	*NEG*	*27.3% (337)*
Do you ever feel that you can never get things done?	*36*	*NEG*	*55.1% (680)*
Do you ever feel that you have only few hobbies or interests?	*37*	*NEG*	*36.4% (450)*
Do you ever feel sad?	*1*	*DEP*	*93.7% (1,157)*
Do you ever feel pessimistic about everything?	*9*	*DEP*	*48.8% (603)*
Do you ever feel as if there is no future for you?	*12*	*DEP*	*27.5% (340)*
Do you ever feel as if you do not want to live anymore?	*14*	*DEP*	*24.9% (308)*
Do you ever cry about nothing?	*19*	*DEP*	*34.9% (431)*
Do you ever feel guilty?	*38*	*DEP*	*73.4% (907)*
Do you ever feel like a failure?	*39*	*DEP*	*48.1% (594)*
Do you ever feel tense?	*40*	*DEP*	*81.2% (1,003)*

Supplementary Figure S1
Path diagrams of the five psychotic experiences' models

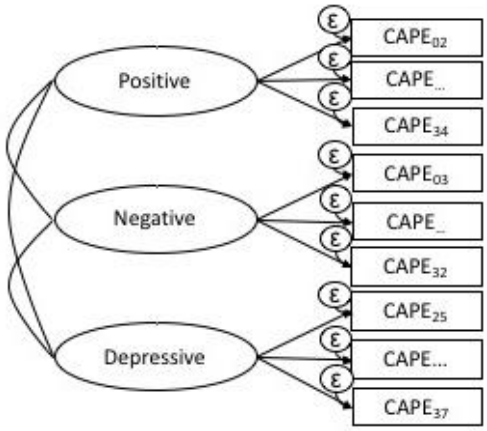
Model A



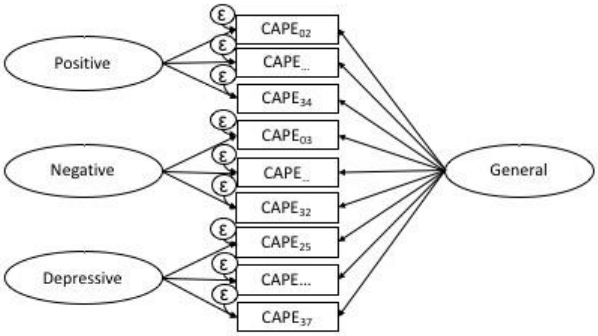
Model B



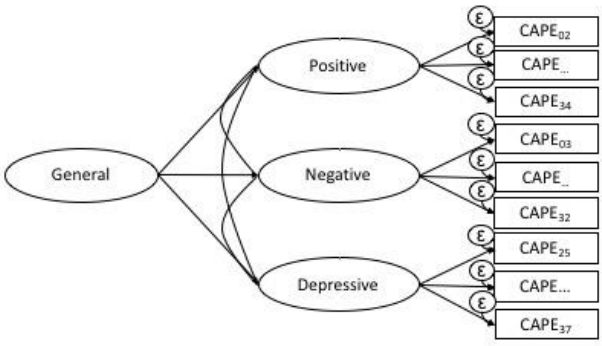
Model C



Model D



Model E



Explanatory note: (▭) Observed symptoms (CAPE items); (Ö) Unobserved variables (latent factors); (→) item loading on latent factors; (ε) item error variance. CAPE item numbers are showed in Tables S1; for simplicity, only three items for each latent factor are presented in the diagrams.

Explanatory note: *Model A*: unidimensional model with one unique general factor; *Model B*: multidimensional model with three uncorrelated specific factors; *Model C*: multidimensional model with three correlated specific factors; *Model D*: bifactor model with one general factor and three

uncorrelated specific factors; Model *E*: hierarchical model with three correlated first-order specific factors and one general second-order factor.

As showed in the main text and in Table 1, the bifactor model for the CAPE (Model D) best reflected the dimensional structure of psychosis in population controls when compared with the other models. This is consistent with our previous findings on the bifactor model for the OPCRIT in patients (Quattrone *et al.*, 2019). The bifactor model allows examining the variance due to each dimension whilst partitioning out the variance due to the common item effect of the whole symptomatology. Thus, in this study, we performed the best possible evaluation of the impact of cannabis use on specific subsets of psychotic symptoms or experiences in patients and controls.

Supplementary Table S4. Model fit statistics of unidimensional, multidimensional, bifactor, second-order models for psychotic experiences and for psychotic symptoms

CAPE (CONTROLS)				
	Full information fit statistics[a]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-23638	47397	47715	47524
B - Multidimensional Model (five uncorrelated factors)	-23844	47808	48126	47936
C - Multidimensional Model (five correlated factors)	-23341	46808	47142	46942
D - Bifactor Model (one general factor and five specific uncorrelated factors)	**-23139**	**46458**	**46935**	**46649**
E - Hierarchical Model (five first-order specific correlated factors and one second order general factor)	-23341	46807	47135	46938
OPCRIT (PATIENTS) (Quattrone *et al.*, 2019)				
	Full information fit statistics[a]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-29965	60126	60618	60306
B - Multidimensional Model (five uncorrelated factors)	-28070	56335	56826	56515
C - Multidimensional Model (five correlated factors)	-27894	56004	56546	56202
D - Bifactor Model (one general factor and five specific uncorrelated factors)	**-27597**	**55489**	**56226**	**55759**
E - Hierarchical Model (five first-order specific correlated factors and one second order general factor)	-27995	56197	56713	56386

LL, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC Sample-size Adjusted Bayesian Information Criterion
A difference of 10 in AIC, BIC and SABIC is considered important. Lower values indicate a statistically better model fit (best values across models are indicated in bold).

