The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults

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Abstract

Objectives: To determine incidence and patterns of natural course of cannabis use and disorders as well as cohort effects in a community sample of adolescents and young adults. Method: Cumulative incidence and patterns of cannabis use and disorders were examined in a prospective longitudinal design (mean follow-up period=42 months) in a representative sample (N=2446) aged 14–24 years at the outset of the study. Patterns of cannabis use, abuse and dependence (DSM-IV) were assessed with the Composite International Diagnostic Interview (M-CIDI). Results: (1) Cumulative lifetime incidence for cannabis use (at second follow-up): 47%; 5.5% for cannabis abuse, 2.2% for dependence. (2) Men used and abused cannabis more often than women. (3) The majority of the older participants (18–24 years at baseline) had reduced their cannabis use at follow-up, while younger participants (14–17 years at baseline) more often had increased their use and developed abuse or dependence. (4) The younger birth cohort (1977–1981) tended to start earlier with substance (ab)use compared to the older birth cohort (1970–1977). (5) Cannabis use was associated with increasing rates of concomitant use of other licit and illicit drugs. Conclusions: Cannabis use is widespread in our sample, but the probability of developing cannabis abuse or dependence is relatively low (8%). The natural course of cannabis use is quite variable: about half of all cannabis users stopped their use spontaneously in their twenties, others report occasional or more frequent use of cannabis.

Keywords: Abuse; Cannabis; Cohort; Dependence; Gender; Longitudinal study; Use

1. Introduction

Across epidemiological studies there is agreement that drug use is widespread among adolescents and young adults. Among substances, alcohol and nicotine are generally found to be the most frequently used, followed by cannabis, which is by far the most widely used illicit substance around the world (Bauman and Phongsavan, 1999). Depending on age group, cohort, country and time examined, between 12 and 50% of all adolescents and young adults in Europe and North America have tried cannabis at least once (Hammer and Vaglum, 1990; Anthony, 1991; Reuband, 1992; Nordlohne et al., 1993; Anthony et al., 1994; Kraus et al., 1994; Konings et al., 1995; Schumann and Kraus, 1995; Miller and Plant, 1996; Adlaf et al., 1997; Kraus et al., 1998; Perkonigg et al., 1998a,b; Weinberg et al., 1998; Bauman and Phongsavan, 1999; Höfler et al., 1999; Ivis and Adlaf, 1999; Merrill et al., 1999; Perkonigg et al., 1999; Kokkevi et al., 2000).

In most studies males report a higher lifetime use than females do. Geographic/cultural differences in cannabis use have been demonstrated, as well as age and birth cohort effects. Highest prevalence of cannabis use have been reported for New Zealand, followed by the US and central Europe; lower rates were found in countries at the periphery of

Europe (e.g. Norway and Greece; Fergusson and Horwood, 2000b; Smart and Ogborne, 2000). In US high school students, the prevalence of cannabis use rose during the late 1960s and 1970s, then declined steadily and substantially throughout the 1980s, only to rise again markedly after 1992 (Bachman et al., 1998; Bauman and Phongsavan, 1999). The comparison of historical trends across various studies and countries is hampered by the fact that most studies do not refer to the concept of 'cohort' (a group defined by calendar year(s) of birth; Neugarten and Datan, 1973) and do not present the years of birth of their study participants (e.g. Bachman et al., 1998).

Fewer representative population-based data are available concerning the prevalence of abuse and dependence of illicit drugs. Using DSM-III-R criteria a similar rank order was found, with highest rates for New Zealand, medium high rates for US (lifetime incidence of cannabis dependence in 15–24 year olds: 5.6%), and lowest in Germany (Lewinsohn et al., 1992; Anthony et al., 1994; Feehan et al., 1994; Perkonigg et al., 1998a,b, 1999; Fergusson and Horwood, 2000a). Males are affected about two to four times as often as females (Offord et al., 1996).

Although a considerable number of longitudinal studies have examined risk factors of starting, continuing and discontinuing cannabis use (e.g. Kandel and Faust, 1975; Newcomb et al., 1986; Kandel and Raveis, 1989; Kendler et al., 1999; Brook et al., 1999), remarkably little systematic research is available on the natural course of substance use disorders in community samples. Thus, our knowledge about transitions from use to patterns of clinically significant abuse and dependence, or regressions from such stages to use without disorder or non-use, is quite limited (Perkonigg et al., 1998b; Weinberg et al., 1998; Nelson and Wittchen, 1998; Cicchetti and Luthar, 1999). These research deficits are mainly due to the facts that most studies: (a) employ cross-sectional rather than longitudinal designs; (b) do not use specified diagnostic criteria for clinically relevant abuse or dependence patterns; (c) focus on the initiation of (ab)use, not on its reduction or cessation; (d) are confined either to drug use or to drug abuse and dependence (only a few studies take 'recreational' (nonpathologic) use as well as clinical criteria into account; Glantz, 1992; Kandel and Davies, 1992; Chen and Kandel, 1998).

Nevertheless there seems to be agreement that in comparison to other illicit drugs, only a small proportion of all lifetime cannabis users go on to develop clinically significant patterns of cannabis abuse or dependence (Weinberg et al., 1998; Perkonigg et al., 1999); cannabis as a substance in itself might not be linked to a strong risk of developing a dependence syndrome. The relative rarity of clinically significant dependence syndrome in cannabis users, even despite continuing regular use, and the research evidence that cannabis use tends to be reduced or terminated with advancing age has led many researchers to describe the predominant pattern of cannabis use as 'transient recreational use' with no major risks and a high rate of spontaneous remission. The major risk for initiation of cannabis use seems to be completed for the most part by age 20, and it seems that about 60% of all cannabis users spontaneously stop their use between ages 23 and 30 years due to changes in social roles (work, marriage, parenthood) that are felt to be incompatible with cannabis use (Kandel and Faust, 1975; Kandel and Logan, 1984; Silbereisen, 1997; Hammer and Vaglum, 1990; Johnston et al., 1992; Chen and Kandel, 1998).

Yet this description does conflict with a considerable body of other studies that have pointed to the fact that of cannabis users who progress to regular use, the majority reveal extended patterns of regular use for at least one year, associated with gradually increasing

dosages and frequencies of use as well as increasing risks to use other illicit drugs, such as amphetamines, hallucinogens, stimulants and opiates (Merrill et al., 1999; Perkonigg et al., 1999; Fergusson and Horwood, 2000a,b). But it may well be that these less optimistic data describe the situation in subjects before they make social transitions in their mid or late twenties. A lack of prospective-longitudinal studies makes it difficult to decide which description of use and abuse patterns is more accurate for the current situation.

