**Marijuana use and the risk of depression: a systematic review and meta-analysis**

A thesis submitted to the University of Arizona College of Medicine—Phoenix
in partial fulfillment of the requirements for the degree of Doctor of Medicine

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**Abstract**

Objective: To conduct a systematic review of the evidence pertinent to the relationship between marijuana use and depression and perform a meta-analysis on the data in order to inform evidenced-based practice. The question of interest is: Is marijuana use associated with increased risk of developing depression?

Methods: The databases MEDLINE (PubMed), The Cochrane Library, CINAHL (EBSCO), psycINFO, and Google Scholar were searched for the topics of marijuana use and depression through October of 2013. Studies were included if they were systematic reviews, randomized controlled trials, prospective or retrospective cohort studies, or case-control studies. No randomized controlled trials were discovered. Quality of cohort and case-control studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale[1]. Overall quality of evidence was determined using the GRADE methodology[2,3]. The Bradford-Hill criteria[4] were used to assess for causation. Studies were assessed by two reviewers. 173 articles were screened for eligibility. Of these fourteen articles were considered to fit the inclusion criteria. Nine homogeneous studies were included in the meta-analysis.

Results: The quality of the evidence reviewed is low to very low. It does not meet Bradford-Hill criteria for causation. There is a slight positive correlation between marijuana use and onset of depression. However, those studies included in the meta-analysis demonstrated a low overall pooled odds ratio (OR = 1.17; 95% CI = 1.06—1.29).

Conclusion: The evidence suggests a slight positive correlation between marijuana use and depression but is not sufficient to draw a conclusion. This evidence is generally of very low quality. It does not demonstrate a dose response, and is without a significant magnitude of effect.

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**Introduction**

Marijuana use for medicinal purposes is currently legal in twenty-three states as well as the District of Columbia and is legal for recreational purposes in the states of Colorado, Washington, and Oregon.[5] It is also the most commonly used illegal drug in the United States.[6] Despite increasing cultural acceptance, its medical value and toxicities are still under investigation. Consequentially, it is evident that more knowledge about the drug is necessary to make a policy and individual decision regarding its use.

The purpose of this analysis is to systematically review the evidence available with respect to depression and marijuana and to understand if using marijuana leads to an increased risk of developing depression. The literature will be evaluated from a perspective of both quality and statistical significance. The quality of observational studies will be evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS)[1,7] while systematic reviews will be evaluated using the Assessment of multiple systematic reviews (AMSTAR) measurement system[8]. The totality of the literature will be analyzed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. This method allows a systematic approach to literature that ranks studies on a four-point scale from high to very low. In order to assess the association between marijuana and depression for causality the Bradford Hill criteria for causation will be utilized.[4] In order to describe quantitatively any association elicited a forest plot will be drawn provided there are homogenous sources. The hypothesis is that although there may not be conclusive evidence to support a causal relationship between marijuana and depression, a strong correlation will likely exist.

## Materials and Methods

**Literature Search and Strategy**: Inclusion criteria for studies to be reviewed included randomized controlled trials, prospective cohort studies, case-control studies, that addressed the key question, and were written in English. The studies had to specifically address the symptom of depression or major depressive disorder.

Studies were excluded if they were case series or cross-sectional, animal studies, or did not address the key question. Studies were also excluded if they only addressed other psychological disorders including bipolar, schizoaffective, anxiety, suicidal ideation, and psychosis. (Figures 1 and 2)

The following databases were searched until October, 2013: Medline (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), psycINFO, and the Cochrane Library. The search string for Medline follows: (("Depression/etiology"[Mesh])) AND ((("Depression"[Mesh] OR "Depressive Disorder"[Mesh])) AND (("Cannabis"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Marijuana Smoking"[Mesh]) OR "Tetrahydrocannabinol"[Mesh])). The other databases were searched using the keywords marijuana OR cannabis AND depression.
The references lists of each study found were also reviewed for additional pertinent studies. Detailed search strategies can be reviewed in Appendix I.

**Data Synthesis and Analysis**:

There were no randomized controlled trials found in the literature search. All studies included were either systematic reviews or cohort studies.

Studies that were homogenous with respect to their methods and outcome measurements were pooled together for a meta-analysis. A meta-analysis using random effects modeling was conducted to estimate an overall, pooled odds ratio from individual odds ratio extrapolated from its respective paper. To estimate percent heterogeneity across the studies, the Higgin's $I^2$

followed by a chi-squared test were conducted to assess heterogeneity[9]. Low heterogeneity would result in 0% while higher percentages would indicate increased heterogeneity. A funnel plot and the small-study effect test proposed by Egger et al were used to assess publication bias and small-study effect bias[10]. A p-value of <0.05 would indicated that there is small-study effect bias. Asymmetry of the funnel plot would indicate publication bias. Analyses were conducted using Stata, Data Analysis and Statistical Software (Version 14, 2014, Statacorp, College Station, TX).

