

The Dutch Cannabis Dependence (CanDep) study on the course of frequent cannabis use and dependence: objectives, methods and sample characteristics

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Abstract

This paper presents an overview of the prospective cohort design of the Dutch Cannabis Dependence (CanDep) study, which investigates (i) the three-year natural course of frequent cannabis use (\geq three days per week in the past 12 months) and cannabis dependence; and (ii) the factors involved in the transition from frequent non-dependent cannabis use to cannabis dependence, and remission from dependence. Besides its scientific relevance, this knowledge may contribute to improve selective and indicated prevention, early detection, treatment and cannabis policies. The secondary objectives are the identification of factors related to treatment seeking and the validation of self report measures of cannabis use.

Between September 2008 and April 2009, baseline data were collected from 600 frequent cannabis users with an average age of 22.1 years, predominantly male (79.3%) and an average cannabis use history of 7.1 years; 42.0% fulfilled a (12-month DSM-IV) diagnosis of cannabis dependence. The response rate was 83.7% after the first follow up at 18 months. The second and last follow-up is planned at 36 months. Computer assisted personal interviews (CAPI) were conducted which covered: cannabis use (including detailed assessments of exposure, motives for use and potency preference); use of other substances; DSM-IV internalizing and externalizing mental disorders; treatment seeking; personality; life events; social support and social functioning. *Copyright* © 2011 John Wiley & Sons, Ltd.

Introduction

Cannabis use is often a transient phenomenon limited to adolescence and early adulthood (Von Sydow *et al.*, 2001).

Approximately 31.6% of European 15–34 year olds have ever used cannabis and although the majority do not continue their use, people who become regular users are at risk of developing cannabis dependence (Coffey *et al.*,

2003; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2008; EMCDDA, 2010). A relationship between frequency of use and dependence has been reported: (near) daily users are at highest risk and people using on 3–4 days a week resemble that risk more closely than less frequent regular users (1–2 days a week). Estimates of the proportion of daily cannabis users with cannabis dependence vary widely from roughly 20% to 50% (Coffey *et al.*, 2002; EMCDDA, 2009). Accordingly, at least half of daily cannabis users do not fulfil criteria for dependence. Although these numbers suggest that cannabis has a relatively low addiction potential (Nutt *et al.*, 2010; Van Amsterdam *et al.*, 2010; van den Brink, 2008), the prevalence of (near) daily cannabis use approximates 2.3% in the population of 15–34 years. This suggests that there are hundreds of thousands young frequent users who are dependent on cannabis in Europe alone, who are exposed to a range of adverse outcomes associated with cannabis dependence. These include higher prevalence of psychiatric disorders, adverse effects on the respiratory system, lower educational achievements, and lower levels of motivation, happiness, and satisfaction with life (Agosti *et al.*, 2002; Hall, 2006; Looby and Earleywine, 2007; Taylor *et al.*, 2000). However, most studies on the transition from cannabis use to cannabis dependence have disregarded the special position of frequent cannabis users and most studies usually included all, and therefore mostly non-frequent, lifetime cannabis users. Moreover, frequency of use is not always considered in studies investigating the transition from cannabis use to cannabis dependence (Lopez-Quintero *et al.*, 2010). The available research consistently reports younger age, tobacco smoking, and use of other illicit drugs to predict the transition from cannabis use to dependence, whereas the role of gender in these studies is less consistent (Chen *et al.*, 2005; Coffey *et al.*, 2003; Lopez-Quintero *et al.*, 2010; Swift *et al.*, 2008; Von Sydow *et al.*, 2002). Early onset of cannabis use has also been identified as a predictor for the transition in most of these studies. However, this observed association might be confounded by socio-economic status, other drug-use and the presence of psychiatric comorbidity (Coffey *et al.*, 2003; Lopez-Quintero *et al.*, 2010). Other proposed risk factors for the transition from cannabis use to cannabis dependence include the presence of a positive first reaction to cannabis, early parental death, deprived socio-economic status and poor financial situation (Chen *et al.*, 2005; Le Strat *et al.*, 2009; Von Sydow *et al.*, 2002).

Factors associated with the presence of cannabis dependence can be grouped into personal and cannabis use related factors. The first include mental disorders, and

while these are common among cannabis dependent persons, evidence for their role in the transition from cannabis use to cannabis dependence is inconclusive (Degenhardt *et al.*, 2003; Fergusson *et al.*, 2010; Lopez-Quintero *et al.*, 2010; Moore *et al.*, 2007; Stinson *et al.*, 2006; Van Laar *et al.*, 2007; Wittchen *et al.*, 2007). Whereas the focus has been on internalizing disorders such as depression and anxiety, research on the role of externalizing disorders is less common and results from available studies are again inconclusive (Elkins *et al.*, 2007; Fergusson *et al.*, 2007; Wittchen *et al.*, 2007). Similarly, impulsivity as a personality trait has been mentioned as a vulnerability factor for several substance use disorders (Acton, 2003), including cannabis use problems (Piechatek *et al.*, 2009; Simons *et al.*, 2005; van Leeuwen *et al.*, 2010; Vangsness *et al.*, 2005). Furthermore, positive and negative life events may influence cannabis consumption patterns, considering that young adulthood is a time of many developmental transitions such as changes in living situation, work and relationships (Hussong and Chassin, 2004; Nation and Heflinger, 2006; Newcomb and Harlow, 1986).

