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Published in:
Drug and Alcohol Dependence

DOI:
10.1016/j.drugalcdep.2013.06.009

Link to publication

Citation for published version (APA):
Predicting the transition from frequent cannabis use to cannabis dependence: A three-year prospective study

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ARTICLE INFO

Article history:
Received 6 February 2013
Received in revised form 27 May 2013
Accepted 14 June 2013
Available online 22 July 2013

Keywords:
Cannabis dependence
Frequent cannabis use
Risk factors
Longitudinal Exposure

ABSTRACT

Background: Frequent cannabis users are at high risk of dependence, still most (near) daily users are not dependent. It is unknown why some frequent users develop dependence, whereas others do not. This study aims to identify predictors of first-incidence DSM-IV cannabis dependence in frequent cannabis users.

Methods: A prospective cohort of frequent cannabis users (aged 18–30, n = 600) with baseline and two follow-up assessments (18 and 36 months) was used. Only participants without lifetime diagnosis of DSM-IV cannabis dependence at baseline (n = 269) were selected. Incidence of DSM-IV cannabis dependence was established using the Composite International Diagnostic Interview version 3.0. Variables assessed as potential predictors of the development of cannabis dependence included sociodemographic factors, cannabis use variables (e.g., motives, consumption habits, cannabis exposure), vulnerability factors (e.g., childhood adversity, family history of mental disorders or substance use problems, personality, mental disorders), and stress factors (e.g., life events, social support).

Results: Three-year cumulative incidence of cannabis dependence was 37.2% (95% CI = 30.7–43.8%). Independent predictors of the first incidence of cannabis dependence included: living alone, coping motives for cannabis use, number and type of recent negative life events (major financial problems), and number and type of cannabis use disorder symptoms (impaired control over use). Cannabis exposure variables and stable vulnerability factors did not independently predict first incidence of cannabis dependence.

Conclusions: In a high risk population of young adult frequent cannabis users, current problems are more important predictors of first incidence cannabis dependence than the level and type of cannabis exposure and stable vulnerability factors.

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1. Introduction

Cannabis is one of the most commonly used illicit substances, yet only a minority of users becomes dependent (Lopez-Quintero et al., 2010). Although frequent cannabis users are at a much higher risk to become dependent (Coffey et al., 2003; Grant and Pickering, 1998; Noack et al., 2011), 'only' 20–50% of the (near) daily users are dependent (Coffey et al., 2002; EMCDDA, 2009). Until now, it is not understood why some frequent users develop dependence, whereas others do not. More knowledge is required concerning the predictors of cannabis dependence among frequent cannabis users, to target the prevention and treatment specifically at frequent users at a high risk of dependence.

The distinction between non-dependent and dependent frequent use is important, because dependent users, by definition, experience significant psychosocial impairments related to reduced control over their cannabis use, whereas other frequent users do not develop such drug-related problems (Budney and Moore, 2002; Looby and Earleywine, 2007; Temple et al., 2011). This distinction is especially important since cannabis use per se is regarded to be relatively harmless (Nutt et al., 2010; Van Amsterdam et al., 2010). Furthermore, there are indications that the risk of comorbid disorders is substantially lower (often not exceeding the general population level) among non-dependent compared to frequent cannabis users (Swift et al., 2001; Van der Pol et al., 2013b).