The Early Developmental Stages of Psychopathology Study (EDSP; Wittchen and Nelson, 1998; Lieb et al., 2000), a prospective-longitudinal community-study, examined the natural course of cannabis use in a representative sample of 14–24 year olds in Munich, Germany. Cannabis use results from the EDSP-baseline and 20 months prospective data for the younger cohort (initially aged 14–17 years) have already been presented (Perkonigg et al., 1998b, 1999; Höfler et al., 1999).

The focus of this paper is to describe the natural course of cannabis use, abuse and dependence over about 4 years in a German sample of adolescents and young adults, aged 14–24 at baseline (birth cohorts 1970–1981), highlighting gender, age and cohort effects. The following questions will be examined:

1. What is the age of onset of cannabis use, abuse and dependence?
2. How prevalent is cannabis use in adolescence and young adulthood?
3. How prevalent is cannabis abuse and dependence according to DSM-IV criteria?
4. How stable are the patterns of cannabis use, abuse and dependence across time, with emphasis on increases, reductions and spontaneous remissions?
5. To what degree is cannabis use associated with the use of other licit and illicit substances? Is the cessation of cannabis use accompanied by a compensative increase in the use of other drugs or by a decrease?

2. Method

The Early Developmental Stages of Psychopathology Study (EDSP; Wittchen et al., 1998; Lieb et al., 2000) explores the prevalence, incidence, comorbidity, risk factors, protective factors and 4-year course of mental disorders, with specific emphasis on substance-use disorders in a representative general population sample. The study is based on three waves, the first conducted in 1995 (t0), the second in 1996–97 (t1: only the younger cohort was assessed), and the third in 1998–99 (t2: again with the total sample).

2.1. Baseline sample and follow-up investigations

The sample was drawn randomly from the 1994 government registries of residents in metropolitan Munich. A total of 3021 participants aged 14–24 years (birth cohorts 1970–1981) were successfully interviewed at baseline, resulting in a response rate of 71%. Since the study was designed with a special interest in early stages of substance use disorders, 14–15 year olds were sampled at twice the probability of 16–21 year olds, and 22–24 year olds were sampled at half the probability. At baseline, almost three-quarters of the participants were students, 36% at the secondary level and 26% at university, and 20% of the participants were employed. Nearly two-thirds (62%) were living with their parents, 23% were living alone, and 12% were living with their partner/spouse. The majority of the respondents were classified as middle class (59%), reflecting the population of Munich.

Two follow-up investigations were completed after the initial baseline assessment, covering an overall period of 42 months (range: 34–50 months). The first follow-up (t1) was conducted in 1996/1997 and confined to the younger subsample (aged 14–17 years at baseline); 1228 interviews were completed, giving a follow-up response rate of 88%. The second follow-up (t2) included all baseline respondents and was conducted in 1998–99, an average of 42 months after the baseline investigation (range 34–50 months); the response rate was 84% (N=2548). Of these, 102 participants did not want to respond to questions about illicit drug use at t0, t1 or t2. Therefore, our dataset is N=2446 with regard to the longitudinal development of cannabis use/abuse across the entire study period: 1101 participants in the younger cohort (aged 14–17 years baseline, born between 1977 and 1981), and 1345 in the older cohort (aged 18–24 years at baseline, born between 1970 and 1977). Data from all three assessments are used in this paper. Noteworthy changes in sociodemographic characteristics from baseline to second follow-up were only found for school/employment status (t2: secondary school: 13%, employed: 36%) and living arrangements (with parents: 40%; with partner: 23%).

2.2. Measures

Face-to-face computer-assisted interviews were administered by professional health interviewers and clinical psychologists at baseline and at the two follow-ups. Diagnostic assessments (t0–t1–t2) were based on the Munich version of the Composite International Diagnostic Interview (M-CIDI; Wittchen and Pfister, 1997). At baseline, lifetime and past 12 month substance use, substance use disorders and other mental disorders were assessed according to DSM-IV criteria. In both follow-up investigations, substance use and diagnoses during the follow-up period(s) and for the previous 12 months were evaluated. The M-CIDI is an updated version of the World Health Organization's CIDI version 1.2 (WHO-CIDI; World Health Organization, 1990), which incorporates questions to cover DSM-IV (American Psychiatric Association, 1994) and ICD-10 criteria. The reliability and procedural validity of the M-CIDI has been established (Lachner et al., 1998; Reed et al., 1998). The assessment of cannabis use, abuse and dependence have been comprehensively described elsewhere (Perkonigg et al., 1998a).

2.3. Data analysis

In line with the WHO–CIDI conventions (World Health Organization, 1990; Lachner et al., 1998), four mutually exclusive patterns of drug use were considered (never; 1 time; 2–4 times; 5 or more times). Additionally, the category of the '5+ times' users was subdivided into those with 'considerable' use (participant never consumed more than two joints during one week) or 'heavy' use (participant consumed at least three joints during one week) according to their peak cannabis- use-per-week period. At second follow-up, the cumulative lifetime consumption of cannabis was assessed: those subjects classified as having a 'considerable' lifetime use on average had consumed cannabis 13–50 times (median; 19.5% 5–12 times, 36.1% 13–50 times, 12.1% 51–100 times, 8.4% 101–150 times, 6.2% 151–200 times, 6.1% 201–365 times and 11.6% > 365 times) and those classified as having a 'heavy' lifetime use actually had an average use of > 365 times (median: 82.5%, only few subjects in this group had consumed less, the minimum being 5–12 times).

Lifetime prevalence at baseline denotes the weighted rate of occurrence of a pattern of use or diagnosis in the total sample or subsamples, and it covers the respondents' lifetime period prior to the assessment at baseline. Follow-up incidence of cannabis use, abuse and

dependence was defined as new outcomes during the follow-up period (t0 to t2) among non-users at baseline. Cumulative lifetime incidence was calculated by adding baseline, t1 and t2 follow-up incident cases. Twelvemonth prevalence rates at follow-up refer to the prevalence of drug use, abuse or dependence during the year preceding the t2-follow-up interview.

To account for different sampling probabilities for the different age-groups, non-contact and non-response, all measures were estimated using weighted data. To account for design effects introduced by the use of weighted data, standard errors were estimated using the software package STATA (StataCorp., 1999) that applies the Huber–White sandwich matrix in this case (Royall, 1986). Survival analyses were used for the examination of age of onset data.

Age-specific cumulative lifetime incidences for cannabis use, abuse and dependence were estimated with the Kaplan–Meier method (Andersen and Keiding, 1996). Differences between curves were assessed with hazard ratios (HR) from the Cox proportional hazards model. The proportional hazards assumption, i.e. hazard ratios being independent of age, was tested with so-called Schoenfeld residuals (Grambsch and Therneau, 1994). When this assumption was violated for cohort differences, a stratified Cox model was used, i.e. different curves in age-cohorts were fitted before testing for group differences (Andersen and Keiding, 1996). In the case that the assumption was violated for gender differences the interaction term female gender×age was added to the model to test whether age is differently associated with the outcome for females as compared to males. A hazard ratio smaller than one then means that women have an earlier onset, conditional on the event that the outcome event is given.