Temple *et al.* (2011) imply that inconsistent findings on risk factors may be attributed to differences in research methods or, more specifically, the contrast of using either low risk general population samples or ultra high risk treatment seeking cannabis users. The authors conclude that to better understand these risk factors, sampling populations should include non-treatment seeking frequent cannabis users, which could be achieved by snowball sampling (Temple *et al.*, 2011). They also stress that traditional measures of cannabis exposure may not adequately represent variations in cannabis exposure since cannabis use related measures are often restricted to age of onset and frequency of use (generally daily, weekly or less frequent use). More detailed information on consumption patterns (e.g. number of joints smoked, type of cannabis, amount of cannabis per joint) is often lacking while such knowledge could help to understand the role of cannabis exposure in the development and persistence of dependence in frequent users (Noack *et al.*, 2009; Temple *et al.*, 2011; Walden and Earleywine, 2008). Furthermore, it has been suggested that cannabis with higher tetrahydrocannabinol (THC) concentrations may induce more adverse health effects than lower potency cannabis (Di Forti *et al.*, 2009; EMCDDA, 2004; Smith, 2005). However, researchers have also indicated that certain cannabis users may adjust the amount and the way they smoke to the cannabis potency (Hall, 2009; Korf *et al.*, 2007; McLaren *et al.*, 2008). In addition, motives for cannabis use have been proposed as a potential moderator variable in the development of cannabis

use problems amongst young people (Bonn-Miller and Zvolensky, 2009; Simons *et al.*, 2005).

Moreover, compared to risk factors for the onset of cannabis dependence, there is a paucity of data on the course of dependence after its onset. Predictors of recovery [absence of a Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) cannabis dependence diagnosis in the previous year] identified by few studies included non-daily use, older age and marriage (Agosti and Levin, 2007; Calabria *et al.*, 2010a), but there are indications that cannabis dependence is fairly persistent (Poulton *et al.* 2001; Swift *et al.* 2000; Von Sydow *et al.* 2001). Treatment for cannabis dependence is another predictor of recovery (Cunningham, 2000). However, relatively few people with cannabis dependence seek treatment (Stinson *et al.*, 2006). Better understanding about the reasons to seek treatment and unmet treatment need, could contribute to a better accessibility of treatment facilities and furthermore contribute to our understanding of this treatment gap: the difference between the prevalence of cannabis dependence and the numbers in treatment. The available information on this subject focuses on barriers to seek treatment and suggest these include the belief that treatment for cannabis use is unnecessary, the fear to be stigmatized when accessing treatment and not being ready to stop using (Gates *et al.*, 2009).

The present study [the Dutch Cannabis Dependence (CanDep) study] aims to enhance our understanding of the course of frequent cannabis use and cannabis dependence and to identify predictors of “state” transitions by taking a wide array of potential predictors into account. Better understanding of personal and cannabis use related risk factors could help to improve selective prevention, and thus help preventing progression to more severe levels of co-occurring mental disorders, which are often associated with higher costs of treatment and special treatment needs (Clark *et al.*, 2008). Secondary aims of this study are to identify factors related to treatment seeking in cannabis dependent users and to improve and validate measures of cannabis exposure.

Rationale and design

While general population surveys are best suited to study risk factors and the course of common mental disorders, such an approach is hampered in relation to cannabis dependence. First, the incidence of cannabis dependence is relatively low (Calabria *et al.*, 2010b; Perkonig *et al.*, 2008; Von Sydow *et al.*, 2001). Second, large general population surveys usually do not allow for an elaborate

assessment of cannabis exposure. CanDep avoids these difficulties using a large community based enriched prospective cohort of 600 frequent cannabis users. Based on 12month DSM-IV diagnosis, participants are classified as frequently using non-dependent users (Cohort I) or frequent using cannabis dependent users (Cohort II). Data are collected with extensive computer assisted personal interviews (CAPI) with follow-ups at 18 and 36months. Table 1 shows topics and timing of these interviews. Within the two cohorts, predictors for transitions from frequent use to dependence and vice versa are investigated. Furthermore, qualitative in-depth interviews are conducted in a sub-sample of 48 participants to further investigate (subjective) underlying dynamics and psychosocial processes. In addition, the relevance of cannabis exposure for the transitions in dependence state is investigated in detail in the cohorts, including drug using habits, dosage per joint, inhalation volumes and self reported preference for (high, moderate or low) cannabis potency. These cohorts are the core element of the present study, as represented in Figure 1, number 1. Figure 1 also depicts a naturalistic experiment that is part of the CanDep study: after the second interview, the self reported potency preference and drug use characteristics are validated with hair analysis, cannabis analysis and *in vivo* smoking measures in a natural setting with a sub-sample of 110 cohort members (Figure 1, number 2).

