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Journal: Journal of Substance Use
Year: 2016
Volume: 21
Issue: 1
Pages: 85-91
DOI: 10.3109/14659891.2014.966342

Associations of age at cannabis first use and later substance abuse with mental health and depression in young men

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Abbreviated title: Age at cannabis first use, mental health and depression

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ABSTRACT

Purpose: This study aimed to determine if the associations between age at cannabis first use and mental health and depression persist after controlling for the misuse of cannabis, other illicit drugs, alcohol and cigarettes.

Methods: Baseline data from an ongoing cohort study on substance use risk factors were used (N=5521). The association between age at cannabis first use and the frequency of cannabis use was assessed using a Cox proportional hazard model. Associations with other illicit drug use, alcohol dependence, nicotine dependence, mental health and depression were tested using linear regressions and logistic regressions.

Results: Participants using cannabis 'almost every day' were on average 2 years younger at cannabis first use than those using cannabis 'once a month or less'. Age at cannabis first use was also associated with other illicit drug use, alcohol dependence and nicotine dependence. Associations with mental health and depression were substantially attenuated after adjustment for the misuse of cannabis and other substances.

Conclusions: These findings show that early cannabis onset is associated with later impairments in mental health and depression, however these are largely explained by later substance abuse. Effective preventive measures are needed to delay cannabis onset and to avoid the progression from cannabis to using other drugs.

Keywords: Cannabis; depression; mental health.

INTRODUCTION

Cannabis is the most widely used illegal substance worldwide, with a prevalence of 3.9% of the population aged 15–64 (United Nations Office on Drugs and Crime, 2013). There is a great heterogeneity in legislation on cannabis consumption between countries, ranging from strict prohibition to legalized use. There is sound evidence that heavy cannabis use is associated with undesirable consequences, such as school dropout (Townsend et al., 2007), increased risk of motor vehicle collisions (Asbridge et al., 2012), mental health problems (Fernandez-Artamendi et al., 2011), earlier onset of psychosis (Burns, 2013), lung function abnormalities (Lee & Hancox, 2011) and a lower quality of life (Gruber et al., 2003).

Although the focus has mainly been on the frequency of cannabis use, research has shown that early use of cannabis is also an important predictor of these undesirable consequences. Adolescence seems to be a particularly vulnerable period during which to be exposed to drugs due to critical neurodevelopmental processes that peak in this period (Lisdahl et al., 2013). Early use of cannabis has been shown to alter executive function (Fontes et al., 2011), as well as the ability to inhibit impulsive behaviors (Gruber et al., 2012). Among adolescents, early initiation to cannabis is associated with engaging in multiple health risk behaviors (Fergusson et al., 1996; Fergusson & Horwood, 1997; DuRant et al., 1999). Age at cannabis first use is also linked to school dropout (Fergusson et al., 1996; Fergusson & Horwood, 1997; van Ours & Williams, 2009), mental health problems (Fernandez-Artamendi et al., 2011), depression (Fergusson et al., 1996; Fergusson & Horwood, 1997; Arseneault et al., 2002), attempts at suicide (Lynskey et al., 2004), schizophrenia (Arseneault et al., 2002; Anglin et al., 2012) and psychosis (Stefanis et al., 2004; Schubart et al., 2011).

Early use of cannabis is also well known for favoring the heavy use of cigarettes (Fergusson et al., 1996), alcohol (Fergusson et al., 1996; Fergusson & Horwood, 1997; Lynskey et al., 2003; Agrawal et al., 2004), cannabis (Fergusson et al., 1996; Fergusson & Horwood, 1997; Lynskey et al., 2003; Agrawal et al., 2004; Lynskey et al., 2012) and other illicit drugs (Fergusson & Horwood, 1997; Agrawal et al., 2004; Lynskey et al., 2012). It is still not clear to what extent the association between early use of cannabis and young people's subsequent health is caused by using cannabis at this vulnerable age, or by the subsequent abuse of cannabis and other substances. Better knowledge of the strength of these relationships is clearly relevant for preventive strategies. If the association between age at cannabis first use and a lower health status remains strong after controlling for substance abuse, then delaying the onset of cannabis

first use would become a high priority. If the association between age at first use and decreased health status does not persist after controlling for substance abuse, then this will highlight the importance of preventing early cannabis users from progressing to using other drugs.