3. Results

3.1. What is the age of onset of cannabis use, abuse and dependence?

Figs. 1–3 show the age-specific cumulative lifetime incidences for use of cannabis, abuse and dependence by gender and birth cohort. First use of cannabis was rarely reported before the age of 13 years. After that age, there was a steep increase in use. Development of abuse and dependence usually occurred after the age of 15 years. While the (cumulative lifetime) use of cannabis was still slightly increasing in the participants' late twenties, none of them developed cannabis abuse or dependence after age 22 (women) or 26 years (men). Users who developed cannabis abuse did so on average 2.0 years after first use (range: 0–10 years), and dependence criteria were fulfilled 2.4 years (mean) after first use (range 0–10 years).

Cohort differences in age of onset could only be analyzed for the period 0-21 years, the highest age reached by members of the younger cohort. With regard to cannabis use we found lower hazard rates in the older cohort (HR=0.61, 95% confidence interval/CI= 0.53–0.69, $P < 0.05$). The curve showing the increase of cannabis use was steeper for the younger than for the older cohort (Fig. 1). Similarly, the cohort differences visible in Figs. 2 and 3 were significant for cannabis abuse (HR=0.45, CI=0.33–0.62, $P < 0.05$), but they did not reach significance for dependence (HR=0.74, CI=0.41–1.32). Interaction effects of age and cohort were found for use (HR=1.32, CI=1.20–1.44; $P < 0.05$), abuse (HR=1.31, CI=1.08–1.59, $P < 0.05$) and did not reach significance with regard to dependence (HR=1.13, CI=0.72–1.80). The younger cohort (born 1977–81) started earlier than the older cohort (born 1970–77) with (ab)use.

Overall, lower hazard rates were found for women with regard to onset of cannabis use (gender differences; HR=0.65, CI=0.57–0.74, P < 0.05), cannabis abuse (HR=0.26, CI=0.17–0.37, P < 0.05) and cannabis dependence (HR=0.41, CI=0.21–0.79; P < 0.05). Interaction effects of age and gender were found for the onset of cannabis use disorders (abuse: HR=0.77, CI=0.63–0.95, P < 0.05; dependence: HR=0.65, CI=0.44–0.95, P < 0.05) but not for first cannabis use (HR=0.97, CI=0.92–1.03). Taken together, these results indicate that fewer females than males started to use cannabis and there is no evidence for a different age of onset pattern among those who started with use. In contrast, among those who fulfilled criteria for disorders, a higher proportion of females started at an earlier age. As shown in Figs. 2 and 3, with increasing age, males' probability of developing a substance use disorder showed a stronger increase than females'. In fact, all female subjects who were diagnosed with cannabis dependence developed their dependence before age 19 years, while men's incidence rate for dependence continued to increase until age 26 years.

3.2. How prevalent is cannabis use?

At baseline (t0), 65.8% of the sample had never used cannabis, 7.0% reported use only on a single occasion, 11.2% reported use '2-4 times', 11.2% reported a 'considerable' and 4.7% a 'heavy use' (see Table 1: first column). The cumulative lifetime incidence by the second follow-up (t0–t1–t2), roughly 4 years later, revealed a substantial decrease in the proportion of subjects with no cannabis use ever (53.4%), and a considerable increase in the proportion of 5+ users ('considerable use': 22.7%; 'heavy use' 6.8%; Table 1: second column). Of the baseline non-users, 81.2% remained abstinent while follow-up incidence results (t2) reveal that 19% started to use cannabis during the follow-up period; there were almost equal proportions of new users with rare use (1 time: 3.5%; 2–4 times: 6.2%) and with regular use ('considerable': 8.3%; 'heavy': 0.8%; Table 1: third column). Taking the follow-up (t2) 12-month prevalence as a rough measure for outcome and particular discontinuation, the fourth column of Table 1 reveals that only one quarter of the entire sample had used cannabis during the year preceding the second follow-up, indicating that almost 50% of all previous lifetime users had stopped their cannabis use during the past 12 months.

Regardless of the period considered, men always revealed a significantly higher rates of use (Table 2).

The older cohort reported higher cannabis use at baseline, but the cumulative lifetime incidence at follow- up, revealed no significant cohort differences in cannabis use. Concerning all other follow-up data (i.e. incidence among baseline non-users and 12-month follow- up prevalence), however, the younger cohort consistently had a higher risk of using cannabis (Table 2).

3.3. How prevalent is cannabis abuse and dependence DSM-IV?

At baseline, 2.5% of the sample fulfilled criteria for cannabis abuse (without dependence), and 1.4% for dependence (Table 3: first column). The cumulative lifetime incidence at follow-up (t2) reveals a substantial increase, with rates of 5.5% for abuse and 2.2% for dependence (Table 3: second column). The follow-up incidences among baseline non-users were low (abuse: 1.8%; dependence: 0.3%; third column), as were follow-up (t2) 12 -month prevalences (abuse: 3.0%; dependence: 0.6%; fourth column).

Men generally had a higher risk of developing cannabis abuse and dependence (the latter did not reach significance with regard to baseline cumulative lifetime incidence and follow-up 12-month prevalence; Table 4).

At baseline, the younger cohort had a significantly reduced risk of meeting criteria for a DSM-IV cannabis dependence, but – similar to the cohort effects in cannabis use – the cumulative incidence data reveal a reversed effect: the younger cohort had overall a significantly higher risk of developing cannabis abuse and dependence (the latter is only significant with regard to the follow-up prevalence; Table 4). Additionally, all of the nine participants who had not used cannabis at baseline but had developed dependence at follow-up came from the younger cohort (Table 3: third column).

3.4. How stable are the patterns of cannabis use, abuse and dependence across time?

Table 5 reports the findings on the change over time in cannabis use by cross-tabulating cumulative lifetime incidence (until 12 months prior the second follow-up t2) and 12-months follow-up findings (t2) along with the estimated conditional probabilities (%) for four patterns (no use, use without disorder, abuse without dependence, dependence). The diagonal values indicate that two patterns were particularly stable in the total sample: namely respondents who had never tried cannabis at baseline were most likely to be classified as non-users at follow-up (95.4%), and cannabis users without a disorder also tended to remain in the same group (44.1%) or to become non-users (54.7%). Half of those diagnosed as having had cannabis abuse had improved during the 12-months follow-up interval — either by going into the ‘user/no disorder’ category (42.8%) or by becoming non-users (13.8%); 41.3% remained abusers and 2.2% developed dependence. Of those with an initial (cumulative lifetime) dependence, 19.0% remained dependent, 20.6% moved to abuse without dependence, while half of this group showed remission (44.2% to use without disorder, and 16.2% to no use).

