**Online supplement:**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **sTable 1 DSM IV diagnosis of cases\* (Operational Criteria Checklist (OPCRIT):**   |  |  |  | | --- | --- | --- | |  | ***n*** | *%* | | No diagnosis | 69 | 10.3 | | Major depressive disorder with psychosis | 56 | 8.4 | | Manic episode with psychosis | 58 | 8.7 | | Schizophrenia | 179 | 26.8 | | Schizophreniform disorder | 115 | 17.2 | | Schizoaffective disorder, depressive type | 13 | 1.9 | | Schizoaffective disorder, bipolar type | 19 | 2.8 | | Delusional disorder | 23 | 3.4 | | Psychosis not otherwise specified (atypical psychosis) | 95 | 14.2 | | Bipolar I disorder | 20 | 3.0 | | *Missing* | 8 | 1.2 | | **Total** | **655\***† | **98.2\***† |   \*Ever cannabis using patients with FEP  † Cases excluded from analysis (not shown in table above) were those with diagnosis of non psychotic disorders (n=12; 1.8%): Moderate Major depressive disorder; Major depressive disorder severe; hypomanic episode; Manic episode without psychosis  **sTable 2: Cases & Controls by site:** | | | | |
|  | |  | | **Total** |
| **Case** | **Control** |
| **Brazil**  Ribeirão Preto |  | 89 (13.6%) | 60 (9.2%) | 149 (11.4%) |
|  |  |  |  |
| **France**  Val-de-Marne (Paris)  Puy-de-Dôme (Clermont-Ferrand) |  | 31 (4.7%) | 38 (5.8%) | 69 (5.3%) |
|  | 8 (1.2%) | 23 (3.5%) | 31 (2.4%) |
| **Holland**  Amsterdam  Gouda and Voorhout |  | 86 (13.1%)  69 (10.5%) | 64 (9.8%)  57 (8.7%) | 150 (11.5%)  126 (9.6%) |
|  |  |  |  |
| **Italy**  Bologna  Palermo |  | 35 (5.3%)  37 (5.6%) | 39 (6.0%)  59 (9.0%) | 74 (5.7%)  96 (7.3%) |
|  |  |  |  |
| **Spain**  Barcelona  Cuenca  Galicia  Madrid  Oviedo  Valencia |  | 22 (3.4%)  13 (2.0%) | 23 (3.5%)  19 (2.9%) | 45 (3.4%)  32 (2.4%) |
|  | 19 (2.9%)  29 (4.4%)  21 (3.2%)  29 (4.4%) | 24 (3.7%)  19 (2.9%)  21 (3.2%)  16 (2.4%) | 43 (3.3%)  48 (3.7%)  42 (3.2%)  45 (3.4%) |
| **United Kingdom**  Cambridge  London |  | 29 (4.4%)  138 (21.1%) | 51 (7.8%)  141 (21.6%) | 80 (6.1%)  279 (21.3%) |
|  |  |  |  |
| **Total** |  | **655 (100.0%)** | **654 (100.0%)** | **1321 (100.0%)** |
|  |  |  |  |

|  |
| --- |
| **sTable 3: Cases & Controls by ethnicity** |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | |  | | | **Total** |
| **Case** | | **Control** |
|  | White |  | 415 (63.4%) | | 547 (83.8%) | 962 (73.5%) |
|  |  | |  |  |
| Black |  | 105 (16.0%) | | 46 (7.0%) | 151 (11.5%) |
|  |  | |  |  |
| Mixed |  | 60 (9.2%) | | 31 (4.7%) | 91 (7.0%) |
|  |  | |  |  |
| Asian |  | 22 (3.4%) | | 12 (4.7%) | 34 (2.6%) |
|  |  | |  |  |
| North African |  | 31 (4.7%) | | 7 (1.1%) | 38 (2.9%) |
|  |  | |  |  |
| Other |  | 22 (3.4%) | | 10 (1.5%) | 32 (2.4%) |
|  |  | |  |  |
| **Total** | |  | **655 (100.0%)** | **653 (99.8%)\*** | **1308 (99.9%)** |
|  |  |  |  |

\*Ethnicity data for one control was missing.

