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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Abstract

Background

Evidence regarding the association between cannabis use and depression remain conflicting, especially as studies have not typically adopted a longitudinal design with a follow-up period that was long enough to adequately cover the risk period for onset of depression.

Method

Males from the Cambridge Study in Delinquent Development (CSDD) (N=285) were assessed 7 times from age 8 to 48 years to prospectively investigate the association between cannabis use and risk of Major Depressive Disorder (MDD). A combination of multiple analyses (logistic regression, Cox regression, fixed-effects analysis) was employed to explore the strength and direction of effect within different developmental stages.

Results

Multiple regression analyses revealed that early onset cannabis use (before age 18) but not late onset cannabis use (after age 27) was associated with a higher risk and shorter time until a subsequent MDD diagnosis. This effect was present in high-frequency ([Odds Ratio (OR) 8.83, 95% Confidence Interval (CI) 1.29-70.79]; [Hazard Ratio (HR) 8.69, 95%CI 2.07-36.52]) and low-frequency early-onset users ([OR2.41, 95%CI 1.22-4.76]; [HR2.09, 95%CI 1.16-3.74]). Effect of increased frequency of cannabis use on increased risk of subsequent MDD was observed only for use during adolescence (age 14-18) but not at later life stages, while controlling for observed and non-unobserved time-invariant factors. Conversely, MDD in adulthood (age 18-32) was linked to a reduction in subsequent cannabis use (age 32-48).

Conclusions

The present findings provide evidence implicating frequent cannabis use during adolescence as a risk factor for later life depression. Future studies should further examine causality of effects in larger samples.

INTRODUCTION

Understanding the nature of the association between use of cannabis, the most widely used illicit drug worldwide (UNODC, 2015), and depressive disorders is important while considering health policies involving cannabis, because depressive disorders are the leading contributor to the global burden of disease attributable to mental and substance use disorders(Whiteford et al., 2013). While evidence is fairly consistent in support of cannabis use as a risk factor for the development of psychosis (Moore et al., 2007) and its relapse (Patel R et al., 2016, Schoeler et al., 2016b, Schoeler et al., 2016a), little consensus exists regarding its association with depressive disorders. This is particularly important in light of marked shifts in public attitudes to cannabis use and its legal standing in society in many countries (Benac and Caldwell, 2013). Although studies have reported feelings of depression, tiredness, lack of motivation, low energy and anxiety as the most commonly reported negative experiences in cannabis users (Reilly et al., 1998) and cross-sectional evidence suggests that higher levels of depressive symptoms may be associated with cannabis use (Schoeler et al., 2015), uncertainty remains regarding the precise nature of this relationship. For instance, integrating data from 4 different cohorts, Horwood et al. (2012) reported that two of the cohorts suggested that cannabis use leads to the development of depression, a third cohort suggested that depression leads to cannabis use, while the fourth one did not find that either of those relationships were significant when employing longitudinal modelling. Another integrative analysis (Silins et al., 2014) using participant-level data from 3 of these cohorts did not find any association with depression by age 25, when they adjusted for potential confounders.

Other investigations that have tested the direction of this association (whether cannabis use leads to depression or vice versa) in the same sample yielded similarly contradictory results. Some

suggest that cannabis use leads to depression (Hayatbakhsh et al., 2007), while others suggest that depression leads to increase(Feingold et al., 2015) or even decreases (Womack et al., 2016) in cannabis use. One study did not find any significant association (Repetto et al., 2008) and another one reported a bi-directional relationship between cannabis use and depression severity (Baggio et al., 2014). Similarly, results from investigations which tested a unidirectional hypothesis about the nature of this association in their sample are equivocal, with some suggesting that depression is a risk factor of subsequent cannabis use (Wittchen et al., 2007) while a larger number suggest that cannabis use is a risk factor for subsequent depression (Brook et al., 2002, Gage et al., 2015) (for a summary of observational studies see *sTable 1*., Supplementary Material).

A recent meta-analysis of longitudinal studies suggest moderate effects of cannabis use on the risk of development of depression (Lev-Ran et al., 2014), though confidence in these effects was offset by large variability across studies as well as methodological concerns. On balance, this suggests that the possibility of other unobserved sources of confounding, such as a common genetic liability influencing both cannabis use and depression cannot be ruled out (Lynskey et al., 2004). Studies that have explored dose-response relationships either did not find a significant effect of frequency of cannabis use on depression (Feingold et al., 2015, Repetto et al., 2008) or found evidence in support of a dose-response relationship (Brook et al., 2002, Gage et al., 2015). Other evidence reported that the ratio between delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in the cannabis plant, and cannabidiol (CBD), the other main cannabinoid present in the extract of cannabis (i.e. the THC:CBD ratio) was not linked to depression scores in users (Schubart et al., 2011). This is supported by experimental studies that did not find that the administration of THC increased depressive symptoms in healthy subjects

(Englund et al., 2015). Another important determinant of the effect of cannabis, i.e., use during a sensitive developmental period (Pope et al., 2003), was not considered by a majority of the studies. Among the few studies that included age of onset of cannabis use in their analyses, some found more adverse effects if started at a younger age (Hayatbakhsh et al., 2007, Horwood et al., 2012), while most were not indicative of moderating effects of age of onset of cannabis use on risk of depression (Horwood et al., 2012, Lev-Ran et al., 2014).

