**SUPPLEMENTARY MATERIAL**

**Developmental sensitivity to cannabis use patterns and risk for Major Depressive Disorder in mid-life: Findings from 40 years of follow-up**

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| **sTable 1.** Summary of observational studies looking at the association between cannabis and depression | | | | | | | | |
| **Study** | **Cohort** | **N** | **Age (M)/ Time point** | **Cannabis definition** | **Depression definition** | **Outcome coding** | **Results** | **Confounders considered** |
| **Cross-sectional studies investigating the association between cannabis use and depression** | | | | | | | | |
| [Lynskey et al. (2004)](#_ENREF_47) | ATW / Australia | 312 | T1: 24-36 (R) | C1: CUD (yes/no) at T1  C2: Use before age 17 (yes/no) | D1: Lifetime diagnosis of MDD (T1) (SSAGA) | Risk prediction (twin-pairs design) | C1 🡪 D1 (NS)  C2 🡪 D1 (NS) | Conduct disorder, childhood sexual abuse, cigarette/alcohol use, depression before age 17, suicidal ideation before age 17, unobserved time-invariant sources of confounding |
| [Chen et al. (2002)](#_ENREF_17) | USNCS / US | 6792 | T1: 15-45 (R) | C1: Frequency of lifetime use | D1: subsequent MDD (CIDI) | Risk prediction | C1 🡪 D1 \* | Gender, birth cohort, cigarette/alcohol use |
| [De Graaf et al. (2010)](#_ENREF_20) | WMHS / worldwide | 50718 | T1: 42.8 (M) | C1: Use (yes/no) before age 17 | D1: Risk of depression spell after age 17 (CIDI) | Risk prediction | C1 🡪 D1 \* | Gender, age, cigarette use, other mental health problems |
| [Poulin et al. (2005)](#_ENREF_54) | SDUSAP / Canada | 12444 | T1: 15 (M) | C1:Frequency of use 1 month prior T1 | D1: Depression (yes/no) at T1(moderate severity) (CES)  D2: Depression (yes/no) at T1 (high severity) (CES | Risk prediction | In females:  C1 🡪 D1 \*  C1 🡪 D2 \*  In males:  C1 🡪 D1 \* | Age, urbanicity, education, alcohol/cigarette use |
| [Rey et al. (2002)](#_ENREF_60) | NSMHW / Australia | 1261 | T1: 13-17 (R) | C1: Ever use (yes/no) | D1: Depression at T1 (CES) | Risk prediction | In females:  IV1 🡪 DV1 \*  In males:  IV1 🡪 DV1 \* | Age of onset of cannabis use |
| [Troisi et al. (1998)](#_ENREF_68) | Italy | 133 | T1: 20 (M) | C1: Use severity (occasional use vs. abuse vs. dependence) | D1: Depression score (BDI) | Severity | IV1 🡪 DV1 \* | Gender |
| **Longitudinal studies investigating effects of cannabis use on subsequent depression outcome** | | | | | | | | |
| [Georgiades and Boyle (2007)](#_ENREF_33) | OCHS / Canada | 854 | T1: 8-16 (R)  T2: 26-34 (R) | C1: Use (yes/no) 6 months prior T1  C2: Use (yes/no) 6 months prior T2  C3: Use prior to T1 and T2 | D1: MDD at T2 (CIDI) | Risk prediction | C1 🡪 D1 (NS)  C2 🡪 D1 \*  C3 🡪 D1 \* | Age, gender, SES, single parent home, family functioning, education, chronic illness, general health status |
| [Harder et al. (2008)](#_ENREF_37) | JHU-RT / US | 1494 | T1: 12-16 (R)  T2: 19-24 (R) | C1: Cannabis dependence (yes/no) before T1 | D1: Depression symptoms (absent/low/moderate/high) at T2 (CIDI) | Risk prediction | C1 🡪 D1 (NS) | SES, cigarette/alcohol/illicit drug use, childhood disturbances, parental monitoring, behavioral intervention status |
| [Pedersen (2007)](#_ENREF_52) | YNLS / Norway | 2033 | T1: 21 (M)  T2: 27 (M) | C1: Never vs. light user (< 10 times used)  C2: Never vs. heavy user (> 10 times used) | D1: Depressed mood (yes/no) 1 year prior T2 (SCL-90) | Risk prediction | C1 🡪 D1 (NS)  C2 🡪 D1 (NS) | Gender, age, SES, parental education, parental divorce, parental smoking and alcohol use, early pubertal maturation, education, conduct problems, cigarette/alcohol use, prior depression, impulsivity, employment |
| [Block et al. (1991)](#_ENREF_12) | LSECD / US | 88 | T1: 14  T2: 18 | C1: Frequency of use at T1 | D1: Depression score at T2 (CES-D) | Severity | In boys:  C1 🡪 D1 \*  In girls:  C1 🡪 D1 (NS) | - |