Table 1 Timing of the CanDep interview topics and additional assessments

Topics	T ₀	T ₁	T ₂
Cannabis use disorders	(CIDI 3.0)	X	X
Alcohol use disorders	(CIDI 3.0)	X	
	(e.g. HSI,		
Other substance use	AUDIT)	X	X
Internalizing mental disorders	(CIDI 3.0)	X	X
Externalizing mental disorders	(CIDI 3.0)	X	X
Socio-demographics		X	X
Personality		X	
Life events and long-term difficulties		X	X
Family history mental disorders		X	
Social support		X	X
Social functioning		X	X
Treatment seeking		X	X
Toxicological data	(n=110)	X	
Behavioural assessment of cannabis			
smoking	(n=110)	X	
In-depth interviews	(n=48)	X	X

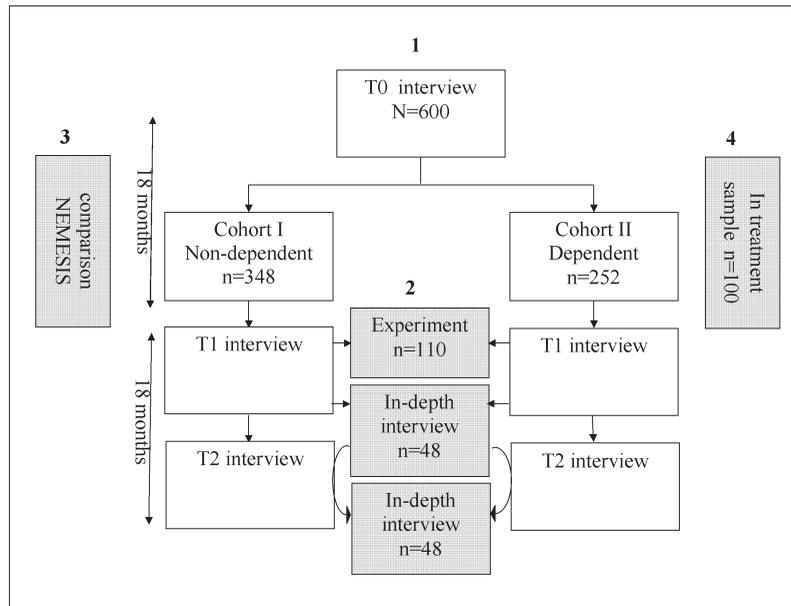


Figure 1 CanDep flowchart. This figure provides an overview of the participant flow in this study.

Third, the baseline data are compared with the baseline data of a Dutch representative general population survey, which studies the prevalence, incidence and course of psychiatric disorders, including cannabis dependence (NEMESIS-2: Netherlands Mental Health Survey and Incidence Study-2) (De Graaf *et al.*, 2010). These samples are compared on demographics, (comorbid) mental disorders, social functioning, and treatment seeking, taking cannabis use (disorders) into account. This allows for better interpretation of the results from the CanDep study regarding predictors for transition and prevalence of comorbidity (Figure 1, number 3).

Finally, an additional sample of 100 patients who sought professional treatment for cannabis use problems are recruited from treatment facilities. They are compared with non-treatment seeking cannabis users from the cohorts on objective characteristics of personal and cannabis use related factors. Also, reasons to seek treatment are evaluated in this additional sample (Figure 1, number 4).

Methods prospective cohort study

Target population

Baseline data for the prospective cohort study were collected between September 2008 and April 2009. To obtain a large enough sample with a current diagnosis of cannabis dependence or at high risk to develop the disorder, the study population had to be a large enriched

community sample ($N=600$) of young adult frequent cannabis users, including both non-dependent and dependent frequent cannabis users. This sample size was indicated by the dichotomous primary outcome variable (transition or no transition). This requires maximum likelihood models with sample sizes of at least 100 participants plus 10 extra participants for each parameter that needs to be estimated (Long, 1997). Thus for a multiple regression model with a liberal amount of nine predictors 200 participants are needed per cohort, with an additional 20% to allow for attrition.

All participants were required to be aged 18–30 years at baseline, speak Dutch fluently, and frequent use was defined as consuming cannabis at least 12 days a month on average in the past year. This cut-off criterion for frequent use was chosen to target a group with a high risk of dependence while maintaining variation in cannabis exposure. This choice is supported by research showing that the risk of dependence among those using 3–4 times per week resembles the risk among daily users more closely than among less frequent users (Coffey *et al.*, 2002). The age range of 18 through 30 years was not only indicated by epidemiological data, but it also makes the study more feasible. Eighteen is the age at which young people legally become adults in the Netherlands and under this age parental consent is required for participation in scientific studies. A sample including youngsters under eighteen could be highly biased, because parents

have to be informed about the frequent use of cannabis of their children and have to consent with the child's participation in the study. Furthermore, 18 years is the minimum age to be allowed to visit "coffee shops" in the Netherlands. These cafe-like outlets, where under certain conditions sale, use, and possession of small amounts of cannabis are legally tolerated, were crucial for the recruitment of study participants.

