

Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population?

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ABSTRACT

Aims To investigate whether cannabis use predicted the first incidence of mood and anxiety disorders in adults during a 3-year follow-up period. **Design and participants** Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a prospective study in the adult population of 18–64 years. The analysis was carried out on 3881 people who had no life-time mood disorders and on 3854 people who had no life-time anxiety disorders at baseline. **Measurements** Life-time cannabis use and DSM-III-R mood and anxiety disorders, assessed with the Composite International Diagnostic Interview (CIDI). **Findings** After adjustment for strong confounders, any use of cannabis at baseline predicted a modest increase in the risk of a first major depression (odds ratio 1.62; 95% confidence interval 1.06–2.48) and a stronger increase in the risk of a first bipolar disorder (odds ratio 4.98; 95% confidence interval 1.80–13.81). The risk of ‘any mood disorder’ was elevated for weekly and almost daily users but not for less frequent use patterns. However, dose–response relationships were less clear for major depression and bipolar disorder separately. None of the associations between cannabis use and anxiety disorders remained significant after adjustment for confounders. **Conclusions** The associations between cannabis use and the first incidence of depression and bipolar disorder, which remained significant after adjustment for strong confounders, warrant research into the underlying mechanisms.

Keywords Anxiety disorders, bipolar disorder, cannabis abuse, major depressive disorder, mood disorders.

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INTRODUCTION

Since the early 1990s, the prevalence of cannabis use has greatly increased in most western countries [1]. While cannabis has generally been perceived to be a relatively harmless drug, concerns about its health effects are growing. In recent years, evidence of the aetiological role of cannabis in the onset of psychotic symptoms and schizophrenia has accumulated [2]. Less information is available on the link between cannabis use and other mental health problems, such as mood and anxiety disorders.

Several cross-sectional studies support associations between cannabis use and measures of depression and/or anxiety [3–6]. For example, Fergusson *et al.* [4] showed that at least weekly use of cannabis among young people aged 14–21 years in New Zealand was associated modestly with a diagnosis of major depression (adjusted odds

ratio 1.7). This effect remained significant after controlling for confounding factors, such as adverse life events, alcohol abuse and deviant peer affiliations. However, opposite findings (no associations) have also been reported [7–10]. The evidence from longitudinal studies with regard to the role of cannabis use as a possible cause of depression and anxiety is also mixed, although most have reported that regular cannabis use predicts an increased risk of later depression and/or anxiety [7,11].

Reasons for inconsistent results between studies may include the different degrees of controlling for confounding factors and the use of heterogeneous measures of cannabis consumption and mental problems, the latter ranging from symptoms to disorders. So far, none of the prospective studies has examined the whole spectrum of mood and anxiety disorders. Moreover, most longitudinal studies investigating the relationship between cannabis use and anxiety or depression have been carried out in

young people. Only one study focused on the adult population [12]. Its results showed that the risk of onset of depressive symptoms (anhedonia and suicidal ideation) was four times greater in people with a baseline indication of cannabis abuse than the risk in people without cannabis abuse. This relationship remained after controlling for confounding demographic factors. Outcome measures of anxiety were not included.

To our knowledge, ours is the first study to determine whether cannabis use predicts the first incidence of a whole spectrum of mood and anxiety disorders in the adult population. We intended to investigate whether cannabis has the potential to cause mental health problems in their more severe manifestations. Therefore, full-blown anxiety and mood disorders were chosen as outcome measures. The associations were examined in different models, including different sets of commonly reported potential confounders.

METHODS

Sample

This study is based on a secondary analysis of data collected by the Netherlands Mental Health Survey and Incidence Study (NEMESIS) among the Dutch population aged 18–64 years. NEMESIS was designed as a longitudinal study with three measurements, in 1996 (baseline) and in 1997 and 1999 (follow-up). A detailed description of the objectives and methods of the study is given in Bijl *et al.* [13]. The subjects were selected by a multi-stage, stratified and random sampling procedure. First, a sample of 90 Dutch municipalities was drawn. Secondly, a sample of private households was drawn. Finally, within each household the member was selected with the most recent birthday, provided he or she was between 18 and 64 years and was sufficiently fluent in Dutch to be interviewed. The selected households were sent an introductory letter by the Ministry of Health inviting them to participate in the study. At baseline (T_0), a total of 7076 people provided informed consent and were interviewed. The response rate was 69.7%. The sample was representative of the Dutch population with regard to gender, civil status and urbanicity. Only the group aged 18–24 years was significantly under-represented, and we therefore post-stratified fully the data to Statistics Netherlands figures. At the first follow-up in 1997 (T_1), 5618 people participated again and a total of 4848 respondents were interviewed in 1999 (T_2).