Heterogeneous studies were subject to qualitative analysis alone. If studies were observational they were reviewed using the Newcastle-Ottawa Scale[1,7]. Studies that were systematic reviews were evaluated using the AMSTAR Criteria[8].

Studies were rated as good, fair or poor based on scores achieved in using the quality assessment tools noted above. The Newcastle-Ottawa Scale allows the reviewer to assign scores based on (1) how well the study groups were selected, (2) how similar they are to each other, and (3) how exposure or outcomes were ascertained and monitored.

**Figure 1**

Methods Flow Chart

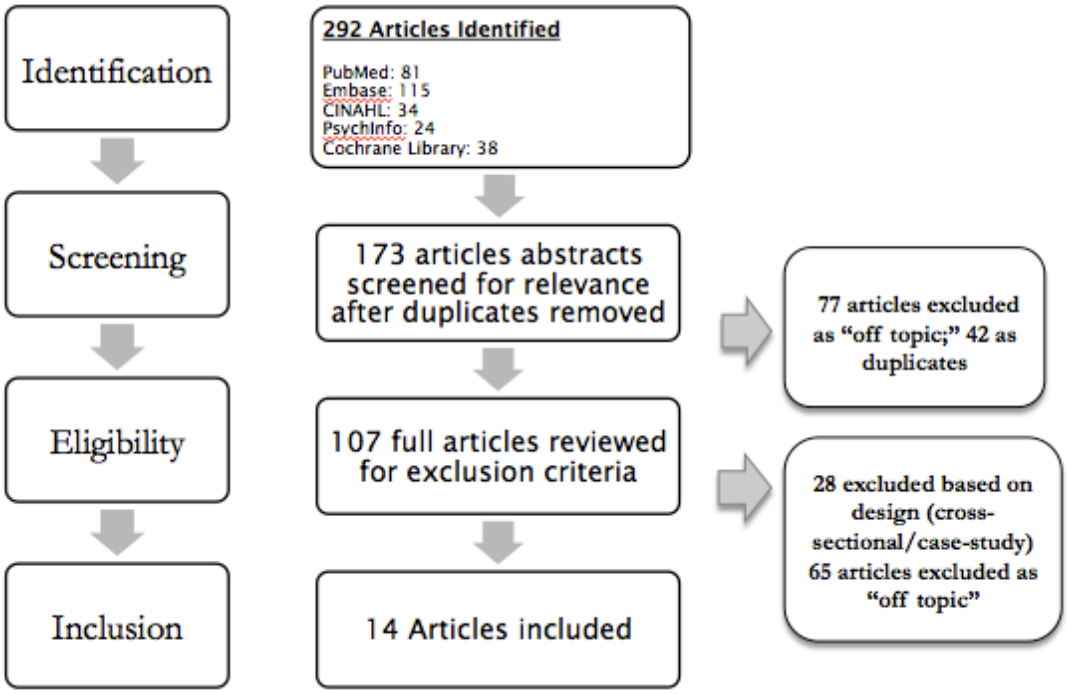
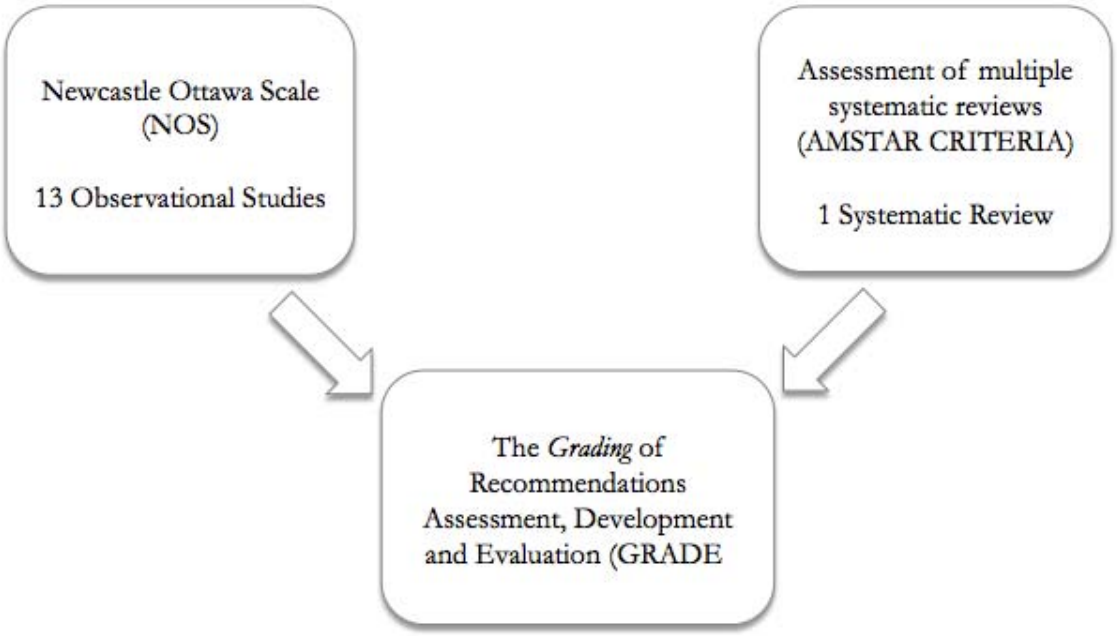


