Cannabis use in early adulthood is prospectively associated with prescriptions of antipsychotics, mood stabilizers and antidepressants

Running title: Cannabis use and psychotropic drugs

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Acknowledgements: Tilmann von Soest's contribution to this article has been supported by a grant from the Research Council of Norway (grant # 288083).

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Abstract

Objective: Cannabis is an acknowledged risk factor for some mental disorders, but for others the evidence is inconclusive. Prescribed medicinal drugs can be used as proxies for mental disorders. In this study, we investigate how use of cannabis is prospectively related to prescription of antipsychotics, mood stabilizers, antidepressants and anxiolytics.

Methods: Data on cannabis exposure and relevant confounders were obtained from 2,602 individuals in the longitudinal Young in Norway Study, providing survey data from four data collection waves between 1992 and 2006. Data were coupled with information about prescriptions for psychotropic drugs from the Norwegian Prescription Database between 2007 and 2015.

Results: Past year cannabis use increased the risk of prescription of antipsychotics (OR = 5.56, 95 % CI 1.64 – 18.87), mood-stabilizers (OR = 5.36, 95 % CI 1.99 – 14.44) and antidepressants (OR = 2.10, 95 % CI 1.36 – 3.25), after accounting for socio-demographic variables, conduct problems, additional drug use, mental distress and prescriptions the year before cannabis use was measured.

Conclusions: In this study of young adults from the general population, past year cannabis use was associated with later prescriptions of antipsychotics, mood-stabilizers and antidepressants.

Key words: cannabis; mental disorders, prescriptions, affective disorders; psychotic disorders

Significant outcomes

1	Cannabis use is associated with a five-fold increased risk for prescription of mood stabilizers and antipsychotics
2	Cannabis use is associated with a smaller but significant increase in risk for prescription of antidepressants

Limitations

1	Using prescriptions as proxy measures for mental disorders may be imprecise
2	A dose-response relationship could not be investigated due to too low statistical power

Data availability statement

Data are not sharable. The consent did not contain permission to share data.

Introduction

Parallel with the past decade changes in cannabis regulation, rates of use, heavy use and addiction have increased (1, 2) and the products have become more potent (3, 4). Evidence suggests that cannabis use may increase the risk of mental disorders, with stronger associations for some disorders than for others.

Numerous studies have described that cannabis use is associated with an increased risk of schizophrenia in a dose-related manner with relatively strong effect sizes (5): While the risk is approximately doubled for any use compared to no use, it increases six-fold when high consumers are compared to non-users (6, 7). The relationship remains strong after adjustment for relevant confounders, and also after accounting for genetic vulnerability (8, 9). Cannabis use is also associated with lower age of onset of schizophrenia (10, 11). Moreover, persons with first episode psychosis who use cannabis show worse functional and symptomatic long term outcomes, and these effects seem to be reversed when the consumption is discontinued (12). In spite of the strong empirical support for a causal association, a steep increase in cannabis consumption over decades unaccompanied by increased incidence of schizophrenia, has been used as an argument against a causal association (13). However, recent evidence suggests that areas with high potency cannabis in fact have higher incidence of schizophrenia (14), and the incidence of schizophrenia has increased in some countries (15).

Bipolar disorder, a disease with some symptom and aetiological overlap with schizophrenia (16, 17), starts at a younger age for cannabis users compared to non-users (18, 19). In clinical samples, cannabis use is associated with increased symptoms (20, 21), rapid cycling (22), lower remission rates (23, 24) and a three-fold increased risk for new onset of manic symptoms (25). While some studies have found that cannabis use increases the risk of first onset of manic symptoms (26) and bipolar disorder (27) by a factor of more than four, others have found the association to be non-significant after adjustment for confounders (28).

There is a growing conception that cannabis use can act as a risk factor for the onset of bipolar disorder (29) though the causal direction is debated (30).

The evidence for depression and anxiety as consequences of cannabis exposure is mixed, with substantially lower effect sizes than for schizophrenia, and with the lower range of the confidence interval often close to the null-effect line (31, 32). A meta-analysis calculated the risk of depression to be increased by 1.62 (95% CI 1.21 – 2.16) for heavy cannabis use and 1.17 (1.05 – 1.30) for any use compared to no use (33). Another meta-analysis including only studies of young adults also found cannabis users to have increased risk for depression relative to non-users (34). The association has remained after adjustment for genetic and environmental factors (35). For anxiety, one meta-analysis found an increased risk of 1.28 (95 % CI 1.06 – 1.54) following cannabis-exposure (36), while another found the association to be non-significant (34). However, several large individual studies have found that cannabis use is unrelated to both major depression and anxiety (28, 37-40).