Instruments and assessments

Subjects were interviewed face to face in their homes using the Composite International Diagnostic Interview (CIDI, version 1.1, computerised version) [14]. The CIDI

is a structured diagnostic interview designed for use by non-clinical interviewers. The CIDI yields Axis I disorders as defined in the DSM-III-R [15]. It has been shown to have an acceptable inter-rater and test-retest reliability, and an acceptable validity for most diagnoses [16]. Interviewers underwent a 3-day training course in recruiting respondents and computer-assisted interviewing, followed by a 4-day training course at the WHO-CIDI training centre of the Academic Medical Centre in Amsterdam.

Variables and data analysis

Cannabis use

Cannabis exposure was measured as the life-time use of cannabis (more than five times) at baseline. Those reporting cannabis use less than five times at baseline are hereafter called 'non-users'. The frequency of use during the period of heaviest use (1–3 days per month, 1–4 days per week, almost every day; reference 'no use') was used as a proxy measure of the intensity of life-time cannabis exposure in order to establish a dose-relationship.

Outcome measures and risk set

Outcome measures included the incidence of a DSM-III-R diagnosis of the main categories mood or anxiety disorders as well as the separate mood or anxiety disorders, occurring for the first time between T_0 and T_2 (over 1997 and 1999). The risk of the first incidence of mood disorders posed by cannabis use was investigated in all subjects who had successfully completed a CIDI interview at T_2 and did not meet criteria for a mood disorder at baseline. Similarly, the risk of the first incidence of anxiety disorders posed by cannabis use was investigated in all subjects who had successfully completed a CIDI interview at T_2 and did not meet criteria for an anxiety disorder at baseline. The risk set of people followed for the first incidence of any mood disorder consisted of 3881 individuals. The risk set of people followed for the first incidence of any anxiety disorder consisted of 3854 individuals. Table 1 gives the sizes of the risk sets for the separate disorders.

Confounders

Confounders were selected on the basis of a previous study on the incidence of mental disorders using the same database [17] and on the basis of other studies investigating the relationship between cannabis use and mental disorders [9,10]. These were: socio-demographic factors, including age, gender, education (four levels), urbanicity (five levels), employment and partner status; neuroticism [18], parental psychiatric history, childhood trauma (emotional neglect, psychological abuse, physical abuse, sexual abuse), life-time alcohol use disorders,

Table 1 Three-year incidence of mood and anxiety disorders among users and non-users of cannabis.

Cannabis use at baseline	3-year incidence																					
	Any mood disorder		Major depression		Dysthymia		Bipolar disorder		Any anxiety disorder		Panic disorder		Agoraphobia		Simple phobia		Social phobia		GAD		OCD	
	n	%	n	%	n	%	N	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
No use	3531	5.0	3662	5.6	3991	1.0	4197	0.3	3474	5.4	4119	1.3	4141	1.3	3869	4.1	3983	1.5	4067	1.4	4239	0.4
Any use	350	11.7	382	11.3	467	3.0	484	2.9	380	8.2	487	2.5	492	2.6	448	4.2	460	2.4	477	5.5	502	0.2

N = number of cases 'at risk' without a life-time disorder at baseline. GAD = generalized anxiety disorder. OCD = obsessive-compulsive disorder.

other substance use disorders (hallucinogens, sedatives, opioids, cocaine, amphetamines, inhalants, PCP) and life-time anxiety disorders (mood cohort), life-time mood disorders (anxiety cohort) and life-time psychotic symptoms. Life-time psychotic symptoms were included because a previous study on the same data set revealed associations between cannabis use and psychotic symptoms [19]. All confounders were measured at baseline and did not incorporate changes during the follow-up period.

Data analysis

According to Long's rule ([20], p. 54) for determining the minimum number of respondents needed to use logistic regression models, a sample size is recommended of at least 100 respondents plus 10 for each parameter (including the intercept) in the model that needs to be estimated. In the full multivariate model (see paragraph below), this would amount to at least 300 respondents. Hence, a sample of over 3800 respondents for each of the mood and anxiety disorders cohorts is more than adequate.

Associations between life-time cannabis use at baseline and the first incidence of mood and anxiety disorders were expressed as odds ratios indicating the risk of developing a mood or anxiety disorder in cannabis users compared to non-users. To examine the impact of confounders on the associations, a series of multivariate logistic regression analyses were carried out in which confounding variables measured at T_0 were entered into four models, each adding new confounders to the previous ones. The first model included socio-demographic factors. The second model included the factors from model 1 plus neuroticism, parental psychiatric history and childhood trauma. The third model added life-time alcohol use disorders and other substance use disorders and the fourth model also took other mental disorders into account. Finally, to investigate a dose-response relationship, a four-level variable based on the frequency of use during the period of heaviest use (see 'cannabis use') was entered into the full model as an independent variable. SPSS version 11.5 [21] was used to carry out these analyses.

The population attributable fraction (PAF) was derived from the associations between any cannabis use at baseline and mood or anxiety disorders at follow-up in the full model of the logistic regression analysis using the Aflogit procedure in STATA. Assuming causality, the PAF describes the percentage by which the incidence rate of mood or anxiety disorders can be reduced, when the exposure to cannabis is eliminated completely from the baseline population.