**sTable 4: Within item and between subscales correlations for Cannabis Experiences Questionnaire**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Fearful* | 1 |  |  |  |  |  |  |  |  |  |  |
| *Crazy, mad* | 0.5073 | 1 |  |  |  |  |  |  |  |  |  |
| *Nervy* | 0.4791 | 0.4349 | 1 |  |  |  |  |  |  |  |  |
| *Suspicious* | 0.5485 | 0.4574 | 0.4862 | 1 |  |  |  |  |  |  |  |
| *Hearing voices* | 0.2535 | 0.4047 | 0.2388 | 0.321 | 1 |  |  |  |  |  |  |
| *Seeing visions* | 0.2642 | 0.3829 | 0.1965 | 0.2619 | 0.4496 | 1 |  |  |  |  |  |
| *Feeling Happy* | -0.0201 | 0.0236 | 0.0454 | 0.1065 | 0.063 | 0.0532 | 1 |  |  |  |  |
| *Full of plans, ideas* | 0.0914 | 0.0984 | 0.1717 | 0.2809 | 0.1779 | 0.1639 | 0.4094 | 1 |  |  |  |
| *Undertanding the world better* | 0.1553 | 0.1084 | 0.1757 | 0.2709 | 0.1656 | 0.1655 | 0.3162 | 0.4857 | 1 |  |  |
| *cPLEs* | 0.7662 | 0.7558 | 0.7161 | 0.7848 | 0.5804 | 0.5397 | 0.0678 | 0.2379 | 0.2545 | 1 |  |
| *cEEs* | 0.0923 | 0.0972 | 0.1656 | 0.2747 | 0.1728 | 0.1619 | 0.7611 | 0.814 | 0.7516 | 0.2343 | 1 |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  | *Fearful* | *Crazy, mad* | *Nervy* | *Suspicious* | *Hearing voices* | *Seeing visions* | *Feeling Happy* | *Full of plans, ideas* | *Undertanding the world better* | *cPLEs* | *cEEs* |

**Legend:** cPLEs: Cannabis induced psychotic-like experiences; cEEs: Cannabis induced euphoric experiences, Pearson’s correlation coefficients colour coded (blue – minimal – red –maximal)

**sTable 5: Missing data rates**

|  |  |  |
| --- | --- | --- |
|  | **Case** | **Controls** |
| Male | *nil* | *nil* |
| White | *nil* | *1 (0.2%)* |
| Age at first contact | *nil* |  |
| Age at assessment | *nil* | *1 (0.2%)* |
| **Years in Education** | ***12 (1.8%)*** | ***2 (0.3%)*** |

|  |  |  |
| --- | --- | --- |
| **Age first tried cbs** | ***15 (2.2%)*** | ***nil*** |
| **Frequency of cbs use** | ***15 (2.3%)*** | ***1 (0.2%)*** |
| Money Spent per week on cbs | *61 (9.3%)* | *47 (7.2%)* |
| Use of high potency cbs | *131 (20.0%)* | *136 (20.8%)* |
| Mean Duration of cbs use (years) | 18 (2.7%) | 28 (4.3%) |
| Current cbs use | *2 (0.3%)* | *1 (0.2%)* |
| **Lifetime DSM IV cbs Dependence** | ***26 (4.0%)*** | ***3/654 (0.5%)*** |
| **Last 12 month DSM IV cbs Dependence** | **26 (5.2%)** | **3 (0.5%)** |
| Number of other drugs tried | *nil* | *nil* |
| **Cigarettes/Roll-ups per day** | ***19 (2.9%)*** | ***8 (1.2%)*** |
| Units of alcohol per day | *143 (21.8%)* | *88 (13.4%)* |
|  |  |  |
| cPLEs | 57 (8.7%) | 39 (6.0%) |
| cEEs | 53 (8.1%) | 38 (5.8%) |

**Legend: cbs:** cannabis**;** Bold typeface indicates significant difference (p<0.05) in missing data between cases and controls (chi squared test or Fisher’s exact test where any single value <=5).

**sTable 6: Supplementary Analyses – cannabis frequency x status interaction regressing for substance type**

In the main analyses we had used ‘*number of illicit substances ever tried’* as in order to control for illicit substance misuse. Reviewers had requested further analyses to control for different drug types as these may conceivable have different effects on cPLEs. We have therefore run a supplementary complete case analysis controlling for different drug types collected in the EU-GEI study: Inhalents, Crack, Cocaine, other Stimulants (such as amphetamines), Sedatives, Opioids, Hallucinogens, Ketamine and Novel Psychoactive Stubstances. We have run two analyses – firstly controlling for ever use of these substances (coded 1 – ever having used and 0 – never having used) and secondly controlling for lifetime misuse (coded 1 – meeting DSM IV abuse or dependence criteria and 0 – not meeting criteria).