**Figure 2**

Methods Flow Chart 2



**Results**

Electronic database searches, followed by reviewing reference lists of the database search results yielded 292 primary articles. The Medline search resulted in 81 articles. The Embase search resulted in 115 articles. The CINAHL search resulted in 34 articles. The Psychinfo search resulted in 24 articles. The Cochrane Library search resulted in 38 articles.

After the articles were screened for obvious irrelevance and duplicates were removed, there were 107 articles that were fully reviewed using inclusion and exclusion criteria. From this list 28 studies were excluded due to cross-sectional or case-study design. 65 were excluded because they were off topic. Ultimately, 14 articles were consistent with the inclusion criteria.

These 14 articles included 13 observational studies (12 cohort and 1 case-control) and 1 systematic review. There were no randomized controlled trials. The entire list of included studies is reviewable in Appendix I. The entire list of excluded studies is reviewable in Appendix II.

**Table 1**

Included Observational Studies

| | Methods | Results |
|---|---|---|
| *Bovasso et al., 2001*[1] | Longitudinal prospective cohort<br><br>Participants: n = 1920<br>Exposure to marijuana: n = 15 without concurrent depressive symptoms at baseline. The low n is consistent with the population sampled which was disproportionately elderly. | OR= 4.49, 95% confidence interval [CI]= 1.51–13.26 (*this is not adjusted for baseline depression)*<br>p < 0.01<br><br>OR = 4.00, 95% confidence interval [CI]= 1.23–12.97 (*this number is adjusted for baseline depression)*<br>p < 0.05<br><br>Of the 267 participants who experienced depressive symptoms during the follow-up period, 3.7% (N=10) had been diagnosed with cannabis abuse at baseline, whereas only 0.9% (N=5) of the 582 participants who did not report depressive symptoms had a baseline cannabis abuse diagnosis. |
| *Brook et al., 1998*[2] | Longitudinal prospective cohort – Follow up at four time periods from adolescence to young adulthood<br><br>Participants: n = 776 | Outcome: Depressive symptoms or disorder<br><br>OR = 1.13; 95% CI (0.95-1.34) |

| | | |
|---|---|---|
| | Exposure: 328 at T0<br>529 at T4 | p > 0.05 |
| *Brook et al., 2002*[3] | Longitudinal prospective cohort<br><br>Participants: n = 736<br>Exposure: n = 219 at T2<br>n = 400 at T4 | Outcome: Depression<br>Control for demographic factors:<br>OR = 1.19; 95% CI = 1.049-1.349<br>p < 0.01<br>Control for demographics and MDD*<br>OR = 1.175; 95% CI = 1.037-1.333<br>p < 0.05<br>These were controlled for MDD during childhood and represent the OR for MDD for those with marijuana use at any point in the past.<br><br>Marijuana use prior to T2:<br>OR 1.565; 95% CI = 1.102-2.222<br>p < 0.05<br><br>Marijuana use prior to T2-T3:<br>OR = 1.438; 95% CI = 1.081-1.912<br>p < 0.05<br>Marijuana use prior to T3-T4:<br>OR = 1.175; 95% CI = 0.887-1.555<br>p not reported<br><br>These were all controlled for prior episodes of MDD during childhood |

| | | |
|---|---|---|
| *Degenhardt et al., 2013*[4] | Longitudinal Prospective Cohort Study | Outcome: Major Depressive Episode |
| | Participants: 1943 Australian secondary school students followed into their late 20's | Daily adolescent marijuana use which ceased in adulthood was not associated with adult depression |
| | Exposure:<br>None/<weekly at t0 → daily at t9<br>n = 85;<br>Weekly + at t0 → daily at t9<br>n = 35 | Marijuana dependence was not associated with depression<br>OR 2.0, 95% CI = 0.63–6.3 (for those with a baseline exposure or none/weekly)<br>OR 1.6, 95% CI = 0.47–5.2 (for those with a baseline exposure of daily use)<br>Odds ratios adjusted for other concurrent substance use and clinically significant depression/anxiety in adolescence |
| *Fergusson et al., 2002*[5] | Longitudinal Prospective Cohort<br>Participants: 1063<br>Exposure:<br>Age 14-15: n = 84<br>Age 17-18: n = 427<br>Age 20-21: n = 473<br>Control:<br>n = 881, 598, 538 respectively | Outcome: Depression<br>Age 14-15: 13<br>Age 17-18: 103<br>Age 20-21: 105<br>Control<br>n = 47, 84, 79 respectively<br>OR (95% CI)<br>Less than monthly:<br>1.2 (1.0-1.9)<br>At least monthly:<br>1.4 (1.0-2.7)<br>At least weekly:<br>1.7, no CI provided<br>p values are not provided |
| *Harder et al., 2006*[6] | Longitudinal Prospective Cohort<br>Marijuana use/depression was assessed at T0 and then reassessed 4 | Outcome: Depression |