It seems reasonable to consider cannabis as a risk factor for schizophrenia, and perhaps also for bipolar disorder. The prospective relationship to depression is weaker and less consistent, and the association to anxiety is unclear and by some even rejected. However, comparison across studies is difficult due to differences in design, setting, definition of exposure and outcome, and inclusion of covariates. Longitudinal, population-based studies comparing all these outcomes would add valuable information.

Due to low incidence rates of the outcomes, large studies, e.g. registry based are warranted. Some of those who have a mental disorder will receive pharmacological treatment for their conditions. Filling a prescription for a mental disorder may thus be used as an indirect measure of the disorders and have been used as such in previous studies (41, 42).

Aims of the study: In this study, we investigate the association between cannabis exposure and later prescription of anti-psychotics, mood stabilizers, antidepressants and

anxiolytics. We include baseline measurement of a multitude of possible confounders, such as several variables of socio-demographic background, conduct problems, mental distress and use of other drugs of abuse. To decrease the possibility of reversed causality, we excluded respondents who received prescriptions the year before the cannabis exposure was measured.

Methods

Procedure and Participants

The study was based on data from the Young in Norway study, described in more detail elsewhere (43). In short, the initial sample at T_1 was composed of students in grades 7 through 12 drawn from 67 junior and senior high schools in Norway (age span 12 to 20 years). The high initial response rate at T_1 of 97 % was achieved by using substantial resources to follow up participating schools (44). The only exclusion criterion was severe lack of reading capability. Students were followed up in 1994 (T_2), 1999 (T_3) and 2006 (T_4).The cumulative response rate across all four waves was 69%. At the last data collection, respondents were asked for their consent to link the data to several registers, to which 2,602 respondents (90%) agreed. The overall participation rate of the final sample was thus 60%. Of the final sample of 2,602 respondents, 1,145 were male (44%) and 1,457 female (56%). The mean age of the participants across the four data collection waves were T_1: 15.1 (SD = 2.0 years), T_2: 16.5, T_3: 23.0 and T_4: 28.5 years.

Information about prescriptions for mental disorders was drawn from the Norwegian Prescription Database (NorPD). This registry is administered by the Norwegian Institute of Public Health and contains information on all prescriptions dispatched to pharmacies outside of institutions, prescribed to individuals, from 2004. The database includes information about date of prescription filling, anatomical-therapeutic-chemical (ATC) code of the drug, and number of daily defined doses. The outcomes in the current study included data from the NorPD from January 1st 2007 to December 31st 2015; 1 to 9 years after T_4.

Measures

Prescription of psychotropic drugs. Subjects were categorized according to ATC-codes in mutually exclusive groups as receiving either anti-psychotics, mood-stabilizers,

antidepressants or anxiolytics during the nine-year period from 2007 to 2015. A fifth group was created to capture prescriptions that due to dose and type of medicine were evaluated to be psychotropic drugs for a non-psychiatric disorder (for instance nausea or epilepsy). The decision rules were hierarchical in the following order: 1) mood-stabilizers, 2) anti-psychotics, 3) antidepressants, 4) anxiolytics and 5) psychotropic drugs on other indications. The hierarchy of categories was relevant for assigning category when a person had received medications from more than one category (e.g. if a person was prescribed both antidepressants and mood-stabilizers, the person was categorized as receiving mood-stabilizers). Some exceptions from the general rules were made to account for only low-dose prescriptions and cases of only one prescription. A detailed description of these categorizing principles is provided in the supplement.

Cannabis use. Based on self-reported use of cannabis at T_4, we divided the material into three categories: those who had never used cannabis; those who had used cannabis at least once in their lifetime, but not in the last 12 months; and those who had used cannabis at least once during the last 12 months.

Socio-demographics. Age, gender and country of birth (Norway or abroad) were assessed at T_1. The same was parental education, which was classified into five levels *from up to 9 years of basic education* (1) to *more than three years of university education* (5) for the parent with highest education. We also asked whether the respondent was living with both biological parents or not at T_1.