The main limitation of evidence to date is the lack of a life-span prospective design, combined with multi-wave assessments to follow up a cohort of individuals. Such an approach makes it possible to investigate the question of whether later life depression results from early onset cannabis use. This is particularly crucial as although cannabis use commonly starts in early or mid-adolescence (Wagner and Anthony, 2002), a diagnosis of depressive disorder typically manifests in middle or later life (Kessler et al., 2007). However, most studies to date have examined cohorts comprising only adolescents or young adults, with a maximum follow-up age of 34 years (cf. *sTable 1*., Supplementary Material), thus limiting their ability to detect the incidence of depression, a substantial proportion of which is likely to have onset beyond the follow-up period of these studies. This may largely explain the conflicting nature of association observed in previous studies. In the present study, we have addressed these limitations by employing a prospective, multi-wave, life-span cohort design (including more than 40 years of follow-up, to age 48). Specifically, we investigated the effects of cannabis use on the risk of developing a Major Depression Disorder (MDD) (First et al., 1998) by age 48, by:

(1) assessing the magnitude of the association between cannabis use and depression

(2) exploring whether the effects vary across different developmental stages

(3) controlling for important observed confounders (other illicit drug use, comorbid mental disorder, employment status) and unobserved time-invariant sources of confounding in multiple fixed-effects analyses

(4) investigating the directionality of the association between cannabis use and depression

METHODS

Study sample

The Cambridge Study in Delinquent Development (CSDD) is a prospective longitudinal study of the development of offending and antisocial behaviour in a cohort of 411 boys born mostly in 1953 and living in an ethnically homogeneous, working-class urban area of London (Farrington et al., 2006). They represented the complete population of boys who were 8 years old at that time (1961/62) and were attending one of six primary schools in a deprived area in London. Multiple waves (T1- T7) of data collection, which included participant interviews [at ages 8 (T1), 10 (T2), 14 (T3), 16 (T4), 18 (T5), 32 (T6) and 48 (T7)] complemented information obtained from parents (annually) and teachers (bi-annually) between ages 8 and 15 years. 97% of the sample was white and most were raised in two-parent working class households. A detailed description of the methods is included as supplementary material (cf. *sAppendix 1*., Supplementary Material). The study was approved by the Ethics Committee of the Institute of Psychiatry, Psychology & Neuroscience.

Measures

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 (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) Axis I Disorders (SCID I) (First et al., 1998)

as part of a psychiatric interview at T7. Frequency of cannabis use was assessed at T3, T5, T6 and T7. 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 (Q_3) for number of times used [Q_3 = 200 times used in those who used it at least once in their lifetime]. Covariates included in the simple analysis were chosen based on previous research, including alcohol, cigarette and other illicit drug use, socioeconomic status, other psychiatric illness, behavioural and emotional problems in childhood, childhood anxiety and childhood conduct problems (for details see sAppendix 1, Supplementary Material). Those variables were included as binary variables, for which the higher category was indicative of disadvantage (e.g. low socioeconomic status, presence of childhood anxiety).

Statistical methods

Data was analysed using R3.1.3 comprising three main statistical approaches, which are described in more detail in the sAppendix 1 (Supplementary Material): First, simple 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). Multiple regression analysis was carried out including those co-variates that were significantly ($p \leq 0.05$) associated with risk of MDD in chi-square tests (*sTable 4*., Supplementary Material). Second, simple and multiple 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. The proportional hazards assumption was checked, confirming that the assumption of proportionality was not violated for any of the variables included. Third, 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. 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 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. We ran a second set of fixed-effects models, in order to investigate any effect that may have occurred in the reverse direction. In the multiple regression models we included other illicit drug use, presence of other mental illness and employment status at age 48 as random-effects.

RESULTS

Out of the 411 boys assessed at baseline, complete multi-wave cannabis use and depression data (T1-T7) at follow up (age 48) was available for a total number of N=285 (for follow-up flow chart see *sFigure 1*., Supplementary Material). Comparison of subjects with and those without complete data who were not included in the present analyses carried out, revealed that there were no significant differences between the two groups in early life demographic variables (substance use, antisocial behavior, conduct problems, social class, anxiety), later life outcomes (substance use and mental health outcomes (DSM-IV based) including depression, anxiety disorders, substance use disorders) and cannabis use across the life span (age 18, 32 and 48) (*sTable 3*., Supplementary Material). As shown in *Table 1*., cannabis use was common in this sample,

comprising a proportion of 38.2% of subjects who used the substance at least once upto age 48. The majority of subjects who had ever used cannabis started using the substance between ages 14 and 18 (76%). Although most of the early-onset cannabis users used the substance only around this age (51.8%) and did not continue subsequently, a quarter continued to use the substance subsequently (i.e. 24.1%reported use also at ages 32 and 48). A total of 58 subjects (20.4%) received a diagnosis of MDD by the age of 48, with an estimated mean age of onset of illness of 38.57 (SD 7.13). Significant ($p \leq 0.05$) associations with risk of depression in exploratory analyses were found for cannabis use (ever used), other illicit drug use (ever used by age 32), other diagnosis of mental illness at age 48 and employment status at age 48 (cf. s*Table 4*., Supplementary Material).