| [Brook et al. (2002)](#_ENREF_16) | CIC / US | 736 | T1: 14 (M)  T2: 16 (M)  T3: 22 (M)  T4: 27 (M) | C1: Frequency of use prior T1  C2: Frequency of use (T1-T2)  C3: Frequency of use (T2-T3)  C4: Frequency of use (T1-T3) | D1: MDD at T4 (CIDI) | Risk prediction | C1 🡪 D1 \*  C2 🡪 D1 \*  C3 🡪 D1 (NS)  C4 🡪 D1 \* | Gender, age, SES, parental education, prior episode of MDD, substance use disorders |
| [Gage et al. (2015)](#_ENREF_32) | ALSPAC / UK | 4561 | T1: 16 (M)  T2: 18 (M) | C1: Frequency of use at T1 | DV1: MDD at T2 (CIS-R) | Risk prediction | C1 🡪 D1 \* | Gender, family history of depression, parental education, urbanicity, IQ at age 8, borderline personality traits, victimization, peer problems, conduct disorder, alcohol/illicit drug use |
| [Van Laar et al. (2007)](#_ENREF_69) | NEMESIS / Netherland | 3881 | T1: 18-64 (R)  T2: 21- 67 (R) | C1: User (> 5 times/lifetime) vs. non-user at T1  C2: Frequency of use between T1 and T2 | D1: MDD between T1 and T2 (CIDI) | Risk prediction | C1 🡪 D1 \*  C2 🡪 D1 (NS) | Gender, age, education, urbanicity, employment, partner status, neurotic personality, family history of psychiatric disorders, childhood trauma, alcohol/illicit drug use, psychosis, lifetime anxiety or depressive disorder at T1 |
| [Marmorstein and Iacono (2011)](#_ENREF_48) | MTFS / US | 1252 | T1: 17 (M)  T2: 20 (M)  T3: 24 (M) | C1: Presence vs. absence of CUD at T1 | D1: MDD between T1 and T3 (SCID) | Risk prediction | C1 🡪 D1 \* | - |
| [Arseneault et al. (2002)](#_ENREF_5) | DMHDS / New Zealand | 759 | T1: 15 (M)  T2: 18 (M)  T3: 26 (M) | C1: User at T1 (used > 3 or more/lifetime) vs. non-user (used < 1/lifetime)  C2: User at T2 (used > 3 or more since T1) vs. non-user (used < 1/lifetime) | D1: MDD at T3 (DIS)  D2: Depression score at T3 (DIS) | Risk prediction / Severity | C1 🡪 D1 (NS)  C2 🡪 D1 \*  C1 🡪 D2 (NS)  C2 🡪 D2 \* | Gender, SES, childhood psychotic symptoms, other drug use |
| [Tien and Anthony (1990)](#_ENREF_67) | ECD / US | 4994 | T1: 18 (M)  T2: 19 (M) | C1: CUD between T1 and T2 | D1: MDD at T2 (DIS) | Risk prediction | C1 🡪 D1\* | Psychotic experiences at T1, gender, education, relationship status, employment |
| [Blanco et al. (2016)](#_ENREF_10) | NESARC / US | 34653 | T1: 18-24 (R)  T2: 21-27 (R) | C1: Use (yes/no) in 12 months preceding T1  C2:Frequency of use in 12 months preceding T1 | D1: MDD between T1 and T2 (AUDADIS-IV) | Risk prediction | C1 🡪 D1 (NS)  C2 🡪 D1 (NS) | Gender, age, education , alcohol/nicotine/illicit drug use, parental loss/separation, self-esteem, lifetime anxiety disorder, antisocial personality, ethnicity |
| **Longitudinal studies effects of depression on subsequent cannabis use** | | | | | | | | |
| [Wittchen et al. (2007)](#_ENREF_75) | EDSP / Germany | 1395 | T1: 14-17 (R)  T2: 16-19 (R)  T3: 18-21 (R)  T4: 21-27 (R) | C1: Presence vs. absence of CUD between T1 and T4  C2: Age of onset of CUD between T1 and T4 | D1: MDD (CIDI) (before T1) | Risk prediction | D1 🡪 C1 \*  D1 🡪 C2 \* | Gender, age, externalizing disorders |
| [King et al. (2004)](#_ENREF_42) | MTFS / US | 1334 | T1: 11 (M)  T2: 14 (M) | C1: Use (> 1 on year before T1) vs. non-use  C2: Regular use (>1/month at T4) vs. non-use | D1: MDD at T1 (DICA) | Risk prediction | D1 🡪 C1 (NS)  D1 🡪 C2 (NS) | Gender |
| **Longitudinal studies investigating bi-directional effects between cannabis use and depression** | | | | | | | | |
| [Horwood et al. (2012)](#_ENREF_39) | VAHCS / Australia | 2032 | T1: 13-16 (R)  T2: 14-18 (R)  T3: 14-18 (R)  T3: 14-18 (R)  T5: 15-18 (R)  T6: 15-18 (R)  T7: 19-22 (R) | C1: Frequency of use in 6/12 months prior assessment (T1-T7)  C2: Frequency of use x age interaction | D1: Depression score (T1-T7) (CIS) | Severity | FEM Model  C1 🡪 D1 \*  C2 🡪 D1 \*  SEM Model  C1 🡪 D1 (NS)  D1 🡪 C1 \* | Unobserved time-invariant factors (FEM Model) |
| [Horwood et al. (2012)](#_ENREF_39) | PATH / Australia | 2404 | T1: 20-25 (R)  T2: 24-29 (R)  T3: 28-34 (R) | C1: Frequency of use in 12 months prior assessment (T1-T7)  C2: Frequency of use x age interaction | D1: Depression score (T1-T3) (GDS) | Severity | FEM Model  C1 🡪 D1 \*  C2 🡪 D1 (NS)  SEM Model  C1 🡪 D1 \*  D1 🡪 C1 (NS) | Unobserved time-invariant factors (FEM Model) |