**sTable 6a: Prevelance of everuse and lifetime misuse by cases and controls**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Ever Use** | | | **Lifetime misuse** | | |
|  | Case | Control | p-value | Case | Control | p-value |
| Inhalents | 92 (14.0%) | 50 (7.7%) | **<0.001** | 9 (1.4%) | 2 (0.3%) | 0.064 |
| Crack | 56 (8.6%) | 24 (3.7%) | **<0.001** | 21 (3.2%) | 9 (1.4%) | **0.0404** |
| Cocaine | 279 (42.6%) | 184 (28.1%) | **<0.001** | 87 (13.3%) | 39 (6.0%) | **<0.001** |
| Stimulants | 203 (31.0%) | 150 (22.9%) | **0.001** | 41 (6.3%) | 23 (3.5%) | **0.029** |
| Sedatives | 51 (7.8%) | 27 (4.1%) | **<0.001** | 14 (2.1%) | 2 (0.3%) | **0.004** |
| Opioids | 46 (7.0%) | 19 (2.9%) | **<0.001** | 19 (2.9%) | 5 (0.8%) | **0.006** |
| Hallucinogens | 142 (21.7%) | 118 (18.0%) | 0.111 | 9 (1.4%) | 6 (0.9%) | 0.605 |
| Ketamine | 61 (9.3%) | 36 (5.5%) | **0.011** | 5 (0.8%) | 1 (0.2%) | 0.217 |
| Novel Psychoactive Substances | 36 (5.5%) | 29 (4.4%) | 0.446 | 9 (1.4%) | 3 (0.5%) | 0.144 |

**Legend**: All tests cases versus control using Fisher’s exact test.

Note all cases and controls in analysis limited to lifetime cannabis users in EUGEI study only.

**sTable 6b: Interaction of cannabis frequency x caseness on cPLEs regressing for illicit substance use**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Coefficient** | **Standard Error** | **t** | **P>|t|** |
|  | Caseness | 1.362 | 0.222 | 6.14 | **<0.001** |
|  | Frequency | 0.798 | 0.172 | 4.63 | **<0.001** |
|  | Casenesss x Frequency | 0.246 | 0.065 | 3.75 | **<0.001** |
|  | cEEs | 0.134 | 0.044 | 3.04 | **0.002** |
| *Lifetime use* | Inhalents | 0.713 | 0.454 | 1.57 | 0.116 |
| Crack | 0.993 | 0.605 | 1.64 | 0.101 |
| Cocaine | 0.123 | 0.276 | 0.45 | 0.654 |
| Stimulants | 0.366 | 0.336 | 1.09 | 0.277 |
| Sedatives | 1.034 | 0.578 | 1.79 | 0.074 |
| Opioids | -0.545 | 0.595 | -0.92 | 0.36 |
| Hallucinogens | -0.370 | 0.311 | -1.19 | 0.235 |
| Ketamine | -0.423 | 0.412 | -1.03 | 0.305 |
| Novel Psychoactive Substances | -0.048 | 0.493 | -0.1 | 0.922 |
|  | Constant | 5.165 | 0.641 | 8.05 | **<0.001** |

**sTable 6c: Interaction of cannabis frequency x caseness on cPLEs regressing for illicit substance misuse**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Coefficient** | **Standard Error** | **t** | **P>|t|** |
|  | Caseness | 1.381 | 0.229 | 6.03 | **<0.001** |
|  | Frequency | 0.809 | 0.164 | 4.95 | **<0.001** |
|  | Casenesss x Frequency | 0.250 | 0.070 | 3.58 | **<0.001** |
|  | cEEs | 0.141 | 0.038 | 3.72 | **<0.001** |
| *Lifetime Misuse* | Inhalents | 3.226 | 1.179 | 2.74 | **0.006** |
| Crack | 2.160 | 0.745 | 2.9 | **0.004** |
| Cocaine | 0.139 | 0.402 | 0.35 | 0.729 |
| Stimulants | 0.245 | 0.546 | 0.45 | 0.654 |
| Sedatives | 2.399 | 0.974 | 2.46 | 0.014 |
| Opioids | -1.619 | 0.840 | -1.93 | **0.054** |
| Hallucinogens | 0.627 | 1.001 | 0.63 | 0.531 |
| Ketamine | -0.189 | 1.511 | -0.13 | 0.9 |
| Novel Psychoactive Substances | 1.361 | 1.175 | 1.16 | 0.247 |
|  | Constant | 5.276 | 0.531 | 9.94 | **<0.001** |

Consequently we observe that the findings of the main analysis remain the same when adjusting for other illicit substance confounders. Additionally we observe that a history of inhalents misuse, crack cocaine misuse are associated with increased cPLEs whereas opioid misuse appears associated with diminished cPLEs. This is broadly in keeping with previous literature in which whereas cannabis and cocaine use are synergistic for psychosis experiences1 whereas opiate withdrawal is associated with psychosis experiences2,3. However we note that overall numbers in the misuse groups for these substances are small (n<=30, see Table 6a) and such findings should be interpreted with caution.

**References:**

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