========== TABLE 1. ABOUT HERE ==========

Simple logistic regression analysis (*Table* 2.) revealed that those who had never used cannabis had the lowest risk for developing a depressive disorder, whilst the highest risk estimates were found for those who had an early onset of cannabis use (age 18 or before) and continued to use the substance throughout their life (cumulative use endorsed more than 450 times) (OR= 10.07[95% CI 2.33-51.61], p=0.002). The risk was reduced in magnitude but still significant for early-onset users who used cannabis less frequently throughout their life (OR= 2.67[95%CI 1.39-5.12], p=0.003). Alternative specifications of cut-off for defining low frequency and high frequency use for the early-onset and late-onset users did not change the direction of these results (data available on request). After controlling for potential confounders that were significantly associated with depression in simple analyses, including other illicit drug use, presence of other mental health illness and employment status, the effects of cannabis use remained significant for

early-onset, high-frequency users (OR=8.83[95%CI 1.29-70.79], *p*=0.03; *Table 2*.) as well as for early-onset-low-frequency users (OR=2.41[95%CI 1.22-4.76], *p*=0.01). Including anxiety reported at age 14 and presence of a lifetime diagnosis of anxiety or other stress disorders in this model did not alter the results (cf. *sTable 5*. and *sTable 6*., Supplementary Material). In line with these results, Cox regression models (cf. *Table 3*.; *Figure 1*) showed that early-onset cannabis use was associated with a shorter time to onset of MDD for both low-frequency ([HR=2.09 [95%CI 1.16-3.74], *p*=0.01) and high-frequency cannabis users ([HR=8.69 [95%CI 2.07-36.52], *p*=0.003).

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As shown in *Table 4*., the results from the multiple, cross-lagged, fixed-effects models suggest that an increase in cannabis use frequency between ages 14-18 was associated with increased odds for the development of MDD in both early adulthood (age 18-32) by 1.08[95% CI 1.03-1.12] (*p*=0.0008) and subsequently (age 33-48) by 1.20[95%CI 1.10-1.31] ($p \leq 0.0001$). Changes in cannabis use frequency at later life stages were not significantly associated with the development of subsequent depression. For instance, a change in cannabis frequency between

age 18-32 was not a predictor for the development of MDD between age 33 to 48 (1.05[95%CI 0.99-1.11], p=0.10). To explore the issue of reverse causation (i.e. whether cannabis use predicts outcome and vice versa, in the form of a two-way causal relationship), we also tested whether the development of MDD was associated with subsequent changes in the frequency of cannabis use. A diagnosis of MDD between age 18 to 32 was linked to a reduction in frequency of cannabis use between ages 32 and 48 by 0.72[95%CI 0.57-0.92] (p=0.009).

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DISCUSSION

These results provide for the first time evidence suggesting early but not late onset cannabis use may be a risk factor for the subsequent development of major depressive disorder. We observed an effect that was not confounded by other observed and unobserved time-invariant risk factors such as shared genetic or environmental influences or factors that change over time such as the use of other substances or the presence of comorbid psychiatric illness. Adverse effects of cannabis use on the risk of development of MDD and on time until MDD diagnosis were present only in those who had used it at a younger age (before age 18) with the effects being greater in high-frequency user (OR 8.83 / HR 8.69, $p \leq 0.05$) than in low-frequency users (OR 2.41 / HR 2.09, $p \leq 0.05$), while no significant adverse effects were present if cannabis use was initiated at an older age (age 27 onwards) (cf. *Table 2*. and *Table 3*.). Early-onset, high-frequency cannabis users experienced depression more than 5 years earlier compared to never users (41 vs. 46.65 years). This is consistent with the idea of developmental sensitivity to the adverse effects of cannabis (Pope et al., 2003), as well as with the results of our fixed-effects (FE) analysis. The

