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ORIGINAL ARTICLE

The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies

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Background. Longitudinal studies reporting the association between cannabis use and developing depression provide mixed results. The objective of this study was to establish the extent to which different patterns of use of cannabis are associated with the development of depression using meta-analysis of longitudinal studies.

Method. Peer-reviewed publications reporting the risk of developing depression in cannabis users were located using searches of EMBASE, Medline, PsychINFO and ISI Web of Science. Only longitudinal studies that controlled for depression at baseline were included. Data on several study characteristics, including measures of cannabis use, measures of depression and control variables, were extracted. Odds ratios (ORs) were extracted by age and length of follow-up.

Results. After screening for 4764 articles, 57 articles were selected for full-text review, of which 14 were included in the quantitative analysis (total number of subjects=76058). The OR for cannabis users developing depression compared with controls was 1.17 [95% confidence interval (CI) 1.05–1.30]. The OR for heavy cannabis users developing depression was 1.62 (95% CI 1.21–2.16), compared with non-users or light users. Meta-regression revealed no significant differences in effect based on age of subjects and marginal difference in effect based on length of follow-up in the individual studies. There was large heterogeneity in the number and type of control variables in the different studies.

Conclusions. Cannabis use, and particularly heavy cannabis use, may be associated with an increased risk for developing depressive disorders. There is need for further longitudinal exploration of the association between cannabis use and developing depression, particularly taking into account cumulative exposure to cannabis and potentially significant confounding factors.

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Key words: Cannabis, depression, epidemiology, meta-analysis, psychiatry.

Introduction

Cannabis is the most widely used illicit substance worldwide (European Monitoring Centre for Drugs and Drug Addiction, 2011; United Nations Office on Drugs and Crime, 2011). It has been reported that cannabis use has stabilized or even decreased in recent years in most high-income countries. However, the continuing high prevalence of use among adolescents and young adults (European Monitoring Centre for Drugs and Drug Addiction, 2011; United Nations Office on Drugs and Crime, 2011), as well as a gradual increase in the strength of cannabis consumed (ElSohly *et al.* 2000), is a cause for concern. These concerns focus, in part, on the perceived association between cannabis use and mental illness.

Evidence for an association between cannabis use and the development of psychotic disorders has accumulated (Moore *et al.* 2007). There is a growing

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consensus that those who use cannabis, particularly heavy users and individuals who initiated cannabis use at a young age, are at increased risk for developing psychotic disorders (Moore *et al.* 2007). However, there is less consensus about the association between cannabis use and the development of depression.

Depression is a common mental health problem and one of the most important contributors to the global burden of disease (Ustün *et al.* 2004; Moussavi *et al.* 2007). Findings of high prevalence of co-morbid cannabis use and depression have been replicated in many large-scale cross-sectional studies. Grant (1995) found that people meeting criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) cannabis use disorders (CUDs, i.e. abuse or dependence) within the past year had 6.4 times the odds of meeting criteria for major depression than those without a CUD. Chen *et al.* (2002) analysed data from the National Comorbidity Survey and found that a greater number of occasions of cannabis use were associated with a higher risk of having experienced a major depressive episode; and that lifetime cannabis dependence was associated with a 3.4 times increased risk of major depression.

Although cross-sectional evidence is informative, it does not allow exploring a causal relationship between cannabis use and developing depression. Fergusson & Horwood (1997) have characterized the possible relationships between cannabis use and mental health based on these cross-sectional data as reflecting either shared common ancestry (e.g. genetic load), earlier cannabis use predicting later mental health disorders, or earlier mental disorders predicting later cannabis use. Longitudinal studies are essential in providing more information on the direction of this association.

Several longitudinal studies have been conducted to explore the possible association between cannabis use and depression. This has been problematic because there has been considerable variation in the methods used including different measures of cannabis consumption and depressive illnesses and different methods for controlling for confounders. To date, two systematic reviews have investigated the association between cannabis use and the development of depression. Degenhardt *et al.* (2003) concluded that longitudinal studies provided mixed evidence on the nature of the association between cannabis use and depression and that though heavy cannabis use may increase depressive symptoms, this relationship may be explained by confounding factors. The more recent systematic review and meta-analysis by Moore *et al.* (2007) concluded that 'the evidence that cannabis use leads to affective outcomes is less strong than for psychosis but is still of concern' (p. 327). Though a meta-analysis was conducted estimating the odds of developing depression based on the most frequent use of cannabis in individual studies, no common criterion for 'frequent' or 'heavy' use across individual studies was used. In addition, no meta-analysis was conducted on the association between cannabis use (opposed to 'heavy use') and developing depression. Since then, a considerable number of longitudinal studies have been published (Georgiades & Boyle, 2007; van Laar *et al.* 2007; Harder *et al.* 2008; Pedersen, 2008; Brook *et al.* 2011; Marmorstein & Iacono, 2011; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013), which may improve our understanding of the links between cannabis and depression. Consequently, a meta-analysis that would examine the longitudinal evidence of the association between cannabis use and depression would be justified as well as needed. This may partially help in forming the societal response to the ongoing high prevalence of cannabis use (Hall & Solowij, 1998; Hall & Babor, 2000). To explore a dose–response association, it is important to differentiate between cannabis use and heavy cannabis use, as the latter is more strongly associated with greater risks for other (e.g. psychotic) psychiatric disorders (Moore *et al.* 2007).

