CHAPTER 2.1

Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender

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Abstract

Background: Cannabis use is associated with an earlier age at onset of psychotic illness. The aim of the present study was to examine whether this association is confounded by gender or other substance use in a large cohort of patients with non-affective psychotic disorder.

Methods: In 785 patients with a non-affective psychotic disorder, regression analysis was used to investigate the independent effects of gender, cannabis use, and other drug use on age at onset of first psychosis.

Results: Age at onset was 1.8 years earlier in cannabis users compared to non-users, controlled for gender and other possible confounders. Use of other drugs did not have an additional effect on age at onset when cannabis use was taken into account. Up to 64% of cannabis using patients had used cannabis most intensively before the onset of psychosis. In males, mean age at onset was 1.3 years lower than in females, controlled for cannabis use and other confounders.

Conclusion: Cannabis use and gender are independently associated with an earlier onset of psychotic illness. Further, our findings support that cannabis use may precipitate psychosis. More research is needed to clarify the neurobiological factors that make people vulnerable for this precipitating effect of cannabis.

Introduction

Since early age at onset of psychotic illness is associated with poor outcome (Lauronen et al 2007) and with more frequent hospitalizations over the course of illness (Rabinowitz et al 2006), better insight in factors that are associated with an early age of onset of psychotic disorders is important.

One of the factors associated with an earlier age at first psychotic episode is cannabis use (Buhler et al 2002, Veen et al 2004, Barnes et al 2006, Mauri et al 2006, Addington and Addington 2007, González-Pinto et al 2008, Barrigon et al 2009, Ongur et al 2009, Sugranyes et al 2009, Foti et al 2010, Pelayo-Terán et al 2010, De Hert et al 2010, Large et al 2011). In a recent meta-analysis, the mean age at onset of psychosis was 2.70 years lower in cannabis users compared to non-users (Large et al 2011). However, some studies did not find differences in age at onset of psychosis between cannabis users and non-users (Bersani et al 2002, Goldberger et al 2010, De Rosse et al 2010).

A second factor associated with age at onset of psychosis is gender: males are 3 to 4 years younger at illness onset compared to females (Hambrecht et al 1992, Castle et al 1998, Szymanski et al 1995, Leung and Chue 2000, Hafner 2003). As cannabis use is more prevalent among male patients with schizophrenia (e.g. Hambrecht and Häfner 1996, Gonzales Pinto et al 2008, Sevy et al 2010), some studies investigated the relation between cannabis use and age at onset of first psychosis after correction for gender. These studies showed that cannabis use remained an independent predictor of an earlier age at first psychotic episode after correction for gender (Veen et al 2004, Barnes et al 2006, Gonzalez Pinto 2008, Barrigon et al 2009, Sugranyes et al 2009, Ongur et al 2009, De Hert 2010). In only one of these studies (Barnes et al 2006) gender remained an independent predictor for age at onset of psychosis after adjusting for cannabis use. This suggests that the frequently reported relation between gender and age at onset is spurious or might be the consequence of a lack of power in the studies that did not find this relationship, since most of these studies included a relatively small number of female patients (range of number of included females was 36-99).

Lack of power was not an issue in the one study that did include a relatively large number (n=236) of females (De Hert et al 2010). However, this study used age at onset of *admission* as a proxy for age at onset of psychosis. Since males have a longer treatment delay than females (e.g. Wunderink et al 2006, Thomas et al 2009), age at onset of *admission* might not be gender-independent and thus not an accurate proxy for the age at onset of psychotic illness. A third factor that could confound the relation between cannabis use and age at onset of psychosis, is use of other illicit drugs that have been reported to precipitate psychotic symptoms, such as stimulants (Brady et al 1991, Satel et al 1991, Landabaso et al 2002, McKetin et al 2006), and hallucinogens (Vardy and Kay 1983). Although these drugs have not yet been shown to have an additional affect on age at onset of psychosis (Barnes et al 2006, Barrigon et al 2009, Gonzalez Pinto et al 2008), the non significant relation between these other Illicit drugs and age of onset might also be the result of insufficient power. This study assesses the independent effects of gender, cannabis use, and the effect of additional drug use on age at onset of first psychosis in a large sample of patients receiving treatment for non-affective psychotic illness, including a relatively large sample of females, and users of drugs other than cannabis.