risk of developing subsequent depression was predicted only by an increase in cannabis use during adolescence (between ages 14 and 18) but not early adulthood (between ages 18 and 32) or subsequently (use between ages 32 and 48). In addition, the results suggest that the effect of early-onset cannabis use cannot be explained by unobserved time-invariant sources of confounding such as shared genetic or stable environmental factors. This may also explain why previous longitudinal analyses of panel data in younger cohorts (up to the maximum age of 34, cf. *sTable 1*., Supplementary Material) have been inconclusive as to whether an increase of cannabis use leads to an increase in risk of depression over time(Horwood et al., 2012, Silins et al., 2014), even when dose-response patterns were tested(Repetto et al., 2008, Womack et al., 2016). Since cigarette use across the life-span was not significantly linked to the risk of MDD, our results were not confounded by smoking, consistent with previous studies(Hayatbakhsh et al., 2007). These findings are also consistent with evidence from animal research, in which long-term exposure of cannabinoids resulted in depression-like symptoms only in adolescent but not adult rats(Bambico et al., 2010). Interestingly, cross-lagged, fixed-effects analysis revealed that a diagnosis of MDD in adulthood (age 18-32) was predictive of reduction in cannabis use subsequently, which is consistent with evidence from a recent longitudinal study(Womack et al., 2016). While subsequent reduction in cannabis use may have been a result of depressed individuals receiving specific therapeutic input following contact with health services as a result of their depression, this was not specifically examined. While these results cannot completely rule out the possibility that depression may also lead to cannabis use (Horwood et al., 2012, Wittchen et al., 2007), e.g. as a form of self-medicating behaviour, this seems less likely. This is also in line with a previous meta-analysis reporting overall significant adverse effects of cannabis use on depression outcome (OR 1.17), with more pronounced effects being present in

heavier users (OR 1.62) (Lev-Ran et al., 2014). As we cannot completely rule out the possibility that depression occurring early on in life led to subsequent initiation or continuation of cannabis us, these results should be treated with caution and future studies should investigate more thoroughly the bi-directional pathways between cannabis use and depression in order to definitively rule out the possibility of reverse causation, as in previous longitudinal studies examining causal nature of associations with cannabis use (Schoeler et al., 2016b, Schoeler et al., 2016c). Since we investigated different groups of cannabis-using subjects based on their usage pattern, future studies may also evaluate continuous measures of cannabis use, such as the number of joints smoked over specified life-periods. These results are to be considered against certain limitations of this study, such as comprising a select group of predominantly white males who grew up in a working class urban environment in the 1960s and 1970s. Therefore, the results may not generalize to the wider population and in particular to females, those from other ethnicities, individuals brought up in rural environments or children from different socio-economic status. Future studies should therefore expand on this and include individuals from more heterogeneous backgrounds. Another limitation is the use of self-report measures of cannabis and other substance use leading to potential under-reporting and the inclusion of only modestly sized cannabis-user groups. The relatively modest size of our sample limits our ability to conclude with certainty that late-onset cannabis use does not increase the risk of depression over the long-term. However, sensitivity analysis carried out by combining the two late-onset groups in order to increase sample power did not change the conclusion ($OR_{late\text{-}onset}$=1.15, p=0.81). Although attrition in this sample was relatively low (Rocque et al., 2017), only the subsample for whom complete information on SCID I was available was included in our study. This reduced the sample size for the present analyses and may have induced bias in our

estimates. However, non-assessed subjects were not strictly drop-outs and, hence, it is unlikely that this reflects a systematic bias linked to individual characteristics that would have confounded the association between cannabis use and risk of development of depression. This is also supported by the fixed effects analysis, which has the advantage of controlling for all unobserved time-invariant individual factors and confirmed the results from our multivariate models. Future studies should therefore include larger samples to assess the association between different trajectories of cannabis use and the risk of depression. Although we assessed a range of covariates at various time points, we cannot draw firm conclusions on whether or when other mediating or modifying factors impact on the relationship between cannabis use and risk of development. The lack of consideration of other potential unmeasured time-variant factors that cannot be accounted for in fixed-effects models (e.g. epigenetic phenomena) could have also affected the results. For instance, 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, as discussed in greater detail as part of supplementary material (Appendix 3.), these factors are unlikely to have affected the direction of results presented here. Regarding the assessment of cannabis use, it is worth noting at the outset that the present cohort study was initiated several decades ago, much before the population level effects of cannabis and other drug use began to be systematically measured. Hence, assessments of exposure were perhaps less optimal than if one were to initiate such a cohort now. Finally, it should be pointed out that MDD was only assessed at the last follow-up assessment (at age 48), which may have resulted in under-reporting. However, this is unlikely to have systematically affected either the cannabis unexposed or exposed groups or the early-onset or late-onset

subgroups of cannabis users. Similarly, if self-reported cannabis use had been under-reported by users, which is usually not the case as data from studies that validated self-report information with biological tests suggest (Di Forti et al., 2012, Basurto et al., 2009, Denis et al., 2012), this is likely to have resulted in an underestimation of effect size. Hence, it is unlikely that under-reporting as a result of recall bias would have affected the direction of relationship that we have observed. It should also be pointed out that we included only a relatively conservative outcome measure (presence of DSM-based diagnosis of MDD), for which reason we could not estimate the effect of cannabis use on more subtle depressive symptomatology across the life-span. Furthermore, we were not able to control for the effect of early life sub-clinical depressive or other affective symptomatology that predate the first onset of depression in our models. However, we attempted to address the possibility that early emotional disturbance or dysregulation may have in turn led to early onset cannabis use, we examined whether anxiety at age 14 was predictive of subsequent cannabis use, which was not the case when we tested the association for cannabis use reported at age 16 (p=0.29), age 18 (p=0.74), age 32 (p=0.74) or age 48 (p=0.21). Hence, future studies should use multi-point assessments across the life-span to prospectively assess depressive outcomes both in terms of syndromal disorder as well as depressive symptoms as done in previous studies in young adults (Horwood et al., 2012) as well as include biological validation of the predictor of interest i.e., cannabis use. Future studies should also investigate other potential risk factors such as poor coping or emotional dysregulation that may influence or mediate the effects of cannabis use on risk of depression. Since the THC levels in the cannabis have increased in recent years (Mehmedic et al., 2010, ElSohly et al., 2016), with THC being only one of the more than 80 different cannabinoids