| | | |
|---|---|---|
| | years later<br><br>Participants: n = 1989<br><br>Exposure: 184 | n = 67<br><br>Unweighted OR 1.78, 95% CI (0.99,3.21)<br><br>p ≤ 0.05<br><br>Weighted OR 1.51, 95% CI (0.63, 3.54) |
| *Harder et al., 2008*[7] | Longitudinal prospective cohort<br><br>Participants: n = 1494<br><br>Exposure: n = 217 | Outcome: Depressive episode<br><br>OR Overall: 1.33, 95% CI (0.76 - 2.33)<br>OR Males: 1.7, 95% CI (0.8 - 3.6)<br>OR Females: 0.7, 95% CI (0.2 - 2.3)<br><br>p = 0.32, 0.54, 0.19 respectively |
| *Marique-Garcia et al., 2012*[8] | Nested Case-Control<br><br>Participants: n = 45087 men<br><br>39978 never used marijuana<br><br>Exposure: 5109 used marijuana to some degree<br><br>855 had used marijuana greater<br><br>than 50 times | Outcome: Depression<br><br>655 depression cases in the never used category<br><br>- HR Crude 1;<br>- HR Adjusted 1<br><br>111 depression cases in the used category<br><br>- HR Crude 1.3, 95% CI (1.1 - 1.6)<br>- HR Adjusted 1.0, 95% CI (0.7 - 1.2)<br>24 depression cases were from those who used greater than 50 times<br><br>- HR Crude 1.8, 95% CI (1.2 - 2.7)<br>- HR Adjusted 0.9, 95% CI (0.5 - 1.6)<br><br>p values not reported |
| *Paton et al., 1977*[9] | Longitudinal prospective cohort<br><br>Participants: n = 8206 high-school students<br><br>Exposure: n = 686 | Outcome: Depressed mood<br><br>44% of non-marijuana users reported symptoms of depressed mood. 47% of marijuana users reported symptoms of depression. The authors conclude this is not a significant difference |
| *Pederson et al.,*<br><br>*2008*[10] | Longitudinal prospective cohort<br><br>Participants: n = 2033 (2902 started the study - 2033 were able to be | Outcome: Depression<br><br>4 models controlling for increasing numbers of<br><br>covariates |

| | | |
|---|---|---|
| | followed for 4 follow-ups)<br>Exposure:<br>Never used by age 16<br>n = 1885<br>Used at age 16<br>n = 94<br>73 used 1-10 times in past 12 months<br>21 used 11+ times in past 12 months<br>Never used by age 21<br>n = 1680<br>Used by age 21<br>n = 299<br>213 used 1-10 times in past 12 months<br>86 used 11+ times in past 12 months | 230 cases of depression at age 21<br>p values not provided<br>OR (95% CI)<br>**Model 1**<br>Never 1<br>1-10 times 1.9 (1.2-2.9)<br>11+ times 2.0 (1.1-3.8)<br>**Model 2**<br>Never 1<br>1-10 times 1.6 (1.0-2.4)<br>11+ times 1.6 (0.8-3.0)<br>**Model 3**<br>Never 1<br>1-10 times 1.4 (0.8-2.5)<br>11+ times 0.9 (0.4-2.8)<br>**Model 4**<br>Never 1<br>1-10 times 1.4 (0.8-2.1)<br>11+ times 0.9 (0.4-2.5) |
| *Repetto et al. 2008*[11] | Longitudinal Prospective Cohort<br>Participants: Highshool aged African American adolescents. n = 681 at T1 | Outcome: Depressive symptoms<br>Marijuana use at Time 1 (Highschool) was correlated with depressive symptoms from Times 3 through 6 (young adulthood), 0.206<br>$p < 0.05$ |
| *van Laar et al., 2007*[12] | Longitudinal Prospective Cohort<br>Total Participants: n = 7076.<br>Those without baseline major depression: n = 4044<br>Exposure:<br>Never exposed: n = 3662 | Outcome: Major depression<br>The authors used 4 models controlling for increasing numbers of covariates. They then analyzed the OR comparing increasing frequency of marijuana consumption – these are all adjusted using the Model 4's covariates. No *P* values are given for this second set of data |