Methods

Participants

Patients took part in the Genetic Risk and Outcome of Psychosis (GROUP) study, a multi-site longitudinal cohort study in The Netherlands and Belgium that focuses on vulnerability and resilience factors for variation in expression and course of treatment seeking patients with non-affective psychotic disorders (Korver and Quee et al submitted). Inclusion criteria for patients were: (1) age between 16 and 50 years, (2) a diagnosis of non-affective psychotic disorder according to DSM-IV (APA 1994), and (3) good command of the Dutch language. In selected representative geographical areas in the Netherlands, patients were identified through clinicians working in regional or academic psychosis centres whose caseloads were screened for inclusion criteria (prevalence sample). In addition, all consecutive patients presenting at these services - either as out- or inpatients - were recruited for the study (incidence sample). All participants gave written informed consent after complete description of the study. The study was approved by the human subject review boards of all four academic centres.

Measures

Clinical measures

To establish a DSM-IV (APA 1994) diagnosis of psychotic disorder, two different structured diagnostic instruments were used in the four GROUP study sites: three sites used the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992) and one site used the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1; Wing et al 1990). All raters had completed training in one of these instruments.

Age at onset of psychosis

Age at onset of first psychosis was defined by the age of the patient at the time of onset of the first psychotic episode. A psychotic episode was defined by the occurrence of at least one of the following psychotic symptoms during at least a week; 1) hallucinations, 2) delusions, and/or 3) formal thought disorders.

Substance use

Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; WHO, 1994) sections B (tobacco use), J (alcohol use) and L (drug use). It comprises items on the quantity of tobacco use and alcohol use in the past year, and items on the quantity and severity of illicit drug use over the past year and lifetime. According to the CIDI, patients were considered drug users if they had used a particular drug five or more times. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. Heavy alcohol use in the past year was defined as having consumed more than 21 alcoholic units per week. In contrast to the age at most intense cannabis use, age at onset of cannabis use was not assessed. Definition of age of most intensive cannabis use was defined as the age at which cannabis was used most intensively lifetime. To determine whether most intense cannabis use had occurred *prior* to psychosis onset, we subtracted age at most intensive cannabis use from age at onset of first psychosis.

In addition to the structured interviews, we used urinalysis to detect current cannabis use (presence of tetrahydrocannabinol (THC) metabolite 11-nor-delta-9-THC-carboxylicacid was assessed with

immunoassays with a cut off of 50ng/ml), current amphetamine use (presence of d-methamphetamine assessed with immunoassays using a cut off of 1000 ng/ml), and current cocaine use (presence of benzoylecgonine assessed with immunoassays using a cut off of 300 ng/ml).
We defined three subgroups based on drug use history:

a) a subgroup of patients who never used drugs (NO DRUG USE), i.e. patients who 1) reported no illicit drug use in the past year or lifetime in the CIDI, and 2) had negative urine screens for THC, cocaine and amphetamines.
b) a subgroup of patients who had used cannabis but no other illicit drugs (ONLY CAN), i.e. patients who 1) reported cannabis use in the past year and/or lifetime but no other drug use in the CIDI, and 2) had negative urine screens for amphetamines en cocaine.
c) a subgroup of patients who had used cannabis and other illicit drugs that can precipitate psychosis (CAN + OTHER DRUGS), i.e. patients who reported cannabis use and other drug use (cocaine, ecstasy , hallucinogens and/or stimulants) in the past year and/or lifetime in the CIDI .

Statistical Analysis

Chi-square tests were used to determine group differences for categorical variables. One-way between-groups analyses of variance (ANOVAs) and T tests were conducted to explore group differences for continuous variables. A linear regression model was fitted with age at onset of first psychosis as dependent variable, and patient subgroup (NO DRUG USE, ONLY CAN, CAN + OTHER DRUGS), gender, and patient subgroup by gender interaction as independent variables. Nicotine use and alcohol use in the past year were entered as covariates. We used Kaplan Meier analyses to assess the effect of drug use history (NO DRUG USE, ONLY CAN, CAN + OTHER DRUGS) on age at onset of first psychosis. The log-rank test was used to compare the survival distributions between the different subgroups. Since the survival curves of the different subgroups crossed, we decided not to perform Cox-regression analysis (because the proportional hazards assumption implies non crossing survival curves). Separate Kaplan Meier analyses were performed for males and females.