identified to date (ElSohly and Gul, 2014), future investigations should also distinguish between different types of cannabis that differ in their potency and cannabinoid constituents.

In summary, we found that cannabis use, especially during a developmentally sensitive period of life is associated with subsequent risk of developing major depression after controlling for potential confounders, suggestive of a potential causal relationship, although future investigations on this topic are necessary in order to draw more definite conclusions. These results have important public health implications given that depressive disorders are one of the top ten causes of disability in the world (Whiteford et al., 2013).

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Contributors

DPF provided the data. SB, DT and DF designed the study and supervised the analyses, TS and DT carried out the data analysis and wrote the first draft together with SB. J-BP and JWC provided data, reviewed the results and contributed to the final draft of the manuscript.

Declaration of interest

None.

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Figure(s)

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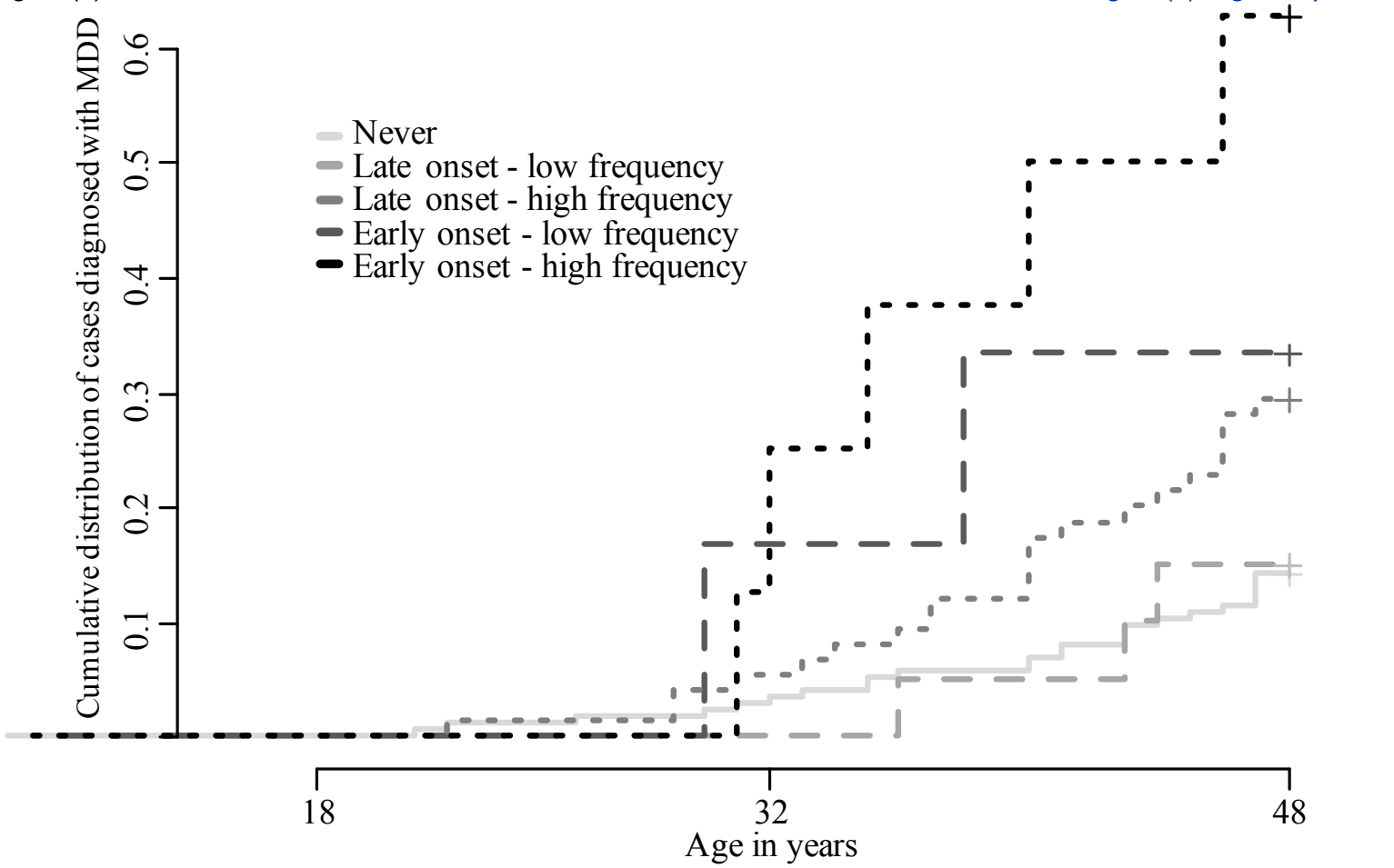