We conducted sensitivity analyses to examine whether differential attrition could have biased the

Table 2 Association between cannabis use at baseline and the 3-year incidence of mood disorders.

Life-time cannabis use at baseline	3-year incidence							
	Any mood disorder		Major depression		Dysthymia		Bipolar disorder	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1	2.83^a	1.89–4.23	2.62^a	1.80–3.81	2.58^c	1.19–5.59	7.58^a	2.93–19.63
Model 2	1.93^b	1.26–2.96	1.72^b	1.15–2.57	1.29	0.57–2.92	4.89^b	1.83–13.06
Model 3	2.03^b	1.30–3.17	1.68^c	1.11–2.55	1.55	0.67–3.58	5.38^b	1.93–14.99
Model 4	1.96^b	1.25–3.08	1.62^c	1.06–2.48	1.52	0.66–3.50	4.98^b	1.80–13.81

Values are given as odds ratios (and 95% confidence intervals) using those subjects who did not report any cannabis use at baseline as the reference category. Bold figures indicate significant associations. Levels of significance: ^a $P < 0.001$; ^b $P < 0.01$; ^c $P < 0.05$. Model 1: adjusted for gender, age, education, urbanicity, employment, partner status. Model 2: adjusted for confounders in model 1 and neurotic personality, parental psychiatric history, traumatic events in childhood. Model 3: adjusted for confounders in model 2 and life-time alcohol use disorders or other substance use disorders. Model 4: adjusted for confounders in model 3 and for life-time psychotic symptoms and life-time anxiety disorders at baseline.

findings. This was performed by multiple imputation of missing values of the outcome measures at T_2 using the Hotdeck command in STATA [22]. The Hotdeck procedure replaces missing values with regression estimates based on the complete cases in the corresponding strata. This is conducted in a number of steps depending on the proportion of missing cases. In this analysis Hotdeck was repeated 100 times, resulting in an equal amount of estimates of the missing values for each case. The final analysis is then based on all these estimates. Imputation of missing values was stratified by known predictors of attrition and incidence of mood/anxiety disorders: gender, age, marital status, employment, education, urbanicity and neuroticism [23,24].

RESULTS

The mean age of the risk set followed for the category mood disorders ($n = 3881$) was 39 years (SD 12.9) at baseline; 54% were male; 31% had a high education level; 83% lived in an urban environment; 29% had no partner and 28% had no paid employment. The mean age of the risk set followed for the category anxiety disorders ($n = 3854$) was also 39 years (SD 12.7) at baseline; 55% were male; 33% had a high education level; 83% lived in an urban environment; 30% had no partner and 27% had no paid employment. The incidence of the category mood disorders, diagnosed between T_0 and T_2 , was 5.6%. The incidence of the category anxiety disorders was 5.7%. Table 1 gives the incidence rates for the specific disorders as defined by baseline cannabis use.

Incidence of mood disorders

In the most simple model (1) correcting only for socio-demographic factors, baseline cannabis use was associated with a more than twofold increased risk of the first incidence of 'any mood disorder' (OR 2.8; Table 2). The

associations were strongest for bipolar disorder (OR 7.6). Cannabis users were also significantly more likely than non-users to have a first diagnosis of major depression or dysthymia (OR 2.6 for both disorders). Additional adjustment for neuroticism, parental psychiatric history and childhood trauma (model 2) resulted in appreciably weaker but still significant associations between cannabis use and both major depression and bipolar disorder (OR 1.7 and 4.9, respectively). The association between cannabis use and dysthymia lost significance.

Additional adjustment for alcohol and other substance use disorders, life-time psychotic symptoms and life-time anxiety disorders (models 3 and 4) had virtually no impact on the size and significance of the association between cannabis use and bipolar disorder, and only minimally reduced the association between cannabis use and major depression.

An analysis of the associations per frequency level in the fully adjusted model (Table 3) suggests that at least weekly or more frequent use of cannabis increased the risk of the first incidence of the category mood disorders. However, this pattern was less clear when the separate mood disorders were considered. For major depression no differences were seen between the different frequency levels. For bipolar disorder a trend towards increasing effect size was seen with increasing frequency of use, except for daily use.

The population attributable fractions based on any use of cannabis at baseline and the first 3-year incidence of the category mood disorders and the separate disorders major depression and bipolar disorder were 7.7%, 5.5% and 34.4%, respectively.

Incidence of anxiety disorders

Any use of cannabis at baseline increased the risk of the category anxiety disorders only in model 1, corrected for socio-demographic factors (OR 1.6; see Table 4).