Results

Sample characteristics

In 785 patients (599 males (76.3%) and 186 females (23.7%)), inclusion criteria for one of the subgroups according to drug use history (NO DRUG USE, ONLY CAN, and CAN + OTHER DRUGS) were met. The numbers of patients per subgroup were: NO DRUG USE 281 (35.8%), ONLY CAN 223 (28.4%), CAN + OTHER DRUGS 281 (35.8%). In the CAN + OTHER DRUG group (n= 281), lifetime prevalence was 51.6% for stimulant use, 52.7% for cocaine use, 48.8% for hallucinogens use, and 66.9% for ecstasy use.
DSM-IV diagnoses of the patients were: schizophrenia (n=528, 67.3%), schizoaffective disorder (n=93, 11.8%), schizophreniform disorder (n=44, 5.6%), psychotic disorder NOS (n=79, 10.1%), and other psychotic disorders (n=41, 5,2%). Sample characteristics stratified by drug use history and gender are shown in table 1a and 1b. For 457 patients (398 males and 59 females), the age at most intensive cannabis use was available, (mean 19.5, SD 4.4; table 1). Age at most intensive cannabis use did not statistically differ (p = 0.148) between males (mean 19.4, SD 4.1) and females (mean 20.5, SD 5.6). In 63.5% of the patients, age at most intensive cannabis use preceded the age at onset of first

psychosis. There were no statistically significant differences between males and females in this percentage (64.3% resp. 57.6%, χ^2 1.0, p = 0.319).

Table 1**.** *Sample characteristics of total study sample (n = 785), stratified by drug use history (a), and stratified by gender (b)*

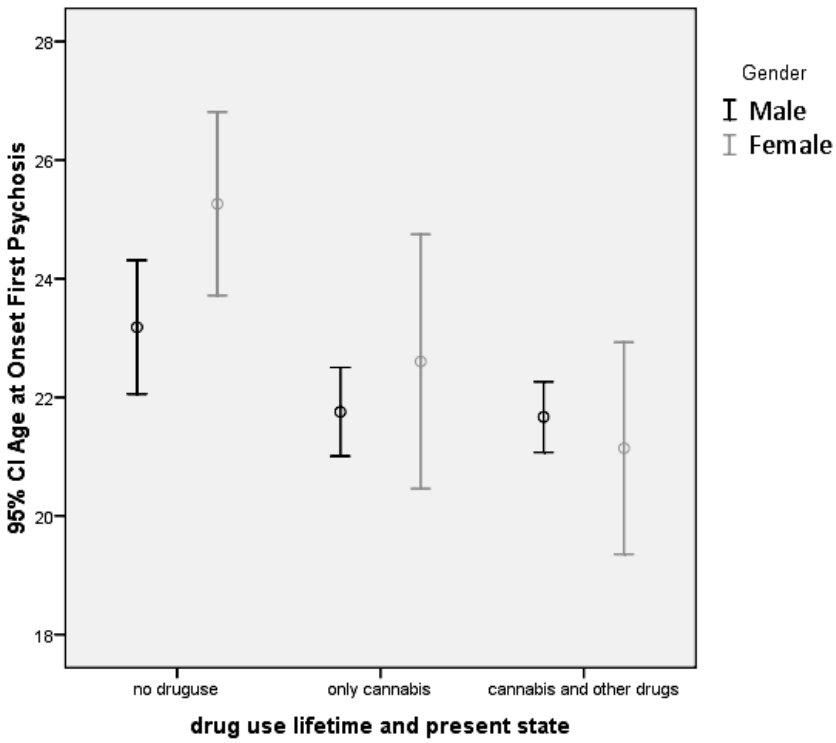
a)	Total	No drug use	Only cannabis	Cannabis and other drugs	χ^2 or *F*	df	*p*-value
	n=785	n=281	n=223	n=281			
Gender, male (%)	599 (76.3)	159 (56.6)	180 (80.7)	**260** (92.5)	103.7	2	< 0.001
Age, mean (SD)	27.2 (7.2)	28.8 (8.5)	26.8 (6.9)	26.1 (5.7)	10.9	2, 782	< 0.001[a]
Illness duration, mean years (SD)	4.1 (3.7)	4.2 (3.8)	4.3 (4.2)	3.9 (3.3)	1.1	2, 782	0.343
Ethnicity, Caucasian (%)	616 (78.5)	233 (82.9)	161 (72.2)	222 (79.0)	8.5	2	0.014
Nicotine use past year, yes (%)	508 (65.0)	85 (30.6)	**178** (79.8)	**245** (87.5)	228.8	2	< 0.001
Alcohol use past year, yes (%)	579 (74.2)	166 (59.7)	172 (77.8)	**241** (85.8)	51.7	2	< 0.001
Alcoholic heavy use past yr, yes (%)	55 (7.0)	5 (1.8)	20 (9.0)	30 (10.7)	18.9	2	< 0.001
Age most intensive cannabis use, mean (SD)	19.5 (4.4)		19.7 (4.8)	19.4 (4.0)	2.9	455	0.456