Table 2. Cannabis profiles and risk of subsequent MDD: Logistic regression analyses*

Simple logistic regression (N=284)	**OR**	**95% CI**	***p***
Cannabis late onset – low frequency	0.71	0.11 – 2.69	0.66
Cannabis late onset – high frequency	3.02	0.40 – 16.34	0.22
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**
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	0.26 - 14.94	0.42
Cannabis early onset – low frequency	2.41	1.22 - 4.76	**0.01**
Cannabis early onset – high frequency	8.83	1.29 - 70.79	**0.03**
Other mental illness (yes)	2.18	1.15 - 4.14	**0.02**
Other illicit drug use (yes)	1.10	0.28 - 3.75	0.88
Employment status (unemployed)	2.34	1.19 - 4.53	**0.01**

Note. Reference group = never cannabis users; Early onset = Cannabis use at age 18 or before; High frequency = $\geq$ 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

Table 3. Cannabis profiles and time until subsequent MDD: Hazard ratios (HR)*

Simple Cox Regression (N=284)	**HR**	**95% CI**	***p***
Cannabis late onset – low frequency	1.05	0.32-3.49	0.93
Cannabis late onset – high frequency	2.90	0.69-12.25	0.15
Cannabis early onset – low frequency	2.26	1.27-4.01	**0.005**
Cannabis early onset – high frequency	6.65	2.54-17.41	**0.0001**
Multiple Cox Regression (N=284)	**HR**	**95% CI**	***p***
Cannabis late onset – low frequency	1.06	0.32-3.54	0.92
Cannabis late onset – high frequency	2.77	0.61-12.51	0.19
Cannabis early onset – low frequency	2.09	1.16-3.74	**0.01**
Cannabis early onset – high frequency	8.69	2.07-36.52	**0.003**
Other mental illness (yes)	1.78	1.05-3.03	**0.03**
Other illicit drug use (yes)	0.73	0.25-2.15	0.56
Employment status (unemployed)	1.97	1.14-3.41	**0.02**

Note. Reference group = never cannabis users; Early onset = Cannabis use at age 18 or before; High frequency = $\geq$ 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

Table 4. Fixed effects regression analysis

	Univariate			Multivariate*		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Effect of Cannabis frequency on MDD in young adolescence (age 18 – 32)						
Cannabis frequency (age 14 - 18)	1.08	(1.04 – 1.13)	**0.0002**	1.08	(1.03 – 1.12)	**0.0008**
Cannabis frequency (age 18 - 32)	1.02	(1.00 – 1.05)	0.07	1.01	(0.99 – 1.05)	0.32
Effect of Cannabis frequency on MDD in adulthood (age 32 – 48)						
Cannabis frequency (age 14 - 18)	1.22	(1.12 – 1.33)	**<0.0001**	1.20	(1.10 – 1.31)	**<0.0001**
Cannabis frequency (age 18 - 32)	1.07	(1.02 – 1.13)	**0.007**	1.05	(0.99 – 1.11)	0.10
Cannabis frequency (age 32 - 48)	1.04	(0.99 – 1.09)	0.17	1.01	(0.95 – 1.07)	0.76
	Univariate			Multivariate*		
	Est.	**95% CI**		**Est.**	**95% CI**	
Effect of MDD on cannabis frequency in adulthood (age 32 – 48)						
MDD (age 18 - 32)	0.77	(0.59 – 0.99)	**0.05**	0.72	(0.57 – 0.92)	**0.009**
MDD (age 32 - 48)	1.07	(0.94 – 1.21)	0.33	1.02	(0.90 – 1.15)	0.77

Note. Increase in frequency = increase in one unit [(0) non-user; (1) low frequency user; (2) high frequency user]

*Controlled for random effects, including (1) other psychiatric illness and (2) other illicit drug use, (3) employment status at age 48

Table 1. Cannabis and depression trajectories (N=285)

Age of onset MDD	Mean in years (SD)	38.57 (7.13)
Diagnosis of MDD	Ever diagnosed (yes) (n)	20.4% (58)
	Before 18 (n)	0% (0)
	Between 18-32 (n)	22.4% (13)
	Between 33-48 (n)	77.6% (45)
Cannabis use trajectory	Ever used (yes)	38.2% (109)
	Onset up to 14 (n)	0% (0)
	Onset between 15-18 (n)	76.1% (83)
	Onset between 27-32 (n)	13.8% (15)
	Onset between 43-48 (n)	10.1% (11)
Cannabis use pattern	Never used (n)	61.8% (176)
	Late onset – low frequency (n)	0.08% (22)
	Late onset – high frequency (n)	0.01% (4)
	Early onset – low frequency (n)	0.27% (78)
	Early onset – high frequency (n)	0.02% (5)
Cannabis-Depression Trajectory	Cannabis → MDD	32 (11.3%)
	Cannabis → no MDD	75 (26.3%)
	Never cannabis, no MDD	152 (53.3%)
	Never cannabis → MDD	25 (8.8%)
	MDD → Cannabis	1 (0.4%)