Conduct problems and drug use. We used a 15-item measure of conduct problems at T_1, which approximates diagnostic criteria for conduct disorder in the DSM-III-R (45). Response options ranged from 1 (*never*) to 6 (*more than 50 times*). Mean scores across all items were computed (Cronbach's $\alpha = 0.75$). We assessed the number of alcohol intoxication episodes at T_1 by asking how often respondents had drunken so much that they felt clearly

intoxicated during the previous 12 months. Response options ranged from 1 (*never*) to 6 (*more than 50 times*). Moreover, we asked at T_1 about daily smoking (no/yes) during the past 12 months. We also assessed use of other illicit drugs than cannabis at T_1 by asking whether the respondent had used "other narcotics than cannabis, such as cocaine, LSD, amphetamine, heroin, or something else" the past 12 months (no/yes).

Mental distress. Mental distress was measured at T_1 by 12 items from the Hopkins Symptom Checklist (46). The measure asks for ratings of symptoms of depression and anxiety the preceding week and applies a 4-point scale with the response options from 1 (*not bothered at all*) to 4 (*extremely bothered*). The items have been used in several studies to measure mental distress and have favorable psychometric properties (47). Mean scores were computed and internal consistency was high (Cronbach's $\alpha = 0.85$).

Analyses

Multinomial logistic regression analysis was conducted with prescription as dependent variable and cannabis use as the independent variable. The categories of "antipsychotics", "mood-stabilizers", "antidepressants", "anxiolytics" and "psychotropic drugs on other indications" were all compared to the reference category "no psychotropic drugs". We compared levels of cannabis exposure ("lifetime use but not last year" and "use last year") with the reference category "no lifetime cannabis use". We adjusted for potential confounders in four steps by including several indicators of socio-demographic background in a first step, adding variables related to conduct problems and drug use in a second step, and adding mental distress in a third step as covariates. Moreover, in a fourth step, we excluded all persons who had obtained prescriptions of psychotropic drugs in 2004 (n = 134), the year before information about cannabis exposure was obtained, to minimize the possibility of prescriptions of psychotropic drugs preceding cannabis use.

A maximum likelihood estimator was used in all analyses. Missing data were handled by means of full information maximum likelihood estimation, thereby providing missing data routines that are considered to be state of the art (48). The statistical program Mplus 7.4 was used for all regression analyses, and the commands “CATEGORICAL”, “ESTIMATOR = MLR” and “INTEGRATION = MONTECARLO” were used to specify the multinomial logistic regression models.

Results

Of the total sample of 2,602 individuals, 317 (12.2%) reported use of cannabis during the past year, while 518 (19.9%) reported earlier use of cannabis but not the past year. During the 9 year follow-up period, 33 individuals (1.3%) had received prescriptions for antipsychotics, 36 individuals (1.4%) for mood-stabilizers, 233 individuals (9.0%) for antidepressants, 104 individuals (4.0%) for anxiolytics and 82 persons (3.2%) had been prescribed psychotropic drugs for presumably other reasons than a mental disorder. The number of individuals who had not received any prescriptions for psychotropic drugs was 2,114 (81.4%).

Those who were not prescribed any psychotropic drugs during follow-up were in adolescence more often living with their parents, had parents with higher education, had less conduct problems, smoked less and had less mental distress, compared to those with some type of prescription (Table 1). There were however considerable differences in how the background variables were distributed between the different psychotropic drug categories. There were differences between the cannabis categories on all variables except being born in Norway and use of other illicit drugs (Table 2).

Insert Tables 1 and 2 here

The unadjusted results of the multinomial regression analyses showed a strong association with later prescription of antipsychotics and mood-stabilizers in those reporting last year cannabis use, and a significant but smaller association to prescription of antidepressants and anxiolytics (Table 3). This pattern remained through the four steps of adjustment, with the final model estimating past year cannabis use to be associated with an increased odds ratio for filling a prescription of antipsychotics of OR = 5.56 (1.64 – 18.87), prescription of mood-stabilizers of OR = 5.36 (95 % CI 1.99 – 14.44) and prescription of

antidepressants of OR = 2.10 (1.36 – 3.25). The association to prescription of anxiolytics became non-significant after adjustments. Through the four steps of modelling the estimates of the associations were only slightly changed, and for some associations the effect size increased after adjustment.