Recruitment procedure

Participants were recruited both in coffee shops and through chain referrals. For a detailed description of the recruitment strategy of the CanDep study, the reader is referred to Liebrechts *et al.* (2011). In short, five Dutch cities were selected based on population size and geographical spread over the Netherlands. An ethnographic mapping was conducted to select coffee shops suitable for recruiting respondents based on field notes on observed number and diversity of visitors (language, ethnicity, gender, age). Fieldworkers approached customers from the 27 selected coffee shops and screened them for the inclusion criteria. All fieldworkers were trained to administer the CAPI and to conduct recruitment in a two day course, and data collection was monitored in semimonthly meetings.

From an international perspective, coffee shops are an exceptional location to recruit frequent cannabis users, since 75% of Dutch users buy their cannabis at these venues (Wouters and Korf, 2009). However, some users visit coffee shops only intermittently and are thus harder to enrol, and others always buy their cannabis elsewhere and are consequently not reached by means of this type of recruitment. Therefore, we also used snowball sampling, to include frequent cannabis from the community who do not (often) visit coffee shops: all participants were asked to bring in a maximum of three frequent cannabis users from their social network, for which they earned at most three vouchers; 7.50 Euro per successful "chain referral". When participants gave permission, an interview appointment was made. Interviews were administered at a time and place of choice of the participant; provided that the ambiance was quiet and confidential. The participants received a 25 Euro incentive after full completion of the interview.

Recruitment results

Willingness to participate in this longitudinal study was relatively high. An estimated 60% of all people approached in coffee shops who fulfilled inclusion criteria did participate. Main reasons for non-response were lack of time or interest. A total of 616 persons were interviewed at baseline of which 16 interviews were

excluded for doubts about the reliability of answers: 12 of those respondents had an inconsistent response pattern and with four interviews there was a suspicion that two respondents had participated twice with different fieldworkers. Of the remaining 600 participants 200 were recruited by the fieldworkers in coffee shops and 400 participants were recruited by chain referral. Liebrechts *et al.* (2011) investigated similarities within these referral chains and found that the networks of frequent cannabis users were mostly heterogeneous (Liebrechts *et al.*, 2011). This suggests that potential multiplication of similar participants is of little influence on representativeness in this sample. No differences between recruitment method were found in 12 month cannabis dependence, gender, education level, and (Western/non-Western) ethnicity. Implications of the finding that chain referrals were younger, more often student, used cannabis less frequently and had a higher lifetime prevalence of cannabis dependence than those recruited from coffee shops are considered in the discussion.

The mean duration of the baseline interview was approximately 2.5 hours (range 1–5 hours; the interview length mainly depended on the number of comorbid mental disorders and the number of short breaks required). The interview location was variable: 31.1% took place at the participant's home; 20.0% at the research institute; 13.1% at a coffee shop; 23.6% at a café, and the remaining 12.2% at a public venue like a park or library. Even though the importance of privacy during the interview was stressed, it could not be prevented that other people were present within hearing distance (e.g. family or partner) for either a considerable or a small part of the interview (2.5% and 5.5% of all interviews, respectively). Participants were asked not to use cannabis during or just prior to the interview. Nonetheless, fieldworkers noticed in 10.5% of the interviews that the concentration of participants could have been influenced by the use of cannabis. In these cases, extra time was taken to repeat questions to establish that the participant had understood them correctly. Only in five of these cases fieldworkers reported that participants had a poor understanding of the questions. However, as this might also have been associated with the presence of a cannabis use disorder or some other psychiatric disorder, these participants were not excluded. When fieldworkers were uncertain about the reliability of the answers as a consequence of cannabis intoxication, they scheduled another appointment. In a sensitivity analysis, these participants will be excluded from the analysis to investigate the possible effect of being under the influence of cannabis during the interview. It should be noted, however, that the answering patterns of patients probably under the influence was not different from the ones

that were probably not under the influence of cannabis, indicated by the very similar internal consistencies that were obtained for different questionnaires for both groups. Correspondingly, interviews conducted at the participants home or at the research facilities did not differ from those conducted elsewhere (these findings are available upon request).

Two cohorts: Cohort I non-dependent and Cohort II dependent frequent cannabis users

During baseline data collection, the Composite International Diagnostic Interview (CIDI 3.0) substance use disorder section was used to establish lifetime and 12-month DSM-IV diagnoses of cannabis dependence. Based on this information, two prospective cohorts were formed. Cohort I consisted of 348 frequent cannabis users who did not meet

criteria for 12-month DSM-IV cannabis dependence. Cohort II consisted of 252 frequent cannabis users with a 12-month diagnosis of DSM-IV cannabis dependence.