Note. MDD = Diagnosis of Major Depression Disorder based on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

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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Includes

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)	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)	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)	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)	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)	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)	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)	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)	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)	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	LSECD /	88	T1: 14	C1: Frequency of use at T1	D1: Depression	Severity	In boys:	-

al. (1991)	US		T2: 18		score at T2 (CES-D)		C1 → D1 * In girls: C1 → D1 (NS)	
Brook et al. (2002)	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)	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)	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)	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)	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)	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)	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)	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.	MTFS /	1334	T1: 11 (M)	C1: Use (≥ 1 on year before T1)	D1: MDD at T1	Risk	D1 → C1 (NS)	Gender

(2004)	US		T2: 14 (M)	vs. non-use C2: Regular use (≥1/month at T4) vs. non-use	(DICA)	prediction	D1 → C2 (NS)	
Longitudinal studies investigating bi-directional effects between cannabis use and depression								
Horwood et al. (2012)	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)	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)	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)	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)	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)	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)	BECA / US	849	T1: 1980 (year), age: > 18 T2: 1995	C1: CUD at T1 C2: CUD between T1 and T2	D1: Depression (yes/no) between T1 and T2 (DIS) D2: Number of	Risk prediction	C1 → D1 * C1 → D2 * D2 → C2 (NS)	Gender, age, SES, ethnicity, education, antisocial behaviour, stressful life events, chronic illness, baseline depressive symptoms

			(year)		depressive symptoms at T1 (DIS)			
Hayatbakhsh et al. (2007)	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)	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)	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)	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)	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); ATP = The Australian Temperament Project (Prior et al., 2000); ATR = Australian Twin Register (Lynskey et al., 2004); AUDADIS-IV = Alcohol Use Disorder and Associated Disabilities Interview Schedule (Grant et al., 2003a); BDI = Beck's Depression Inventory (Beck et al., 1987); BECA = Baltimore Epidemiologic Catchment Area study (Anthony and Helzer, 1991); BSI = Brief Symptom Inventory (Degoratis and Spencer, 1982); CES-D = Centre for Epidemiological Studies - Depression Scale (Radloff, 1977); CIC = Children in the Community sample (Brook et al., 2002); CHDS = The Christchurch Health and Development Study (Fergusson and Horwood, 2001); CIDI = Composite International Diagnostic Interview (Robins et al., 1983); CIS = Clinical Interview Schedule (Lewis et al., 1988); CIS-R = computerized revised Clinical Interview Schedule (Lewis et al., 1992); C-SURF = Cohort Study on Substance Use Risk Factors (Baggio et al., 2014); CUD = Cannabis Use Disorder; DASS = Depression Anxiety Stress Scale (Lovibond and Lovibond, 1995); DICA = Diagnostic Interview for Children and Adolescents (Reich, 2000); DIS = Diagnostic Interview Schedule (Robins et al., 1981); DISC = Diagnostic Interview Schedule for Children (Costello et al., 1982); DMHDS = Dunedin Multidisciplinary Health and Development Study (Silva and Stanton, 1996); ECD = Epidemiologic Catchment Area Program (Tien and Anthony, 1990); EDSP = Early Developmental Stages of Psychopathology (Wittchen et al., 1998); FEM = Fixed Effects Model; GDS = Goldberg Depression Scale (Goldberg et al., 1988); JHU-RT = John Hopkins University – Randomized Trial (Harder et al., 2008); LAT = Life Across Time: A Longitudinal Study; LSECD = Longitudinal Study of Ego and Cognitive Development (Block and Block, 1980); M = Mean; MUSP = Mater University Study of Pregnancy (Najman et al., 2005); NESARC = National Epidemiologic Survey on Alcohol and Related Conditions (Grant et al., 2003b); MTFS = Minnesota Twin Family Study; NESPAR = National Epidemiologic Survey on Alcohol and Related Conditions (Blanco et al., 2016); NEMESIS = Netherlands Mental Health Survey and Incidence Study; NSMHW = National Survey of Mental Health and Wellbeing (Sawyer et al., 2000); OCHS = Ontario Child Health Study (Boyle et al., 1987); PART (by Swedish acronym) = Mental Health, Work and Relations study (Danielsson et al., 2016); PATH = The Personality and Total Health Study (Anstey et al., 2011); PMCP = Pitt, Mother & Child Project (Shaw et al., 2003); R = Range; SCL = John Hopkins Symptom Checklist (Derogatis, 1992); SCID = Structured Clinical Interview for DSM-III-R (Spitzer et al., 1987); SDUSAP = Student Drug Use Survey in the Atlantic Provinces ; SEM = Structural Equation Model; SMFQ = Short Mood and Feelings Questionnaire (Angold et al., 1995); SSAGA = Semi-Structured Assessment for the Genetics of Alcoholism (Lynskey et al., 2004); T = Time point of assessment; USNCS = United States National Comorbidity Study (Kessler, 1994); VAHCS = Victorian Adolescent Health Cohort Study (Patton et al., 2007); WHO-MDI = World Health Organization – Major Depressive Inventory (Bech et al., 2001); WMHS = World Mental Health Survey (Kessler and Üstün, 2008); YASR = Young and Adult Self-Report (Achenbach, 1997); YNLS = Young in Norway Longitudinal Study (Pedersen, 2007).