There is currently important heterogeneity in the definition of what early cannabis use actually constitutes. The great majority of studies have used cut-off ages for defining early use of cannabis, such as before the ages of 12 (DuRant et al., 1999), 14 (Zullig et al., 2001; Anglin et al., 2012), 15 (Fergusson et al., 1996; Arseneault et al., 2002; Fontes et al., 2011), 16 (Fergusson & Horwood, 1997; Stefanis et al., 2004; van Ours & Williams, 2009), 17 (Lynskey et al., 2004; de Graaf et al., 2010) or 18 (Arseneault et al., 2002; Agrawal et al., 2004; Fairman & Anthony, 2012). The use of a cut-off age is somewhat arbitrary, however, and provides neither a comparison between age groups nor the possibility of identifying the most vulnerable one. We therefore chose to consider several age groups in order to provide a more detailed picture of the associations between age at cannabis first use and subsequent abuse of other substances, mental health and depression. This picture should be more useful for the development or improvement of preventive strategies targeted towards limiting the negative consequences of cannabis use.

The present study aimed to determine the associations between age at cannabis first use and mental health and depression, and to test whether these potential relationships persist after controlling for the frequency of cannabis use and for the misuse of other illicit drugs, alcohol and cigarettes.

METHODS

Study design

Baseline data from the Cohort Study on Substance Use Risk Factors (C-SURF) were used. C-SURF is a large cohort study designed to assess substance use patterns and their related consequences in young Swiss men. Details about C-SURF enrollment procedures are provided in Studer et al. (2013a, 2013b). Briefly, participants were enrolled in three of Switzerland's six army recruitment centers, covering 21 of 26 cantons (including all French-speaking ones). Since army recruitment is mandatory in Switzerland, and involves no pre-selection, this provided a representative sample of young Swiss men. Assessments were done outside the army context, by means of questionnaires sent to participants' private addresses. They were informed that data would be kept strictly confidential and would not be shared with third parties, including the army. With their responses hidden from the army, participants had no reason to conceal answers which might have influenced the recruitment process. Data were collected between September 2010 and March 2012.

Participants

A total of 5990 conscripts consented to participate and completed the questionnaire. Missing values were listwise deleted and analyses were based on a final sample of 5521 participants (92% of responders). Detailed analyses indicated only small differences between consenters and non-consenters (Studer et al., 2013b) and between responders and non-responders (Studer et al., 2013a). Ethical approval for the study was granted by the Ethics Committee for Clinical Research of Lausanne University Medical School (Protocol No. 15/07).

Measurements

Mental health

Mental health was measured using the Medical Outcomes Study 12-item Short Form Health Survey (SF-12v2) (Ware et al., 2002). The mental component summary (MCS) score was computed. Norm-based scores were obtained by linear transformations (mean=50; SD=10). Based on a clinically meaningful change in health-related quality of life measures of half a standard deviation (Norman et al., 2003), poor mental health was defined as an MCS score below 45 (Dey et al., 2013).

Depression

States of depression were assessed using the Major Depressive Inventory (MDI). The MDI contains 10 items answered on a six point Likert scale, from 0 'never' to 5 'all the time'. This provides a total score for the severity of symptoms ranging from 0 (no depression) to 50 (extreme depression) (Olsen et al., 2003). In addition, major depression can be scored diagnostically according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (Bech et al., 2001).