Table 3 Associations between cannabis use at baseline and 3-year incidence of mood disorders by frequency of use during the period of heaviest use.¹

Frequency of use	Any mood disorder		Major depression		Dysthymia		Bipolar disorder	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No use	1		1		1		1	
1–3 days a month	1.38	0.70–2.71	1.49	0.82–2.71	1.03	0.28–3.74	2.85	0.56–14.53
1–4 days a week	2.57^b	1.33–4.98	1.79	0.94–3.40	2.27	0.72–7.23	8.93^a	2.77–28.82
Almost every day	2.38^c	1.09–5.19	1.60	0.75–3.42	1.54	0.37–6.46	3.13	0.56–17.47

Values are given as odds ratios (and 95% confidence intervals) using those subjects who did not report any cannabis use at baseline as the reference category. Bold figures indicate significant associations. Levels of significance: ^a $P < 0.001$; ^b $P < 0.01$; ^c $P < 0.05$. ¹Adjusted for gender, age, education, urbanicity, employment, partner status, neurotic personality, parental psychiatric history, traumatic events in childhood, life-time alcohol use disorders or other substance use disorders, life-time psychotic symptoms and life-time anxiety disorders at baseline (model 4).

Disorder-specific analyses revealed significant associations for panic disorder and generalized anxiety disorder (OR 2.4 and 2.8, respectively). Correcting for neuroticism, parental psychiatric history and childhood trauma (model 2) reduced odds ratios and none of them remained significant. The third model, which also corrected for life-time alcohol use and other substance use disorders, further reduced the strength of the (non-significant) associations between cannabis use and panic disorder and agoraphobia. Additional adjustment for life-time psychotic symptoms and mood/anxiety disorders had little impact on the associations.

There were no significant linear trends in the associations between frequency levels of cannabis use and anxiety disorders.

Sensitivity analyses

Based on 100 imputation sequences, in which missing values of incidences of mood or anxiety disorders at follow-up were stochastically imputed on the basis of predictors of attrition, the (estimated average) associations between any use of cannabis at baseline and the first incidence of any mood disorder, major depression or bipolar disorder remained significant (OR any mood 2.51, 95% CI 1.62–3.87; major depression 1.93, 95% CI 1.26–2.95; bipolar disorder 5.44, 95% CI 1.75–16.89).

DISCUSSION

Key findings

This longitudinal study in the adult population showed that after statistical adjustment for a series of strong confounders, cannabis use increased the risk of first incidence of major depression by a factor of 1.6 and the risk of first incidence of bipolar disorder by a factor of 5.0. None of the associations between cannabis use and anxiety disorders remained significant after correcting for potential confounders.

Limitations

Before discussing these findings we have to address a number of limitations. First, this study relied on self-reported use of cannabis. As is the case with all illegal drugs, this may lead to under-reporting and misclassification. However, this bias is assumed to be fairly small. In the Netherlands, the use of cannabis (and to a lesser extent other recreational drugs, such as cocaine and ecstasy) is generally not stigmatized and there are no risks of legal sanctions and associated social costs, which might make people reluctant to admit this substance use. Nevertheless, any under-reporting of cannabis use can be assumed to result in an underestimation of risks rather than giving rise to spurious associations. A second potential limitation is the fact that this study was conducted between 1996 and 1999, while the average delta(9)-tetrahydrocannabinol (THC) concentration in Nederwiet (Dutch-grown weed—the most consumed Dutch marijuana brand) has doubled from 9% in 1999 to 18% in 2005 [25]. This may indicate that the reported associations are underestimated, at least in so far as the higher concentrations of THC in cannabis have resulted in an increased internal body exposure and in so far as the link between cannabis use and mental disorders is explained by a pharmacological mechanism. Thirdly, in order to avoid sparsely filled cells in the multivariate model, which might hamper the statistical analysis, cannabis use at baseline was defined as the life-time use of cannabis. This life-time use might potentially have been far in the past. None the less, a *post-hoc* analysis on data for last-year cannabis use revealed a similar pattern of effects, including significant associations for the main category of mood disorders (OR 2.47, 95% CI 1.32–4.63; $P < 0.005$) and marginally significant associations for the separate disorders, major depression (OR 1.81, 95% CI 0.99–3.29; $P = 0.051$) and bipolar disorder (OR 3.13, 95% CI 0.89–11.05; $P = 0.076$). These results suggest that the findings are (also) related to more proximal use. Finally, the

Table 4 Association between cannabis use at baseline and the 3-year incidence of anxiety disorders.

Life-time cannabis use at baseline	3-year incidence percentage													
	Any anxiety disorder		Panic disorder		Agoraphobia		Simple phobia		Social phobia		GAD		OCD	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1	1.62^b	1.00–2.61	2.37^b	1.22–4.62	2.07	0.99–4.31	1.34	0.79–2.27	1.39	0.65–2.94	2.80^a	1.55–5.04	0.43	0.05–3.41
Model 2	1.19	0.73–1.95	1.68	0.84–3.35	1.36	0.64–2.88	1.01	0.59–1.73	0.92	0.42–1.99	1.75	0.95–3.23	0.29	0.04–2.35
Model 3	1.27	0.77–2.12	1.36	0.64–2.88	1.18	0.55–2.56	0.95	0.54–1.65	0.81	0.36–1.80	1.90	1.01–3.58	0.11	0.01–1.24
Model 4	1.18	0.71–1.97	1.29	0.61–2.71	1.14	0.53–2.46	0.91	0.52–1.58	0.80	0.36–1.79	1.83	0.97–3.44	0.12	0.01–1.28