b)	Total	Males	Females	χ^2 or *t*	df	*p*-value
	n=785	n= 599	n=186			
Gender, male (%)	599 (76.3)					
Age, mean (SD)	27.2 (7.2)	26.7 (6.6)	29.0 (8.9)	3.3	250.6[b]	0.001
Illness duration, mean years (SD)	4.1 (3.7)	4.1 (3.7)	4.4 (4.0)	0.7	783	0.460
Ethnicity, Caucasian (%)	616 (78.5)	464 (77.5)	152 (81.7)	1.5	1	0.217
Nicotine use past year, yes (%)	508 (65.0)	**421** (70.6)	87 (47)	34.6	1	< 0.001
Alcohol use past year, yes (%)	579 (74.2)	**462** (77.5)	117 (63.6)	14.3	1	< 0.001
Alcoholic heavy use past yr, yes (%)	55 (7.0)	50 (8.3)	5 (2.7)	7.0	1	0.008
Age most intensive cannabis use, mean (SD)	19.5 (4.4)	19.4 (4.1)	20.5 (5.6)	1.5	67.6[b]	0.148

Figures in bold have adjusted standardised residuals > 3.0; figures underlined have adjusted standardised residuals < -3.0.
Percents in the columns and means are sometimes based on less than n presented in the top row, because of missing data in the CIDI data.
[a] Post-hoc Bonferroni test :no drug use > only can, no drug use > can + other drugs
[b] equal variances not assumed

Comparison of age at onset of first psychosis between subgroups according to drug use history

Figure 1 shows mean age at onset of first psychosis with 95% confidence intervals, stratified for subgroups according to drug use history and gender. Since no statistically significant gender by drug use history interaction was found in the prediction of age at onset of first psychosis, only main effects without the gender by drug use history interaction are presented (table 2).



Males: mean age (95% CI) NO DRUG USE 23.2 (22.0-24.3), ONLY CAN 21.8 (21.0-22.5), CAN + OTHER DRUGS 21.7 (21.0-22.3)
Females: mean age (95%CI) NO DRUG USE 25.3 (23.7-26.8), ONLY CAN 22.6 (20.5-24.8), CAN + OTHER DRUGS 21.1 (19.4-22.9)

Figure 1. *Mean ages at onset of psychosis with 95% confidence intervals, stratified for subgroups according to drug use history and gender.*

Table 2. *Summary of general linear regression analysis, with total patient sample (n= 785)* [a,b]

	Age at onset of psychosis			
	B	SE B	*t*	
Intercept	25.2			
Drug use history, only cannabis compared to no drug use	-1.7	0.6	-2.6	**
Drug use history, cannabis and other drugs compared to no drug use	-1.8	0.7	-2.7	**
Gender, male/ female	-1.3	0.6	-2.3	*
Covariates				
Nicotine use, yes/no	-0.2	0.6	-0.4	
Alcohol use, yes/no	-0.4	0.5	-0.8	