We describe a meta-analysis of longitudinal studies examining the association between cannabis use and depression. The study investigates the association between cannabis use and the development of depression and whether this association is different for heavy or frequent cannabis use and for those who use cannabis as adults as opposed to during adolescence.

Method

The methods were based on the guidelines for Meta-analysis in Observational Studies in Epidemiology (Stroup *et al.* 2000).

Literature search

Inclusion/exclusion criteria

Studies were included if they met the following criteria: (1) reported in an original paper in a peer-reviewed journal; (2) included population-based data that were collected longitudinally and prospectively; (3) the exposure variable referred specifically to cannabis use (not 'substance use', which clusters together different substances, including cannabis); (4) outcome measures referred specifically to depression (and not mixed anxiety–depressive symptoms, for example); (5) the outcome variable (depression) was controlled for at baseline, or individuals with baseline depression were excluded; and (6) data were either presented as odds of developing depression following cannabis use or allowed the odds ratio (OR) to be calculated.

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In cases in which multiple studies were found reporting on the same population cohort at different time points, only one study reporting on the respective cohort was included. When more than one study from the same cohort met the inclusion criteria, the most recent study was selected. In cases in which the most recent publication did not fulfill the inclusion criteria (e.g. data presentation did not allow for calculation of ORs), the next most recently publication from the same cohort was included.

Search strategy

In consultation with a professional mental health librarian we established a search strategy of electronic databases (EMBASE, Medline, PsycINFO and ISI Web of Science) for publications from longitudinal studies reporting on the association between cannabis use and depression. The search was conducted between 1 August 2012 and 1 December 2012. There was no time span specified for date of publication. All references in which the word 'cannabis' or 'marijuana' or 'marihuana' and in which the words 'depression/depressed/depressive disorder', 'mood/mood disorder', 'affective disorder' or 'dysthymia' were included, collected and reviewed. The search was not limited by the inclusion of 'longitudinal' in the search terms. There were no language restrictions.

We examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate (S.L. and M.R.) we read the papers and determined whether they met inclusion criteria. Disagreements were resolved by consensus and in discussion with J.R. References of papers meeting inclusion criteria and of previous systematic reviews on cannabis use and depression were hand-searched for further relevant studies.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) for assessing the quality of studies included in the meta-analysis. The NOS includes a 'star system' in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest [e.g. controlling for the outcome variable (depression) at baseline] (Wells *et al.* 2005). We determined a score of 8 or more on the NOS to indicate 'high methodological quality'.

Data extraction and analysis

An extraction form was developed and used to collect the following data from studies: year of publication, country where study was conducted, sample size at follow-up, mean age at baseline and at follow-up, gender, measurement of cannabis use (in terms of time before assessment and frequency if provided), measurement of depression and control variables (Table 1).

Definition of cannabis use. Studies were divided into two categories according to the measurement of cannabis use. Studies defining cannabis use as either (1) any cannabis use (within a specific time-frame or lifetime) with non-users as the control group or (2) using specific cut-off criteria (e.g. monthly cannabis use, lifetime use on five occasions) with non-users or those using less frequently than the cut-off criteria as the control group were included in the 'cannabis use' category. Studies that used an exposure measure of either (1) DSM-IV CUD or (2) at least weekly cannabis use were included in the 'heavy cannabis use' category. The control group in the 'heavy cannabis use' category included non-users, individuals using cannabis less than weekly or not having a CUD. These categories were based on several studies using these categories of frequency of cannabis use when examining association between cannabis use and mental illness (Moore *et al.* 2007; Hall & Degenhardt, 2009).

Definition of depression. We included studies that evaluated major depressive disorder, dysthymia, or depressive symptoms using validated clinical tools. Studies were subdivided into two categories: studies assessing a clinical depression diagnosis and studies assessing depressive symptoms. This subdivision was made according to the outcome presented by the authors in each study.

Statistical analysis

ORs were treated as measures of risk. We recorded adjusted OR estimates when these were available and calculated ORs from the raw number of cases and controls when odds were not reported. When multiple exposure or control groups were reported, we combined these to derive one risk estimate per primary study. We calculated one estimate of the OR for depression for each article, and pooled the effect size for developing depression after cannabis use across studies using random-effects models (DerSimonian & Laird, 1986). When ORs were presented separately for different populations (e.g. by gender) in the original article, we reported them separately for each population provided. All analyses were conducted on the log scale. Publication bias was assessed by visual inspection of funnel plots depicting the risk estimates (on the log scale) against their standard error and by Egger's regression-based test (Egger *et al.* 1997). In

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Table 1. *Characteristics of included studies*