Substance use

Participants were asked to report any lifetime use of cannabis and their age at first use. The latter was subsequently split into the following age groups: <13 years old, 13–15 years old, 16–18 years old, >18 years old, and lifetime non-users. The frequency of cannabis use over the past 12 months was assessed using the following response choices: no use, once a month or less, 2–4 times per month, 2–3 times per week, 4–5 times per week, and almost every day. Alcohol dependence status was determined using the DSM-IV diagnostic criteria, as defined by a positive response to any three or more of seven dependence criteria (Knight et al., 2002). Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991), a six-item questionnaire yielding a score ranging between 0 'no symptoms of dependence' and 10 'high number of symptoms of dependence'. A score of 4 or above was used to define a nicotine dependent status (Huang et al., 2008). Participants were asked to report any lifetime use of illicit drugs other than cannabis, covering the following categories: 1) hallucinogens, magic mushrooms, psilocybin, peyote, mescalin; 2) other hallucinogens (LSD, PCP/Angel Dust, 2-CB, 2-CI); 3) salvia divinorum; 4) speed; 5) amphetamine,

metamphetamine, amphetamine sulfate (e.g. dexedrine, benzedrine); 6) crystal meth (Ice); 7) poppers (amyl nitrite, butyl nitrite); 8) solvent sniffing (e.g. glue, solvent and gases such as benzine, ether, toluene, trichloroethylene, nitrous oxide); 9) ecstasy, MDMA; 10) cocaine, crack, freebase; 11) heroin; 12) ketamine (Special K), DXM; 13) GHB/GBL/I-4 Butanediol (BDB); 14) research chemicals (e.g. mephedrone, butylone and methedrone); and 15) Spice or similar substances.

Socio-demographics

Socio-demographic variables were measured and recorded as follows: *age*, *language* ('German'; 'French'), perceived *family financial situation* ('below average'; 'average'; 'above average'), *education* ('primary school'; 'vocational secondary school'; 'general secondary school' [high school or equivalent]; 'tertiary' [university or other graduate school]), *parental education* ('primary school'; 'vocational secondary school'; 'general secondary school' [high school or equivalent]; 'tertiary' [university or other graduate school]), *occupation* ('employed'; 'student'; 'inactive' [unemployed, social or disability pension]), *place of residence* ('rural' [below 10,000 inhabitants]; 'urban' [10,000 inhabitants or above]).

Statistical analysis

The analyses were conducted using SPSS 21 software (IBM, Armonk, NY). Descriptive statistics were used to present socio-demographics according to age group at cannabis first use. Differences between age groups at first use were tested using one-way ANOVA (continuous variables) or Chi-squared tests (categorical variables). When tests showed significant ANOVA or Chi-squared results, post-hoc analyses were computed using Tukey HSD tests or standardized residuals (difference between observed and expected frequencies), respectively. P-values of pairwise comparisons were corrected to adjust for multiple post-hoc comparisons with an overall $p<.05$ used as the significance level.

The associations between age at cannabis first use and alcohol dependence, nicotine dependence and illicit drug use were tested using logistic regressions, with lifetime non-users of cannabis as a reference, and controlling for socio-demographics. Among cannabis users, the Cox proportional hazard model (Cox, 1972) was used to measure the association between age at cannabis first use and the frequency of cannabis use over the past 12 months, controlling for socio-demographics. Common graphic procedures were undertaken to ensure that the proportional hazard assumption was not violated.

The associations between age at cannabis first use and mental health and depression were tested in two ways. First, two linear regressions were used with age at cannabis first use as the independent variable, and the SF12-MCS score and the MDI total score as the dependant variables. Second, two logistic regressions were used with age at cannabis first use as the independent variable (with lifetime non-users as a reference), and poor mental health and major depression as the dependant variables. Linear regression and logistic regression models were run controlling for socio-demographics (model 1), for the frequency of cannabis use over the past 12 months (model 2), and for alcohol dependence, nicotine dependence and lifetime illicit drug use (model 3).