| [Horwood et al. (2012)](#_ENREF_39) | ATP / Australia | 2443 | T1: 15-16 (R)  T2: 17-18 (R)  T3: 19-20 (R)  T4: 23-24 (R) | C1: Frequency of use 1 month prior assessment (T1-T7)  C2: Frequency of use x age interaction | D1: Depression score (T1-T4) | Severity | FEM Model  C1 🡪 D1 \*  C2 🡪 D1 (NS)  SEM Model  C1 🡪 D1 (NS)  D1 🡪 C1 (NS) | Unobserved time-invariant factors (FEM Model) |
| [Horwood et al. (2012)](#_ENREF_39) | CHDS / New Zealand | 1265 | T1: 15 (M)  T2: 16 (M)  T3: 18 (M)  T4: 21 (M)  T5: 25 (M)  T6: 30 (M) | C1: Frequency of use in 12 months prior assessment (T1-T7)  C2: Frequency of use x age interaction | D1: Depression score (T1-T6) (DISC/CIDI) | Severity | FEM Model  C1 🡪 D1 \*  C2 🡪 D1 (NS)  SEM Model  C1 🡪 D1 \*  D1 🡪 C1 (NS) | Unobserved time-invariant factors (FEM Model) |
| [Danielsson et al. (2016)](#_ENREF_19) | PART / Sweden | 8598 | T1: 20-64 (R)  T2: 23-67 (R) | C1: Use (ever used) before T1  C2: Use (use > 1 in 12 months prior T2) | D1: MDD at T2 (MDI)  D2: MDD at T1 | Risk prediction | C1 🡪 D1 (NS)  D2 🡪 C2 (NS) | Gender, age, alcohol, illicit drug use, education, family tension, place of upbringing |
| [Repetto et al. (2008)](#_ENREF_59) | US | 622 | T1: 15 (M)  T2: 16 (M)  T3: 17 (M)  T4: 18 (M)  T5: 19 (M)  T6: 20 (M) | C1: Changes in frequency of use in 30 days prior T (T1-T6) | D1: Changes in depressive symptoms (BSI) (T1-T6) | Severity | C1 🡪 D1 (NS)  D1 🡪 C1 (NS) | Gender, age, substance use |
| [Bovasso (2014)](#_ENREF_13) | BECA / US | 849 | T1: 1980 (year), age: > 18  T2: 1995 (year) | C1: CUD at T1  C2: CUD between T1 and T2 | D1: Depression (yes/no) between T1 and T2 (DIS)  D2: Number of depressive symptoms at T1 (DIS) | Risk prediction | C1 🡪 D1 \*  C1 🡪 D2 \*  D2 🡪 C2 (NS) | Gender, age, SES, ethnicity, education, antisocial behaviour, stressful life events, chronic illness, baseline depressive symptoms |
| [Hayatbakhsh et al. (2007)](#_ENREF_38) | MUSP / Australia | 3239 | T1: 0 (M)  T2: 14 (M)  T3: 21 (M) | C1: Age of onset of (ever) use  C2: Frequency of use 1 month prior assessment (T3) | D1: Anxiety and depression (yes/no) (YASR) at T3  D2: Anxiety and depression (yes/no) at T2 | Risk prediction | C1 🡪 D1 \*  C2 🡪 D1 \*  D2 🡪 C2 (NS) | Gender, SES, mother’s age, mother’s education, maternal marital status, maternal mental health, maternal substance use, adolescent mental health, cigarette/alcohol use |
| [Patton et al. (2007)](#_ENREF_51) | VAHCS / Australia | 1601 | T1: 13 (M)  T2: 14 (M)  T3: 14 (M)  T4: 15 (M)  T5: 16 (M)  T7: 20 (M) | C1: Frequency of use in 6 months prior T (T1-T6)  C2: Frequency of use in 12 months prior T7 | D1: Presence of depression (yes/no) at T7 (CIS) | Risk prediction | D1 🡪 C2 (NS)  In females:  C1 🡪 D1 \*  In males:  C1 🡪 D1 (NS) | Childhood depression and anxiety, alcohol use, antisocial behaviour, parental separation, parental education |
| [Feingold et al. (2015)](#_ENREF_29) | NESARC / US | 34653 | T1: > 18  T2: 3 Y FU | C1: Frequency of cannabis use 1 year prior T1  C2: Initiation of use between T1 and T2 | D1: Incidence MDD between T1 and T2  D2: Incidence MDD 1 year prior T1 | Risk prediction | C1 🡪 D1 (NS)  D2 🡪 C2 \* | Gender, age, SES, education, marital status, urbanicity, alcohol/illicit drug use, comorbid psychiatric disorders |
| [Windle and Wiesner (2004)](#_ENREF_74) | LAT / UK | 829 | T1: 15-17 (R)  T2: 15-17 (R)  T3: 17-19 (R)  T4: 17-19 (R)  T5: 24 (M) | C1: Use profile (T1-T4) [Abstainers vs. Experimenters vs. Increasers vs. Decreases vs. High chronic]  C2: Use profile (T1-T5) [cf. above] | D1: Depression (yes/no) at T5 (CIDI)  D2: Depression score at T5 (CES-D)  D3: Depression score at T1 (CES-D) | Risk prediction / Severity | C1 🡪 D1 (NS)  C1 🡪 D2 (NS)  D3 🡪 C2 \* | Cannabis use at T5 |
| [Womack et al. (2016)](#_ENREF_77) | PMCP / US | 264 | T1: 17 (M)  T2: 20 (M)  T3: 22 (M) | C1: Frequency of cannabis use (T1-T2)  C2: Frequency of cannabis use (T2-T3) | D2: Depression score (T2-T3) (BDI)  D2: Depression score (T1-T2) (BDI) | Severity | C1 🡪 D1 (NS)  D2 🡪 C2 (reduced) | Education, SES, ethnicity, IQ, family history mental illness, childhood antisocial behaviour, alcohol/nicotine use |