| | | |
|---|---|---|
| | Use: n = 382 | |
| | | OR (95% CI) |
| | | No use 1<br>Model 1 2.62 (1.8-3.81)[a]<br>Model 2 1.72 (1.15-2.57)[b]<br>Model 3 1.68 (1.11-2.55)[c]<br>Model 4[i] 1.62 (1.06-2.48)[c]<br>No use 1<br>1-3 days/month 1.49 (0.82-2.71)<br>1-4days/week 1.79 (0.94-3.40)<br>Almost daily[i] 1.60 (0.75-3.42)<br><br>[a]$P < 0.001$; [b]$P < 0.01$; [c]$P < 0.05$<br><br>[i]Adjusted 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 |
| *Windle et al., 2004*[13] | Longitudinal Prospective Cohort<br><br>Participants: Adolescent school children, n = 1205<br><br>Exposure to marijuana surveyed intermittently in 5 waves over an 8 year period | Outcomes: Major depressive disorder<br><br>**One way ANOVA data:**<br><br>*Abstainers*: 10.83<br>*Experimental Users*: 11.35 *Those that decreased use over time*: 10.84 *Those that increased use over time*: 14.01 *Chronic Users*: 10.64 *F-statistic*: 0.72<br><br>Windle et al.'s interpretation: Marijuana use was not associated with major depressive disorders |

**Table 2**

Newcastle Ottawa Scale[14]: Quality assessment of observational studies

| Author, Year | Representativeness of exposed cohort | Selection of non-exposed cohort | Method to ascertain exposure | Showed that outcome absent before study started? | Control for confounders? Comparability of cohorts | Outcome assessment | Appropriate duration follow-up | Adequate number of follow-ups | Total Score | Quality Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| *Bovasso et al., 2001*[1] | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | **7** | Good |
| *Brook et al., 1998*[2] | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | **5** | Fair |
| *Brook et al., 2002*[3] | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | **5** | Fair |
| *Degenhardt et al., 2013*[4] | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 1 | **7** | Good |
| *Fergusson et al., 2002*[5] | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | **8** | Good |
| *Harder et al., 2006*[6] | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 0 | **6** | Poor |
| *Harder et al., 2008*[7] | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 1 | **7** | Good |
| *Marique-Garcia et al., 2012* | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | **7** | Good |
| *Paton et al., 1977*[9] | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | **4** | Poor |
| *Pederson et al., 2008*[10] | 1 | 1 | 0 | 0 | 2 | 0 | 1 | 1 | **6** | Fair |
| *Repetto et al., 2008* | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 0 | **6** | Fair |
| *van Laar et al., 2007*[12] | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | **8** | Good |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Windle et al., 2004*[13] | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | **5** | Fair |

Scoring algorithm*

| **Quality rating** | **# Points in Selection Domain** | **# Points in Comparability Domain** | **# Points in Outcome Domain** |
|---|---|---|---|
| Good | ≥3 | ≥2 | ≥2 |
| Fair | 2 | ≥1 | ≥2 |
| Poor | 0-1 | 0 | 0-1 |

**Included Systematic Reviews**

One systematic review was found via our search strategy. According to criteria *Moore et al., 2007*[6] produced a high quality study (Complete AMSTAR assessment data is located in Table 3). They conclude that there is concerning but weak evidence to support a claim that marijuana use is associated with an increased risk of depression. They report that the evidence was not clear enough to support a recommendation to inform individuals of an increased risk of depression associated with marijuana consumption.

**Overall Evidence Quality**

There is very low quality evidence that marijuana use is associated with depression. GRADE criteria rank studies based on 5 points: risk of bias, publication bias, imprecision, inconsistency, and indirectness[24]. Quality was not downgraded due to any of these criteria as discussed below.

By default observational studies are qualified as low quality evidence and can be upgraded in quality based on evidence of a 2 fold or greater magnitude of effect, evidence of a dose related response, and when unaccounted for confounders might reasonable raise the estimated effects[25]. There was a high overall risk of bias throughout the evidence that downgraded the overall quality of the evidence to very-low quality. Of the studies evaluated in this review none were upgraded to a higher level due to these criteria[25].

**Risk of Bias**

The quality of evidence was downgraded based on risk of bias[26]. 6 out of the 13 observational studies had a high risk of bias in at least one category (Table 2). Bovasso et al.[11], was considered to have a high risk of bias with respect to incomplete follow-up. In this study, the number of participants exposed to marijuana was quite low (n = 15). On follow-up, 298 participants refused to participate and 415 participants were not found. These numbers represent a large group of people who could have been exposed to marijuana. Repetto et al. and Harder et al. had a high risk of bias in the follow-up category as well. This group lost 25.3%