Lifetime cannabis use but no use during the past year, showed no significant associations with any prescription outcome in any model.

Insert Table 3 here

Discussion

In this longitudinal cohort study of a population-based sample of young adults, we found that past year cannabis use was associated with later prescription of antipsychotics, mood-stabilizers and antidepressants. The associations remained significant and with almost unaltered effect-sizes after adjustment for relevant background variables including baseline mental distress and when excluding those with prescription for psychotropic drugs the year before the measurement of cannabis use. The association to anxiolytics was not significant after adjustment.

The association between cannabis exposure and prescription of antipsychotics is in accordance with existing knowledge on the association between cannabis and psychosis. Several large, prospective, longitudinal epidemiologic and clinical studies have found that cannabis use, particularly heavy exposure that starts at an early age, increases the risk of developing schizophrenia (6-8, 11, 49, 50) and psychotic symptoms (9, 51, 52). To our knowledge, prescription data on antipsychotic medication has not been used as outcome in previous studies, and the present investigation thus supplements the evidence.

Our result of a robust association between cannabis use and prescription of mood stabilizers strengthens the relatively new assumption of cannabis use as a risk factor for bipolar disorder (29, 30). The effect size for the association between cannabis and mood stabilizers was comparable to the effect size for association between cannabis and antipsychotics, a magnitude similar also to the effect sizes found in studies using a diagnosis of bipolar disorder as outcome (26, 27, 53). It has been shown that cannabis use increases the risk for earlier onset bipolar disorder (19, 54), and the participants in this study were quite young adults.

The smaller but significant association between cannabis use and antidepressants prescriptions found in this study is in accordance with most of the literature on cannabis and

depression (31-34). Further, the absence of an association between cannabis and anxiolytics in our study is informative for the understanding of the effect of cannabis use on anxiety, as meta-analysis provide conflicting results (34, 36). We have earlier commented that the use of benzodiazepines is greater in cannabis users (55), but the more careful grouping of psychotropic drug users in the present study indicates that this may be because benzodiazepines often are used also for other psychiatric illnesses than anxiety disorder.

Only "past year use" significantly predicted prescriptions of the psychotropic drugs, while "lifetime use but not during the past year" seemed to infer no increased risk. This may reflect that the "past year use" category included those who continued their cannabis habits from youth into early adulthood, thus indicating longer exposure. Many studies demonstrate stronger association between frequent use and the outcome than for the association between *any* use and the same outcome (5, 31, 33), a dose-response pattern consistent with inferring causality. The "lifetime use but not during the past year" is a broad category, encompassing individuals who may have tried cannabis only a few times in their youth, or even just once.

No particular variable or set of variables explained the association between cannabis use and later prescriptions in the sample. Adjusting for socio-demographic variables increased the effect size somewhat for all outcomes except antipsychotics. School truancy and conduct problems were associated with cannabis use, in line with previous research documenting cannabis use to be associated with school drop-out and poor educational attainments (56, 57). However, adjusting for school-variables, conduct problems and drug use imposed only a small decrease in the ORs. It should however be noted that drug use was measured at T_1, leaving open the possibility that later drug use may have affected the outcome. Also, despite the significant differences in baseline mental distress between those with and without prescriptions, adjusting for baseline mental distress did not alter the effect sizes. Removing persons who had received prescriptions of psychotropic drugs the year prior to the self-

reported cannabis use limits the risk of reversed causality. However, mental disorders may develop slowly, the prodromal phase of psychosis may for instance last years (58), and we cannot rule out that some have used cannabis to relieve early symptoms of mental illness.

We do not know how well prescriptions function as a measure for a mental disorder. Most psychotropic drugs may have several uses. Before the rules of categorization were applied to the dataset, we reviewed each person's total history of prescriptions to examine if the rules seemed reasonable. In spite of this effort to increase likelihood of correct approximation, it must be kept in mind that the psychotropic categories where only proxies for mental health diagnosis. Most significantly, antidepressants are also used for the treatment of anxiety and benzodiazepines are not recommended for long-term anxiety treatment, making the "antidepressants" and "anxiolytics" categories less valid as proxies for a mental disorder. Also, the proportion receiving treatment of those who have a mental disorder may not be equal across diagnostic categories, and the treatment-coverage is probably highest for psychotic disorders (59). It is however unlikely that this could explain the entire difference in associations between cannabis use and later psychotic vs. non-psychotic prescriptions found in the present study. Lastly, we do not know if the prescribed drugs in fact were taken, but when using prescriptions as a proxy for disease, compliance is less of an issue.