| ALSPAC =Avon Longitudinal Study of Parents and Children ([Boyd et al., 2012](#_ENREF_14)); ATP = The Australian Temperament Project ([Prior et al., 2000](#_ENREF_55)); ATR = Australian Twin Register ([Lynskey et al., 2004](#_ENREF_47)); AUDADIS-IV = Alcohol Use Disorder and Associated Disabilities Interview Schedule ([Grant et al., 2003a](#_ENREF_35)); BDI = Beck’s Depression Inventory ([Beck et al., 1987](#_ENREF_9)); BECA = Baltimore Epidemiologic Catchment Area study ([Anthony and Helzer, 1991](#_ENREF_4)); BSI = Brief Symptom Inventory ([Degoratis and Spencer, 1982](#_ENREF_21)); CES-D = Centre for Epidemiological Studies - Depression Scale ([Radloff, 1977](#_ENREF_57)); CIC = Children in the Community sample ([Brook et al., 2002](#_ENREF_16)); CHDS = The Christchurch Health and Development Study ([Fergusson and Horwood, 2001](#_ENREF_30)); CIDI = Composite International Diagnostic Interview ([Robins et al., 1983](#_ENREF_62)); CIS = Clinical Interview Schedule ([Lewis et al., 1988](#_ENREF_44)); CIS-R = computerized revised Clinical Interview Schedule ([Lewis et al., 1992](#_ENREF_43)); C-SURF = Cohort Study on Substance Use Risk Factors ([Baggio et al., 2014](#_ENREF_6)); CUD = Cannabis Use Disorder; DASS = Depression Anxiety Stress Scale ([Lovibond and Lovibond, 1995](#_ENREF_46)); DICA = Diagnostic Interview for Children and Adolescents ([Reich, 2000](#_ENREF_58)); DIS = Diagnostic Interview Schedule ([Robins et al., 1981](#_ENREF_61)); DISC = Diagnostic Interview Schedule for Children ([Costello et al., 1982](#_ENREF_18)); DMHDS = Dunedin Multidisciplinary Health and Development Study ([Silva and Stanton, 1996](#_ENREF_65)); ECD = Epidemiologic Catchment Area Program ([Tien and Anthony, 1990](#_ENREF_67)); EDSP = Early Developmental Stages of Psychopathology ([Wittchen et al., 1998](#_ENREF_76)); FEM = Fixed Effects Model; GDS = Goldberg Depression Scale ([Goldberg et al., 1988](#_ENREF_34)); JHU-RT = John Hopkins University – Randomized Trial ([Harder et al., 2008](#_ENREF_37)); LAT = Life Across Time: A Longitudinal Study; LSECD = Longitudinal Study of Ego and Cognitive Development ([Block and Block, 1980](#_ENREF_11)); M = Mean; MUSP = Mater University Study of Pregnancy ([Najman et al., 2005](#_ENREF_50)); NESARC = National Epidemiologic Survey on Alcohol and Related Conditions ([Grant et al., 2003b](#_ENREF_36)); MTFS = Minnesota Twin Family Study; NESPAR = National Epidemiologic Survey on Alcohol and Related Conditions ([Blanco et al., 2016](#_ENREF_10)); NEMESIS = Netherlands Mental Health Survey and Incidence Study; NSMHW = National Survey of Mental Health and Wellbeing ([Sawyer et al., 2000](#_ENREF_63)); OCHS = Ontario Child Health Study ([Boyle et al., 1987](#_ENREF_15)); PART (by Swedish acronym) = Mental Health, Work and Relations study ([Danielsson et al., 2016](#_ENREF_19)); PATH = The Personality and Total Health Study ([Anstey et al., 2011](#_ENREF_3)); PMCP = Pitt, Mother & Child Project ([Shaw et al., 2003](#_ENREF_64)); R = Range; SCL = John Hopkins Symptom Checklist ([Derogatis, 1992](#_ENREF_22)); SCID = Structured Clinical Interview for DSM-III-R ([Spitzer et al., 1987](#_ENREF_66)); SDUSAP = Student Drug Use Survey in the Atlantic Provinces ; SEM = Structural Equation Model; SMFQ = Short Mood and Feelings Questionnaire ([Angold et al., 1995](#_ENREF_2)); SSAGA = Semi-Structured Assessment for the Genetics of Alcoholism ([Lynskey et al., 2004](#_ENREF_47)); T = Time point of assessment; USNCS = United States National Comorbidity Study ([Kessler, 1994](#_ENREF_40)); VAHCS = Victorian Adolescent Health Cohort Study ([Patton et al., 2007](#_ENREF_51)); WHO-MDI = World Health Organization – Major Depressive Inventory ([Bech et al., 2001](#_ENREF_8)); WMHS = World Mental Health Survey ([Kessler and Üstün, 2008](#_ENREF_41)); YASR = Young and Adult Self-Report ([Achenbach, 1997](#_ENREF_1)); YNLS = Young in Norway Longitudinal Study ([Pedersen, 2007](#_ENREF_52)). | | | | | | | | |