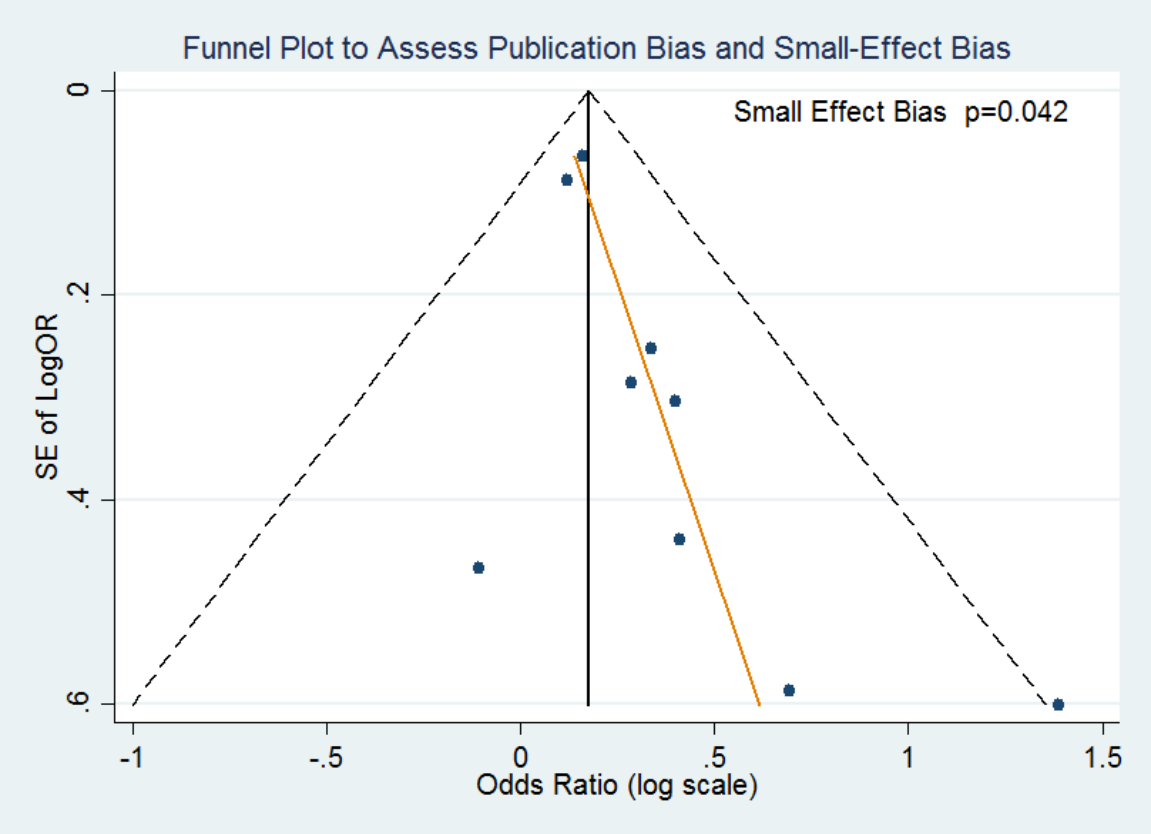
of its participants. Those that were lost were more likely to have low GPAs, which is a potentially significant confounder. Van Laar et al.[22] did not provide characteristics of those participants lost to follow-up. Windle et al.[23] did not adjust for confounders including but not limited to baseline depression and concurrent elicit drug use. Paton et al's study[19] fulfilled criteria for high risk of bias in two categories: adjusting for covariants and loss to follow-up. Paton et al. did not adjust for covariants and had a 52% loss to follow-up without a description of those lost and was therefore characterized as high risk for bias in both categories.

The seven other studies were all considered to be of low bias risk[12-16,18,20]. However, all studies, except for van Laar et al did not include information in the section for prognostic imbalance. This category includes adjusting for other potential covariants not included in the first section. In van Laar's study for example, family history of depression was controlled for. It is unclear whether adjusting for this variable would affect the measured outcomes.

**Publication Bias**[27]

There was evidence for publication bias due to a small study-effect. The p-value for bias is statistically significant (p = 0.042), which is consistent with the biasing effects of small studies. A visual evaluation of the funnel plot (Figure 2) shows a majority (6 out of 9) of the studies lie to the right side of the funnel's midline. There was no industry support noted in the literature and the overall number. The evidence led to down grading based on publication bias[27].

**Figure 3**


Funnel Plot to Assess Publication Bias and Small-Effect Bias
Small Effect Bias p=0.042
SE of LogOR
0
.2
.4
.6
-1
-.5
0
.5
1
1.5
Odds Ratio (log scale)

**Imprecision**[28]

According to GRADE criteria, data is imprecise based on the characteristics of the 95% confidence intervals (CI). If an evaluation of the high end compared to the low end of the CI would result in a different clinically management strategy, that data is said to be imprecise. If there is imprecision in the literature the quality of evidence should be rated down. Of the studies pooled in the meta-analysis, the overall confidence interval (CI = 1.17 [1.06-1.29]) would not cause a change in practice at the extremes of range. Therefore, when considered in totality the evidence was not graded down for imprecision. (Figure 4)

**Inconsistency**

The included studies were not down-graded based on inconsistency. Inconsistency describes a wide variability among the studies in the magnitude of effect of the exposed drug or meaningful heterogeneity among studies demonstrated by the $I^2$ statistic. According to the grade criteria, the body of evidence should be down-graded if there is 1) inconsistency demonstrated by wide variation in point estimates, 2) minimal to no overlap in confidence intervals, 3) an $I^2$ p-value which is low, or 4) a large $I^2$, defined as greater than 50%[24].