[a] General linear regression analysis, with age at onset of psychosis as dependent variable and drug use history and gender as independent variable. The covariance structure is unstructured. The B coefficient indicates the individual contribution of each predictor to the model. This value indicates that as the predictor increases by one unit, age at onset of psychosis increases by the B value. A positive B value means that compared to the reference category, the component score increases. A negative sign means that compared to the reference category, the component score decreases. The t indicates whether the predictor is making a significant contribution to the model. The larger the value of t, the greater the contribution to the model.
[b] Bold is reference category
*p < .05, ** p < .01

After controlling for gender, nicotine use and alcohol use in the past year, mean age at onset of psychosis was significantly different between patients from the NO DRUG USE, ONLY CAN and CAN + OTHER DRUGS subgroups (F (2, 772)= 4.3, p = 0.014). Mean age at onset of first psychosis in patients from the ONLY CAN group was significantly lower than mean age at onset of psychosis in patients from the NO DRUG USE group (adjusted difference of 1.7 years; B = -1.7, SE B 0.6, t = -2.6, p = 0.009). Further, mean age at onset of first psychosis in patients from the CAN + OTHER DRUGS group was also significantly lower than the mean age at onset of psychosis in patients from the NO DRUG USE group (adjusted difference 1.8 years; B = -1.8, SE 0.6, t = -2.7, p = 0.008). There was no significant difference in age at onset between the ONLY CAN and CAN + OTHER DRUGS group.

Comparison of age at onset of first psychosis between males and females

Gender was significantly related to age at onset of psychosis, above and beyond illicit drug use, nicotine use and alcohol use. Mean age at onset of psychosis was significantly lower in males than in females (adjusted difference 1.3 years; F (1,772) = 5.6, p = 0.018).

Figure 2a and 2b show Kaplan-Meier survival curves for onset of first psychosis stratified by drug use history for male and female patients, respectively. Log-rank tests showed that both in males and in females, age at onset of psychosis was significantly different between the NO DRUG USE, ONLY CAN and CAN+ OTHER DRUGS subgroups (males: log rank χ^2 =11.40, df 2, p=0.003, females: χ^2 11.05, df 2, p = 0.004). As shown in figure 2 and 3, differences in age at onset of first psychosis between the NO DRUG USE group and the ONLY CAN and CAN+OTHER DRUGS are most pronounced in the later onset group, i.e. onset of first psychosis after the age of 23 for males and after the age of 20 for females.