Studies on predictors of cannabis dependence are predominantly performed in the general population, which generally...
includes a minority of current frequent users (Bruns and Geist, 1984; Chen et al., 2005; EMCDDA, 2011; Grant and Pickering, 1998; Lopez-Quintero et al., 2010; McGee et al., 2000; Swift et al., 2008; Von Sydow et al., 2002). Therefore, these studies are limited in predicting the transition from non-dependent to frequent frequent use of cannabis and subsequently fail to detect the risk factors in this high risk population of cannabis users. Despite this limitation, some of these general population studies have identified predictors of dependence that may also apply to the transition from non-dependent frequent cannabis use to cannabis dependence. These include: younger in age, being male, deprived socioeconomic status, poor financial situation (Chen et al., 2005; Hayatbakhsh et al., 2009; Lopez-Quintero et al., 2010; Poulton et al., 1997; Von Sydow et al., 2002), early onset of cannabis use, use and dependence of other substances including nicotine, alcohol, and cocaine (Chen et al., 2005; Lopez-Quintero et al., 2010; Von Sydow et al., 2002), and the presence of cannabis dependence symptoms without meeting criteria for a DSM-IV diagnosis of cannabis dependence (Degenhardt et al., 2008). Some of these symptoms are predictive of the persistence of cannabis use (Perkonigg et al., 2008). However, they have not been assessed as predictors of incident cannabis dependence. Other risk factors for cannabis dependence that were identified in general population studies include a family history of substance use disorders, parents’ marital problems, early life events, impulsivity, aggressive or delinquent behaviour, and the presence of externalising disorders (Bruns and Geist, 1984; Coffey et al., 2002; Ferguson et al., 2007; Florez-Salamanca et al., 2013; Hayatbakhsh et al., 2006, 2009; Hyman and Sinha, 2009; Lopez-Quintero et al., 2010; Perkonigg et al., 2008; Pingault et al., 2012; Swift et al., 2008; Von Sydow et al., 2002; Wittchen et al., 2007). The role of internalising disorders is still unclear (Moore et al., 2007). Yet, there is increasing evidence for an association between mood/anxiety disorders and heavy or problematic cannabis use (Degenhardt et al., 2003). The onset of dependence has also been predicted specifically by the presence of social phobia (Buckner et al., 2008), whereas recurrence of dependence has been predicted by the presence of mood disorders (Florez-Salamanca et al., 2013). Therefore, it may be hypothesised that these disorders may be important for the transition from non-dependent frequent cannabis use to cannabis dependence (Florez-Salamanca et al., 2013). Together, these factors can be grouped as ‘vulnerability’ factors. Furthermore, current stressful factors may increase the risk of both cannabis use (Hyman and Sinha, 2009) and cannabis dependence (Harris, 2000). However, information on stress factors associated with the transition from non-dependent cannabis use to cannabis dependence is almost non-existent. Examples of acute stress factors include recent negative life events, and lack of social support (Bruns and Geist, 1984; Hyman and Sinha, 2009; Windle and Wiesner, 2004).

Remarkably little is known about the intensity of cannabis exposure as a risk factor for the development of cannabis dependence. Even though prospective studies have shown that the number of days when using drugs is a strong predictor of dependence, most studies implicitly assume that a higher number of days when using drugs equates to higher cannabis exposure. Only few studies also assessed the quantity of cannabis use such as the number of ‘joints’ per day (e.g., Chen et al., 1997; Grant and Pickering, 1998; Looty and Earleywine, 2007; Moss et al., 2012), while quantity has been shown to discriminate dependent and non-dependent users independently from the number of using days (Walden and Earleywine, 2008; Zeisser et al., 2011). The quantity and quality (potency) of the cannabis consumed may be of particular importance among (near) daily high risk users, since their cannabis consumption may vary widely from a single joint of low potent cannabis to numerous high potency joints per day (Temple et al., 2011; Zeisser et al., 2011).

Finally, potential predictors of the transition from non-dependent frequent cannabis use to cannabis dependence are suggested from cross-sectional studies, but these have not yet been investigated prospectively. These factors include setting (of use), such as solitary use versus use with others and daytime versus evening cannabis use (Noack et al., 2005; Van der Pol et al., 2013b). In addition, cannabis users with coping-oriented reasons to use cannabis may be at a higher risk to develop dependence than other users (Bonn-Miller and Zvolensky, 2009; Bujarski et al., 2012; Chabrol et al., 2005; Fox et al., 2011; Johnson et al., 2010; Simons et al., 2005).

To our knowledge, the only prospective study among frequent cannabis users investigating predictors of dependence is an exploratory study following long term (heavy) cannabis users for one year (Swift et al., 2000). However, most cannabis users in this sample were already cannabis dependent at baseline, and therefore little information is given about predictors of first incidence of cannabis dependence. It concluded that quantity (number of cones in water pipes per day) and severity of cannabis dependence at baseline were the main predictors of cannabis use and cannabis dependence (persistence) at follow-up.

This study aims to identify predictors of the transition from non-dependent frequent cannabis use to cannabis dependence. A broad range of predictors identified in previous prospective studies (sociodemographic variables, substance use characteristics, and vulnerability factors) is investigated in a large sample of non-dependent frequent cannabis users aged 18–30 who were followed for a period of three years. In addition, novel risk factors suggested by cross-sectional studies are considered, including stress indicators (e.g., recent life events, lack of social support), cannabis consumption variables (e.g., pattern of use, habits, motives) and symptoms of abuse and dependence (without full-blown diagnoses). The predictive value of the abuse and dependence symptoms will be assessed individually, but also cumulatively, because the presence of these symptoms may represent a subclinical underlying continuum of severity (Compton et al., 2009).