We did not find significant gender differences in the observed transitions from cumulative lifetime use and the 12-months prevalence at second follow-up. But it is remarkable that none of those females initially classified as ‘user, no disorder’ had developed a disorder at follow-up, while 16 men have done so (Table 5).

A comparison of the two age cohorts revealed significant differences for the courses of those initially diagnosed as ‘never using’ cannabis or ‘use/no disorder’ (Table 5). Of the initially abstinent participants from the older group, nearly all remained abstinent (97.6%), whereas only 90.5% of the initially abstinent younger participants remained non-users. Similarly, participants in the older cohort initially grouped as ‘use/no disorder’ mostly stopped their cannabis use (62.2%) or — less often — remained in the same group (37.7%); only 0.2% developed a disorder. But in the younger cohort, 4.0% of the baseline ‘use/no disorder’ participants developed cannabis related disorders by second follow-up and the majority remained users without disorder (63.0%); only a minority had stopped their cannabis use at follow-up (33.1%).

Table 6 summarizes the cumulative incidence use pattern in the sample (until 12 months prior the second follow-up) and the proportion of non-users at t2 (12- months status). The lower the cumulative lifetime cannabis use, the higher the probability that participants did not use this substance during the 12 months preceding the second follow-up.

3.5. To what degree is cannabis use or the cessation of cannabis use associated with the use of other substances?

Table 7 reveals substantial associations between use of other licit and illicit drugs and cannabis use status (12-months prevalence at second follow-up). Continuous cannabis users had the highest 12-month use of other substances, followed by ex-cannabis-users (who had not taken cannabis during the past 12 months) and never-users of cannabis described a comparatively low consumption of drugs. The risk of using licit (alcohol, nicotine) as well as illicit drugs was significantly higher for continuous cannabis users as well as ex-users of cannabis compared to never users of cannabis. Odds ratios were particularly high for continuous (and to a lesser degree for ex-)cannabis users to use certain illicit drugs (opioids, cocaine, stimulants, sedatives, hallucinogens); odds ratios were lower but still increased for licit drugs (alcohol and nicotine). But there was no tendency of a compensative increased drug use of exusers of cannabis: this group used other licit and illicit drugs distinctly less often than those who had continued to use cannabis.

4. Discussion

In this paper data on the natural course of cannabis use, abuse and dependence over four years are presented, from a prospective-longitudinal representative community sample of 2446 German adolescents, aged 14–24 years at baseline and 17–28 years at the second follow-up. The data presented here are comparable to US studies (e.g. Kessler et al., 1994; Warner et al., 1995) with regard to the design, sampling, data-analysis and instruments employed. Data were collected in personal interviews with an established reliable and valid standardized, computerized instrument (M-CIDI; Wittchen and Pfister, 1997; Lachner et al., 1998; Reed et al., 1998).

4.1. Limitations of the study

Some limitations of the study should be considered:

1. Interpretation of some of the analyses for cannabis abuse and dependence is hampered by the fact that relatively few cases developed a cannabis disorder.
2. Some attrition occurred from baseline to t2-followup that might have had an effect on the data. For example, users of any illegal drugs and participants with drug use disorders had a slightly but non-significant higher probability of not participating at the second follow-up (OR=1.5–1.7). Further, 102 participants of the study did not want to answer to questions about illicit drug use at one or more of the assessments. This potential selective attrition might have resulted in the description of a more favorable pattern of course for cannabis use, abuse and dependence.
3. Cannabis users in the US on average use more of the drug; therefore, German ‘heavy use’ is not equivalent to US ‘heavy use’ (e.g. Kandel and Chen, 2000).
4. Complexity of the field work resulted in a relatively variable follow-up length (range: 34–50 months). Therefore, follow-up incidence data are reduced in their precision because they refer to varying time-intervals.
5. Because of the focus of our study on early stages of substance use, the younger cohort was assessed three times (t0–t1–t2), the older group only two times (t0–t2). Therefore, higher estimations of use, abuse and dependence in the younger cohort could be related to the shorter follow-up intervals of the younger group, which reduces the chance of recall bias.

4.2. Prevalence of cannabis use and disorders in Germany

The overall cumulative lifetime incidence rate of 47% for cannabis use at the second follow-up for our then 17–28 year old participants is similar to estimates found in US or French studies for this age group (Anthony et al., 1994: 15–24 year olds: 36.5%; Chabrol et al., 2000: 16–20 year olds: 49%), but is higher than the federal German prevalence estimates of 26% for 21–24 year old adults in West Germany in 1995 (Kraus et al., 1998) and results from Greece (Kokkevi et al., 2000: 18–24 year olds: 22%). Overall, ages 14–20 are peak hazard ages for initiation of cannabinoid use, and after age 16 is the peak risk period for developing abuse and dependence (Anthony et al., 1994; Kandel et al., 1997).

Our cumulative lifetime incidence assessed at the second follow-up (t2) for CIDI-DSM-IV-defined cannabis dependence in 17–28 year-olds (2.2%) is considerably lower than the 5.6% cannabis dependence rate for 15–24 year olds found in recent US studies of this age group (Anthony et al., 1994). This raises important questions about why German young adults make the transition into dependence less frequently. Is this due to lower use rates, more favorable psychosocial factors, the established lower prevalence of associated psychopathological factors in German samples, or the lower prevalence of concomitant use of other drugs? We are currently examining these issues in a follow-up paper.

While we did not find significant gender differences in the (previously published) analyses of the younger subsample (Perkonigg et al., 1999), we found gender differences in the full baseline data set (Perkonigg et al., 1998a) and in the four-year follow up data presented here for the complete sample. As most other researchers have reported, we found that men use and abuse cannabis more often than women do (Schumann and Kraus, 1995; Kandel et al., 1997). Similar to other studies (Offord et al., 1996), females revealed in our second follow-up a slightly lower cumulative lifetime incidence (49.0% compared to 54.1% in male respondents), as well as distinctly lower rates for abuse and dependence (although the difference for dependence did not reach significance). All females with a cannabis use disorder developed the disorder before age 19 (dependence) or 23 years (abuse), while men's incidence rate continued to increase throughout their twenties.

4.3. Cannabis use — a transient phase-specific phenomenon?

There is indeed a considerable variability in patterns of cannabis use and disorder over time. The proportion of subjects who had stopped cannabis use even after prolonged and heavy use is quite substantial. As expected from our previous analyses (Perkonigg et al., 1999), our follow-up outcome analyses reveal that subjects with previous occasional cannabis use only (prior to the 12 months preceding second follow-up) had the highest probability of being grouped as non-users at second follow-up (12-months status: 74–78%). Regular users ('considerable use': 39%; 'heavy use' without disorder: 25%) and subjects that had been diagnosed as having had a DSM-IV cannabis abuse (14%) or dependence (16%) were considerably less likely to have stopped their cannabis use during the 12 months preceding second follow-up.