**sAppendix 1. Methods**

*Study sample*

The Cambridge Study in Delinquent Development (CSDD), originally designed by Donald J. West and directed since 1982 by David P. Farrington, is a prospective longitudinal study of the development of offending and antisocial behavior in a cohort of 411 boys born mostly in 1953 living in a homogeneous, working class urban area of South London [a review of major findings may be found in several books ([West and Farrington, 1977](#_ENREF_73), [West and Farrington, 1973](#_ENREF_72), [West, 1982](#_ENREF_71), [West, 1969](#_ENREF_70), [Piquero et al., 2007](#_ENREF_53), [Farrington et al., 2013](#_ENREF_24), [Farrington et al., 2009](#_ENREF_27)) as well as in several summary papers ([Farrington et al., 2006a](#_ENREF_23), [Farrington, 1995](#_ENREF_25), [Farrington and West, 1990](#_ENREF_28))]. The sample comprised a complete population of boys from six primary schools who were aged 8-9 in 1961/62 in a deprived area in South London. Most of the boys (357, 87%) were White in appearance and of British origin([Farrington et al., 2006b](#_ENREF_26)). There were multiple waves (T1- T7) of data collection which included participants being interviewed in their school [at ages 8 (T1), 10 (T2), 14 (T3), in research offices (at ages of 16 (T4) and 18 (T5)] or in their homes (at ages 32 (T6) and 48 (T7)] by social science graduates. Parents were interviewed (about once per year) and questionnaires were completed by the boys’ teachers (about once every two years) between ages 8 and 15 to complement information about troublesome/aggressive behavior in school and difficulties at home.

*Measures*

Presence of Major Depressive Disorder (MDD)

Lifetime diagnosis of Major Depressive Disorder (MDD) and age of onset of MDD were assessed by a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) ([First et al., 1998](#_ENREF_31)) as part of a psychiatric interview at T7. Subjects were classified as those with or without a lifetime diagnosis (MDD) by age 48 (T7).

Cannabis use

Cannabis use at the ages of 14 (T3) and 18 years (T5) was assessed in terms of frequency of use (number of times used in past 6 months) and ever used (vs. never used) before that time-point of assessment. Cannabis use at ages 32 (T6) and 48 years (T7) was assessed in terms of frequency of use (number of times used in the preceding 5 years) and presence (vs. absence) of use (used more than once in the 5 years preceding the interview).

Covariates

Covariates included in the simple analysis were chosen based on previous research, reporting a link between depression and:

1. Alcohol use ([Brook et al., 2002](#_ENREF_16), [Bovasso, 2014](#_ENREF_13)):
2. Self-reported presence (vs. absence) of binge drinking ( at least 13 units of alcohol drunk in one evening in the last month yes/no) was assessed at T5, T6, and T7 and an ordinal variable was computed based on whether binge-drinking was present or not at each of the 3 time-points assessed (score ranging from 0-3).
3. Presence (vs. absence) of a DSM-IV lifetime diagnosis of alcohol use and/or dependence was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) ([First et al., 1998](#_ENREF_31)) as part of the psychiatric interview conducted at age 48 (T7).
4. Cigarette use ([Brook et al., 2002](#_ENREF_16), [Georgiades and Boyle, 2007](#_ENREF_33), [Pedersen, 2007](#_ENREF_52)): Self-reported cigarette use defined as presence of smoking (over 20 cigarettes/ day) was assessed at T5, T6 and T7 and a score (from 0 to 3) was computed based on whether smoking was present or not at each of the 3 time-points assessed (scored from 0 - 3).
5. Other illicit drug use ([Brook et al., 2002](#_ENREF_16)):
6. Self-reported presence (vs. absence) of illicit drug use (other than cannabis) was assessed at T6 (used > 1 prior to age 32) and was coded as a dichotomized variable.
7. DSM-IV diagnosis of substance use and/or dependence other than cannabis use disorder was assessed using the SCID-I as part of the psychiatric interview at age 48 (T7).
8. Socioeconomic status ([Lorant et al., 2003](#_ENREF_45)): Social class assessed at age 10 (T2) was coded as “low” if the family breadwinner had an unskilled manual job. Social class assessed at age 48 (T7) was coded as “low” if a subject had an unskilled manual job or was not working.
9. Employment status: Employment status assessed at age 48 was coded as “unemployed” if there was a period of > 5 months of unemployment in the last 5 years.
10. Other psychiatric illness: Presence (vs. absence) of a diagnosis of mental illness other than depression or substance abuse/dependence was assessed using the SCID-I as part of a psychiatric interview at age 48 (T7). *sTable 2.* displays the prevalence rates of other DSM diagnoses in the sample.
11. Behavioural and emotional problems in childhood ([Rey et al., 2002](#_ENREF_60), [Windle and Wiesner, 2004](#_ENREF_74), [De Graaf et al., 2010](#_ENREF_20)) including:
12. Antisocial personality: Antisocial traits were assessed at age 10 (T2) based on teacher, peer, or parent ratings using the antisocial personality scale (AP) (Farrington 1991).
13. Childhood anxiety: Anxiety was assessed at age 10 (T2).
14. Childhood conduct problems: Conduct problems were assessed at age 8 (T1) based on teacher and parent ratings of being “troublesome” and at age 14 (T3) were based on a teacher’s rating of being aggressive in school.