Values are given as odds ratios (and 95% confidence intervals) using those subjects who did not report any cannabis use at baseline as the reference category. Bold figures indicate significant associations. Levels of significance: ^a $P < 0.01$; ^b $P < 0.05$. GAD = generalized anxiety disorder. OCD = obsessive-compulsive disorder. Model 1: adjusted for gender, age, education, urbanicity, employment, partner status. Model 2: adjusted for confounders in model 1 and neurotic personality, parental psychiatric history, traumatic events in childhood. Model 3: adjusted for confounders in model 2 and life-time alcohol use disorders or other substance use disorders. Model 4: adjusted for confounders in model 3 and for life-time psychotic symptoms and life-time mood disorders at baseline.

average age of the respondents at baseline was 39 years, which is appreciably higher than the average age of the onset of mood and anxiety disorders (29 years for any mood disorder and 20 years for any anxiety disorder in the full NEMESIS sample) [26]. This is related to the fact that subjects with a life-time diagnosis of any mood or anxiety disorder were excluded at baseline. This implies that the results of this study apply to mood and anxiety disorders with a relatively late onset and may not generalize to disorders emerging during adolescence and early adulthood.

Role of confounding factors

The different statistical models showed that early predisposing factors, such as neuroticism, parental psychiatric history and childhood trauma were strong confounders in the relationship between cannabis use and both mood and anxiety disorders. This is consistent with the literature demonstrating that these are broad and strong risk factors for a whole range of (comorbid) disorders, including substance use disorders and internalizing disorders [27–30]. Moreover, alcohol use and other drug use disorders also appeared to be confounders in the (already non-significant) relationship between cannabis use and panic disorder and agoraphobia, but did not have a major impact on the association between cannabis use and either major depression or bipolar disorder. This is in contrast to the study of Degenhardt *et al.* [9], suggesting that other drug use was a main confounder in the relationship between cannabis and major depression. To some extent, this difference might be explained by the order of entering variables in the regression analysis. A *post-hoc* analysis on our data, in which we corrected for socio-demographic factors and alcohol and other drug use disorders only, indicated that drug use disorders did indeed have a small impact on the association between cannabis use and major depression (but not bipolar disorder). Apparently, prior adjustment for early predisposing factors (in model 2) removed the impact of this confounder.

Major depression

We found a smaller increase in the risk of the first incidence of major depression among adult cannabis users compared to the study by Bovasso [12], i.e. 1.6 against 4. This difference might be explained in part by the differences in outcome measure. Bovasso [12] assessed 'any' symptom of depression instead of the clinical disorder major depression, which lowers the threshold for counting as a 'positive' outcome of cannabis use.

The association between cannabis use and first incidence of major depression remained significant after being scrutinised with a fairly conservative analytical approach incorporating a wide number of potential con-

founders, suggesting a direct relationship. However, the lower limit of the 95% confidence interval in the final model was close to 1 and the size of the association was relatively small. This raises the question of whether any uncontrolled confounding may have been overlooked that may ultimately move the association towards the null. In this regard, a recent study suggests that much of the association between cannabis dependence and major depression may be explained by shared or correlated genetic vulnerabilities [31]. To some extent, this genetic vulnerability may have been controlled for by statistical adjustment for 'parental psychiatric history', but we cannot exclude this factor fully. Another, perhaps more important, factor is that we have not controlled for tobacco smoking status, which was assessed only at the follow-up assessments' and not at baseline. Because tobacco smoking may increase the risk of depression [32,33] and regular tobacco smokers are over-represented among cannabis users [10], it might have contributed to the reported association. This may hold especially for countries such as the Netherlands, where cannabis is smoked predominantly in a joint mixed with tobacco.

Besides significant associations between variables and adjustment for confounders, a direct or causal relationship may be supported by a dose-response relationship. This study showed no clear pattern between the separate frequency levels and the risk of major depression. It should be noted, however, that version 1.1 of the CIDI does not allow a detailed assessment of cannabis exposure. The dose-response relationship was based on the frequency of use during the period of heaviest use, without taking into account the age at onset, the number of joints per occasion and the duration of heaviest use. Future longitudinal studies should apply more detailed measures of cannabis use. None the less, the dose-response relationships between cannabis and the onset of psychosis reported in various studies quantifying cannabis exposure in the same way suggests that it may be sufficiently valid as a proxy measure of the intensity of cannabis exposure [19,34].

Further, although cannabinoids exert complex effects on various brain neurotransmitter and neuroendocrine systems that have also been implicated in depression, plausible evidence of the specific neurophysiological pathways through which cannabis use leads to depressed mood is missing [35].