2. Methods

Data were derived from the CanDep study, investigating a prospective cohort of 600 frequent cannabis users. The reader is referred to a previous publication (Van der Pol et al., 2011). In summary, 600 Dutch frequent cannabis users (≥ 3 days per week for 12 months) between 18 and 30 years were recruited from cannabis outlet, coffee shops) and through chain referral. Baseline measures (T0, September 2008–April 2009) included a face-to-face interview to assess the presence of DSM-IV cannabis dependence and a range of potential predictors of cannabis dependence. In addition, there were two face-to-face follow-up interviews after 18 months (T1, March–November 2010) and after 36 months (T2, September 2011–March 2012) assessing DSM-IV cannabis dependence. To allow the investigation of first incidence of cannabis dependence, only participants who had never met DSM-IV criteria for cannabis dependence at baseline (n = 289) were included in the current study. Response rates relative to T0 were 80.3% (n = 216) at T1 and 74.0% at T2 (n = 199).

2.1. Outcome

Participants who fulfilled a diagnosis of DSM-IV cannabis dependence for the first time between T0 and T2 were identified as incident cases. DSM-IV cannabis dependence was measured with the Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler and Ustun, 2004), and required the presence of three or more of seven symptoms within the 12-month period since the previous interview (without requiring the presence of all symptoms at the same time). It should be noted that the CIDI includes a withdrawal symptom, which is not included in the DSV-IV manual. The Severity of Dependence Scale (SDS, 5 items on a 0–3 scale) was assessed at all interviews to address measurement error in the dependence diagnosis (Section 2.3.1; Gossop et al., 1995; Van der Pol et al., 2013a).

2.2. Baseline predictors of cannabis dependence

2.2.1. Sociodemographic variables. The following sociodemographic variables were included: age, sex, ethnicity (Western vs. non-Western), educational level (primary or lower secondary, higher secondary, higher professional or university),
employment situation (employed, unemployed or unable to work, student), and living arrangement (living alone vs. living with others).

2.2.2. Cannabis and other substance use. Baseline cannabis use was assessed in detail and included four categories of variables. First, variables related to cannabis use disorders (CUD; cannabis abuse and dependence) were assessed with the CIDI. These included the presence of 12-month cannabis abuse at baseline, the lifetime presence of individual CUD symptoms, and the total number of lifetime positively endorsed CUD symptoms at baseline. Second, besides age of onset of first cannabis use, cannabinoids related to (a typical cannabis using day in) the last four weeks. Exposure variables included: number of cannabis using days in the past four weeks, presence for herbal cannabis (yes/no), estimated potency (high, medium, low), number of joints per using day, dosage of cannabis per joint (measured as 1/number of joints from 1g). In addition, total cannabis exposure (in grams) in the last four weeks was measured by multiplying the number of cannabis using days by the number of joints per day and the dose per joint. Third, the setting of cannabis use was defined by location (non-selective, home, coffee shop), solitary use or use with others, using at night or (also) at daytime, number of hours 'high' per using day, continuous smoking a joint (rarely to never pause, sometimes to always pause), average intensity of perceived intoxication during cannabis consumption measured on a visual analogue scale ranging from 1 (light buzz) to 10 (very 'high'). Fourth, motives for cannabis use were assessed with the Marijuana Motives Measure (MMM; Simons et al., 2005). The MMM is a 25-item self-report questionnaire with five internally consistent subscales of five items each (subscale range 5–25) measuring enhancing, conformity, expansion, coping, and social motives.

Problematic use of other substances was also assessed. This included 12-month alcohol use and related problems measured with the Alcohol Use Disorders Identification Test (AUDIT), a screening instrument with excellent psychometric qualities (Bohn et al., 1995). Also, the Heaviness of Smoking Index (HSI) was used to measure smoking and related problems in the past four weeks (Burling and Burling, 2003). Finally, any 12-month use of ecstasy, cocaine, or amphetaamines was assessed.

2.2.3. Vulnerability factors. We identified four types of vulnerability factors. First, family history of mental problems (anxiety, depression, psychosis) or substance use problems (alcohol, cannabis, other drugs). Second, two types of distress during childhood were evaluated (Hovens et al., 2010; Janssen et al., 2004; Konings et al., 2012; Zeisser et al., 2011): (i) the presence of one or more (dichotomous) of the following childhood family adversities before the age of 16 was assessed: parental divorce, parental death, and not being brought up by both parents; and (ii) a history of any child abuse before the age of 16 years: emotional, psychological, physical, and sexual abuse. Because these abuse experiences may not always occur in isolation and may have an additive effect, the cumulative number of these four types of child abuse was used as the main predictor (Van der Pol et al., 2013b).