RESULTS

Table 1 displays socio-demographics stratified by age at cannabis first use. More than half of the participants had never used cannabis (N=2901). Among those who reported having used cannabis, age at first use was most frequent in the 16–18 years old group (N=1472), followed by 13–15 years old (N=901), >18 years old (N=126) and <13 years old (N=121). All socio-demographic variables were significantly associated with age at cannabis first use (ANOVA or Pearson Chi-squared test). Lifetime non-use of cannabis was negatively associated with tertiary parental education (p=.002) and an inactive occupational status (p=.023). An age at cannabis first use of <13 years old was positively associated with below-average family financial situation (p<.001) and an inactive occupational status (p<.001). Age at cannabis first use of 13–15 years old was negatively associated with a vocational secondary school parental education (p=.001). Age at cannabis first use of 16–18 years old was negatively associated with a primary school parental education (p=.015) and the employed occupational status (p=.012). Age at cannabis first use >18 years old was positively associated with being a French speaker (p=.025).

Age at cannabis first use was strongly associated with substance abuse (Table 2). The younger the age at cannabis first use, the higher the risk for alcohol dependence, nicotine dependence and illicit drug use. As illustrated in Figure 1, the cumulative incidence of cannabis use according to age exhibited a similar shape for each frequency of cannabis use over the past 12 months, but participants declaring the highest level of cannabis use were on average 2 years younger at cannabis first use than those declaring the lowest level. The hazard ratios increased progressively among the frequencies of cannabis use, as compared to the lowest frequency.

Table 3 summarizes the associations between age at cannabis first use and mental health and depression, analyzed using either linear regression models (right-side columns, with SF12 – MCS and MDI scores as dependent variables) or logistic regression models (left-side columns, with mental health and depression dichotomized as poor mental health and major depression respectively). The independent contribution of each of the explanatory variables is also indicated. In model 1, linear regression showed that age at cannabis first use was significantly associated with mental health (β=-0.74, p<.001), and showed a dose-response relationship. This was confirmed in the logistic regression predicting poor mental health. Age at cannabis first use was significantly associated with depression (β=0.61, p<.001), yet the logistic regression predicting major depression was only significant for the 13–15 years old group, as compared to lifetime non-users (OR 1.64, p=.028). When controlling for the frequency of cannabis use

(model 2), age at cannabis first use was still significantly associated with mental health (β=-0.44, p<.001) and depression (β=0.33, p<.001), but the strengths of these relationships were about half of those in model 1. Interestingly, frequency of cannabis use was not associated with poor mental health as a dichotomous outcome in a dose-response manner, but odds ratios were highest for intermediate use frequencies. The logistic regression model analyzing major depression was not significant. When additionally controlling for alcohol dependence, nicotine dependence, and lifetime illicit drug use (model 3), the association between age at cannabis first use and mental health was once again reduced by half (β=-0.24, p=.037). The association between age at cannabis first use and depression was not significant (β=0.08, p=.393), and the logistic regression models were not significant either. Finally, it is worth noting that in all three models linear and logistic regressions were not significant for the >18 years old group.

DISCUSSION

The aim of this study was to determine whether the associations between age at cannabis first use and mental health and depression persist after adjusting for the use of cannabis and other substances. The results confirmed that cannabis first use at a young age is an important risk factor in the progression to other drug use. Mental health and depression were significantly predicted by age at cannabis first use. However, after controlling for the frequency of cannabis use and for the misuse of alcohol, cigarettes and other drugs, the association with depression did not persist and the association with mental health was much attenuated. This underlines the importance of preventing early cannabis users from progressing to other drugs.

This study builds on the current knowledge of the association between early use of cannabis and subsequent impairments in mental health (Fernandez-Artamendi et al., 2011) and depression (Fergusson et al., 1996; Fergusson & Horwood, 1997; Arseneault et al., 2002). Prior studies used a variety of cut-off ages to define early use, and did not systematically control for the misuse of cannabis and other substances. Interestingly, however, Schubart et al. (2011) grouped ages at cannabis first use as <12 years old, 12–15 years old, 15–18 years old, 18–20 years old and >20 years old. Subclinical psychiatric experiences were assessed using the Community Assessment of Psychic Experiences (CAPE) questionnaire. Compared to the 15–18 years old group, the 12–15 years old group, and more importantly the <12 years old group were associated with subclinical positive and negative symptoms of psychosis, but not with the depressive dimension. Analyses were adjusted for a set of sociodemographic variables and the amount of cannabis use. In line with the present study, this showed that simply dichotomizing age at cannabis cannabis first use — which is the most frequently adopted approach when analyzing or controlling for the onset of cannabis use — causes a substantial loss of information. Continuous or categorical variables should be preferred to the use of cut-offs.