Cohorts I and II did not significantly differ in mean age (22.1 years), gender (79.3% male), level of education and ethnicity. However, non-dependent frequent cannabis users were more often employed and less often student and the average duration of cannabis use was shorter in this cohort (Cohort I, Table 2). Of the persons from Cohort I, who were not dependent in the last 12 months, 22.4% had a lifetime diagnosis of cannabis dependence, and another 43.4% had a lifetime diagnosis of cannabis abuse, of which 21.0% in the past 12 months. These prior disorders will be taken into account as risk factors for transitions in the direction of cannabis dependence. However, whereas the first onset of cannabis dependence may involve other factors than recurring dependence,

Table 2 Baseline demographic and cannabis use characteristics for CanDep Cohorts I and II and the NEMESIS-2 subsample

		CanDep total (%)	Cohort I non-dependent (%)	Cohort II dependent (%)	NEMESIS 18–30 years	
					<i>n</i>	(%) ^a
Sample size	<i>N</i>	600	348	252	1118	1118
Gender	Male	79.3	79.3	79.4	490	49.1
Age	(mean, SD)	22.1 (3.1)	22.0 (3.1)	22.1 (3.0)		24.1 (4.0)
Ethnicity	Western (versus non-Western)	71.8	69.8	74.6	1011	87.5
Education	Primary education	9.2	8.9	9.5	32	6.4
	Lower secondary	20.5	23.0	17.1	192	28.3
	Higher secondary	37.5	37.4	37.7	460	42.4
	Higher professional, university	32.8	30.7	35.7	434	23.0
Employment status	Employed	41.5 ^b	46.3	34.9	760	65.6
	Student	43.7	40.5	48.0	276	26.0
	Unemployed, homemaker	12.8	11.8	14.3	67	6.8
	Unable to work	2.0	1.4	2.8	15	1.6
Cannabis use disorders	Lifetime dependence	55.0 ^b	22.4	100	29	4.0
	12 month dependence	42.0	0	100	10	0.9
	Lifetime abuse	25.2	43.4	n/a	55	5.0
	12 month abuse	12.2	21.0	n/a	12	1.0
Cannabis use	Years of use (mean, SD)	7.1 (3.2) ^b	6.9 (3.3)	7.4 (3.1)		4.0 (3.3) ^c
Past year average	Daily	31.5	31.9	31.0	11	12.5 ^d
	Near daily	36.8	34.2	40.5	8	5.2 ^d
	3–4 days per week	31.5	33.6	28.6	7	4.6 ^d

^aObserved numbers in NEMESIS-2 (*n*) and population based weighed proportions (%).

^bStatistical significant difference between cohort I and cohort II.

^cEstimation based on (*n*=450) lifetime cannabis users.

^dProportion based on (*n*=163) past year cannabis users.

separate analyses will be conducted excluding those with a lifetime cannabis dependence diagnosis at T_0 .

Attrition minimization

Respondents from both cohorts were re-interviewed at 18 months (T_1) between April and November 2010, with a follow-up response rate of 83.7%. The last interview (T_2) will take place 36 months after baseline. In order to reduce attrition during follow up, all participants were asked to give their name, address, phone number and e-mail address at baseline and T_1 . Moreover, at baseline the same information was asked from two significant others, preferably relatives and/or long lasting friends. These personal data were stored separately from their questionnaires, and are only available to the researchers. Between baseline assessment and follow-up interviews, participants are contacted every five months to check whether their personal data are still correct and updated when required. They are also asked to answer a minimal number of questions regarding their cannabis use in order to obtain a more detailed picture of the dynamics of cannabis use between the assessments. Participants receive a voucher (7.50 Euro) at each of these interim assessments.

Outcome measures

The CIDI 3.0 was used to assess the primary outcome of the prospective cohort study; 12 month DSM-IV cannabis dependence diagnosis. State transitions or stability between T_0 and T_1 and between T_1 and T_2 are based on this measure. A dimensional approach (change in number of symptoms) is used in addition to this dichotomous approach, since dependence symptoms may represent an underlying continuum (Compton *et al.*, 2009). Moreover, a categorical approach ignores the issue of sub-clinical disorders, which may be clinically relevant (Temple *et al.*, 2011). Other secondary outcomes include: (a change in) cannabis use pattern during the follow-up periods, including frequency, amount and estimated monthly cannabis dose.

Predictors of state transitions

The timing of measurement of potential predictors is summarized in Table 1 and described in more detail below.

Mental disorders

The presence of lifetime and 12 month DSM-IV diagnoses of mental disorders was established with the CIDI 3.0. Internalizing disorders measured at T_0 and T_2 include

major depression, bipolar disorder, dysthymia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder. Externalizing disorders included in the study at T_0 and T_2 were adulthood attention deficit hyperactivity disorder (ADHD) and lifetime antisocial personality disorder. In addition, childhood ADHD and conduct disorder (CD) were assessed at T_0 .