Third, the personality characteristic impulsivity was measured with the Dutch version of the Barratt Impulsiveness Scale (BIS-15). This is a 15-item reliable measure of impulsivity, which consists of three subscales: motor, attentional, and non-planning impulsivity (Spinella, 2007). Finally, the personal history of psychiatric disorders was assessed. This was associated with the data was categorized in three major diagnostic categories of lifetime DSM-IV diagnoses: any mood disorder (major depression, bipolar disorder, dysthymia); any anxiety disorder (social phobia, panic disorder, agoraphobia, generalised anxiety disorder); any externalising disorder (childhood ADHD, conduct disorders). Lifetime psychotic symptoms such as hallucinations and delusions (yes, no) were measured with a selection of six items of the psychosis section of CIDI 1.1 (Van der Pol et al., 2011).

2.2.4. Stress factors: life events and social support. The sum of negative and positive life events were included as two count variables. Major negative recent life events (Table 4 (Brugha et al., 1985)). Positive life events included: establishing close friendships; commencing a steady relationship; having a baby; graduation or completion of a course/training; starting a new job; substantial financial gain. Finally, perceived lack of social support from network members was measured as two dichotomised variables: ‘heart unburdening below expectations’ and ‘practical help below expectations’. These were each based on two questions: the degree to which participants could count on their social network, and whether this support was below their expectations.

2.3. Statistical analysis

To determine any bivariate association between aforementioned baseline predictors and the dependent variable, i.e., first incidence of cannabis dependence at some time during the three-year follow-up, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated using logistic regression analyses. Subsequently, to identify the unique contribution of predictors of cannabis dependence onset and to reduce the risk of missing unique predictors, all bivariate predictors with p ≤ 0.10 were entered into a multivariable logistic regression (Mansoor and Lemeshow, 2013). Yet, only variables significant at the 5% level in the multivariable model were considered unique predictors. Finally, McFadden’s pseudo R² is reported for the multivariable model.

CUD symptoms are strong predictors of first incidence cannabis dependence (Compton et al., 2009; Degenhardt et al., 2008) and this may overshadow the effects of all other predictors that may be important for clinical practice (without diagnostic assessment). Therefore, the multivariable model was first tested with the CUD variables and then without the CUD variables in the model. Moreover, besides the sum of CUD symptoms as predictor of dependence, each criterion was assessed separately, both as a bivariate and as independent multivariable predictor. For all other aggregated variables (e.g., number of childhood adversities, number of recent life events) that significantly predicted first incidence cannabis dependence, the same procedure was applied, i.e., assessing each original item in the bivariate model and the combination of items in a multivariable logistic regression.

2.3.1. Measurement error. Measurement errors are inherent to survey data. When several indicators of a concept are available, a latent class Markov model enables estimation of classification probabilities of ‘latent’ variables represented by the measured indicators (Van de Pol and Mannari, 2002). Using the CIDI dependence diagnosis (yes/no) and the total SDS score at T0, T1 and T2 as indicators, three latent variables of cannabis dependence were constructed with PanMark 3.2 software (Humphreys et al., 1994; Van de Pol et al., 2007). Both T0 dependent and non-dependent participants (with complete data N = 460) were included, because at least three waves with all possible transition options are needed.

2.3.2. Missing data. While missing data of predictor variables was limited (only four variables had a maximum of eight missing values), 26.0% of participants were lost during follow-up. Although this is not disconcerting in a population of young adult frequent substance users, performing complete case analyses may introduce bias. Imputing missing values with multiple imputation by chained equations is preferable when data are missing at random, which means that any systematic differences between missing and observed values can be explained by differences in observed data (Molenberghs et al., 2009). Therefore, imputation was preferred, as predictors associated with attrition included: non-Western ethnicity, lower education, being employed, being ‘high’ longer, using higher doses per joint, use at coffee shops, less illicit substance use, less (motor) impulsivity, and more negative life events. To impute missing data, 20 complete datasets were created, using 50 imputation cycles for each dataset. The analyses described above were conducted on the imputed datasets using ‘mi estimate’ in Stata 12.0, which combines results of analyses on the 20 completed datasets and adjusts standard errors using Rubin’s rules (Rubin, 1987). A detailed description of the imputation models and a discussion of the comparison with complete case analyses can be found in Supplementary Material.1

3. Results

There were 73 incident cases of cannabis dependence within the three-year follow-up (n = 47 T0–T1, n = 26 T1–T2), which is 36.7% of the 199 complete cases. Similarly, the imputed (mean) incidence rate was 37.2% (95% CI = 30.7, 43.8).