It would have been preferable with a more fine-graded differentiation of the cannabis exposure, enabling an investigation of potential dose-response relationships to the psychotropic drugs outcomes. The number of individuals in each group was however too small for such analysis to be conducted.

Despite these limitations, an advantage of using this prescription database is that both patients from primary health care and the specialized health care are included. As Norway is a country with a comprehensive publicly financed health care system, access to mental health care (including prescriptions) should be based on illness severity, not on private economy

(60). Also, most limitations affect all the diagnostic categories equally and cannot explain the differences in results for the psychotropic drugs outcomes found in this study.

This study is informative to the field as it has a relative large population-based sample, includes numerous relevant confounders, and expands the knowledge from previous studies by using prescription data as outcome. The results are indicative of a prospective association between cannabis use and psychosis, bipolar disorder and depression. This is important information in a world where cannabis is increasingly stronger and more available.

Table 1. Cannabis use, socio-demographics, conduct problems, drug use, and depression according to filling prescriptions for psychotropic drugs

		No psychotropic drugs	Antipsychotics	Mood stabilizers	Antidepressants	Anxiolytics	Other psychotropic drugs	Difference test
		n=2,114 (81.2%)	n=33 (1.3%)	n=36 (1.4%)	n=233 (9.0%)	n=104 (4.0%)	n=82 (3.2%)	*p*
Cannabis use								
never used	n (%)	1,428 (69.1%)	14 (45.2%)	15 (45.5%)	133 (58.6%)	62 (60.8%)	54 (66.7%)	
used before but not last year	n (%)	419 (20.3%)	4 (12.9%)	7 (21.2%)	51 (22.5%)	23 (22.5%)	14 (17.3%)	
used last year	n (%)	220 (10.6%)	13 (41.9%)	11 (33.3%)	43 (18.9%)	17 (16.7%)	13 (16.0%)	
Socio-demographics								
Female gender	n (%)	1,137 (53.8%)	15 (45.5%)	25 (69.4%)	154 (66.1%)	71 (68.3%)	55 (67.1%)	< 0.001
Age	mean (SD)	15.24 (1.87)	14.88 (3.18)	15.14 (3.04)	15.28 (2.15)	15.34 (1.92)	15.41 (2.42)	0.818
Born in Norway	n (%)	1,925 (97.0%)	27 (93.1%)	32 (94.1%)	214 (96.8%)	96 (97.0%)	75 (98.7%)	0.667
Parental education	mean (SD)	3.42 (1.12)	3.08 (1.13)	3.33 (1.18)	3.16 (1.07)	3.33 (1.13)	3.20 (1.08)	0.023
Living with both parents	n (%)	1,450 (71.5%)	20 (64.5%)	24 (70.6%)	130 (57.5%)	57 (55.3%)	55 (70.5%)	< 0.001
Conduct problems and drug use								
Conduct problems	mean (SD)	1.34 (0.37)	1.36 (0.35)	1.37 (0.46)	1.41 (0.40)	1.44 (0.53)	1.42 (0.45)	0.022
Alcohol intoxication	mean (SD)	1.88 (1.42)	1.54 (1.10)	1.57 (1.25)	2.11 (1.46)	2.08 (1.60)	2.12 (1.48)	0.043
Daily smoking	n (%)	176 (9.1%)	3 (10.0%)	5 (14.7%)	37 (17.0%)	20 (20.2%)	7 (10.0%)	< 0.001
Other illicit drugs than cannabis	n (%)	11 (0.6%)	0 (0.0%)	1 (3.3%)	5 (2.3%)	2 (2.0%)	0 (0.0%)	0.026
Self-reported depression								
Mental distress	mean (SD)	1.57 (0.45)	1.70 (0.55)	1.65 (0.48)	1.80 (0.53)	1.64 (0.43)	1.65 (0.46)	< 0.001

Table 2. Socio-demographics, conduct problems, drug use, and mental distress according to cannabis use