Since our sample includes the age span 14–24 years at baseline and 17–28 years at follow-up, we have examined how these findings differ by age and cohort. About two-thirds (62%) of the older (birth cohort: 1970–77) cumulative lifetime cannabis users without disorder did not use cannabis during the 12 months preceding the second follow-up assessment; one third (38%) continued to use cannabis without developing a disorder, and

only 0.2% developed an abuse (none developed dependence). But results were considerably different for the younger cohort (1977–81): only onethird (33%) of the users without disorder stopped their use, 63% continued as before, 3% developed abuse and 0.7% developed cannabis dependence at follow-up (Table 5). These findings suggest (1) that users — and especially female users — who have not developed a DSM-IV cannabis use disorder by age 20 years have a fairly low probability of doing so at a higher age. (2) Incident use as well as continued use of cannabis is a characteristic of adolescents and young adults. Irrespective of the fact that there is a high proportion even among regular users after age 25 years in our sample that do not entirely stop taking the drug, these findings are partially consistent with the notion of cannabis use as a transient 'experimental period in adolescence' (Kandel and Faust, 1975; Kandel and Logan, 1984; Hammer and Vaglum, 1990; Johnston et al., 1992; Silbereisen, 1997; Chen and Kandel, 1998). Spontaneous changes from use to non-use occurred relatively often in our older subsample (aged 22–28 years at follow-up). The partiality of agreement is due to the fact that the length of cannabis use clearly stretches over almost a decade in our sample into the late 20s which makes the use of the word 'transient' somewhat questionable. But nevertheless the findings seem to be consistent with the speculation that a large proportion of cannabis use is of experimental 'adolescence-limited' nature (Moffitt, 1993) that for the most part stops during the 20s because of new responsibilities (job, relationship, parenthood).

4.4. The bad news

The good news about significant rates of spontaneous reduction or stop of cannabis use in almost 50% in our sample is offset by three problematic implications of our study.

4.4.1. Increasing use of cannabis in younger German cohorts

As has been found in studies in the US (Bachman et al., 1998; Bauman and Phongsavan, 1999) and Greece (Kokkevi et al., 2000), we demonstrated a cohort effect with regard to the age of onset of cannabis (ab)use. The younger cohort (birth cohort 1977–81), tended to use and abuse cannabis more often and at an earlier age than those born 1970–77.

4.4.2. Cannabis use is accompanied by an elevated use of other drugs

Like several other researchers (e.g. Merrill et al., 1999; Fergusson and Horwood, 2000a,b), we found that (continuous and ex-)cannabis users compared to non-users have significantly higher risks for use of other illicit substances like cocaine, stimulants, hallucinogens and opioids as well as for alcohol and nicotine. But increased risks do not necessarily prove a cause-effect relationship in the sense of the 'gateway' theory (Kandel and Faust, 1975). Although several studies show that use of other illicit substances usually is preceded by the use of cannabis (e.g. Fergusson and Horwood, 2000b), it is also obvious that the use of cannabis is usually preceded by the use of alcohol and nicotine (e.g. Kandel and Faust, 1975; Pederson and Skrondal, 1999). It is still an open question concerning whether cannabis use in adolescence causes use of other illicit drugs, or whether cannabis use is a marker for other factors that also cause the use of other illicit drugs (Merrill et al., 1999).

Further, our analyses show that those former cannabis users who had stopped to use this substance at follow-up also had a lower follow-up use of other licit and illicit drugs

compared to continuous users of cannabis — but they still tended to use other substances more often than never users of cannabis.

4.4.3. Cannabis abuse and dependence tends to remain stable across four years

More than 40% of the cumulative lifetime users that had fulfilled DSM-IV criteria for either cannabis abuse or dependence (prior to the 12 months before the second follow-up assessment) remained DSM-IV-cases of abuse or dependence at the 12-months follow-up. Additionally, only 0.2% of the older baseline cannabis users without disorder developed an abuse during follow- up (none developed a dependence), but a higher percentage of younger baseline users without disorder had become cases at 12-months follow-up (3.3% abuse, 0.7% dependence). Although it is not entirely clear whether this pattern is due to cannabis use per se or whether it is linked to the concomitant use of other substances, this finding raises clinical and public health concerns.

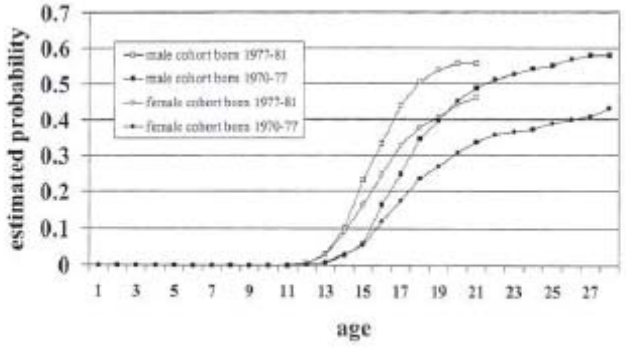

Fig. 1. Onset of cannabis use.

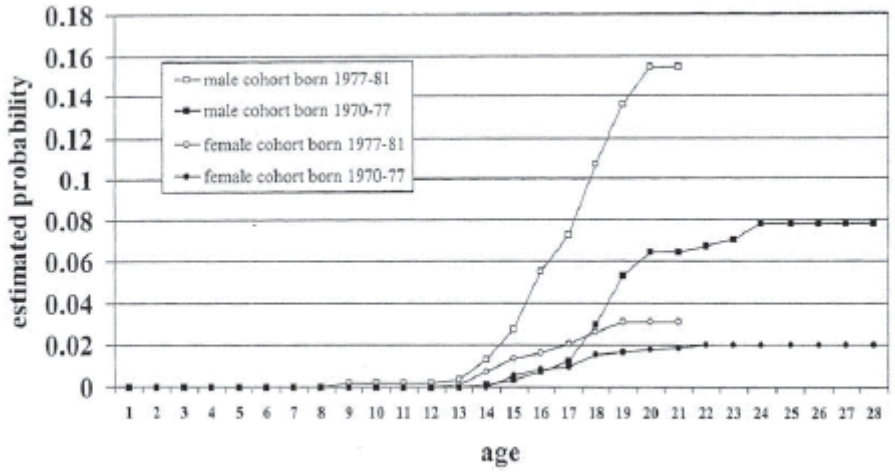

Fig. 2. Onset of cannabis abuse (without dependence).