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, West and Farrington, 1973, West, 1982, West, 1969, Piquero et al., 2007, Farrington et al., 2013, Farrington et al., 2009) as well as in several summary papers (Farrington et al., 2006a, Farrington, 1995, Farrington and West, 1990)]. 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). 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) 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, Bovasso, 2014):
    a. 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).
    b. 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) as part of the psychiatric interview conducted at age 48 (T7).
(2) Cigarette use (Brook et al., 2002, Georgiades and Boyle, 2007, Pedersen, 2007): 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).
(3) Other illicit drug use (Brook et al., 2002):
    a. Self-reported presence (vs. absence) of illicit drug use (other than cannabis) was assessed at T6 (used $\geq$ 1 prior to age 32) and was coded as a dichotomized variable.
    b. 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).
(4) Socioeconomic status (Lorant et al., 2003): 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.

(5) 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.
(6) 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.
(7) Behavioural and emotional problems in childhood (Rey et al., 2002, Windle and Wiesner, 2004, De Graaf et al., 2010) including:
    a. 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).
    b. Childhood anxiety: Anxiety was assessed at age 10 (T2).
    c. 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) 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 ($\geq$ 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 (Q_3) for number of times used [Q_3 = 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 ($p \leq 0.05$) 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 Q_3 per assessment); (2) high-frequency user = $\geq$ 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) 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

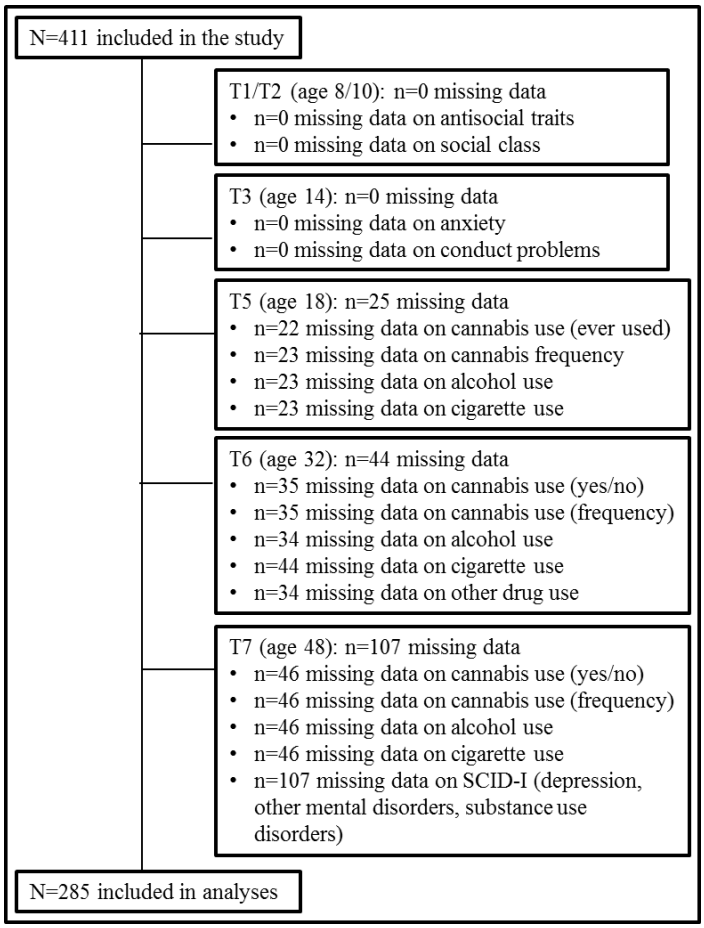
Out of the 411 boys assessed at baseline, complete multi-wave cannabis and depression data (T1-T7) at follow up 48 years later was available for a total number of N=285 (cf. Flow chart, *sFigure 1*.). Comparing subjects that dropped out throughout follow up (n=126) to completers (n=285) in demographic 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, Poulin et al., 2005). 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).

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)

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/n_{av} (%)[a]	Incomplete data n/n_{av} (%) [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 n_{av} (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

sTable 4. Childhood and life factors associated with risk of MDD by age 48 (N=284)*

	χ^2	*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); SR = Self-reported.

[1] missing data for n=2

*n=1 cases excluded since MDD was diagnosed prior to cannabis use

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

sTable 6. Anxiety/stress disorder and risk of MDD: Logistic regression analysis[a]

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/Stress[b]	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)
[a]n=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

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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