Supplementary Table S5. Prevalence of OPCRIT symptoms in patients (Quattrone *et al.*, 2019)

OPCRIT ITEM	**Item no.**	**Factor**	**Valid frequency**
Persecutory Delusions	54	POS	71.6% (794)
Well organised delusions	55	POS	41.6% (458)
Delusions of influence	58	POS	24.1% (267)
Bizarre Delusions	59	POS	23.3% (259)
Widespread Delusions	60	POS	42.4% (437)
Delusions of passivity	61	POS	15.2% (168)
Primary delusional perception	62	POS	26.2% (286)
Other primary delusions	63	POS	19.4% (213)
Delusions & hallucinations last for one week	64	POS	47.9% (495)
Persecutory delusions & hallucinations	65	POS	30.1% (311)
Thought insertion	66	POS	16.4% (180)
Thought broadcast	68	POS	15.5% (171)
Third person auditory hallucinations	73	POS	29.3% (322)
Running commentary voices	74	POS	24.1% (266)
Abusive/accusatory/persecutory voices	75	POS	31.8% (329)
Other (non-affective) auditory hallucinations	76	POS	23.3% (264)
Non-affective hallucination in any modality	77	POS	26.7% (294)

Negative formal thought disorder	29	NEG	19% (209)
Restricted affect	32	NEG	36.4% (404)
Blunted affect	33	NEG	21.9% (243)
Bizarre behaviour	17	DIS	44.9% (496)
Speech difficult to understand	26	DIS	20.9% (230)
Incoherent	27	DIS	13% (13)
Positive formal thought disorder	28	DIS	24.3% (268)
Inappropriate affect	34	DIS	19.6% (216)
Excessive activity	19	MAN	25.5% (283)
Reckless activity	20	MAN	21% (233)
Distractibility	21	MAN	47.4% (521)
Reduced need for sleep	22	MAN	30.8% (340)
Agitated activity	23	MAN	41.3% (457)
Pressured speech	30	MAN	23% (255)
Thoughts racing	31	MAN	33% (365)
Elevated mood	35	MAN	20.6% (229)
Irritable mood	36	MAN	47.7% (529)
Increased self esteem	56	MAN	24.1% (267)
Grandiose Delusions	57	MAN	23.3% (259)
Slowed activity	24	DEP	23.6% (261)
Loss of energy/tiredness	25	DEP	40.1% (444)
Dysphoria	37	DEP	48.7% (540)
Loss of pleasure	39	DEP	43.2% (477)
Poor concentration	41	DEP	61% (676)
Excessive self-reproach	42	DEP	25.8% (286)
Suicidal ideation	43	DEP	34.2% (380)
Initial insomnia	44	DEP	52.4% (576)
Middle insomnia (broken sleep)	45	DEP	38.4% (423)
Early morning waking	46	DEP	24.9% (274)
Excessive sleep	47	DEP	15.2% (168)
Poor appetite	48	DEP	37% (407)
Weight Loss	49	DEP	29.3% (315)

Supplementary Table S6.1. Symptom dimensions in patients by frequency of use and potency of cannabis[a]

Model	Lifetime frequency of use B (95% CI)		Potency of cannabis B (95% CI)	
	Less than daily *(v. never used)*	Daily *(v. never used)*	low potency *(v. no use)*	high potency *(v. no use)*
Positive symptom dimension	0.1 (-0.21 to 0.22)	**0.23**** (0.07 to 0.39)	0.09 (-0.12 to 0.28)	**0.22**** (0.02 to 0.29)
Negative symptom dimension	-0.07 (-0.29 to 0.15)	-0.09 (-0.26 to 0.09)	**-0.24**** (-0.41 to -0.06)	-0.2* (-0.39 to -0.02)
Depressive symptom dimension	-0.12 (-0.31 to 0.06)	-0.1 (-0.24 to 0.04)	-0.13 (-0.28 to 0.03)	-0.13 (-0.29 to 0.03)
Disorganization symptom dimension	0.26* (0.05 to 0.47)	0.11 (-0.04 to 0.27)	-0.02 (-0.19 to 0.15)	0.13 (-0.04 to 0.32)
Manic symptom dimension	0.02 (-0.17 to 0.22)	0.13 (-0.02 to 0.28)	**0.23**** (0.06 to 0.39)	**0.27**** (0.1 to 0.44)
General Psychosis factor	0.17* (0.01 to 0.33)	0.12* (0.01 to 0.25)	0.06 (-0.07 to 0.19)	0.02 (-0.12 to 0.17)