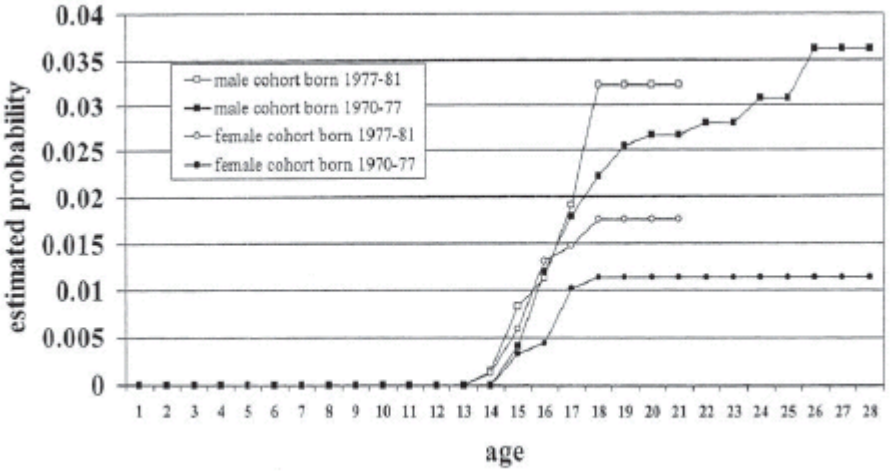

Fig. 3. Onset of cannabis dependence.

Table 1
Cannabis use at baseline (t_0) and follow-up (t_2) ($N = 2\,446$)[a]

(Sub)group	Use pattern	Baseline (t_0) cum. Lifetime incidence			Follow-up (t_0–t_1–t_2) cum. lifetime incidence			Follow-up (t_2) incidence among baseline non-users			Follow-up (t_2) 12-month prevalence		
		N	%w	95% CI	N	%w	95% CI	N	%w	95% CI	N	%w	95% CI
Total	Never use	1723	65.8	(63.65–67.96)	1327	53.4	(51.20–55.64)	1327	81.2	(79.16–83.00)	1766	74.6	(72.66–76.42)
	One time-use	156	7.0	(5.87–8.22)	137	6.1	(5.05–7.25)	65	3.5	(2.66–4.59)	128	5.1	(4.18–6.14)
	2–4 times use	245	11.2	(9.88–12.75)	264	11.0	(9.68–12.46)	123	6.2	(5.08–7.48)	185	7.1	(6.10–8.35)
	Considerable use	221	11.2	(9.81–12.82)	552	22.7	(0.91–24.56)	185	8.3	(7.15–9.71)	298	10.8	(9.58–12.17)
	Heavy use	101	4.7	(3.86–5.82)	166	6.8	(5.77–7.99)	23	0.8	(0.54–1.27)	69	2.4	(1.84–3.10)
14–17 years at baseline	Never use	907	80.6	(77.84–83.07)	608	54.1	(50.87–57.21)	608	67.1	(63.71–70.27)	722	65.0	(61.89–67.98)
	One time-use	57	5.2	(3.97–6.86)	48	4.1	(3.02–5.48)	39	4.0	(2.88–5.58)	59	4.9	(3.76–6.38)
	2–4 times use	72	7.3	(5.77–9.26)	119	10.8	(9.01–12.93)	86	9.4	(7.57–11.62)	106	10.3	(8.45–12.46)
	Considerable use	41	4.3	(3.07–5.85)	252	24.1	(21.41–26.95)	151	17.2	(14.69–20.04)	170	15.9	(13.66–18.37)
	Heavy use	24	2.6	(1.71–3.97)	74	7.0	(5.50–8.83)	23	2.3	(1.50–3.52)	44	3.9	(2.88–5.37)
18–24 years at baseline	Never use	816	59.7	(56.86–62.48)	719	53.2	(50.30–56.01)	719	89.1	(86.64–91.07)	1044	78.6	(76.17–80.79)
	One time-use	99	7.7	(6.26–9.37)	89	6.9	(5.56–8.5)	26	3.2	(2.15–4.79)	69	5.1	(4.01–6.57)
	2–4 times use	173	12.9	(11.09–14.88)	145	11.1	(9.40–12.99)	37	4.4	(3.11–6.08)	79	5.8	(4.63–7.33)
	Considerable use	180	14.1	(12.21–16.29)	300	22.2	(19.88–24.63)	34	3.4	(2.37–4.79)	128	8.7	(7.28–10.37)
	Heavy use	77	5.6	(4.47–7.09)	92	6.7	(5.44–8.28)	0	0.0		25	1.7	(1.16–2.64)
Male	Never use	830	60.2	(57.09–63.31)	595	45.9	(42.76–48.97)	595	76.1	(72.89–79.05)	827	68.3	(65.42–71.10)
	One time-use	86	7.4	(5.88–9.30)	73	6.4	(4.98–8.15)	34	4.1	(2.78–5.93)	69	5.3	(4.06–6.79)
	2–4 times use	143	13.0	(11.00–15.29)	135	10.8	(9.05–12.89)	60	6.4	(4.89–8.45)	95	7.6	(6.10–9.38)
	Considerable use	128	13.3	(11.20–15.80)	335	27.7	(24.96–30.60)	122	11.9	(9.84–14.27)	201	14.7	(12.67–16.91
	Heavy use	63	6.0	(4.64–7.74)	112	9.3	(7.60–11.23)	19	1.5	(0.93–2.41)	58	4.2	(3.13–5.52)
Female	Never use	893	71.4	(68.36–74.23)	732	61.0	(57.81–64.00)	732	85.4	(82.84–87.60)	939	80.8	(78.28–83.09)
	One time-use	70	6.5	(5.05–8.31)	64	5.7	(4.39–7.45)	31	3.0	(2.04–4.46)	59	4.9	(3.66–6.49)
	2–4 times use	102	9.5	(7.76–11.56)	129	11.2	(9.30–13.34)	63	5.9	(4.52–7.77)	90	6.7	(5.33–8.41)
	Considerable use	93	9.1	(7.38–11.25)	217	17.8	(15.52–20.32)	63	5.4	(4.13–6.99)	97	7.0	(5.65–8.60)
	Heavy use	38	3.5	(2.47–4.91)	54	4.4	(3.25–5.83)	4	0.3	(0.10–0.72)	11	0.6	(0.34–1.17)

[a]Considerable use: peak time use $\leq$2 times per week; heavy use: peak time use >2 times per week; information about the weighted N can be obtained from the first author.