The presence of hallucinations and delusions were measured with a selection of six items of the psychosis section of CIDI 1.1 (G4, G5, G7, G8, G15, G16, in the CanDep study: Cronbach's $\alpha=0.58$). This selection of questions was based on a secondary analysis of NEMESIS-1 data; only those questions with the best sensitivity or the best positive predictive value in relation to a diagnosis of psychosis were included.

Substance use

Besides a diagnosis of cannabis abuse and dependence, the substance use section of the CIDI 3.0 included age of onset of the disorder, number of symptoms of abuse and dependence, age of first use, and frequency of cannabis use in the past 12 months. A more detailed assessment of cannabis use was obtained with items from a self-report questionnaire used in previous research (Korf *et al.*, 2007). Monthly cannabis dose was estimated based on the number of cannabis days in the past four weeks, and the number of joints per cannabis day. More specific subjective estimates of cannabis use include the preferred cannabis potency, the pace of smoking, and the depth of inhalation using a visual analogue scale. Finally, the dosage of cannabis per joint was based on a prompt card with dosages of 0.05, 0.10, 0.20 and 0.30 gram and on the estimate of the number of joints made from one gram of cannabis.

Motives for cannabis use were assessed by using the Marijuana Motives Measure (MMM) (Simons *et al.*, 2005). The MMM is a 25-item questionnaire with five internally consistent subscales consisting of: enhancement, conformity, expansion, coping and social. Based on a pilot study of the Dutch version of the MMM among 12 cannabis users, four questions were added to cover motives of some of the more experienced cannabis users; "using out of boredom", "using out of habit", "using to relax", and "using to sleep (better)".

The pilot phase demonstrated that inclusion of the CIDI alcohol and complete substance use sections would unacceptably lengthen the interview. Therefore, alcohol use and alcohol related problems were assessed at baseline with the Alcohol Use Disorders Identification Test (AUDIT); a screening instrument used to detect alcohol

abuse and dependence with excellent psychometric qualities (Bohn *et al.*, 1995). For ecstasy, cocaine, and amphetamines, questions on lifetime use (dichotomous), most recent use (last month/last 12 months/before), and frequency of use in the past year [rarely/less than monthly/monthly/weekly/(near) daily] as well as age of onset were included. Finally, nicotine use and nicotine related problems were assessed with the Heavy Smoking Index (HSI); a two-item measure including “time to first cigarette of day” and “number of daily cigarettes” (Burling and Burling, 2003). Age of first smoking and last month tobacco use were also assessed. These substance use questionnaires were administered at all waves.

Treatment

Treatment seeking can be both a predictor of state transition as well as a consequence of changes in cannabis use. Lifetime and 12-month service use related to cannabis use or any emotional or mental problems were assessed among all respondents of Cohorts I and II at baseline. Reasons for *not* seeking treatment, unmet treatment need, and attitudes towards treatment were also recorded. All these assessments will be repeated for 36-month service use at T_2 plus a limited assessment of cannabis related service use at T_1 .

Socio-demographics

Age, gender, education, employment status, and urbanization of the place of residence were recorded. Participants' living conditions were also recorded; which refers to persons living alone, with a partner, children, or parents.

Personality

Neuroticism was measured with the neuroticism scale of the shortened Eysenck Personality Questionnaire (the EPQ-RSS) (Eysenck *et al.*, 1985). Impulsivity was measured with the Dutch version of the Barratt Impulsiveness Scale (BIS-15), a 15-item measure of impulsiveness (Spinella, 2007). Both were administered at baseline and are reliable self-report scales with good psychometric properties, including high stability over time.

Life events

Questions on negative childhood experiences were recorded at T_0 , including parental death, emotional, physical, psychological or sexual abuse before age 16. Items on abuse were scored on a five-point frequency

scale (ranging from “never” to “very often”). In addition, the occurrence of major life events in the previous 12 months were assessed at each interview using Brugha's List of Threatening Experiences (Brugha *et al.*, 1985) and their positive equivalents.

Family history

Finally, family history of depression, psychosis, anxiety, and problematic use of alcohol, cannabis and other drugs were assessed at T_0 for biological parents and siblings. For each domain it was assessed which (if any) family member it concerned and whether any professional treatment was received.

Social support

Assessment of perceived social support from network members included the following questions: ‘to what degree can you unburden your heart to someone?’ and ‘to what degree can you count on practical help?’ on a four-point scale.

Social functioning

This was assessed in two ways. The first was a general scale of functioning not specifically related to cannabis dependence: Short-Form-36 Health Survey (SF-36), which includes four subscales: emotional role limitations, vitality, social functioning and general health perceptions (Ware *et al.*, 1993). Furthermore, among cases of cannabis abuse or dependence, disorder specific functions or impairments in the past 12 months were assessed at the end of the substance use section in the CIDI 3.0 by the Sheehan Disability Scales (SDS) (Sheehan, 1983). The SDS asks respondents to rate the impairment caused by the disorder in four areas of life (household, employment/education, social life, close personal relationships). It also includes a single question regarding the number of days in the past 12 months when the respondent was completely unable to work or carry out his or her usual activities due to the cannabis use disorder.