Source	Country	Sample size, *n*	Age of cannabis measurement, years	Cannabis measure	Age of depression measurement, years	Type of depression assessment	Depressive scale	Control variables
Paton *et al.* (1977)	USA	4785	High school students[a]	Any cannabis use in the previous 30 days	6 months after initial assessment[a]	Depressive symptoms	Six-item depressive mood index	Depression at baseline[b]
Fergusson & Horwood (1997)	New Zealand	927	16	Any previous cannabis use	18	Clinical diagnosis (MDD or dysthymia)	DISC	Depression at baseline, family functioning, association with delinquent or substance using peers, cigarette smoking, family history of drug/alcohol dependence, most alcohol consumed, gender, self-report offending, conduct/oppositional disorders at baseline, conduct problems at age 8 years, truancy at baseline, alcohol problems at baseline, IQ at age 8 years, plans for future secondary education at baseline, intentions to enter university at baseline, anxiety disorders at baseline, suicidal ideation at baseline
Bovasso (2001)	USA	849	18 and above[a]	CUD	14–16 years after initial assessment[a]	Depressive symptoms	DIS	Depression at baseline[b], gender, age, marital status, race, education, household income, stressful life events, chronic illness
Brook *et al.* (2001)	Columbia	2226	12–17	Cannabis use one or more times per month	14–19	Depressive symptoms	Johns Hopkins Symptoms Checklist	Depression at baseline, age, gender, SES
Brook *et al.* (2002)	USA	736	14, 16, 22[c]	Any previous cannabis use	27	Clinical diagnosis (MDD)	University of Michigan CIDI	Depression at baseline, age, gender, parental educational level, family income

Harder *et al.* (2006)	USA	8033	34–41	Any cannabis use=any use in the previous year. Heavy cannabis use=at least once per week in the previous 30 days	38–45	Depressive symptoms	CES-D	Depression at baseline, age, race, gender, aptitude (measure by the Armed Forces Qualifications Test score), general health limitations, region of residence, urban versus rural residence, past-year residence, criminal activity, adolescent alcohol use, residence at age 14, number of siblings, number of older siblings, mother's education, father's education, family income and family poverty status, cigarette use, excessive alcohol use, ever used hard drugs (cocaine or heroin), neighborhood ratings, educational achievement, income, marital status, employment status, hours worked and number of children living in the house
van Laar *et al.* (2007)	Netherlands	4848	18–64	Any cannabis use=at least five previous occasions of cannabis use. Heavy cannabis use=at least weekly	21–67	Clinical diagnosis (MDD or dysthymia)	CIDI	Depression at baseline[b], gender, age education, urbanicity, employment, partner status, neurotic personality, parental psychiatric history, traumatic events in childhood, lifetime alcohol and substance use disorders, lifetime psychotic symptoms and lifetime anxiety disorders at baseline
Georgiades & Boyle (2007)	Canada	1282	12–16	Any cannabis use in the previous 6 months	26–34	Clinical diagnosis (MDD)	CIDI-SF	Depression at baseline, family SES (family income, parental years of education, occupational prestige), single parent home and family functioning
Pedersen (2008)	Norway	2033	21	Any cannabis use in the previous 12 months	27	Depressive symptoms	Johns Hopkins Symptoms Checklist	Depression at baseline (age 16 and 21 years), age, gender, parental educational level, parents unemployed or received social welfare benefits, parental divorce, parental smoking and alcohol problems, parental support and monitoring measured at age 16 years, early pubertal maturation, school marks at age 16 years, conduct problems and daily smoking at age 16 and 21 years, alcohol intoxication at age 16 years, alcohol problems at age 21 years, impulsivity at age 21 years, level of education at age 21 years, unemployment and income from social security, marriage/cohabitation and being a parent at age 21 years

Table 1 (*cont.*)

Source	Country	Sample size, *n*	Age of cannabis measurement, years	Cannabis measure	Age of depression measurement, years	Type of depression assessment	Depressive scale	Control variables
Harder *et al.* (2008)	USA	1494	17	CUD	19–24	Clinical diagnosis (MDD)	CIDI	Depression at baseline, race, family income, parental supervision and monitoring, concentration problems, behavioral problems, shyness, anxiety, tobacco, drug use
Marmorstein & Iacono (2011)	USA	1165	17	CUD	20, 24[c]	Clinical diagnosis (MDD)	SCID	Depression at baseline, gender, psychosocial failure, occupational failure, crime
Brook *et al.* (2011)	USA	837	14, 19, 24[c]	More than four occasions of cannabis use per month in a 5-year period	29	Depressive symptoms	Symptoms Checklist 90-R	Depression at baseline, gender, ethnicity, criminal behavior, school achievement
Manrique-Garcia *et al.* (2012)	Sweden	45087	18–20	Any previous cannabis use	22–58	Clinical diagnosis (MDD)	ICD-8, ICD-9, ICD-10	Depression at baseline[b], personality disorders at conscription, IQ, disturbed behavior in childhood, social adjustment, risky use of alcohol, smoking, early adulthood socio-economic position, use of other drugs, brought up in a city
Degenhardt *et al.* (2013)	Australia	1756	15–17, 20, 24[c]	Any previous cannabis use. Heavy cannabis use =at least weekly	29	Clinical diagnosis (major depressive episode)	ICD-10	Depression at baseline, anxiety symptoms at baseline, gender, non-metropolitan school location, low parental education, parental divorce/separation by age 17 years, concurrent substance use