		Never used cannabis	Used cannabis before but not last year	Used cannabis last year	Difference test
		n=1,706 (67.1%)	n=518 (20.4%)	n=317 (12.5%)	*p*
Socio-demographics					
Female gender	n (%)	1,024 (60.0%)	271 (52.3%)	123 (38.8%)	< 0.001
Age	mean (SD)	15.34 (1.98)	15.20 (1.89)	14.75 (1.84)	< 0.001
Born in Norway	n (%)	1,559 (97.4%)	472 (96.7%)	286 (95.7%)	0.214
Parental education	mean (SD)	3.32 (1.10)	3.51 (1.11)	3.55 (1.20)	< 0.001
Living with both parents	n (%)	1,204 (73.8%)	318 (63.3%)	175 (56.6%)	< 0.001
Conduct problems and drug use					
Conduct problems	mean (SD)	1.29 (0.32)	1.46 (0.45)	1.52 (0.49)	< 0.001
Alcohol intoxication	mean (SD)	1.77 (1.33)	2.22 (1.59)	2.13 (1.54)	< 0.001
Daily smoking	n (%)	126 (8.0%)	72 (15.3%)	47 (16.2%)	< 0.001
Other illicit drugs than cannabis	n (%)	10 (0.6%)	6 (1.3%)	3 (1.0%)	0.375
Self-reported depression					
Mental distress	mean (SD)	1.57 (0.44)	1.67 (0.51)	1.58 (0.47)	< 0.001

Table 3. Results of logistic regression analyses with prescription of psychotropic drugs as outcome

	Antipsychotics		Mood stabilizers		Antidepressants		Anxiolytics		Other psychotropic drugs	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Baseline Model: Unadjusted associations										
Cannabis use										
never used	(reference)		(reference)		(reference)		(reference)		(reference)	
used before but not last year	0.98	0.32-3.01	1.59	0.65-3.89	1.31	0.93-1.84	1.27	0.78-2.07	0.88	0.49-1.61
used last year	5.92***	2.77-12.62	4.66***	2.15-10.09	2.10***	1.45-3.04	1.78*	1.02-3.10	1.56	0.84-2.92
Model 1: Control for socio-demographics										
Cannabis use										
never used	(reference)		(reference)		(reference)		(reference)		(reference)	
used before but not last year	0.94	0.29-3.04	1.87	0.76-4.56	1.31	0.92-1.87	1.26	0.76-2.09	0.96	0.52-1.75
used last year	5.49***	2.29-13.16	6.50***	3.01-14.06	2.29***	1.54-3.41	1.91*	1.06-3.43	1.92*	1.01-3.67
Model 2: Additional adjustment for conduct problems and drug use[†]										
Cannabis use										
never used	(reference)		(reference)		(reference)		(reference)		(reference)	
used before but not last year	0.96	0.29-3.18	1.95	0.78-4.84	1.25	0.87-1.78	1.16	0.71-1.91	0.92	0.49-1.72
used last year	5.73***	2.44-13.47	6.60***	2.98-14.62	2.11***	1.42-3.16	1.66	0.91-3.02	1.83	0.95-3.56
Model 3: Additional adjustment for mental distress										
Cannabis use										
never used	(reference)		(reference)		(reference)		(reference)		(reference)	
used before but not last year	0.94	0.29-3.07	1.94	0.78-4.82	1.21	0.85-1.73	1.16	0.71-1.91	0.92	0.49-1.72
used last year	6.06***	2.49-14.76	6.77*	3.05-14.99	2.18***	1.45-3.26	1.66	0.91-3.25	1.83	0.94-3.55
Model 4: Additional adjustment for use of psychotropic drugs in 2004[‡]										
Cannabis use										
never used	(reference)		(reference)		(reference)		(reference)		(reference)	
used before but not last year	1.11	0.28-4.34	1.53	0.41-5.63	1.19	0.80-1.75	1.15	0.69-1.93	0.99	0.51-1.93
used last year	5.56**	1.64-18.87	5.36***	1.99-14.44	2.10***	1.36-3.25	1.61	0.84-3.07	1.80	0.87-3.70

Note. OR = Odds ratio; 95% CI = 95% confidence interval of OR; *p < 0.05, **p < 0.01, **p < 0.001.

[†]Illicit drug use was not included as covariate because the model did not converge due to low frequencies of such use in some of the drug prescription groups.

[‡]All who obtained prescriptions for psychoactive drugs in 2004 (*n* = 134) were removed from the analyses.

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