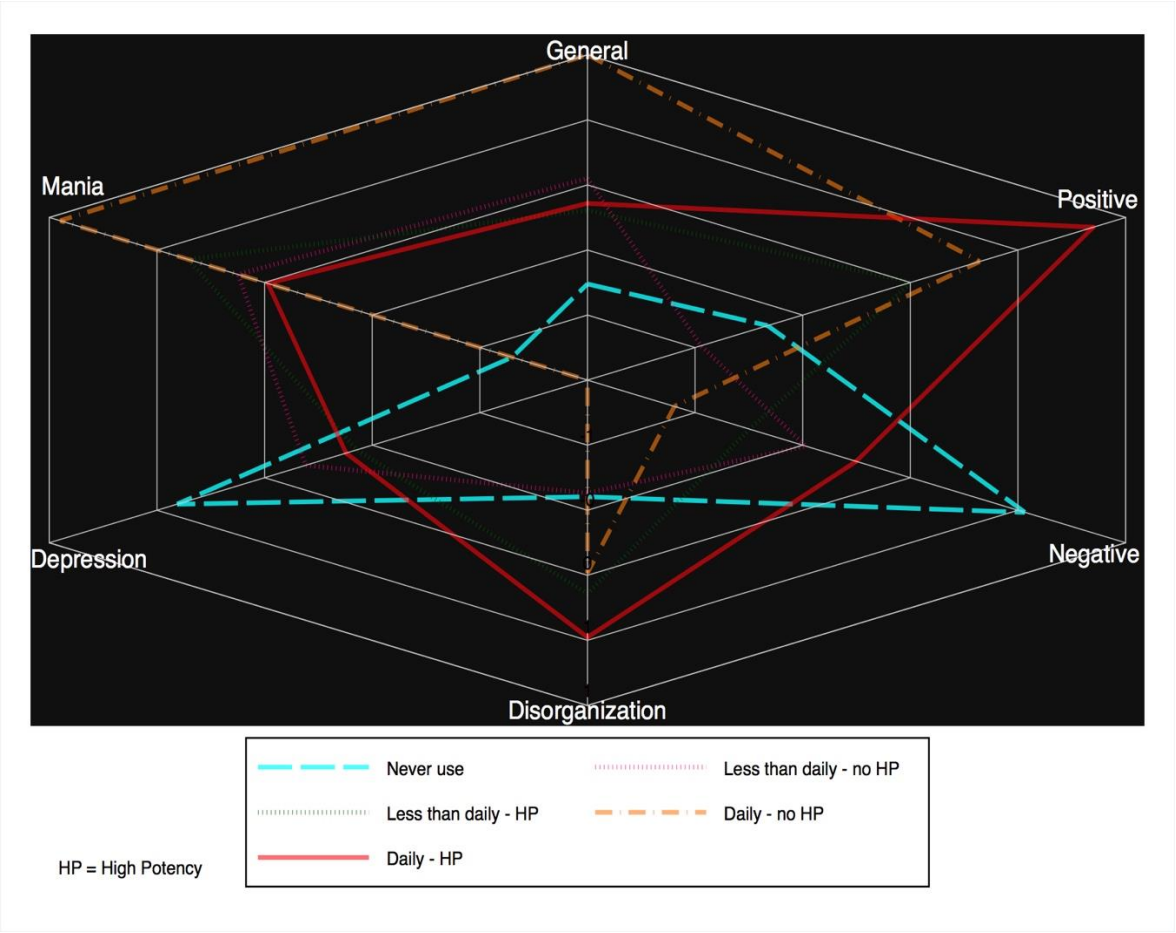
[a]All models were adjusted for age, sex, ethnicity, current use of other recreational/illicit substances, and diagnosis. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; associations that hold after Benjamini-Hochberg procedure are showed in bold.

Supplementary Table S6.2. Psychotic experience dimensions in controls by frequency of use and potency of cannabis[a]

Model	Lifetime frequency of use B (95% CI)		Potency of cannabis B (95% CI)	
	Less than daily *(v. never used)*	Daily use *(v. rare and never use)*	Low Potency *v. no use*	High potency *v. no use*
Positive psychotic experience dimension	0.04 (-0.08 to 0.16)	0.17 (-0.05 to 0.38)	0.08 (-0.06 to 0.22)	0.03 (-0.13 to 0.19)
Negative experience dimension	0.11 (-0.02 to 0.24)	0.14 (-0.09 to 0.38)	0.09 (-0.05 to 0.24)	0.12 (-0.05 to 0.29)
Depressive experience dimension	0.08 (-0.05 to 0.2)	0.17 (-0.08 to 0.4)	0.08 (-0.07 to 0.23)	0.05 (-0.11 to 0.22)
General psychotic experience factor	0.03 (-0.1 to 0.16)	0.13 (-0.11 to 0.37)	0.08 (-0.07 to 0.23)	-0.02 (-0.19 to 0.15)

[a]All models were adjusted for age, sex, ethnicity, current use of other recreational/illicit substances. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary Figure S2. Symptom dimensions by frequency of use and potency of cannabis



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