As mentioned in the introduction, strong associations have previously been reported between age at cannabis first use and later use of cigarettes, alcohol, cannabis and illicit drugs. The dose-response relationship observed in the present study was also recently found by Lynskey et al. (2012). The mechanisms underlying these associations are still not fully understood, but several possible explanations have been theorized (van Leeuwen et al., 2011; Vanyukov & Ridenour, 2012). First, the gateway hypothesis posits a stage-like sequence of drug use progression, starting from licit drug use such as tobacco and alcohol, followed by illicit soft drug use such as

cannabis, ending with illicit hard-drug use such as cocaine and heroine. Second, the common liability model does not assume such order in the sequence of drug use, but rather a common liability including genetic and individual factors that make certain young people more prone to both cannabis and other illicit drug use. More recently, the route of administration model has proposed that the use of a given substance favors later use of another one if both substances share a common route of administration. Controversy exists regarding which model best explains substance use patterns in young people. The present study does not support the route of administration model, since age at cannabis first use significantly predicted alcohol dependence. More genetic and individual factors would be required to take a clear position in favour of the gateway hypothesis or the common liability model.

Among individuals whose first use of cannabis is early in life, the present results suggest that the risks of mental health problems and depression are subsequently mediated by abusive consumption of cannabis or other substances. Early onset does not appear to be an indicator of later mental health problems *per se*, as long as it is not followed by harmful patterns of substance use. However, it is likely that later substance abuse predominantly occurred in participants whose initial cannabis use was at a high frequency, rather than those who initially consumed cannabis only once or at a very low frequency. A 2002 cohort study indicated that frequent cannabis use during the period from 15 to 18 years old predicted higher rates of depression and anxiety at 21 years old in women, but not in men (Patton et al., 2002). The authors controlled for frequency of drinking and a set of socio-demographic variables, but not for smoking or the use of other illicit drugs. Fergusson et al. (1997) reported a dose-response relationship between the frequency of cannabis use at 15–16 years old and the rates of major depression and anxiety disorder at 16–18 years old. However, the relationship did not persist after controlling for the use of cannabis, alcohol and other substances at 16–18 years old. The present findings suggest, however, that frequent cannabis use earlier in adolescence may play a more important role. This would be consistent with animal studies showing that cannabis use during adolescent development increases the risk of psychiatric diseases (Chadwick et al., 2013). The frequency of cannabis use in early adolescence might be a key parameter in predicting which early cannabis users are at risk of later substance abuse and mental health problems. This issue still needs to be addressed using a prospective study design.

The frequency of cannabis use was assessed for its contribution to the prediction of mental health and depression, and was therefore not the main focus of this study. Strikingly, however,

the risk for poor mental health and major depression was highest for intermediate rather than maximal frequencies of cannabis use. The highest frequencies of use may provide short-term and transient improvements, whereas mental health problems may result from prolonged use at intermediate frequencies. Stefanis et al. (2004) obtained a similar pattern, yet on the contrary, Schubart et al. (2011) reported a dose-response relationship between depressive symptoms and the amount of money spent on cannabis per week.

The present study's main strength is that it is based on a large, nationally representative sample, with adjustment for a broad set of confounders. A detailed analysis of age at cannabis first use was performed, which has rarely been done before. Some limitations must however be considered. First, the present study's retrospective nature precludes causal inference and may have introduced recall bias in the self-reported age at cannabis first use. A similar study design has been used in adult populations, and the relatively young age of the participants attenuates this potential bias. Second, the present findings were obtained from a sample of young men, and cannot be generalized to women.