MDD, Major depressive disorder; DISC, Diagnostic Interview Schedule for Children; IQ, intelligence quotient; CUD, cannabis use disorder; DIS, Diagnostic Interview Schedule; SES, socio-economic status; CIDI, Composite International Diagnostic Interview; CES-D, Center for Epidemiologic Studies Depression Scale; CIDI-SF, Composite International Diagnostic Interview – Short Form; SCID, Structured Clinical Interview for DSM-III-R; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases.

[a] Mean age not provided.

[b] Individuals with depression at baseline excluded from study.

[c] Multiple assessments.

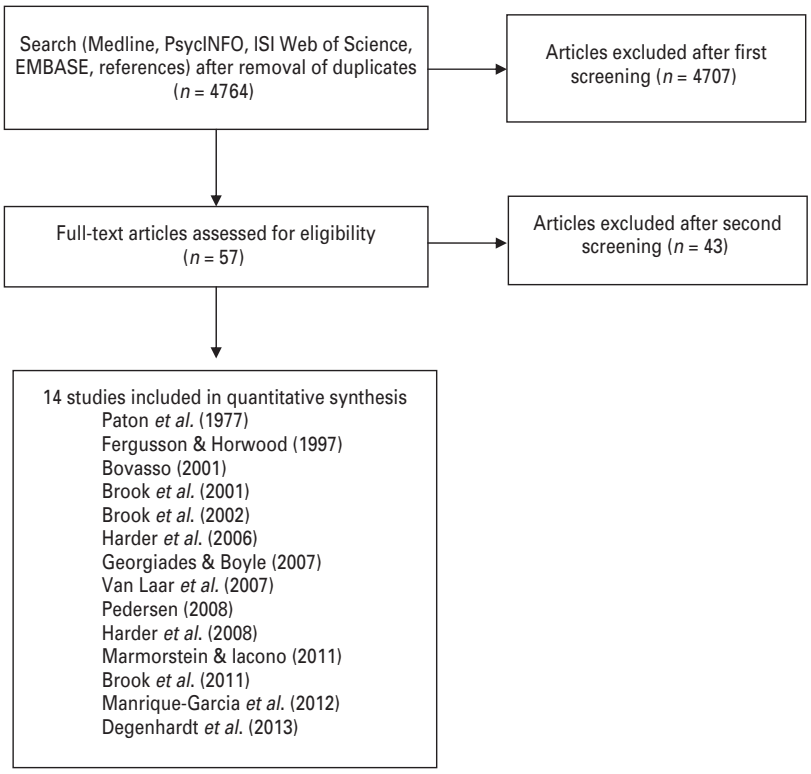

Fig. 1. Flowchart of search strategies and results.

the case of presence of such bias we conducted sensitivity analyses using Duval and Tweedie's trim-and-fill method (Duval & Tweedie, 2000). The influence of any particular study on the pooled OR was examined by re-estimating the pooled effect excluding studies one by one. Since considerable heterogeneity was expected, all analyses were performed with a random-effects model. Between-study heterogeneity was quantified by I^2 and Cochran's Q (Lipsey & Wilson, 2001). I^2 can be interpreted as the percentage of the total variance due to between-study heterogeneity.

To determine whether factors such as age of cannabis exposure or follow-up duration modified the cannabis-depression association, meta-regressions were performed. We also conducted three sets of sensitivity analysis including: (1) only studies with 'high methodological quality'; (2) only studies using clinical diagnosis of depression as the outcome variable; and (3) only studies with non-cannabis-users serving as the control group. All analyses were conducted in Stata statistical software version 11.2 (StataCorp LP, USA).

Results

Search results

(Fig. 1) Of the 4764 abstracts reviewed, 4707 were excluded based on title and abstract. In total, 57 articles were retrieved and assessed for eligibility and 14 articles met the inclusion criteria (Paton *et al.* 1977; Fergusson & Horwood, 1997; Bovasso, 2001; Brook *et al.* 2001, 2002, 2011; Harder *et al.* 2006, 2008; Georgiades & Boyle, 2007; van Laar *et al.* 2007; Pedersen, 2008; Marmorstein & Iacono, 2011; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013). A total of 76058 subjects were included in the meta-analysis.

Quality assessment

All studies included in this meta-analysis scored at least 5 out of 9 in the NOS, and eight of the studies scored 8 out of 9. The mean NOS score of all studies included was 7.21 (±1.25 S.D.) stars.