Bivariate logistic regression on the imputed data was performed to identify potential predictors of incident cannabis dependence. Table 1 shows that none of the sociodemographic variables predicted incident cannabis dependence, except living alone. Baseline cannabis use variables that predicted incident cannabis dependence included a diagnosis of 12-month abuse, number of lifetime CUD symptoms, (also) using at daytime, continual smoking, and coping motives for cannabis consumption. Remarkably, cannabis exposure variables were not predictive of the transition from non-dependent to dependent cannabis use. Lifetime and current mental disorders were frequent in both family members and participants but these disorders were not predictive for the development of first incident cannabis dependence, and neither was family childhood adversity. However, the number of childhood adversities and the number of recent negative life events were associated with the development of dependence and so were two of the three impulsivity subscales. Finally, the lack of ‘heart unburdening’ social support was a significant predictor (p < 0.10).

All predictor variables that were significant at the 10% level were included in a multivariable logistic regression to identify independent predictors of the incidence of cannabis dependence. Living

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1 Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: ...
alone, baseline number of lifetime CUD symptoms, and number of negative life events were unique predictors (Table 2: Model 11), with a pseudo $R^2$ of 23%. In a separate model without the CUD variables as predictors (Table 2: Model 21), coping as a motive for cannabis use was also an independent predictor. In this model, the pseudo $R^2$ was 17%.

Table 3 shows that the dependence symptoms “using larger amounts or longer than intended” and “tolerance” were the most frequently reported CUD symptoms. While most baseline lifetime CUD symptoms were bivariately associated with the incidence of dependence, “impaired control over use” was the strongest and only independent multivariable predictor.

Finally, Table 4 shows the specific negative life events associated with the incidence of cannabis dependence in a post hoc analysis: the frequently occurring event “major financial crisis” was the only independent multivariable predictor.
Table 2
Independent predictors of incidence of first cannabis dependence in young adult frequent cannabis users (n = 269): multivariable model including (1) and excluding cannabis abuse and dependence variables (2).

<table>
<thead>
<tr>
<th></th>
<th>Model 1. Including CUD</th>
<th>Model 2. Excluding CUD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (vs. with others)</td>
<td>3.85** (1.69, 8.77)</td>
<td>3.38** (1.55, 7.36)</td>
</tr>
<tr>
<td><strong>CUD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last year abuse</td>
<td>1.37 (0.65, 2.86)</td>
<td>–</td>
</tr>
<tr>
<td>Mean number CUD symptoms</td>
<td>1.42** (1.14, 1.79)</td>
<td>–</td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using (also) at daytime</td>
<td>1.82* (0.92, 3.62)</td>
<td>1.79* (0.94, 3.41)</td>
</tr>
<tr>
<td>No pauses while smoking joint</td>
<td>1.70 (0.85, 3.38)</td>
<td>1.84* (0.96, 3.54)</td>
</tr>
<tr>
<td>Mean coping motive</td>
<td>1.07 (0.94, 1.21)</td>
<td>1.13* (1.01, 1.26)</td>
</tr>
<tr>
<td><strong>Vulnerability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of child abuse</td>
<td>0.97 (0.69, 1.36)</td>
<td>0.99 (0.72, 1.36)</td>
</tr>
<tr>
<td>Mean motor impulsivity</td>
<td>1.04 (0.91, 1.20)</td>
<td>1.05 (0.92, 1.20)</td>
</tr>
<tr>
<td>Mean attentional impulsivity</td>
<td>1.06 (0.92, 1.22)</td>
<td>1.08 (0.95, 1.23)</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of negative recent life events</td>
<td>1.43** (1.18, 1.73)</td>
<td>1.35** (1.14, 1.60)</td>
</tr>
<tr>
<td>Lack 'heart unburden' social support</td>
<td>1.35 (0.58, 3.14)</td>
<td>1.36 (0.61, 3.01)</td>
</tr>
</tbody>
</table>

Model 1: multivariable logistic model predicting incidence of cannabis dependence with all variables in the model (pseudo R² = 23%). Model 2: excludes last year abuse and the number of dependence and abuse symptoms (pseudo R² = 17%).

*: not included in the model. CUD: cannabis use disorder.
**: p < 0.10.
***: p < 0.05.
****: p < 0.01.
****: p < 0.001.

Table 3
Lifetime cannabis abuse and dependence symptoms at baseline predicting incidence of first cannabis dependence among young adult frequent users (n = 269).