In conclusion, age at cannabis first use significantly predicted mental health and depression in emerging adulthood, but the association with depression did not persist, and the association with mental health was considerably reduced, after controlling for the frequency of cannabis use and for the use of other illegal substances, alcohol dependence and nicotine dependence. These findings highlight the need to implement programs and policies that discourage early cannabis first use, but more importantly, the need to develop preventive strategies aimed at avoiding the progression from cannabis use to the misuse of other substances.

ACKNOWLEDGEMENTS

This work was supported by the Swiss National Science Foundation [grant number 33CS30_139467]. The funding source had no role in: study design; data collection, analysis, and interpretation; preparation of the manuscript; or the decision to submit this paper for publication. The authors are grateful to Charlotte Eidenbenz for her extensive contribution to study coordination.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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FIGURE LEGEND

Figure 1. Cumulative incidence of cannabis use by age group for different frequencies of use. HR = hazard ratio (95% confidence interval).

Table 1. Socio-demographics by age at cannabis first use (N=5521).

Characteristics [*]	Age at cannabis first use					
	<13 years (n=121)	13 to 15 years (n=901)	16 to 18 years (n=1472)	>18 years (n=126)	Lifetime non-users (n=2901)	P [†]
Age [mean (SD)]	20.14 (1.32) [a]	20.02 (1.20) [a]	20.01 (1.24) [a]	21.02 (1.40) [b]	19.91 (1.17) [a]	<.001
Language						
German	56 (46.3%)	419 (46.5%)	645 (43.8%)	35 (27.8%) [-]	1341 (46.2%)	.001
French	65 (53.7%)	482 (53.5%)	827 (56.2%)	91 (72.2%) [+]	1560 (53.8%)	
Family financial situation						
Below average	33 (27.3%) [+]	150 (16.6%)	191 (13.0%)	23 (18.3%)	393 (13.5%)	<.001
Average	43 (35.5%)	337 (37.4%)	582 (39.5%)	62 (49.2%)	1254 (43.2%)	
Above average	45 (37.2%)	414 (45.9%)	699 (47.5%)	41 (32.5%)	1254 (43.2%)	
Education						
Primary school	64 (52.9%)	453 (50.3%)	712 (48.4%)	48 (38.1%)	1375 (47.4%)	.009
Vocat. secondary school	30 (24.8%)	230 (25.5%)	338 (23.0%)	34 (27.0%)	792 (27.3%)	
General secondary school	24 (19.8%)	200 (22.2%)	395 (26.8%)	38 (30.2%)	683 (23.5%)	
Tertiary	3 (2.5%)	18 (2.0%)	27 (1.8%)	6 (4.8%)	51 (1.8%)	
Parental education						
Primary school	6 (5.0%)	48 (5.3%)	65 (4.4%) [-]	14 (11.1%)	212 (7.3%)	<.001
Vocat. secondary school	34 (28.1%)	254 (28.2%) [-]	513 (34.9%)	46 (36.5%)	1093 (37.7%)	
General secondary school	27 (22.3%)	156 (17.3%)	236 (16.0%)	15 (11.9%)	512 (17.6%)	
Tertiary	54 (44.6%)	443 (49.2%) [+]	658 (44.7%)	51 (40.5%)	1084 (37.4%) [-]	
Occupational status						
Employed	66 (54.5%)	480 (53.3%)	656 (44.6%) [-]	57 (45.2%)	1495 (51.5%)	<.001
Student	34 (28.1%) [-]	355 (39.4%)	726 (49.3%) [+]	57 (45.2%)	1270 (43.8%)	
Inactive	21 (17.4%) [+]	66 (7.3%)	90 (6.1%)	12 (9.5%)	136 (4.7%) [-]	
Place of residence						
Rural	60 (49.6%)	517 (57.4%)	864 (58.7%)	74 (58.7%)	1820 (62.7%)	.001
Urban	61 (50.4%)	384 (42.6%)	608 (41.3%)	52 (41.3%)	1081 (37.3%)	

Notes: [*] Data are N (%), unless otherwise indicated ; [†]ANOVA (age) or Pearson Chi-squared test (all other variables) ; [a, b] means with different subscript letters differ significantly (post-hoc Tukey HSD tests at p<.05) ; [+] significantly higher prevalence than expected (standardized residuals >2.58 to adjust for multiple testing) ; [-] significantly lower prevalence than expected (standardized residuals <-2.58 to adjust for multiple testing).