Meta-analyses results

In order to examine whether cannabis use was associated with increased odds for developing depression, we pooled results from 10 studies (Paton *et al.* 1977; Fergusson & Horwood, 1997; Brook *et al.* 2001, 2002; Harder *et al.* 2006; Georgiades & Boyle, 2007; van Laar *et al.* 2007; Pedersen, 2008; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013). The pooled OR for depression among cannabis users compared with controls was 1.17 [95% confidence interval (CI) 1.05–1.30, I^2=2.1%] (Fig. 2). In order to examine whether heavy cannabis use was associated with increased

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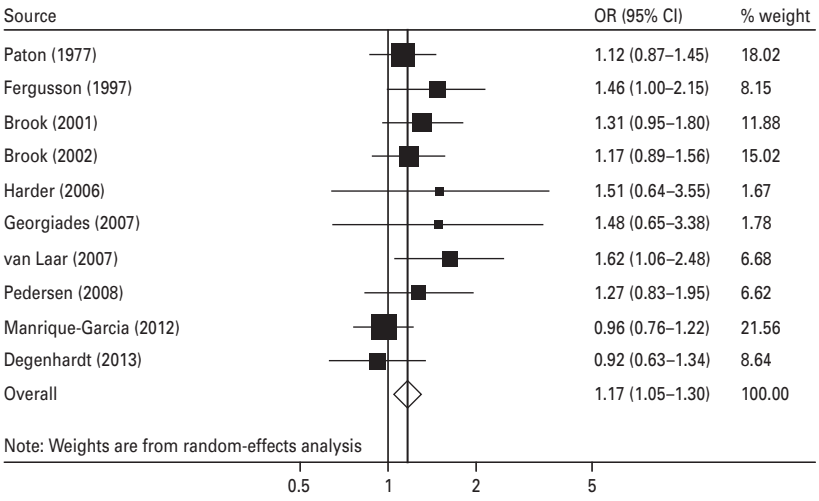

Fig. 2. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for any depressive outcome according to cannabis use in individual studies (random effects).

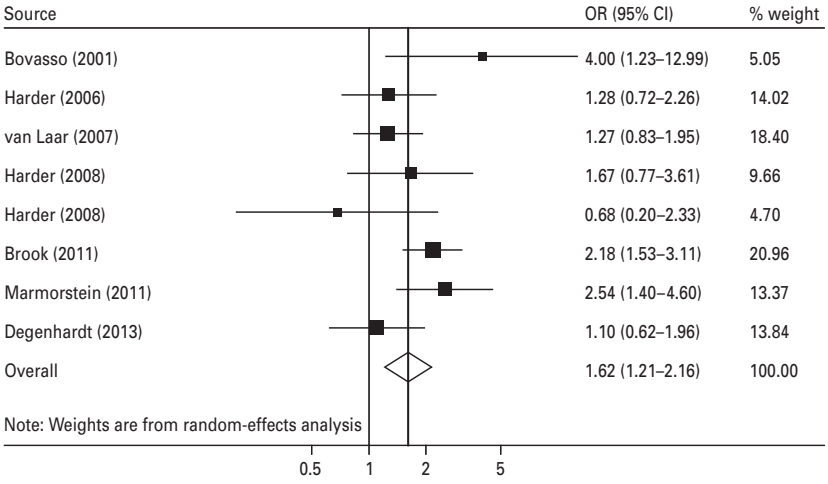

Fig. 3. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for any depressive outcome according to heavy cannabis use (defined as a cannabis use disorder or at-least weekly use) in individual studies (random effects).

odds for depression, we pooled results from seven studies (Bovasso, 2001; Harder *et al.* 2006, 2008; van Laar *et al.* 2007; Brook *et al.* 2011; Marmorstein & Iacono, 2011; Degenhardt *et al.* 2013). The OR for depression among heavy cannabis users compared with controls was 1.62 (95% CI 1.21–2.16, I^2=47.3%) (Fig. 3).

Sensitivity analyses

We conducted additional meta-analyses including only studies that scored at least 8 out of 9 possible stars on the NOS. To examine whether cannabis use was associated with increased odds for depression, we pooled results from eight studies that scored at least 8 on the NOS (Fergusson & Horwood, 1997; Bovasso, 2001; Brook *et al.* 2002; Harder *et al.* 2006; van Laar *et al.* 2007; Pedersen, 2008; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013). The pooled OR for depression among cannabis users compared with controls was 1.12 (95% CI 1.03–1.37, I^2=20.2%). For heavy cannabis use, we pooled results from four studies (Bovasso, 2001; Harder *et al.* 2006; van Laar *et al.* 2007; Degenhardt *et al.* 2013) and the OR was 1.34 (95% CI 0.96–1.87, I^2=21.6%).

In order to examine whether cannabis use was associated with increased odds for a diagnosis of major depression or dysthymia (excluding studies reporting depressive symptoms as the outcome), we pooled results from six studies (Fergusson & Horwood, 1997; Brook *et al.* 2002; Georgiades & Boyle, 2007; van Laar *et al.* 2007; Manrique-Garcia

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et al. 2012; Degenhardt *et al.* 2013). The pooled OR for cannabis users was 1.17 (95% CI 0.97–1.41, I^2=36.9%). For heavy cannabis use we pooled results from four studies (van Laar *et al.* 2007; Harder *et al.* 2008; Marmorstein & Iacono, 2011; Degenhardt *et al.* 2013) and the OR was 1.43 (95% CI 1.00–2.05, I^2=35.8%).