<table>
<thead>
<tr>
<th>Dependence incidence</th>
<th>Yes %</th>
<th>No %</th>
<th>Bivariate OR</th>
<th>95% CI</th>
<th>Multivariable OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse Role impairment</td>
<td>40.1</td>
<td>25.4</td>
<td>1.97*</td>
<td>[1.10, 3.54]</td>
<td>1.38</td>
<td>[0.69, 2.76]</td>
</tr>
<tr>
<td>Hazardous use</td>
<td>28.0</td>
<td>32.0</td>
<td>0.83</td>
<td>[0.46, 1.50]</td>
<td>0.90</td>
<td>[0.46, 1.77]</td>
</tr>
<tr>
<td>Legal problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social problems</td>
<td>22.7</td>
<td>13.8</td>
<td>1.83*</td>
<td>[0.90, 3.72]</td>
<td>1.31</td>
<td>[0.58, 2.96]</td>
</tr>
<tr>
<td>Dependence Tolerance</td>
<td>55.9</td>
<td>41.5</td>
<td>1.79*</td>
<td>[0.96, 3.32]</td>
<td>1.44</td>
<td>[0.72, 2.87]</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>30.3</td>
<td>17.6</td>
<td>2.03*</td>
<td>[1.06, 3.90]</td>
<td>1.39</td>
<td>[0.66, 2.91]</td>
</tr>
<tr>
<td>Larger/larger</td>
<td>88.4</td>
<td>63.1</td>
<td>2.38*</td>
<td>[1.24, 4.57]</td>
<td>1.76*</td>
<td>[0.93, 3.36]</td>
</tr>
<tr>
<td>Impaired control over use</td>
<td>43.2</td>
<td>17.0</td>
<td>3.72*</td>
<td>[1.88, 7.36]</td>
<td>2.95*</td>
<td>[1.41, 6.15]</td>
</tr>
<tr>
<td>Much time spent</td>
<td>25.5</td>
<td>13.9</td>
<td>2.11*</td>
<td>[1.06, 4.20]</td>
<td>1.48</td>
<td>[0.67, 3.27]</td>
</tr>
<tr>
<td>Reduced activities</td>
<td>27.7</td>
<td>13.1</td>
<td>2.54*</td>
<td>[1.25, 5.16]</td>
<td>1.53</td>
<td>[0.66, 3.54]</td>
</tr>
<tr>
<td>Use despite problems</td>
<td>20.1</td>
<td>8.1</td>
<td>1.50</td>
<td>[0.77, 2.94]</td>
<td>1.28</td>
<td>[0.75, 2.05]</td>
</tr>
</tbody>
</table>

*: legal problems omitted due to the low prevalence (1.9% of total sample) which led to perfect prediction of dependence.
*: p < 0.10.
*: p < 0.05.
*: p < 0.01.
*: p < 0.001.

Table 4
Negative life events predicting incidence of first cannabis dependence among young adult frequent users (n = 269) (post hoc).

<table>
<thead>
<tr>
<th>Dependence incidence</th>
<th>Yes %</th>
<th>No %</th>
<th>Bivariate OR</th>
<th>95% CI</th>
<th>Multivariable OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separation from someone important</td>
<td>44.6</td>
<td>27.4</td>
<td>2.14*</td>
<td>[1.24, 3.68]</td>
<td>1.72</td>
<td>[0.95, 3.11]</td>
</tr>
<tr>
<td>Broke off steady relationship</td>
<td>48.4</td>
<td>42.9</td>
<td>1.25</td>
<td>[0.73, 2.13]</td>
<td>0.99</td>
<td>[0.54, 1.82]</td>
</tr>
<tr>
<td>Death of a loved-one</td>
<td>39.2</td>
<td>27.1</td>
<td>1.73*</td>
<td>[0.96, 3.13]</td>
<td>1.75</td>
<td>[0.87, 3.51]</td>
</tr>
<tr>
<td>Dropped out of school</td>
<td>28.6</td>
<td>21.0</td>
<td>1.51</td>
<td>[0.80, 2.83]</td>
<td>1.15</td>
<td>[0.56, 2.37]</td>
</tr>
<tr>
<td>Sacked from job or became unemployed</td>
<td>36.6</td>
<td>28.0</td>
<td>1.48</td>
<td>[0.82, 2.67]</td>
<td>1.14</td>
<td>[0.59, 2.22]</td>
</tr>
<tr>
<td>Major financial crisis</td>
<td>37.1</td>
<td>17.0</td>
<td>2.88*</td>
<td>[1.57, 5.29]</td>
<td>2.44</td>
<td>[1.27, 4.71]</td>
</tr>
<tr>
<td>Problems with police</td>
<td>16.0</td>
<td>12.4</td>
<td>1.34</td>
<td>[0.61, 2.97]</td>
<td>1.12</td>
<td>[0.47, 2.67]</td>
</tr>
<tr>
<td>Moved house</td>
<td>48.4</td>
<td>37.0</td>
<td>1.60</td>
<td>[0.91, 2.80]</td>
<td>1.38</td>
<td>[0.74, 2.55]</td>
</tr>
<tr>
<td>Serious illness or injury</td>
<td>17.7</td>
<td>9.1</td>
<td>2.16*</td>
<td>[0.98, 4.75]</td>
<td>1.58</td>
<td>[0.62, 3.99]</td>
</tr>
<tr>
<td>Serious illness or injury to close relative</td>
<td>32.1</td>
<td>28.9</td>
<td>1.16</td>
<td>[0.65, 2.09]</td>
<td>0.92</td>
<td>[0.47, 1.79]</td>
</tr>
<tr>
<td>Serious illness or injury to friend</td>
<td>24.5</td>
<td>13.9</td>
<td>2.01*</td>
<td>[1.04, 3.91]</td>
<td>1.52</td>
<td>[0.72, 3.18]</td>
</tr>
</tbody>
</table>