Table 3
DSM-IV Cannabis abuse/dependence at baseline (t_0) and follow-up (t_2) ($N = 2446$)[a]

(Sub)group	Abuse pattern	Baseline (t_0) cum. lifetime incidence			Follow-up (t_0–t_1–t_2) cum. Lifetime incidence			Follow-up (t_2) incidence among baseline non-users			Follow-up (t_2) 12-months prevalence		
		N	%w	95% CI	*N*	%w	95% CI	*N*	%w	95% CI	*N*	%w	95% CI
Total	Use, no disorder	632	30.2	(28.15–32.36)	913	38.8	(36.65–41.00)	346	16.8	(15.00–18.69)	574	21.8	(20.10–23.68)
	Abuse, no dependence	61	2.5	(1.95–3.32)	150	5.5	(4.65–6.56)	41	1.8	(1.27–2.44)	89	3.0	(2.39–3.77)
	Dependence	30	1.4	(0.95–2.08)	56	2.2	(1.67–3.00)	9	0.3	(0.16–0.64)	17	0.6	(0.33–0.97)
14–17 years at baseline	Use, no disorder	168	16.9	(14.57–19.54)	387	36.0	(33.02–39.14)	254	28.0	(24.94–31.21)	312	29.1	(26.26–32.09)
	Abuse, no dependence	19	1.9	(1.15–3.01)	79	7.6	(5.98–9.49)	36	4.1	(2.88–5.71)	55	4.9	(3.68–6.38)
	Dependence	7	0.6	(0.28–1.41)	27	2.4	(1.58–3.53)	9	0.9	(0.44–1.78)	12	1.1	(0.57–1.95)
18–24 years at baseline	Use, no disorder	464	35.7	(33.03–38.54)	526	40.0	(37.18–42.80)	92	10.5	(8.49–12.86)	262	18.8	(16.72–21.13)
	Abuse, no dependence	42	2.8	(2.06–3.87)	71	4.7	(3.68–5.95)	5	0.5	(0.20–1.14)	34	2.2	(1.57–3.18)
	Dependence	23	1.7	(1.12–2.66)	29	2.2	(1.49–3.21)	0	0.0		5	0.4	(0.14–0.92)
Male	Use, no disorder	362	34.4	(31.44–37.53)	497	42.1	(39.05–45.25)	190	19.7	(16.99–22.77)	330	25.4	(22.79–28.13)
	Abuse, no dependence	40	3.5	(2.55–4.92)	120	8.8	(7.31–10.68)	37	3.5	(2.51–4.96)	81	5.5	(4.33–6.95)
	Dependence	18	1.8	(1.10–2.89)	38	3.2	(2.25–4.48)	8	0.6	(0.30–1.34)	12	0.8	(0.42–1.57)
Female	Use, no disorder	270	26.0	(23.26–29.00)	416	35.5	(32.52–38.61)	156	14.3	(12.08–16.81)	244	18.3	(16.09–20.83)
	Abuse, no dependence	21	1.6	(0.99–2.43)	30	2.2	(1.52–3.26)	4	0.3	(0.10–0.77)	8	0.5	(0.26–1.11)
	Dependence	12	1.0	(0.53–1.98)	18	1.3	(0.76–2.26)	1	0.1	(0.01–0.38)	5	0.3	(0.13–0.82)

[a]Considerable use: peak time use ≤2 times per week; heavy use: peak time use >2 times per week; information about the weighted *N* can be obtained from the first author. The weighted percent do not sum up to 100% because the data about the 'never use' participants have been excluded from this table (see Table 1).

** $p < 0.05$.

Table 2
Cannabis use: gender and age cohort differences (odds ratios) ($N = 2446$)

		Male versus female			Young cohort versus old cohort		
		OR	p**	95% CI	OR	p**	95% CI
Baseline (t_0) Cum. lifetime incidence	Use vs. no use	1.7	*	(1.39–2.07)	0.4	*	(0.29–0.43)
	Use, no disorder vs. no use	1.6	*	(1.31–1.99)	0.3	*	(0.28–0.43)
Follow-up (t_0–t_1–t_2) Cum. lifetime incidence	Use vs. no use	1.8	*	(1.54–2.21)	1.0	ns	(0.81–1.14)
	Use, no disorder vs. no use	1.6	*	(1.30–1.91)	0.9	ns	(0.74–1.07)
Follow-up (t_2) incidence Among baseline non-users	Use vs. no use	1.8	*	(1.36–2.30)	3.9	*	(2.99–5.16)
	Use, no disorder vs. no use	1.5	*	(1.15–1.99)	3.5	*	(2.66–4.66)
Follow-up (t_2) 12-month prevalence	Use vs. no use	2.0	*	(1.60–2.42)	2.0	*	(1.64–2.42)
	Use, no disorder vs. no use	1.7	*	(1.33–2.05)	1.9	*	(1.54–2.32)
Follow-up (t_1–t_2) Prevalence	Use vs. no use	1.9	*	(1.55–2.26)	1.9	*	(1.56–2.24)
	Use, no disorder vs. no use	1.5	*	(1.25–1.86)	1.7	*	(1.41–2.06)

Table 5
Longitudinal development of cannabis use, abuse and dependence ($N = 2446$): cross-tabulation of cumulative lifetime incidence 12 months prior to the t_2-assessment and 12-months status at t_2[a]

(Sub)group	Cumulative lifetime incidence 12 months prior t_2 assessment	12-months status at second follow-up (t_2)											
		No use			Use, no disorder			Abuse, no dependence			Dependence		
		N	%w	95% CI	N	%w	95% CI	N	%w	95% CI	N	%w	95% CI
Total	No use	1327	95.4	(94.14–96.32)	84	4.5	(3.52–5.68)	4	0.2	(0.07–0.48)	0	0.0	
	Use, no disorder	416	54.7	(51.02–58.39)	414	44.1	(40.49–47.84)	13	1.0	(0.54–1.73)	3	0.2	(0.06–0.54)
	Abuse, no dependence	16	13.8	(8.40–21.76)	55	42.8	(33.88–52.13)	61	41.3	(32.65–50.56)	2	2.2	(0.43–10.00)
	Dependence	7	16.2	(7.65–31.00)	21	44.2	(29.74–59.71)	11	20.6	(11.01–35.23)	12	19.0	(10.42–32.21)
14–17 years at baseline	No use	608	90.5	(87.95–92.58)	66	9.1	(7.08–11.65)	3	0.4	(0.12–1.16)	0	0.0	
	Use, no disorder	110	33.1	(27.94–38.65)	212	63.0	(57.31–68.27)	12	3.3	(1.81–5.91)	3	0.7	(0.22–2.09)
	Abuse, no dependence	3	4.5	(1.27–14.95)	24	41.8	(29.13–55.58)	36	52.5	(39.08–65.48)	1	1.3	(0.17–8.39)
	Dependence	1	4.0	(0.55–23.54)	10	44.2	(24.44–66.06)	4	15.1	(5.58–34.71)	8	36.8	(18.49–59.82)
18–24 years at baseline	No use	719	97.6	(96.09–98.48)	18	2.4	(1.45–3.82)	1	0.1	(0.01–0.61)	0	0.0	
	Use, no disorder	306	62.2	(57.62–66.50)	202	37.7	(33.33–42.21)	1	0.2	(0.02–1.19)	0	0.0	
	Abuse, no dependence	13	18.9	(11.06–30.28)	31	43.3	(31.71–55.69)	25	35.2	(24.45–47.65)	1	2.7	(0.38–16.43)
	Dependence	6	21.3	(9.58–0.81)	11	44.2	(26.13–63.91)	7	22.9	(10.68–42.46)	4	11.6	(4.32–27.80)
Male	No use	595	93.9	(91.67–95.50)	48	5.9	(4.26–8.05)	3	0.3	(0.09–0.84)	0	0.0	
	Use, no disorder	219	53.0	(47.97–57.97)	231	44.9	(39.99–49.93)	13	1.8	(0.99–3.16)	3	0.3	(0.10–0.99)
	Abuse, no dependence	10	11.0	(5.76–19.81)	38	39.2	(29.40–49.93)	55	47.1	(36.91–57.61)	2	2.7	(0.55–12.45)
	Dependence	3	10.5	(3.25–28.92)	13	44.7	(27.65–63.15)	10	28.5	(15.02–47.29)	7	16.3	(7.31–32.59)
Female	No use	732	96.5	(95.02–97.55)	36	3.4	(2.36–4.86)	1	0.1	(0.02–0.74)	0	0.0	
	Use, no disorder	197	56.8	(51.28–62.15)	183	43.2	(37.85–48.72)	0	0.0		0	0.0	
	Abuse, no dependence	6	24.3	(11.15–45.16)	17	56.1	(36.74–73.75)	6	19.6	(8.58–38.72)	0	0.0	
	Dependence	4	28.5	(10.54–57.30)	8	43.1	(19.44–70.32)	1	3.7	(0.49–22.63)	5	24.8	(9.54–50.87)