The pooled studies did not have a wide variability. There is substantial overlap in confidence intervals. The $I^2$ p=value was 0.95 and the $I^2$ magnitude was 0.0%.

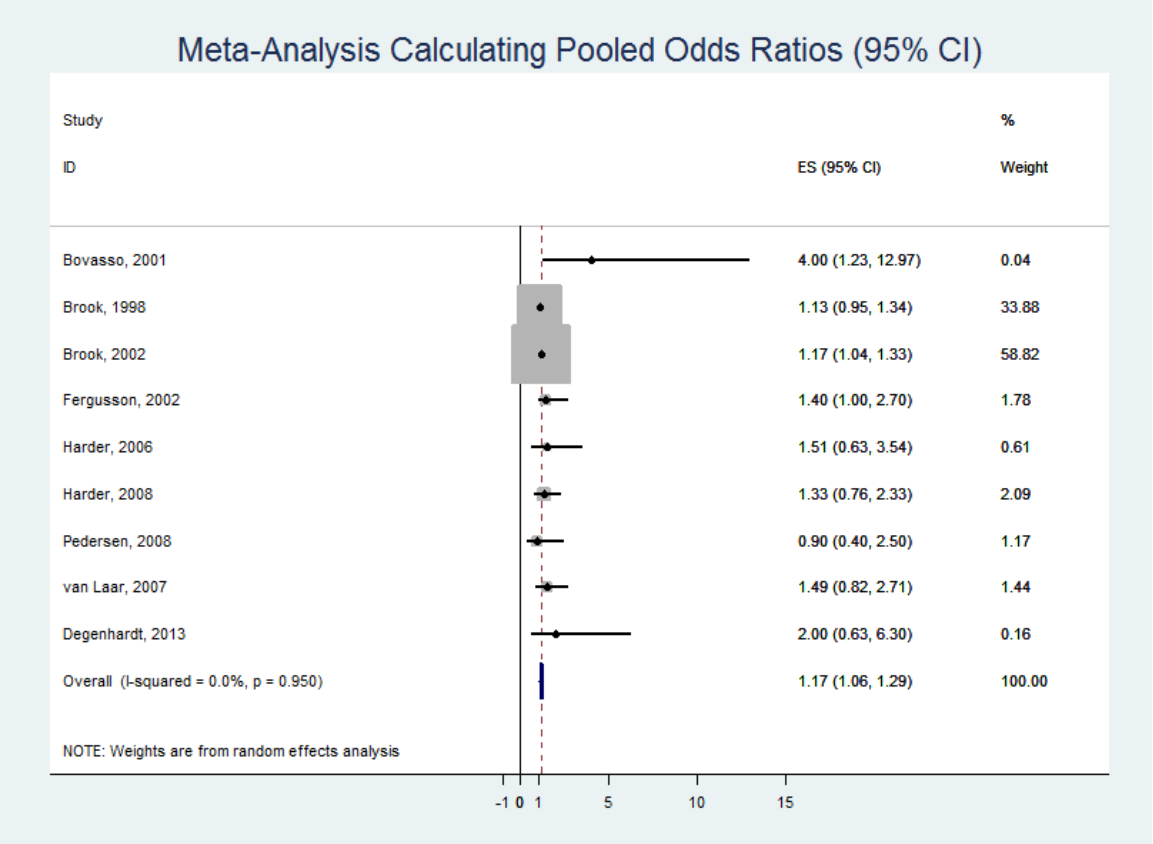
**Indirectness**

The body of evidence was not graded downward based on indirectness. Direct evidence is evidence that addresses the exposed drug's effect on the intended population and measures an outcome that is relevant to that population[29]. The totality of the evidence reviewed addressed each of these issues.

**Meta-Analysis Results**

Where possible evidence was pooled for meta-analysis. Of the included studies, 9 studies used odds ratios (OR) to evaluate risk of depression associated with marijuana. The $I^2$ value for these studies was 0.0% indicating homogeneity. The other studies were heterogeneous with respect to their statistical analysis and were not included in the meta-analysis (Figure 4) The overall data demonstrated a pooled odds ratio of 1.17 (95% CI 1.06-1.29). This OR was not of a magnitude that was significant enough to increase the ranking of the quality of evidence.