Finally, we conducted a meta-analysis excluding studies where only non cannabis-users were included in the control group. We pooled results from nine studies (Paton *et al.* 1977; Fergusson & Horwood, 1997; Brook *et al.* 2002; Harder *et al.* 2006; Georgiades & Boyle, 2007; van Laar *et al.* 2007; Pedersen, 2008; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013) and the OR was 1.15 (95% CI 1.02–1.30, I^2=7.0%).

Meta-regression

Meta-regressions were performed based on differences in age of exposure (⩽18 years *versus* >18 years at baseline), and length of follow-up (continuous in years, and dichotomized at 5 years).

Regarding any use of cannabis, including follow-up length as a predictor variable, was marginally related to the strength of the pooled OR in a continuous (p=0.07) and dichotomized (p=0.09) form, showing attenuation of risk with longer follow-up. Investigation of age as a predictor of the pooled OR did not reveal any evidence for such an effect (p=0.37). Regarding heavy cannabis use, including follow-up length as a predictor variable, was not significantly related to the strength of the pooled OR in neither the continuous (p=0.79) nor the dichotomized (p=0.85) form, and the investigation of age as a predictor of the pooled OR did not reveal any evidence for such an effect (p =0.77). These tests were underpowered because of the small number of studies included; therefore cautious interpretation is necessary. Removing studies one by one had very little influence on the pooled OR in all analyses.

Publication bias

We found some evidence of publication bias in the analysis involving cannabis use (p=0.08), and none regarding heavy use (p=0.76). Imputing possibly missed studies yielded a pooled OR of 1.13 (95% CI 1.01–1.27) with three studies being imputed.

Discussion

We found that cannabis use was associated with a modest increased risk for developing depressive disorders. We further found that heavy cannabis use was associated with a stronger, but still moderate, increased risk for developing depression. These associations remained the same in sensitivity analyses, and were consistent for cannabis use both in adolescence and in adulthood. There was large heterogeneity in the number and type of control variables in the different studies, and we cannot exclude the possibility that study-specific characteristics had an influence on the pooled effects. Although we detected some evidence of publication bias, the adjusted pooled effect for cannabis use was only slightly attenuated and still statistically significant.

In comparison with the most recent systematic review and meta-analysis on the association between cannabis use and depression conducted by Moore *et al.* (2007), we excluded several studies based on the following criteria: over-representation of individuals with mental illness (Beard *et al.* 2006), exposure variable clustering together cannabis and other substances (Kandel & Davies, 1986), outcome measures of mixed anxiety–depression (McGee *et al.* 2000; Patton *et al.* 2002), presentation of results in a manner which did not allow calculation of OR (Block & Gjerde, 1991; Brook *et al.* 1998; Windle & Wiesner, 2004) and inclusion of other studies based on the same cohort (Fergusson *et al.* 1996, 2002). We added the following: (1) eight studies published during or after 2007; (2) a meta-analysis on the association between cannabis use and depression; (3) a meta-analysis on the association between 'heavy cannabis use' and depression using a single common criterion for 'heavy use' across individual studies; and (4) additional meta-analyses based on quality of studies and clinical diagnosis of depression as the outcome variables.

Results from individual studies on the association between cannabis use and depression varied between showing no significant association to showing significantly increased risks for developing depression following cannabis use. Many of the studies have been criticized for having small sample sizes, making interpretation of null results difficult. Nevertheless, the large variability in definitions of cannabis use and of depression, as well as in the number and type of control variables included in the individual studies should be acknowledged.

One of the most important considerations when examining the potential effect of cannabis on developing depression is ruling out differences in level of depression at baseline. This is based on reports showing an increased risk of subsequent depression following major depressive episodes and following brief subsyndromal depression (Patten *et al.* 2012). We therefore included only studies controlling for baseline depression, or otherwise excluded individuals with baseline depression. Despite this, additional confounding factors not accounted for in the vast majority of the studies, which may contribute to the reported

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association, should be noted. There was large variability in the number and type of confounding factors accounted for in the different studies, ranging from no additional factors (Paton *et al.* 1977) to more than 20 factors, including demographics, socio-economic variables, parental substance use and additional substance use and mental health (e.g. Pedersen, 2008). One half of the studies accounted for additional (non-cannabis) substance use (Ferguson & Horwood, 1997; van Laar *et al.* 2007; Harder *et al.* 2006, 2008; Pedersen, 2008; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013) though alcohol and drug use are common among cannabis users and are associated with increased rates of depression independently (Rehm *et al.* 2004; Jané-Llopis & Matytsina, 2006) and in cannabis users (Degenhardt *et al.* 2001). Regarding the impact of adjustment for control variables on the reported results: in seven of the studies included, results did not change after adjusting for control variables (Bovasso, 2001; Georgiades & Boyle, 2007; Harder *et al.* 2008; Brook *et al.* 2011; Marmorstein & Iacono, 2011; Degenhardt *et al.* 2013), four of the studies showed a substantial reduction in effect following adjustment (Fergusson & Horwood, 1997; Harder *et al.* 2006; Pedersen, 2008; Manrique-Garcia *et al.* 2012), one study showed a reduced, yet still significant, association between cannabis use and developing depression (van Laar *et al.* 2007), and two studies did not specifically report on differences between adjusted and unadjusted analysis (Paton *et al.* 1977; Brook *et al.* 2001). Given these findings, it would seem that confounding is not the sole factor for the observed heterogeneity.