*Statistical methods*

Data was analysed using R3.1.3 ([R Core Team, 2015](#_ENREF_56)) comprising three main statistical approaches:

1. Logistic regression analysis to estimate the effect of cannabis use group on risk of subsequent diagnosis of MDD (presence vs. absence of MDD by age 48). Given the focus on risk of subsequent MDD, we excluded one case where depression was diagnosed prior to the reported use of cannabis [diagnosis received at age 36, admitted to cannabis use at T7 (age 43-48) but not T6 (age 27-32)]. Three cases were classified as cannabis-using subjects prior to the diagnosis of MDD, although we were unable to establish accurately whether onset of cannabis use actually preceded the diagnosis of MDD [n=1 reported cannabis use at T6 (age 27-32) and received diagnosis of MDD at age 30, n=2 reported cannabis use at T7 (age 43-48) and received diagnosis of MDD at age 44/43]. To address the potential effects of reverse causation, we carried out further analysis using longitudinal modelling that specifically elaborated on the issue of directionality (cf. fixed-effects analysis below). The cannabis use predictor was coded as a categorical variable that took into account age of first reported use [early-onset user (reported use at age 18 or before) vs. late-onset user (reported use subsequent to age 18)] and frequency of use [high-frequency user (> 450 times used across T3, T5, T6, T7) vs. low-frequency user (< 450 times used)]. This cut-off was chosen to generate a “high-frequency” cannabis group based on cannabis use pattern reported by our sample, here defined as greater than twice the third quantile (Q3) for number of times used [Q3 = 200 times used in those who used it at least once in their lifetime]. In the regression analyses, these 4 different cannabis use groups were compared to a non-user group as the reference group (no reported use of cannabis at T3, T5, T6 and T7). Multiple regression analysis was carried out including those co-variates that were significantly (p<0.05) associated with risk of MDD in chi-square tests.
2. Cox proportional hazard regression analysis was employed to test whether the time until diagnosis of MDD was significantly different between the different cannabis use groups. Person years of follow up (age 0 to age 48) were used as the underlying time-scale. Simple and multiple analyses were carried out, including the same categorical cannabis predictor and covariates as in the logistic regression analysis. The Hazard Ratio (HR) was reported for the cannabis groups, as well as all covariates included in the model (cf. *Table 3*.).The proportional hazards assumption was checked, revealing that the assumption of proportionality was not violated for any of the variables included.
3. Fixed-effects logistic regression models were fitted in order to extend the ordinary logistic regression by adjusting for time-invariant, non-observed, fixed factors that vary across individuals, such as family background, genetic influences, personality or pre-existing depressive traits. In order to investigate the potential moderating effect of age of onset and frequency of use, we set up two developmental dependent models, including one that assessed the effect of changes in cannabis frequency [(0) non-user; (1) low frequency user = < 150 times used at time of assessment (i.e. use less than Q3 per assessment); (2) high-frequency user = > 150 times used at time of assessment] on risk of development of MDD within the age range of 14-18 years, one within the age range of 18-32 years and one within the age range of 32-48 years. In order to investigate any effect that may have occurred in the reverse direction (i.e. reverse causation: development of MDD predisposing to a subsequent increase in cannabis frequency)*,* we ran a second set of fixed-effects models that examined the effect of occurrence of MDD during two distinct developmental periods (diagnosis between 18 to 32 years and diagnosis between 33 to 48 years) as a predictor for subsequent changes in frequency of cannabis use. The simple and multiple regression models were fitted using the R package lme4 ([Bates et al., 2015](#_ENREF_7)) for binary (risk of depression) and categorical outcomes (increase in cannabis frequency category). In the multiple model we included other illicit drug use and presence of other mental illness as random-effects.

**sAppendix 2. Supplementary Results**

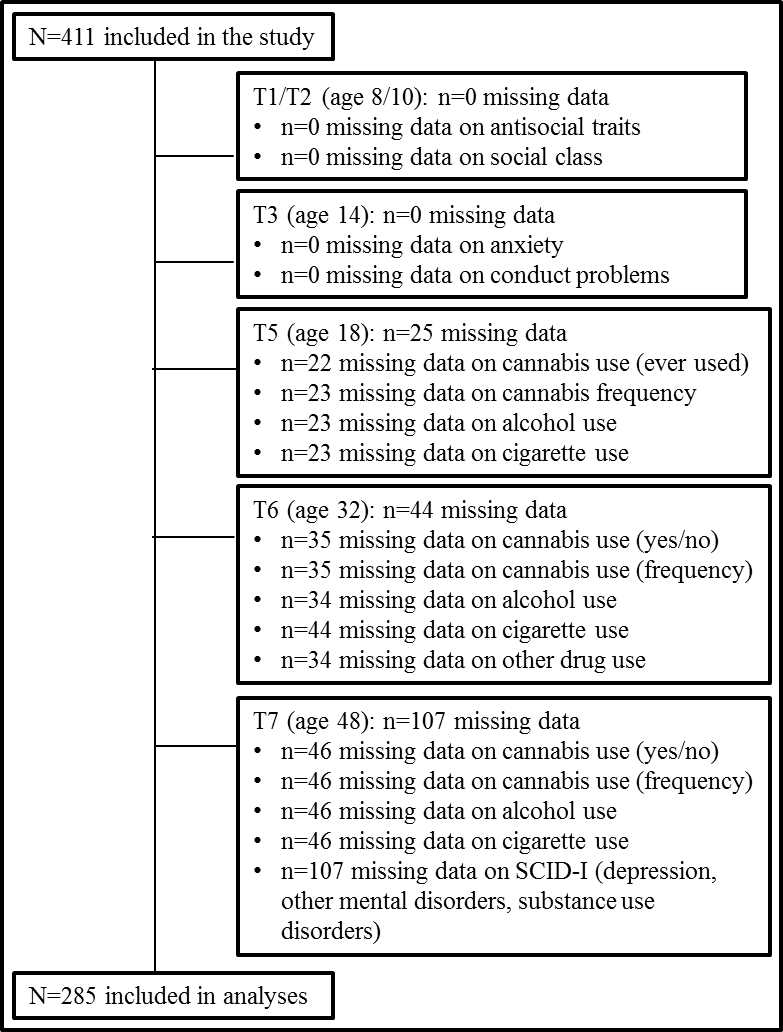
Out of the 411 boys assessed at baseline, complete multi-wave cannabis and depression data (T1-T7) at follow up 48 years later was available for a total number of N=285 (cf. Flow chart, *sFigure 1.*). Comparing subjects that dropped out throughout follow up (n=126) to completers (n=285) in demographic variables and outcome data revealed that there were no significant differences between the two groups (cf. *sTable1*).