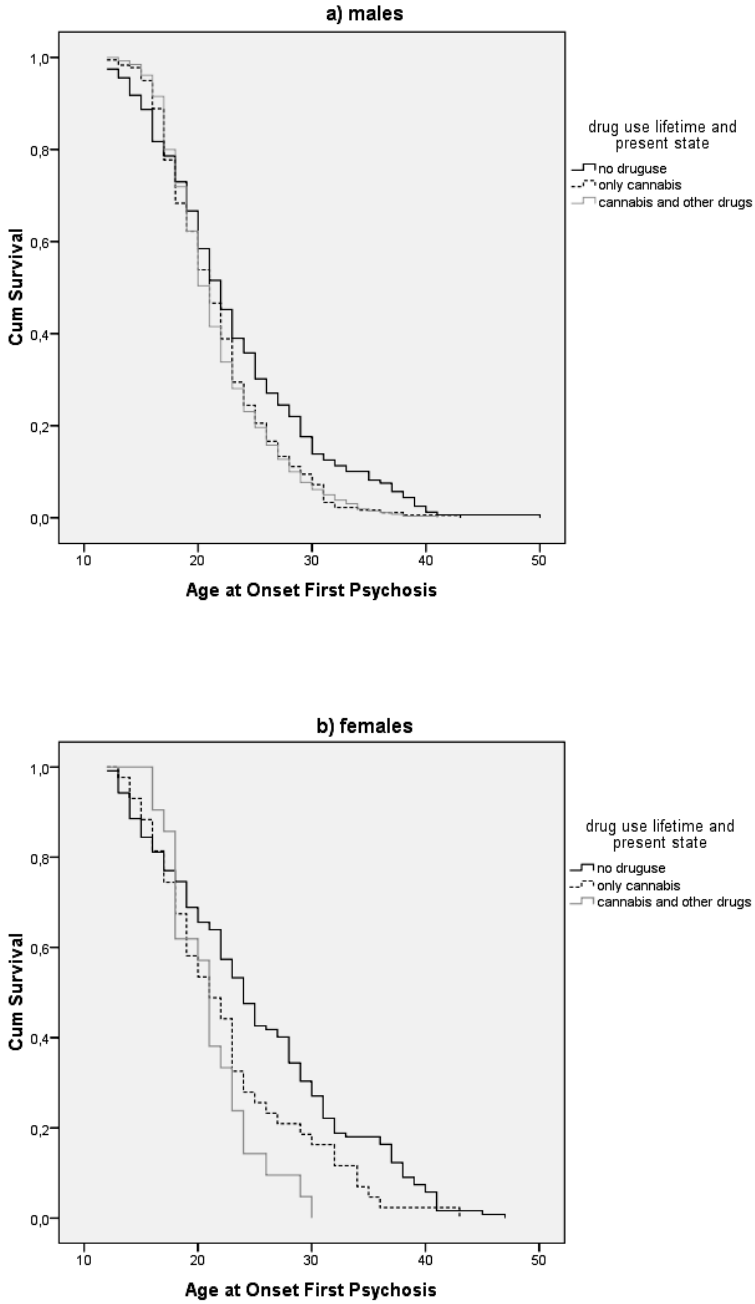


Figure 2. *Kaplan Meier survival curves for age at first psychosis stratified by drug use history for a) males (n= 599) and b) females (n=186)*

Discussion

This large cohort study of patients treated for non-affective psychotic illness confirms previous findings that a history of cannabis use is associated with a lower age at onset of first psychosis, independent of the effects of gender or use of other drugs. Further, males had an earlier age at onset of psychotic illness compared to females irrespective of the use of cannabis, and the majority of both males and females that had used cannabis, had done so most intensively *prior* to onset of psychotic illness.

Our finding that cannabis use was associated with earlier age at onset of psychotic illness, independent of the effect of gender, is in line with the results of a recent meta-analysis on this topic (Large et al 2011). We speculate that earlier onset of first psychosis in cannabis using patients could be explained by (early) cannabis use precipitating the onset of psychotic illness in vulnerable subjects Support for this hypothesis comes from studies in which age at onset of cannabis use is positively associated with age at onset of high risk symptoms for psychosis (Dragt et al 2010) and with age at onset of psychotic illness (Barnett et al 2007, Estrada et al 2010). Interestingly, the difference in age of onset between the cannabis users and non-cannabis users seem to manifest itself most pronouncedly in the group with a relatively late age of onset, i.e. onset after the age of 23 for males and 20 for females (figure 2a and 2b). The survival curve from the study of Gonzales-Pinto et al. (2008), with comparable subgroups of patients, shows a similar pattern. This may also explain why some studies in schizophrenia patients did not find differences in age at onset between cannabis users and non-users: the age at onset of psychosis in these studies was around 20 years, which is earlier than the age range where differences occurred in our study (De Rosse et al 2010, Bersani et al 2002, Goldberger et al 2010). It may also explain why the absolute differences in age at onset between cannabis users and non- users substantially differs across studies. Studies with a later age at onset than in our study will probably find a larger difference in age at onset between users of cannabis and non-users. This corresponds with the finding of a meta-analysis on cannabis use and age at onset of psychosis (Large et al 2011) that the use of an upper age limit (< 45 years of age) as inclusion criterion inflated effect sizes. However, in the meta-analysis, the finding of an association between the proportion of cannabis users and earlier age at onset was statistically independent of age inclusion criteria.

Our finding that cannabis-related differences in age at onset of psychosis seem to manifest itself only in the group with a relatively late age of onset, could be explained by recent findings from a genetic study (Pelayo- Terán et al 2010). In this study, age of onset of first psychosis in *non*-users of cannabis was significantly later in the COMT Met/Met genotype carriers than in the COMT Val/Val and COMT Val/ Met genotype carriers, while this association was absent in users of cannabis. The authors suggest that use of cannabis could exert a modulator effect on the genotype, suppressing the delay effect for the age of onset in the case of the Met allele patients. Although this could be an explanation for our findings, further studies are needed to confirm our preliminary findings and to clarify possible other neurobiological mechanisms that make people vulnerable for the precipitating effects of cannabis on psychotic illness.