The heterogeneity between individual studies in measurement of depression should also be noted. This relates both to differences between studies using clinical diagnosis of depression (Fergusson & Horwood, 1997; Brook *et al.* 2002; Georgiades & Boyle, 2007; van Laar *et al.* 2007; Harder *et al.* 2008; Marmorstein & Iacono, 2011; Manrique-Garcia *et al.* 2012; Degenhardt *et al.* 2013) and to those using depressive symptoms (Paton *et al.* 1977; Bovasso, 2001; Brook *et al.* 2001, 2011; Harder *et al.* 2006; Pedersen, 2008) as the outcome variable, as well as different scales and cut-off points to define 'depressive symptoms'. Paton *et al.* (1977) used the six-item checklist developed by Manheimer *et al.* (1972), with the index cutting point for depressive symptoms as the median of the distribution of index scores. Brook *et al.* (2001) used the Johns Hopkins Symptoms Checklist (Derogatis *et al.* 1974) and defined 'depressive symptoms' as the upper quartile of the results. Bovasso (2001) used the Diagnostic Interview Schedule (Robins *et al.* 1981) and defined 'depressive symptoms' as the occurrence of any of the nine symptoms in the follow-up period. Pedersen (2008) use the six-item checklist from the Johns Hopkins Symptoms Checklist (Kandel & Davies, 1982) (range 0–18) and used a dichotomized measure, with a cut-off between 8 and 9, to define 'depressive symptoms'. Brook *et al.* (2011) used the eight-item Symptoms Checklist 90-R (Derogatis, 1994) and used a dichotomized measure, with a cut-off at the 84th percentile, to define depressive symptoms. There is no single criterion for cut-off points across different scales of depressive symptoms representing increased risk for a diagnosis of major depression or dysthymia. Given the described variability in methods (e.g. tools, cut-off points) used to assess depressive symptoms, interpretation of results is complicated.

Nevertheless, sensitivity analyses partially addressing these methodological issues did not substantially alter our findings on the increased risk for developing depression among cannabis users. There are two broad classes of explanation for the association between cannabis use and developing depression. The first is a possible neurobiological link between cannabinoid effects and symptoms of depression (Degenhardt *et al.* 2003). The primary psychoactive ingredient of cannabis, Δ^9-tetrahydrocannabinol, acts upon the cannabinoid system in the brain, which appears to be related to regulation of emotional experience (and therefore of depression). There is little research evidence to support this possible direct effect of cannabis. Recent research, for example, has suggested that action at cannabinoid receptors is linked to a reduction in depressive behaviours (Degenhardt *et al.* 2000). Furthermore, there is repeated evidence linking rimonabant, a cannabinoid CB1 receptor antagonist, and depression. Increased rates of depression have been observed in clinical trials using rimonabant, a finding that has led to the suspension of rimonabant by both the European Medicines Agency and the United States Food and Drug Administration (Hill & Gorzalka, 2009). These findings, together with human studies showing depressive symptoms following acute administration of rimonabant (Horder *et al.* 2010), imply that cannabinoids may actually have an antidepressant action (Le Foll *et al.* 2009). A second possibility is that cannabis use causes life events or circumstances that increase the likelihood of depression (Degenhardt *et al.* 2003; Marmorstein & Iacono, 2011), meaning that the perceived association between cannabis use and increased risk for depression is socially mediated (Degenhardt *et al.* 2003). Cannabis use is associated with reduced educational attainment (Kendler *et al.* 1993), unemployment and crime (Kendler *et al.* 1993; Fergusson & Horwood, 1997), all factors that may increase risks of depression (Marmorstein & Iacono, 2011). Longitudinal

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epidemiological research is warranted to further establish the mediators that link cannabis use to depression.