DNA

There is substantial evidence for an important role of genetic factors in the development of cannabis dependence, and for gene by environment interactions (e.g. Verweij *et al.*, 2010). All participants in the CanDep study were (after written informed consent) asked to donate saliva for DNA extraction, to investigate candidate genes associated with the transition from frequent cannabis use to dependence and vice versa.

Methods qualitative sub-study

Factors underlying transitions in cannabis dependence have been investigated with quantitative methods before (Perkonig *et al.*, 2008; Swift *et al.*, 2000). However CanDep combines this quantitative approach (in the prospective cohort study) with in-depth qualitative information about the dynamics and psychosocial processes underlying such transitions. Knowledge about the motives of cannabis users to change their pattern of use is crucial for the development of selective and indicated prevention and treatment. While the focus in the prospective cohorts was on factors predicting transitions in cannabis use and dependence, the in-depth interviews in a subgroup of users will generate additional knowledge on the mechanisms of change as well as social conditions which may support these changes. Qualitative interviews also provide an opportunity to describe how drug users perceive the way they have changed, and this can improve our understanding of transitions in cannabis dependence over time.

For this qualitative study, 48 cannabis users from Cohort I ($n=24$) and Cohort II ($n=24$) will be interviewed in-depth twice (shortly after T_1 and T_2) with emphasis on the dynamics underlying changes in cannabis use and the development or remission of a cannabis dependence diagnosis. Interviewees will be selected on the basis of change or persistence in cannabis dependence status between T_0 and T_1 . The interview schedule is semi-structured, using a topic list that includes questions about “cannabis career”, previous and intermediate changes in patterns of use, motivations for use, lifestyle and living conditions, motives for change and the possible role of treatment, life events and social network.

Methods for the comparison with the general population

Characteristics of frequent and dependent cannabis users (CanDep) will be compared cross-sectionally with subjects in the same age range from a representative sample of the general population and a sub-sample of last 12 month regular users (NEMESIS-2) in terms of comorbidity, social functioning and treatment for mental health problems. Furthermore, differences in personality characteristics, life events and substance use history are investigated. The variables and assessment instruments in both samples are closely matched which allows a direct comparison. Collection of baseline data in NEMESIS-2 took place between November 2007 and July 2009 and contains information on 6646 men and women from the general population aged 18–64 years, including 1118

respondents aged 18–30 years. For this sub-sample, the numbers of cases of cannabis use (450 lifetime, 163 last year), abuse (55 lifetime, 12 last year) and dependence (29 lifetime and 10 last year) are shown in Table 2. All subjects in NEMESIS-2 were also asked to donate saliva for DNA extraction.

Methods for comparison with treatment seekers

At baseline only 32 of a total of 252 (12.7%) cannabis dependent subjects in the cohort study had contacted a professional health care worker in the past 12 months. Only for 15 of these cases this contact was reported to be related to cannabis use problems, of which 10 were at specialized treatment facilities (4.0% of cannabis dependent Cohort II).

There were two approaches to investigate reasons for (not) seeking treatment, unmet treatment need and attitudes towards treatment. First, within Cohort II, treatment seekers ($n=32$) and non-treatment seekers ($n=220$) are compared regarding cannabis exposure, motives to use, substance use history, personality, comorbidity, history of mental health care, recent life events, and social functioning. Because of the small numbers of treatment seekers in Cohort II, these comparisons are likely to lack statistical power. Therefore, the second approach is to duplicate these analyses comparing non-treatment seekers from Cohort II with an additional sample of 100 cannabis users currently in treatment for cannabis-related problems. This additional sample is recruited from specialized addiction treatment facilities through referral by the care givers and through posters and flyers in the treatment facilities. The inclusion criteria resemble those of the respondents in the cohorts and the interview is similar to the baseline interview in Cohort II, except for an extra focus on subjective reasons for treatment seeking and unmet treatment needs. Representativeness of the additional sample is determined by comparing the demographic characteristics of this population with those of cannabis clients in the same age group recorded in a national treatment registry of addiction care. There is no follow-up of this treatment seeking patient group recruited through the treatment facilities.