Table 2. Associations between age at cannabis first use and substance abuse.

Predictor	Alcohol dependence †	Nicotine dependence †	Illicit drug use †
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Age at cannabis first use			
Lifetime non- users	1.00	1.00	1.00
>18 years old	2.00 (1.07-3.72) *	3.95 (2.13-7.31) ***	3.21 (1.1-9.37) *
16 to 18 years old	2.58 (2.07-3.22) ***	6.11 (4.68-7.97) ***	4.89 (3.19-7.51) ***
13 to 15 years old	3.85 (3.04-4.86) ***	11.54 (8.80-15.13) ***	10.91 (7.2-16.53) ***
<13 years old	5.12 (3.23-8.09) ***	20.49 (13.14-31.94) ***	25.11 (14.28-44.16) ***

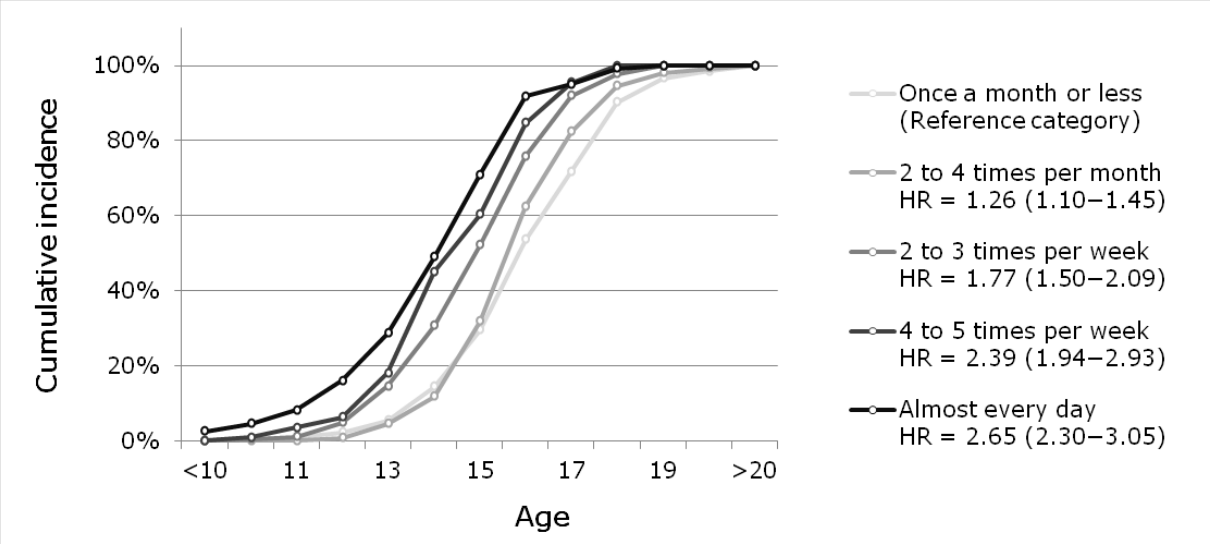
Notes: CI=confidence intervals of the odds ratios (OR); † adjusted for socio-demographics ; *p<.05 ; ***p<.001.

Table 3. Associations between age at cannabis first use and mental health and depression, controlling for socio-demographics and substance abuse.