We did not find a significant difference in age at onset between patients who had used *only* cannabis and patients who had used both cannabis *and* other illicit drugs. Our findings suggest that the additional use of other drugs has no independent effect on age at onset of psychosis when adjusted for cannabis use.

We found that male patients had a lower age of onset of first psychotic episode compared to female patients, irrespective of the use of cannabis or other illicit drugs. This is similar to findings of Barnes et al (2006), but in contrast to findings of other studies (Veen et al 2004, Gonzales Pinto et al 2008, Ongur et al 2009, Sugranyes et al 2009, Barrigon et al 2009, De Hert et al 2010), which may be explained by the low power due to small groups of female patients in most of these studies. Later age at onset of psychosis in females has been related to the modulating effect of estrogen, which is thought to play a protective role in the disease process of schizophrenia, resulting from a hypothesized anti-dopaminergic effect that could delay the development of the disease (Szymanski et al 1995). Another explanation might be that psychosis in females is later recognized by the environment resulting in treatment delays (Aleman et al 2003). Although we found significant gender differences in age at onset of psychosis irrespective of the use of cannabis, we did not find gender differences for the mean age at most intensive use of cannabis (males 19.4 and females 20.5 years of age). Although other studies on gender and age at most intensive cannabis use are lacking, there are a few studies comparing age at onset of *first* cannabis use between males and females. Those studies did not find a difference between age at first use of cannabis between male and female patients (mean 15.5 and resp. 15.4 years; Dekker et al 2008), or found a trend towards earlier *first* use of cannabis in males (mean 15.6 years) than females (mean 17.9 years) (Barnett et al 2007).

In the current study, 64% of cannabis users had used cannabis most intensively *prior* to the onset of first psychosis, with no statistical difference in proportion of males and females. As many patients from both sexes use cannabis prior to first psychosis and cannabis effects age at onset of first psychosis in both males and females, treatment interventions for cannabis use in prodromal and ultrahigh risk populations should focus on both males and females. Finally, as the largest proportion of patients used cannabis most intensively before the onset of psychosis, the self-medication hypothesis is not supported in this study, at least not in the majority of patients.

A limitation of the current study is that the age of first cannabis use was not assessed. A comparison between patients that started cannabis use prior to the onset of psychosis versus non using patients might have provided more robust conclusions about the possible contribution of cannabis use to the onset of psychotic illness. However, many of the cannabis using patients (64%) in the current study had used cannabis most intensively prior to onset of psychosis, which corresponds with previous first-episode studies reporting that 62-98% of cannabis using patients had started using cannabis before the onset of the first psychosis (Linszen et al 1994, Buhler et al 2002, Mauri et al 2006, Barnett et al 2007, Sevy et al 2010, Goldberger et al 2010). Further, studies in comparable patient populations have reported a mean age at first cannabis use of 15.6 and 15.4 years (Dekker et al 2009, Dekker et al 2010) , which is at least 5 years earlier than the mean age at onset of psychosis in the current sample.

Strengths of our study are: (1) the large study sample, (2) the fact that we included patients presenting consecutively either as out-patients or in-patients, reflecting a sample of treated patients which enhances the generalizability of our findings, (3) a larger number of females than in most of the previous studies, which enables us to perform a sufficiently powered regression analysis in which the independent effect of gender on age at onset of psychosis was tested, and (4) the fact that we checked urine for the presence of drugs in addition to self reported drug use.

In summary, this study shows that both cannabis use and gender are independently associated with an earlier age at onset of psychotic illness, above and beyond the effect of possible confounders, and that the difference in age at onset between cannabis users and never users seems to manifest itself in the subgroup with a relatively late age of onset, i.e. from the age of 23 in males and 20 in females.

Our findings do not support the self-medication theory, but point toward cannabis as a precipitating factor in the development of psychosis. Future studies are needed to clarify the neurobiological factors that make people vulnerable for the precipitating effects of cannabis us on age at onset of psychotic illness.

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