Methods to explore the validity of cannabis exposure measures

As previously stated, self-reported cannabis use is assessed thoroughly at all three stages of assessment (T_0 , T_1 and T_2) using a questionnaire and interviews. To validate and better understand the meaning of these subjective measures, additional objective assessments of cannabis

exposure were performed after the first follow-up interview (T_1) among a subgroup of 110 cannabis users from Cohorts I and II. First, these additional assessments included hair analysis, which has a great potential in determining longer term substance use (Skopp *et al.*, 2007): detailed self-reported assessment of cannabis will be compared with concentrations of major cannabinoids and metabolites in hair. Second, self-reported doses per joint and pace of smoking will be validated by objective measures, for which data were collected in a natural setting, such as the participant's home or a coffee shop. Participants were asked to bring along a gram of their commonly used cannabis, for which they were financially compensated. They were asked to make a joint in their habitual manner (in the Netherlands, cannabis is usually mixed with tobacco) in order to validate the self-reported amount of cannabis in a single joint. Subsequently their smoking behaviour (smoking topography) was measured using a portable Cress Micro Transducer (Lee *et al.*, 2003). The Cress Micro Transducer is a small device used to measure the total smoke inhaled during a smoking session. This method has been applied successfully in field research of tobacco smoking topography. Finally, preference of cannabis potency will be validated by analysing the participant's cannabis sample for levels of THC, cannabidiol and cannabinol.

Initially, all participants who still used cannabis at T_1 , had sufficient scalp hair and consented to participate, were included in the assessment to ensure sufficient enrolment. After 70 participants were included, recruitment was targeted to those that were under-represented regarding their level of cannabis exposure and their potency preference.

Informed consent and medical ethics committee

In order to recruit respondents and reduce attrition, respondents received 25 Euros after completion of every interview (cohorts, treatment sample, in-depth interview) and after the measurements of cannabis exposure. All respondents had to provide written informed consent at the start of their participation in the study and also for the measurements of exposure. The project proposal was approved by an independent Medical Ethics Committee (METIGG).

Discussion

A total of 600 dependent ($n=252$) and non-dependent ($n=348$) frequent cannabis users were enrolled in the CanDep study at baseline, of which 83.7% was retained at 18 months follow up (T_1). This unique cohort from a

population which is often considered to be difficult to reach for scientific research, could be enrolled amongst others by using coffee shops as a special recruitment location specific for the Netherlands in combination with the use of snowball sampling.

While this study was designed to achieve a large sample of frequent dependent and non-dependent users, this recruitment method can not guarantee full representativeness. However, this is still a community based sample and snowball sampling has been suggested to produce more representative data than sampling from treatment facilities, since treatment seeking cannabis users are assumed to be more severe cases than non-treatment seeking individuals (Temple *et al.*, 2011). Besides, compared to representative general population surveys, the CanDep method has the advantage of very detailed cannabis use measures and a much higher prevalence of cannabis dependence, thus allowing to investigate exposure in more detail than "never use" versus "ever use".

This does not mean that limitations regarding the representativeness of the CanDep population do not need to be taken into account. First, the incentive in the chain referral could have encouraged invitation of non-eligible persons. To restrain this kind of dishonesty and the possible source of selection bias, there was a maximum of three referrals per participant. Furthermore, for this reason the incentive was chosen to be modest, but still high enough for sufficient enrolment. Second, the use of referral chains could result in a multiplication of chain referrals with similar but non-representative characteristics. While Liebrechts *et al.* (2011) found that the CanDep networks were mostly heterogeneous, it is still difficult to determine to which extent the sample is truly representative. Unfortunately there is no other suitable data available on characteristics of representative samples of frequent cannabis users that could be used to weigh the data from chain referrals. Neither can data from participants recruited in coffee shops be used to weigh the chain referral data because differences could both be interpreted as a result of a successful recruitment method in which various types of cannabis users were included, and as a selection of specific cannabis users as a side effect of the chain referral.

However, while representativeness of the CanDep sample cannot be determined, this does not necessarily mean that it is highly biased. After all, most frequent cannabis users in the Netherlands do visit coffee shops, which is why coffee shops are appropriate recruitment sites. Besides, there was satisfactory readiness to participate in the study. In order to explore the representativeness of the CanDep sample, frequent cannabis users and

cannabis dependent subjects from the CanDep study will be compared with (the limited numbers of) frequent and dependent cannabis users from NEMESIS-2, respectively. Furthermore, to account for the possibility of clustering within the chain referrals, robust standard errors will be obtained to produce correct 95% confidence intervals and *P* values (Skinner *et al.*, 1989). Furthermore, it should be noted that extrapolation to younger age groups may not be appropriate since the onset of cannabis dependence peaks at 17–18 years while the CanDep sample is restricted to persons older than 18 due to practical restrictions. (EMCDDA, 2010; Wagner and Anthony, 2002),

Finally, most data are based on self-report. While measures on cannabis consumption were validated externally, self-report has also been accepted as a suitable way to gain information about population behaviours (Harrison, 1997; Zaldivar Basurto *et al.*, 2009). Another issue regarding data quality is that a minority of the participants were difficult to interview while they were under the influence of cannabis. Since this may be associated with (the severity of) cannabis dependence or other relevant characteristics, excluding these interviews was deemed to be a larger violation of data integrity than maintaining them in the dataset. However, sensitivity analysis excluding these participants will be conducted.

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Declaration of interest statement

The authors have no competing interests.

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