Meta-regressions revealed no significant effect of age of cannabis use on the risk of developing depression. Though it seems intuitively compelling to assume that earlier age of cannabis use carries an increased risk for depression, there is no evidence in this meta-analysis to support this. Furthermore, our findings are in line with previous multiple-wave studies (such as the Christchurch Health and Development Study) reporting no significant effect of age of cannabis use on the risk of developing depression (Fergusson & Horwood, 1997; Fergusson *et al.* 1996, 2002). It is possible, though, that when combined with increased cumulative exposure to cannabis, younger age of use would affect the risk for developing depression. Definitions of cannabis use in the studies included referred to specific time-frames, ranging from any previous lifetime use (Fergusson *et al.* 1996) to any use in the previous 30 days (Paton *et al.* 1977). None of the studies included provided data regarding cumulative exposure to cannabis, both in the period of exposure measurement as well as in the follow-up period. It is possible that the cumulative exposure to cannabis during the follow-up period, and not the duration itself, has an effect on the association between cannabis use and the development of depression. Longitudinal studies that include data on cumulative exposure to cannabis are essential in elucidating the complex relationship between age of use, dose and frequency of use, and the risk for developing depression.

Our findings are in line with an integrative data analysis recently published by Horwood *et al.* (2012) based on four Australian cohorts. Though two of the studies there had been excluded from our meta-analysis based on our inclusion criteria [not reported in a peer-reviewed journal (Prior *et al.* 2000) and not including cannabis exposure in the published data (Anstey *et al.* 2012)], results published there similarly show a dose–response relationship between cannabis use and depressive symptoms. Results showed a consistent and highly significant effect across all cohorts in frequency of cannabis use associated with higher mean depressive scores. Weekly users of cannabis had depressive scores that were higher than non-users, a finding that was reduced but remained significant after adjustment for confounding. This analysis used methods of integrative data analysis in which the assessment of cannabis use was consistent across studies, depressive symptoms were measured on common metrics and confounding was controlled using fixed effects regression.

In addition to the considerations discussed above regarding measurement of cannabis use, variability in controlling for confounding factors and measurement of depression, this study has several limitations. First, the overall number of included articles is relatively small. This is due mainly to our strict inclusion criteria, particularly including only population-based longitudinal studies controlling for baseline depression. The small number of included studies may have limited our findings, particularly regarding the effect of heavy cannabis use on developing depression. Second, although we restricted studies to those controlling for depression at baseline, controlling for other potentially important confounders was not designated in the inclusion criteria. For example, though gender is known to affect both prevalence of depression (Weissman *et al.* 1996) as well as prevalence of cannabis use and CUDs (Compton *et al.* 2004), we did not restrict studies to those controlling for gender. Though these additional confounders might have affected the results of the individual studies and hence the estimates of the pooled ORs, further restricting inclusion would have substantially reduced the number of included articles and not allowed a proper meta-analysis of results. Fixed-effects modelling has been used in longitudinal studies to control for non-observed sources of confounding (Rehm *et al.* 1992). This makes it possible to control for stable characteristics of the individual, even when these cannot be measured. Fixed-effects regression models require detailed estimates from all individual studies which were not fully available. Moreover, time-varying covariates still may bias the results. Third, our definition of 'heavy cannabis use' was based both on frequency (Harder *et al.* 2006; van Laar *et al.* 2007; Brook *et al.* 2011; Degenhardt *et al.* 2013) and symptoms (i.e. DSM-IV criteria for CUD) (Bovasso, 2001; Harder *et al.* 2008; Marmorstein & Iacono, 2011), and though CUD commonly reflects regular and frequent cannabis use (Grant & Pickering, 1998), these measures are not synonymous and differences may have an effect on the estimated risk for developing depression.

As is the case in all meta-analyses, our meta-analysis was subject to limitations as they were inherent in the primary studies. The assessment tools used in the individual studies did not clearly differentiate primary mental disorders and substance-induced disorders. This may be particularly important when exploring the association between cannabis use and depression, as it is otherwise difficult to conclude whether the measured depression is higher even when cannabis-induced mental disorders are ruled out (Grant *et al.* 2004). Finally, in addition to the substantial differences in the definition of cannabis use in individual studies, it is possible that the type of cannabis used may affect the risk for developing depression. Large variation in biologically available cannabinoid concentrations, resulting from different sources of cannabis and from

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different intake practices (Moore *et al.* 2007), may have different effects in terms of psychiatric outcomes.

Conclusions

Despite the methodological considerations mentioned, this meta-analysis is important and timely. It seems likely that many of the limitations mentioned will be part of any study exploring the association between cannabis use and the development of depression, and our report represents the current state of knowledge on this association. As rates of cannabis use continue to be high (European Monitoring Centre for Drugs and Drug Addiction, 2011; United Nations Office on Drugs and Crime, 2011), pressing questions regarding education of the public as to potential risks associated with cannabis use, and particularly with heavy cannabis use, arise. Furthermore, though recognizing the potential risks associated with heavy cannabis use is particularly important in adolescents, the group with the highest rates of cannabis use (Degenhardt *et al.* 2003), it is also important to note that the majority of cannabis is used by adults. Given the modest pooled results and numerous methodological considerations, results pertaining to increased risk for depression among cannabis users should be regarded with caution. Rather, the focus should be on the possibly increased risk for developing depression among frequent cannabis users and individuals with CUDs, and potential factors mediating this increased risk. There is need for further longitudinal exploration of the association between cannabis use and developing depression, particularly taking into account cumulative exposure to cannabis and significant confounding factors.

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Declaration of Interest

None.

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