*: p < 0.10.
*: p < 0.05.
*: p < 0.01.
*: p < 0.001.
3.1. Measurement error

Compared to the latent dependence diagnose, false positive rates of the CIDI dependence diagnose at T0, T1 and T2 were estimated at 12.6 (SD = 0.06), 10.6 (SD = 0.03) and 4.9% (SD = 0.02), respectively. False negative rates were 25.6 (SD = 0.05), 25.2 (SD = 0.05) and 24.8% (SD = 0.05), respectively.

4. Discussion

4.1. Findings

To our knowledge, this study is the first prospective exploration of factors predicting the incidence of cannabis dependence in a high risk population of frequent cannabis users. Six hundred (near) daily cannabis users were recruited to reach an adequate sample of 269 frequent users without a lifetime diagnosis of cannabis dependence. The response rate after three years was 74%. During this period, approximately one in three frequent users developed a first diagnosis of cannabis dependence (37.2%, 95% CI = 30.7, 43.8), emphasising both the importance and the potential of prevention targeted specifically at high risk frequent users.

Interestingly, most risk factors for the development of cannabis dependence from general population studies had no predictive value in our sample of frequent cannabis users, including most of the sociodemographic factors, the presence of internalising and externalising mental disorders, childhood family adversity, and family history of substance use or mental health problems. Moreover, while impulsivity and child abuse were bivariately associated, they did not survive in multivariable prediction models. This finding suggests that in a group of high risk frequent cannabis users other factors are involved in the development of cannabis dependence than in a general population sample of cannabis users. It may also indicate that predictors established in general population studies actually predict progression to frequent cannabis use rather than the development of cannabis dependence. This interpretation is supported by our baseline comparison of dependent and non-dependent frequent users from the CanDep cohort with a representative general population sample (Van der Pol et al., 2013b). While dependent and non-dependent users were similar in this study, this comparison showed that both groups of frequent cannabis users differed from the general population particularly on risk factors previously reported in prospective general population studies. Together with the finding that the incidence of cannabis dependence in general population studies is strongly associated with frequent cannabis use, this may indicate that predictors from general population studies are mainly related to the transition from incidental to frequent cannabis use and not to the transition from frequent cannabis use to cannabis dependence.

It is also remarkable that neither total levels of cannabis exposure or several detailed exposure measures were predictive of the development of cannabis dependence among frequent cannabis users. Similarly, only weak associations between alcohol consumption and the diagnosis of alcohol dependence have been reported (Tuithof et al., 2013). However, cannabis use may be dynamic, while only recent cannabis exposure at baseline was investigated as a predictor in the current study. Therefore, in future studies, transitions in exposure should be added as predictors of cannabis dependence incidence.

Notably, coping as the motive for cannabis use was among the less commonly investigated variables (i.e., not inspired by previous prospective general population studies) which emerged as a predictor of the transition from non-dependent to dependent frequent cannabis use. In addition, cannabis consumption patterns and habits such as daytime cannabis use and continual smoking were significant bivariate and borderline significant multivariable predictors of cannabis dependence incidence. Together, this suggests that among frequent cannabis users cannabis consumption motives and habits are more important predictors of future dependence than the actual cannabis (THC) exposure level.