[a] Information about the weighted N can be obtained from the first author.

Table 4
Cannabis abuse and dependence: gender and age cohort differences (odds ratios) ($N = 2446$)

			Male versus female			Young cohort versus old cohort		
			OR	P[b]	95% CI	OR	P[b]	95% CI
Cum. Lifetime incidence Baseline (t_0)	Abuse wo dependence	vs. no disorder	2.4	*	(1.33–4.19)	0.6	ns	(0.35–1.15)
	Dependence	vs. no dependence	1.8	ns	(0.77–4.02)	0.4	*	(0.14–0.91)
Follow-up (t_0–t_1–t_2)	Abuse wo dependence	vs. no disorder	4.3	*	(2.80–6.75)	1.7	*	(1.16–2.39)
Cum. lifetime incidence	Dependence	vs. no dependence	2.5	*	(1.28–4.79)	1.1	ns	(0.61–1.90)
Follow-up (t_2) incidence	Abuse wo dependence	vs. no disorder	12.1	*	(4.14–35.47)	8.4	*	(3.21–21.92)
Among baseline non-users	Dependence	vs. no dependence	10.3	*	(1.25–84.59)	–[a]		–
Follow-up (t_2)	Abuse wo dependence	vs. no disorder	10.8	*	(5.00–23.52)	2.3	*	(1.42–3.62)
12-month prevalence	Dependence	vs. no dependence	2.5	ns	(0.80–7.84)	2.9	ns	(0.94–8.90)
Follow-up (t_1–t_2)	Abuse wo dependence	vs. no disorder	7.8	*	(4.36–13.92)	2.4	*	(1.58–3.54)
Prevalence	Dependence	vs. no dependence	2.9	*	(1.29–6.63)	2.7	*	(1.22–6.00)

[a] Cannot be computed because one cell is empty.
[b] *$P < 0.05$.

Table 6
Cannabis use disorder pattern (cumulative lifetime incidence 12 months prior to the second follow-up) and outcome (proportion of non-users at second follow-up: 12-months status)[a]

Total	Cannabis use disorder pattern			Proportions of non user at t_2		
	N	%w	95% CI	N	%w	95% CI
No use	1415	56.0	(53.81–58.24)	1327	95.3	(94.14–96.32)
One time-use	141	6.3	(5.23–7.47)	101	77.9	(69.83–84.27)
2–4 times use	246	10.6	(9.31–12.06)	168	73.8	(67.78–79.09)
Considerable use, no disorder	408	17.6	(15.96–19.41)	135	38.8	(33.56–44.33)
Heavy use, no disorder	51	2.3	(1.68–3.07)	12	25.3	(14.14–41.12)
Abuse, no dependence	134	5.2	(4.29–6.17)	16	13.8	(8.40–21.76)
Dependence	51	2.1	(1.52–2.80)	7	16.2	(7.65–31.00)

[a] Information about the weighted *N* can be obtained from the first author.

Table 7
Use of other substances during 12-month follow-up according to cannabis use status at 12-month follow-up (t_2) ($N = 2446$)[a]

Follow-up use of	Follow-up cannabis use status (12-month prevalance at t_2)				Risk of substance use according to type of cannabis use									
	No use $N = 1327$		Ex-use $N = 450$	Continous use $N = 669$	Ex-cannabis user — never user			Continuous cannabis user — never user			Continuous cannabis user — ex-user			
	%w	%w	%w		OR	P[c]	95% CI	OR	P[c]	95% CI	OR	P[c]	95% CI	
Alcohol	70.3	83.2	89.5		1.9	*	(1.4–2.5)	3.4	*	(2.5–4.5)	1.8	*	(1.3–2.7)	
Nicotine	20.2	53.5	68.0		4.9	*	(3.7–6.4)	8.3	*	(6.5–10.5)	1.7	*	(1.3–2.2)	
Cocaine	0.2	3.3	11.5		19.7	*	(4.3–89.3)	77.5	*	(18.6–322.2)	3.9	*	(2.0–7.8)	
Stimulants	0.2	2.3	8.6		12.3	*	(3.1–49.5)	44.7	*	(13.1–152.5)	3.6	*	(1.6–8.5)	
Hallucinogens	0.2	1.0	6.1		4.5	ns	(0.8–24.8)	25.3	*	(7.1–90.8)	5.6	*	(1.5–21.3)	
Sedatives	0.1	2.2	1.0		24.6	*	(2.9–212.6)	14.6	*	(1.54–137.6)	0.6	ns	(0.2–2.1)	
Opioids	0.0	2.0	2.7		105.4	*	(13.1–850.8)	140.1	*	(18.4–1065.4)	1.3	ns	(0.5–3.4)	
Inhalants	0.0	0.2	0.4		_[b]			_[b]			1.2	ns	(0.1–12.0)	
PCP	0.0	0.2	0.2		_[b]			_[b]			1.0	ns	(0.0–41.7)	
Other drugs	0.4	0.0	0.9		_[b]			2.2	Ns	(0.6–8.7)	_[b]			

[a] Alcohol: alcohol use at least 12 times per year; nicotine: daily at least one cigarette for at least 4 weeks.
[b] Cannot be computed because at least one cell is empty.
[c] * $P \leq 0.05$.

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