**sAppendix 3. Supplementary Discussion**

Certain limitations should be taken into consideration when interpreting these results. Firstly, the sample included a select group of predominantly white males who grew up in in a working class urban environment in the 1960s and 1970s, for which reason the results may not generalize to females, other ethnicities or social classes. This also limited our ability to investigate any potential moderating effects of gender, as examined in previous studies ([Patton et al., 2007](#_ENREF_51), [Poulin et al., 2005](#_ENREF_54)). Despite the use of longitudinal panel data, this design does not allow us to make definitive conclusions regarding causality since fixed-effects models can neither account for individual unmeasured factors that vary over time nor do they address sufficiently the possibility of reverse causality. However, by exploring a range of potential confounders as well as by testing bi-directional cross-lagged relationships (cannabis on depression and vice versa), the results provide a higher level of evidence in support of cannabis use as a causal risk factor for depression than the majority of the prior studies. Such an analytical design is considered as a quasi-experimental design that is only second best to randomised control trials when identifying causal risk factors ([Murray et al., 2009](#_ENREF_49)).

Absence of effects of late-onset cannabis use on the risk of subsequent depression may reflect a lack of power to detect such effect. Nevertheless, we found that the effect of changes in cannabis frequency became more pronounced as the age of onset of exposure decreased, suggesting that initiation of cannabis use in later life was associated with a lower risk of developing subsequent MDD. This was further supported by combining the two late-onset groups in order to increase sample power (cf. *sTable 7.*). Nevertheless, future studies including larger samples should model the effects of cannabis use at different stages across the life-span in order to derive more precise estimates for age-dependent effects of cannabis use. The inclusion of more frequent follow-up assessments at shorter intervals (e.g. yearly assessments), especially in early neurodevelopmental stages could help explore developmental sensitivities to cannabis use in greater detail. In this context, future studies should also investigate the potential mechanisms of effects of cannabis over the life span. Furthermore, the inclusion of narrower and more numerous follow ups (e.g. yearly assessments), especially in early neurodevelopmental stages, could help to explore questions on developmental sensitivities to cannabis use in more detail.

**sFigure 1. Follow up flow chart**



**Note.** SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders ([First et al., 1998](#_ENREF_31))

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| --- | --- | --- |
| **sTable 2.** Prevalence of diagnosis of other mental illness | | |
| DSM Diagnosis | Number of subjects diagnosed | Percentage |
| Bipolar | 0/285 | 0% |
| Schizophrenia | 1/285 | 0.004% |
| Anxiety/Stress\* | 77/285 | 27% |
| Eating disorder | 2/285 | 0.007% |
| \* Includes panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorder, somatoform disorder, adjustment disorder | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **sTable 3.** Differences in demographics and outcome in later life and between completers and drop outs | | | |
|  | **Complete data n/nav (%)a** | **Incomplete data n/nav (%) a,b** | ***p*** |
| **Sample size** | **n=285** | **n=126** |  |
| **Cannabis variables** | | | |
| Cannabis at age 18 (yes) | 82/285 (29%) | 27/105 (28%) | 0.86 |
| Cannabis at age 32 (yes) | 50/285 (17.5%) | 19/91 (21%) | 0.47 |
| Cannabis at age 48 (yes) | 44/285 (15%) | 11/80 (14%) | 0.71 |
| **Mental health outcome (DSM diagnosis)** | | | |
| Lifetime diagnosis depression (yes) | 58/285 (20%) | 2/19 (11%) | 0.30 |
| Lifetime diagnosis anxiety disorder (yes) | 73/285 (26%) | 4/19 (21%) | 0.19 |
| Other substance use disorder (yes) | 29/285 (10%) | 2/19 (11%) | 0.96 |
| Alcohol use disorder (yes) | 56/285 (20%) | 3/19 (16%) | 0.68 |
| Any mental health diagnosis (yes)b | 171/285 (40%) | 5/19 (21%) | 0.24 |
| **Early life variables** | | | |
| Alcohol use at 18 (yes) | 57/285 (20%) | 24/103 (23%) | 0.48 |
| Cigarette use at 18 (yes) | 78/284 (28%) | 26/104 (25%) | 0.63 |
| Antisocial Personality at age 10 (yes) | 65/285 (23%) | 33/126 (26%) | 0.46 |
| Low social class at age 10 (yes) | 50/285 (18%) | 29/126 (23%) | 0.19 |
| Anxiety at age 14 (yes) | 25/285 (9%) | 13/126 (10%) | 0.62 |
| Conduct problems at age 14 (yes) | 99/285 (35%) | 35/126 (28%) | 0.17 |
| **Late life variables** | | | |
| Other illicit drug use at age 32 (yes) | 25/285 (9%) | 11/92 (12%) | 0.37 |
| Cigarette use at 48 (yes) | 71/285 (25%) | 20/80 (25%) | 0.99 |
| Alcohol use at 48 (yes) | 59/285(21%) | 19/80 (24%) | 0.56 |
| **Note.** *p*= p-value for chi-square test  **a** Prevalence reported for n (number of subjects scoring “yes” for the variable of interest) out of nav (total number of subjects for which data was available)  b Subjects with incomplete data include those who dropped out (n=107 that did not complete the SCID-I interview) and those with missing data in other variables (n=19)  c Including bipolar, schizophrenia, depression, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorder, somatoform disorder, adjustment disorder, any substance use disorder | | | |