The number of negative life events was also an independent predictor; the risk of dependence increased with 43% with every additional negative event. This implies that in a young adult population, acute stressful events are stronger predictors of dependence than the presence of relatively stable vulnerability factors. A major financial problem was the strongest predictor among all negative life events. Also, living alone was a strong predictor, which corresponds very well with general population studies indicating that not living with a partner is associated with (any drug) dependence (Grant et al., 2009). The role of parents and partners in the development of cannabis dependence will be analysed in depth on the basis of qualitative interviews among 47 CanDep participants in a future report of our research group.

Finally, it is not surprising that presence of last year cannabis abuse and lifetime number of CUD symptoms at baseline were important predictors of the onset of full-blown cannabis dependence. Of all CUD symptoms, “impaired control over use” was the strongest predictor of dependence. However, it should be noted that cultural differences may be important. For example, legal problems due to cannabis use are rare in the Netherlands (1.9% in the current sample) and no OR could be calculated, but legal problems might be an important predictor in countries with more restrictive regulations (Perkonigg et al., 2008). Similarly, interviewers reported that hazardous use in this age group was mainly restricted to riding a bike under the influence of cannabis, a CUD criterion that was not associated with the risk of the future development of cannabis dependence in the current study.

4.2. Strengths and limitations

The most important strengths of the current study are the large sample size, the impressive follow-up rate and the broad range of predictors that were assessed using adequate instruments. However, some limitations have also emerged. Primarily, those with a lifetime diagnosis of cannabis dependence were excluded to assess first incidence of dependence. However, the minimum age of the current sample was relatively high (18 years) considering the fact that cannabis dependence on average has been shown to emerge at age 18 (for males) (Wittchen et al., 2008). It can therefore not be excluded that those frequent users with a lifetime diagnosis of cannabis dependence at baseline (who were excluded in the current analyses) were more vulnerable and that the risk profile of these youngsters is different from the ones who developed cannabis dependence only after the age of 18, i.e., after the baseline assessment. Second, although power was sufficient to identify a series of unique predictors, some of the bivariate predictors did not survive the competition in the multivariable models either because a lack of power or due the overlapping variance. However, when backward selection was manually applied (although this is a data driven method not recommended after multiple imputation (Wood et al., 2008)), the results were very similar, suggesting that overlapping variance is the more plausible explanation. Finally, although a broad range of predictor variables were assessed, including CUD symptoms, the pseudo $R^2$ was only 23% in the multivariable model. Other factors that were not considered in this study may be important in the prediction of cannabis dependence incidence in this high risk population. For example role transition has shown to be of great relevance in the development of alcohol dependence (Copeland et al., 2012). It should also be noted that the current study was mainly restricted to phenotypic predictors and that intermediate phenotypes/endophenotypes (e.g., Cousijn et al., 2012a, 2012b) and (epi)genetic factors (e.g., Agrawal et al., 2011;
Jutras-Aswad et al., 2012) were not included as potential predictors for the development of cannabis dependence. Nevertheless, 23% is significant considering that the model has to predict the onset of a complex multi-factorial disorder over a substantial period of time and includes baseline variables of which some may change during follow-up. However, it should be considered that inaccuracy or bias caused by self-report may partly explain the limited pseudo \( R^2 \). Specifically, the estimated 25% false negative rate using latent Markov modelling suggests that part of our sample should have been excluded and a similar proportion of incident cases were missed. The estimated proportion false positive was much smaller and the effect would be opposite. Altogether, misclassification may have diluted associations, resulting in underestimated or even missed associations. Unfortunately, analyses could not be adjusted for this measurement error, because baseline dependent users had to be included in the Markov model in order to perform the analyses. However, measurement error may also have been overestimated because only the CIDI diagnosis and the SDS score were available to construct the latent cannabis dependence variable, and the SDS has previously been reported to poorly correlate with cannabis dependence (Van der Pol et al., 2013a). Therefore, it is most likely that the current findings are a reasonable representation of the real world possibly with some underestimation of the real associations between predictors and outcomes.

4.3. Conclusion

In summary, our findings imply that young adult non-dependent frequent cannabis users are at considerable risk (37%) to develop cannabis dependence in the near future, especially when they show the following risk factors: CUD symptoms, coping motives for their (frequent) use of cannabis, acute stressful negative life events and living alone. Unexpectedly, the actual level of cannabis exposure and the presence of stable vulnerability factors seem to be less significant.

Role of funding source

The CanDep study was financially supported by a grant of the Netherlands Organisation for Health Research and Development (NWO, grant number 31160009). The NWO had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Contributors

M. van Laar, W. van den Brink, D.J. Korf and R. de Graaf designed the study and wrote the protocol. N. Liebregts and P. van der Pol collected the data, and P. van der Pol managed the literature searches and summaries of previous related work, undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2013.06.009.

References