With all these caveats in mind, Degenhardt *et al.* [7] argue that a relationship between cannabis use and depression might also be indirect, or socially mediated. Some studies report associations between regular and early onset of cannabis use among adolescents and negative social consequences, such as educational failure, unemployment and crime [36,37], and it has been

hypothesized that all these factors may increase risks of later mental health problems. Whether similar mechanisms might have been at work in the present study remains to be investigated.

In conclusion, the results of this study provide additional evidence of an association between cannabis use and clinically relevant levels of depression in adults. However, we should be cautious in drawing conclusions on causality, because we lack evidence on a dose-response relationship and a plausible mechanism underlying the association. Moreover, competing explanations, such as concurrent tobacco smoking, cannot be ruled out.

Bipolar disorder

Substance use—especially alcohol, cannabis and stimulants—is exceptionally common in people with bipolar disorder [38]. The specific reasons for this comorbidity remain equivocal. Approximately 60% of the bipolar patients in clinical studies appear to develop substance abuse disorders before the onset of their bipolar illness, but there is also anecdotal evidence that cannabis is used as self-medication [39]. According to our knowledge, this is the first prospective population-based study to demonstrate that cannabis use is associated with a (fivefold) increase in the risk of a first diagnosis of bipolar disorder.

The decrease in strength of the association by 34% after adjusting for neurotic personality, parental psychiatric history and traumatic events in childhood indicates that part of the association is due to common risk factors. However, after additional adjustment for confounders the association remained stable and significant. Further, the dose-response relationship suggested that at least weekly use of cannabis was associated with an increased risk of bipolar disorder, although the daily dose level failed to reach significance, due possibly to the low number of daily cannabis users.

There is converging evidence that cannabis use increases the risk of psychotic symptoms and schizophrenia [40]. As psychotic symptoms are also common in bipolar disorder, it is possible that the association between cannabis use and bipolar disorder in this study is due (partly) to its link with new onset psychotic symptoms. However, an analysis at symptom level rather than diagnostic category suggests that cannabis use also has a unique contribution to the incidence of non-psychotic manic symptoms [41].

The increase in (positive) psychotic symptoms by cannabis has been linked, among others, to the capacity of its main psychoactive component THC to enhance mesolimbic dopaminergic activity [42]. There is also limited evidence from pharmacological and brain imaging studies

that (mesolimbic) dopaminergic hyperactivity may underlie both psychosis/schizophrenia and mania [43]. Thus, dopaminergic hyperactivity may also underlie the association between cannabis and bipolar disorder. Moreover, glutamate/glutamine levels in the prefrontal cortex have been shown to be elevated in patients with acute mania and bipolar disorder [44–46], and THC has been reported to increase (prefrontal) cortical glutamate levels [47].

Ashton *et al.* [48] have argued that cannabis may have both psychotic/mania-like properties and antipsychotic/mood stabilizing properties, the former being mediated by THC and the latter by cannabidiol (CBD). The concentration ratio of CBD/THC in domestic-grown marihuana, which has by far the greatest market share in the Netherlands and the United States, is very low [49,50]. Therefore it is probable that, in these countries, the psychological effects of cannabis can be attributed to THC. On the other hand, relative CBD content is appreciably higher in some forms of hashish [49,50], which might perhaps explain why some patients with bipolar disorder seem to benefit from cannabis. However, trials confirming the therapeutic efficacy of cannabis with high CBD content are still being awaited.

In addition to a causal relationship, another explanation for the reported association proposes that cannabis use is just a symptom of the prodrome of bipolar disorder [51,52]. In the current study respondents with a full-blown bipolar disorder were excluded at baseline, but people with subclinical symptoms of the disorder might have been included. It is possible that periods of changes in mood, impulsivity and poor judgement associated with the prodrome of bipolar disorder have promoted cannabis use.

In conclusion, the strength of the association between cannabis use and bipolar disorder and indications of a dose–response relationship suggests that the results merit further attention. However, a validation of the findings in other studies is important. In addition, the symptom overlap between bipolar disorder and psychosis/schizophrenia provides a clue about a physiological mechanism, but the specific pathways through which cannabis is linked to bipolar disorder remain to be elucidated.

Possible implications

Both major depression and bipolar disorder are highly debilitating disorders, in terms of quality of life, work absenteeism, morbidity and risk of suicide (attempts) [53–55]. With regard to the practical significance of our findings, the population attributable fraction indicated that some 6% of new cases of major depression and 34% of new cases of bipolar disorder over a 3-year period

might be prevented, assuming that any intervention can remove cannabis use completely and that the association is fully causal, thus without residual confounders. As both assumptions can be questioned, these figures most definitely reflect the upper limit of the public health impact of cannabis use. While the population attributable fraction is nearly six times greater for bipolar disorder than for major depression, the absolute numbers of new cases due to cannabis use may be smaller for bipolar disorder, because of the lower overall incidence rate. Taking into account a current 3-year incidence of 6.1% for major depression and 0.5% for bipolar disorder, the fractions indicate that the maximum health gain would consist of preventing the incidence of major depression in 34 000 people and of bipolar disorder in 17 000 people in the Dutch population aged 18–64 years (some 10 million).