		Logistic regression				Linear regression			
		Poor mental health		Major depression		Mental health (SF12 - MCS)		Depression (MDI)	
		$\chi^{2\,\dagger}$	OR (95% CI)	$\chi^{2\,\dagger}$	OR (95% CI)	F †	β (SE)	F †	β (SE)
Model 1 #	Age at cannabis first use	38.64 ***		6.49		17.52 ***		17.16 ***	
	Lifetime non- users		1.00		1.00		Ref		Ref
	>18 years old		1.30 (0.88-1.93)		0.99 (0.30-3.25)		-0.99 (0.77)		0.65 (0.64)
	16 to 18 years old		1.41 (1.22-1.63) ***		1.09 (0.71-1.67)		-1.62 (0.27) ***		1.12 (0.22) ***
	13 to 15 years old		1.57 (1.32-1.87) ***		1.64 (1.06-2.55) *		-2.12 (0.32) ***		1.83 (0.27) ***
	<13 years old		1.71 (1.14-2.55) **		2.15 (0.89-5.18)		-2.97 (0.78) ***		2.83 (0.65) ***
Model 2 #	Age at cannabis first use	13.56 **		0.57		6.08 ***		4.14 **	
	Lifetime non-users		1.00		1.00		Ref		Ref
	>18 years old		1.29 (0.87-1.91)		0.97 (0.29-3.20)		-0.95 (0.76)		0.62 (0.63)
	16 to 18 years old		1.29 (1.11-1.50) ***		0.87 (0.55-1.36)		-1.23 (0.27) ***		0.75 (0.23) ***
	13 to 15 years old		1.28 (1.06-1.55) *		1.02 (0.61-1.73)		-1.12 (0.34) **		0.90 (0.29) **
	<13 years old		1.17 (0.76-1.79)		0.99 (0.37-2.61)		-1.11 (0.81)		1.11 (0.67)
	Cannabis use disorder	33.17 ***	1.90 (1.53-2.37) ***	17.32 ***	3.04 (1.82-5.05) ***	60.37 ***	-3.32 (0.43) ***	75.29 ***	3.08 (0.36) ***
Model 3 #	Age at cannabis first use	5.88		3.52		2.45 *		0.44	
	Lifetime non-users		1.00		1.00		Ref		Ref
	>18 years old		1.23 (0.83-1.83)		0.79 (0.24-2.64)		-0.73 (0.76)		0.32 (0.63)
	16 to 18 years old		1.19 (1.02-1.40) *		0.67 (0.42-1.08)		-0.85 (0.28) **		0.28 (0.23)
	13 to 15 years old		1.11 (0.91-1.36)		0.68 (0.39-1.20)		-0.44 (0.36)		0.07 (0.30)
	<13 years old		0.98 (0.63-1.53)		0.51 (0.18-1.47)		-0.26 (0.82)		0.00 (0.68)
	Cannabis use disorder	19.82 ***	1.68 (1.34-2.11) ***	8.29 **	2.25 (1.31-3.87) **	36.37 ***	-2.67 (0.44) ***	41.04 ***	2.34 (0.37) ***
	Alcohol dependence	21.04 ***	1.6 (1.31-1.95) ***	20.09 ***	2.82 (1.84-4.31) ***	41.54 ***	-2.43 (0.38) ***	97.45 ***	3.07 (0.31) ***
	Nicotine dependence	0.19	1.05 (0.85-1.3)	7.93 **	2.02 (1.26-3.25) **	1.55	-0.49 (0.39)	18.09 ***	1.37 (0.32) ***
	Other illicit drug use	8.65 **	1.31 (1.1-1.56) **	1.27	1.32 (0.82-2.11)	12.13 ***	-1.18 (0.34) ***	10.73 **	0.91 (0.28) **

Notes: SF12=12-item Short Form Health Survey; MCS=Mental Component Summary (high score indicates good mental health); MDI=Major Depressive Inventory (high score indicates elevated symptoms of depression); SE=standard error of the regression coefficients (β) ; CI=confidence intervals of the odds ratios (OR) ; † independent contribution to the model ; # adjusted for socio-demographics ; * p<.05 ; ** p<.01 ; *** p<.001.

Figure 1


Cumulative incidence
100%
80%
60%
40%
20%
0%
<10
11
13
15
17
19
>20
Age
Once a month or less
(Reference category)
2 to 4 times per month
HR = 1.26 (1.10–1.45)
2 to 3 times per week
HR = 1.77 (1.50–2.09)
4 to 5 times per week
HR = 2.39 (1.94–2.93)
Almost every day
HR = 2.65 (2.30–3.05)