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| **sTable 4.** Childhood and life factors associated with risk of MDD by age 48 (N=284)\* | | |
|  | *χ2* | *p* |
| Cannabis use (ever/SR) | 9.93 | **0.002** |
| Cigarette use (cum/SR)1 | 4.18 | 0.24 |
| Alcohol use (cum/SR) | 0.03 | 1.00 |
| Alcohol (DSM Diagnosis) | 3.14 | 0.08 |
| Presence other illicit substance use (SR) | 6.79 | **0.009** |
| Presence substance use disorder (DSM) | 1.14 | 0.29 |
| Other mental illness (DSM Diagnosis) | 6.85 | **0.008** |
| Anxiety at age 14 (yes) | 0.26 | 0.61 |
| Antisocial at age 10 (yes) | 0.52 | 0.47 |
| Conduct problems at age 14 (yes) | 1.31 | 0.25 |
| Low social class at age 10 (yes) | 0.20 | 0.65 |
| Low social class at age 48 (yes) | 1.13 | 0.29 |
| Employment status at age 48 (unemployed) | 10.54 | **0.001** |
| Note. DSM = Diagnosis based on Structured Clinical Interview for DSM-IV Axis I Disorders ([First et al., 1998](#_ENREF_31)); SR = Self-reported.  1 missing data for n=2  \*n=1 cases excluded since MDD was diagnosed prior to cannabis use | | |

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| **sTable 5.** Anxiety and risk of subsequent MDD: Logistic regression analysis\* | | | |
| Multiple logistic regression (N=284) | **OR** | **95% CI** | ***p*** |
| Cannabis late onset – low frequency | 0.68 | 0.10 – 2.65 | 0.63 |
| Cannabis late onset – high frequency | 2.23 | 0.25 – 15.10 | 0.42 |
| Cannabis early onset – low frequency | 2.41 | 1.22 – 4.76 | **0.01** |
| Cannabis early onset – high frequency | 8.83 | 1.29 – 70.97 | **0.03** |
| Other mental illness | 2.18 | 1.15 – 4.14 | **0.02** |
| Other illicit drug use | 1.10 | 0.28 – 3.76 | 0.89 |
| Employment status (unemployed) | 2.34 | 1.18 – 4.58 | **0.01** |
| Anxiety at age 14 | 1.01 | 0.32 – 2.81 | 0.99 |
| **Note.** Early onset = Cannabis use at age 18 or before; High frequency = > 450 cumulative number of times used across time points (age 18, 32, 48)  \*n=1 cases excluded since MDD was diagnosed prior to cannabis use. Reference group = never cannabis users | | | |

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| **sTable 6.** Anxiety/stress disorder and risk of MDD: Logistic regression analysisa | | | |
| Multiple logistic regression (N=284) | **OR** | **95% CI** | ***p*** |
| Cannabis late onset – low frequency | 0.67 | 0.10 – 2.62 | 0.62 |
| Cannabis late onset – high frequency | 2.51 | 0.28 – 17.42 | 0.36 |
| Cannabis early onset – low frequency | 2.43 | 1.22 – 4.80 | **0.01** |
| Cannabis early onset – high frequency | 8.78 | 1.27 – 71.62 | **0.03** |
| Anxiety/Stressb | 2.41 | 1.26 – 4.60 | **0.01** |
| Other illicit drug use | 1.11 | 0.28 – 3.87 | 0.87 |
| Employment status (unemployed) | 2.32 | 1.18 – 4.52 | **0.01** |
| **Note.** Early onset = Cannabis use at age 18 or before; High frequency = > 450 cumulative number of times used across time points (age 18, 32, 48)  an=1 cases excluded since MDD was diagnosed prior to cannabis use. Reference group = never cannabis users  b Includes panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorder, somatoform disorder, adjustment disorder | | | |

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| --- | --- | --- | --- |
| **sTable 7.** Sensitivity analysis: Cannabis profiles and risk of subsequent MDD (Logistic regression analyses)\* | | | |
| Simple logistic regression (N=284) | **OR** | **95% CI** | ***p*** |
| Cannabis late onset | 1.15 | 0.32 - 3.34 | 0.81 |
| Cannabis early onset – low frequency | 2.67 | 1.39 - 5.12 | **0.003** |
| Cannabis early onset – high frequency | 10.07 | 2.33 - 51.61 | **0.002** |
| **Note.** Reference group = never cannabis users; Early onset = Cannabis use at age 18 or before; High frequency = > 450 cumulative number of times used across time points (ages 18, 32, 48)  \*n=1 cases excluded since MDD was diagnosed prior to cannabis use | | | |

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