CONCLUSIONS

In conclusion, this study showed that cannabis use predicts a fairly modest increase in the risk of a first major depression and a somewhat greater increase in the risk of a first bipolar disorder in the adult population. While we have corrected for quite strong confounders, conclusive evidence on the causality of the associations cannot be drawn from this research because competing explanations cannot be excluded fully. However, considering the strength of the association, as well as indications of a dose–response relationship and plausibility of a physiological mechanism, a causal relationship is more likely for bipolar disorder than major depression. However, a confirmation of the findings in other studies is needed, especially studies that include more precise measures of cannabis exposure. Finally, this study failed to find an increase in the risk of anxiety disorders in cannabis users. Given the average age of the respondents, the results mainly apply to relatively late onset mood and anxiety disorders.

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References

1. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Annual Report 2005: the State of the Drugs Problem in the European Union and Norway*. Lisbon: EMCDDA; 2005.
2. Smit F., Bolier L., Cuijpers P. Cannabis use and the risk of later schizophrenia: a review. *Addiction* 2004; 99: 425–30.
3. Agosti V., Nunes E., Levin F. Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. *Am J Drug Alcohol Abuse* 2002; 28: 643–52.

4. Fergusson D. M., Horwood L. J., Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* 2002; **97**: 1123–35.
5. Rey J. M., Tennant C. C. Cannabis and mental health. *BMJ* 2002; **325**: 1183–4.
6. Poulin C., Hand D., Boudreau B., Santor D. Gender differences in the association between substance use and elevated depressive symptoms in a general adolescent population. *Addiction* 2005; **100**: 525–35.
7. Degenhardt L., Hall W., Lynskey M. Exploring the association between cannabis use and depression. *Addiction* 2003; **98**: 1493–504.
8. Monshouwer K., Van Dorsselaer S., Verdurmen J., Bogt T. T., De Graaf R., Vollebergh W. Cannabis use and mental health in secondary school children: findings from a Dutch survey. *Br J Psychiatry* 2006; **188**: 148–53.
9. Degenhardt L., Hall W., Lynskey M. The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Soc Psychiatry Psychiatr Epidemiol* 2001; **36**: 219–27.
10. Degenhardt L., Hall W., Lynskey M. Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. *Addiction* 2001; **96**: 1603–14.
11. Patton G. C., Coffey C., Carlin J. B., Degenhardt L., Lynskey M., Hall W. Cannabis use and mental health in young people: cohort study. *BMJ* 2002; **325**: 1195–8.
12. Bovasso G. B. Cannabis abuse as a risk factor for depressive symptoms. *Am J Psychiatry* 2001; **158**: 2033–7.
13. Bijl R. V., Ravelli A., Van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol* 1998; **33**: 587–95.
14. Smeets R. M. W., Dingemans P. M. A. J. *Composite International Diagnostic Interview (CIDI)*, version 1.1. Amsterdam/Geneva: World Health Organization; 1993.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-III-R*. Washington, DC: American Psychiatric Association; 1987.
16. Wittchen H. U. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994; **28**: 57–84.
17. De Graaf R., Bijl R. V., Ravelli A., Smit F., Vollebergh W. A. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatr Scand* 2002; **106**: 303–13.
18. Ormel J. Moeite met leven of een moeilijk leven [Difficulty with living or a difficult life]. Groningen: Uitg. Konstapel; 1980.
19. Van Os J., Bak M., Hanssen M., Bijl R. V., De Graaf R., Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol* 2002; **156**: 319–27.
20. Long J. S. *Regression Models for Categorical and Limited Dependent Variables: Advanced Quantitative Techniques in the Social Sciences*, no. 7. Thousand Oaks, CA: Sage Publications; 1997.
21. SPSS, Inc. *SPSS [computer program]*, version 11.5. Chicago, IL: SPSS, Inc.; 2003.
22. StataCorp. *Stata Statistical Software*, release 7.0. College Station, TX: Stata Corporation; 2001.
23. De Graaf R., Bijl R. V., Smit F., Ravelli A., Vollebergh W. A. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 2000; **152**: 1039–47.
24. De Graaf R., Bijl R. V., Smit F., Vollebergh W. A., Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry* 2002; **159**: 620–9.
25. Niesink R. J. M., Rigter S., Hoek J. *THC-Concentraties in Wiet, Nederwiet En Hasj in Nederlandse Coffeeshops (2004–05)* [THC concentrations in marijuana, nederwiet and hashish in Dutch coffee shops]. Utrecht: Trimbos Institute; 2005.
26. De Graaf R., Bijl R. V., Spijker J., Beekman A. T. F., Vollebergh W. A. M. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Soc Psychiatry Psychiatr Epidemiol* 2003; **38**: 1–11.
27. Khan A. A., Jacobson K. C., Gardner C. O., Prescott C. A., Kendler K. S. Personality and comorbidity of common psychiatric disorders. *Br J Psychiatry* 2005; **186**: 190–6.
28. Dube S. R., Felitti V. J., Dong M., Chapman D. P., Giles W. H., Anda R. F. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 2003; **111**: 564–72.
29. De Graaf R., Bijl R. V., Ten Have M., Beekman A. T., Vollebergh W. A. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J Affect Disord* 2004; **82**: 461–7.
30. Sareen J., Fleisher W., Cox B. J., Hassard S., Stein M. B. Childhood adversity and perceived need for mental health care: findings from a Canadian community sample. *J Nerv Ment Dis* 2005; **193**: 396–404.
31. Lynskey M. T., Glowinski A. L., Todorov A. A., Bucholz K. K., Madden P. A., Nelson E. C. *et al.* Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Arch Gen Psychiatry* 2004; **61**: 1026–32.
32. Klungsoyr O., Nygard J. F., Sorensen T., Sandanger I. Cigarette smoking and incidence of first depressive episode: an 11-year, population-based follow-up study. *Am J Epidemiol* 2006; **163**: 421–32.
33. Breslau N., Peterson E. L., Schultz L. R., Chilcoat H. D., Andreski P. Major depression and stages of smoking. A longitudinal investigation. *Arch Gen Psychiatry* 1998; **55**: 161–6.
34. Henquet C., Krabbendam L., Spauwen J., Kaplan C., Lieb R., Wittchen H. U. *et al.* Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 2005; **330**: 11.
35. Kalia M. Neurobiological basis of depression: an update. *Metabolism* 2005; **54**: 24–7.
36. Fergusson D. M., Horwood L. J. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* 1997; **92**: 279–96.
37. Lynskey M., Hall W. The effects of adolescent cannabis use on educational attainment: a review. *Addiction* 2000; **95**: 1621–30.
38. Cassidy F., Ahearn E. P., Carroll B. J. Substance abuse in bipolar disorder. *Bipolar Disord* 2001; **3**: 181–8.
39. Grinspoon L., Bakalar J. B. The use of cannabis as a mood

- stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoact Drugs* 1998; **30**: 171–7.
40. Semple D. M., McIntosh A. M., Lawrie S. M. Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol* 2005; **19**: 187–94.
 41. Henquet C., Krabbendam L., De Graaf R., Ten Have M., Van Os J. Cannabis use and expression of mania in the general population. *J Affect Disord* 2006; **95**: 103–10.
 42. D'Souza D. C., Abi-Saab W. M., Madonick S., Forselius-Bielen K., Doersch A., Braley G. et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005; **57**: 594–608.
 43. Murray R. M., Sham P., Van Os J., Zanelli J., Cannon M., McDonald C. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res* 2004; **71**: 405–16.
 44. Michael N., Erfurth A., Ohrmann P., Gossling M., Arolt V., Heindel W. et al. Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex. *Psychopharmacology (Berl)* 2003; **168**: 344–6.
 45. Ketter T. A., Wang P. W. The emerging differential roles of GABAergic and antilglutamatergic agents in bipolar disorders. *J Clin Psychiatry* 2003; **64**: 15–20.
 46. Friedman S. D., Dager S. R., Parow A., Hirashima F., Demopoulos C., Stoll A. L. et al. Lithium and valproic acid treatment effects on brain chemistry in bipolar disorder. *Biol Psychiatry* 2004; **56**: 340–8.
 47. Tomasini M. C., Ferraro L., Bebe B. W., Tanganelli S., Cassano T., Cuomo V. et al. Delta(9)-tetrahydrocannabinol increases endogenous extracellular glutamate levels in primary cultures of rat cerebral cortex neurons: involvement of CB(1) receptors. *J Neurosci Res* 2002; **68**: 449–53.
 48. Ashton C. H., Moore P. B., Gallagher P., Young A. H. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. *J Psychopharmacol* 2005; **19**: 293–300.
 49. Pijlman F. T., Rigter S. M., Hoek J., Goldschmidt H. M., Niesink R. J. Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addict Biol* 2005; **10**: 171–80.
 50. ElSohly M. A., Wachtel S. R., De Wit H. Cannabis versus THC: response to Russo and McPartland. *Psychopharmacology* 2003; **165**: 433–4.
 51. Levin F. R., Hennessy G. Bipolar disorder and substance abuse. *Biol Psychiatry* 2004; **56**: 738–48.
 52. Strakowski S. M. I., Bello M. P. The co-occurrence of bipolar and substance use disorders. *Clin Psychol Rev* 2000; **20**: 191–206.
 53. Ten Have M., Vollebergh W., Bijl R., Nolen W. A. Bipolar disorder in the general population in The Netherlands (prevalence, consequences and care utilisation): results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord* 2002; **68**: 203–13.
 54. Alonso J., Angermeyer M. C., Bernert S., Bruffaerts R., Brugha T. S., Bryson H. et al. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004; **420**: 38–46.
 55. Mitchell P. B., Malhi G. S. Bipolar depression: phenomenological overview and clinical characteristics. *Bipolar Disord* 2004; **6**: 530–9.