**Figure 4**


Meta-Analysis Calculating Pooled Odds Ratios (95% CI)
Study
ID
ES (95% CI)
%
Weight
Bovasso, 2001
4.00 (1.23, 12.97)
0.04
Brook, 1998
1.13 (0.95, 1.34)
33.88
Brook, 2002
1.17 (1.04, 1.33)
58.82
Fergusson, 2002
1.40 (1.00, 2.70)
1.78
Harder, 2006
1.51 (0.63, 3.54)
0.61
Harder, 2008
1.33 (0.76, 2.33)
2.09
Pedersen, 2008
0.90 (0.40, 2.50)
1.17
van Laar, 2007
1.49 (0.82, 2.71)
1.44
Degenhardt, 2013
2.00 (0.63, 6.30)
0.16
Overall (I-squared = 0.0%, p = 0.950)
1.17 (1.06, 1.29)
100.00
NOTE: Weights are from random effects analysis
-1 0 1 5 10 15

**Bradford-Hill Criteria**

The Bradford-Hill Criteria are an established method of determining a causal relationship[4]. In his seminal work determining association versus causation, Sir Austin Bradford-Hill described nine criteria to determine causality: 1) Strength of association – what is the observed magnitude of effect, 2) consistency – has the association been seen many times, in different people, and different places, 3) specificity – does the association seem to affect certain groups and lead to unique outcomes, 4) temporality – is the relationship unidirectional, 5) biological gradient – is there a dose response, 6) plausibility – is there a physiological rationale to describe the relationship, 7) coherence – the association should not conflict with what is already known, 8) experiment – is there experimental evidence to support an causal relationship, 9) analogy – it may be meaningful to use similar situations to support a case for causality.

Hill argues that none of these criteria can bring "hard-and-fast rules of evidence[4]" but they do provide guidelines to help make a rational decision about causality. Given the evidence presented above, there is not a strong case for a causal relationship between marijuana and depression. The association does not meet Bradford-Hill's criteria of strength of association, significant magnitude of effect, consistency, specificity, temporality, or experimentation. There have been proposed biological mechanisms[30] to support a causal relationship, the observed findings are not incoherent with what is known about depression, and there are analogous cases of a drug leading to a psychiatric symptom or disease.

**Discussion**

The hypothesis tested in this paper was that marijuana use is positively correlated with the development of depression. The current body of evidence does not provide reasonable evidence to either reject or accept the hypothesis that marijuana use causes depression. The evidence gathered for this review does show, a slight positive correlation between marijuana use and depression.

Nonetheless, given the overall-low quality of the studies as well as minimal magnitude of effect it is not reasonable to draw conclusions based on this evidence. Of the 13 included observational studies 6 were considered good quality studies by Newcastle Ottawa Criteria[11,14-16,22]. Of these 6, the Bovasso et al. study and the van Laar study both had a high risk of bias with respect to follow-up[11,22]. The Bovasso study had only 15 exposed individuals from their follow-up cohort, which represented an over-sampling of an older population. The van Laar study failed to document the characteristics of those whom they followed-up with and in accordingly had a high potential for bias.

These 6 good quality studies demonstrated a mixed set of conclusions regarding the hypothesis that marijuana use is associated with depression. Bovasso et al.[11] concluded there was an increased risk, OR 4.0, 95% CI: 1.23-12.97, again his follow-up sample was biased.

Fergusson et al.[15] also concluded that there was increased risk of depression associated with marijuana use OR 1.4, 95% CI 1.0-2.7 for those consuming at least monthly and OR 1.7 for weekly users, although they do not provide a confidence interval for this last data point. The Fergusson study does suggest a dose response, but does not have a magnitude of effect greater or equal to 2. Harder et al[17]. concludes that adolescent exposure to marijuana is not associated with depression, OR: 1.33, 95% CI: 0.76 - 2.33 and was a good study according to the Newcastle Ottawa scale. The van Laar et al.[22] study concluded that there was some correlation between marijuana and depression, but when the data was adjusted for frequency of use, they were not able to demonstrate a dose response and the overall correlation became insignificant OR 1.60 95% CI: 0.75-3.42. Table 1 and Appendix V provide more details.

Degenhardt et al[14] and Marique-Garcia et al.'s[18] study were perhaps the most compelling. Both were good studies by the Newcastle Ottawa scale. Degenhardt et al. concluded that marijuana dependence at age 29 and a baseline of marijuana abstinence was not association with depression at age 29, OR 2.0, 95% CI: 0.63–6.3. In this same study similar results were seen when observing patterns of depression in those with baseline weekly use who progressed to daily use and dependence, OR 1.6, 95% CI 0.47–5.2. This data suggests that those who consumed the highest levels of marijuana, when controlled for sex, non-metropolitan school location, low parental education, parental divorce/separation, concurrent alcohol or illicit drug use, baseline depression and anxiety, were not significantly different than their non-marijuana-using peers with respect to the development of depression. It is possible that if these individuals were followed for another period of time they would develop depression, but the results at hand suggest otherwise.

Manrique-Garcia et al.'s study was a large case-control study of 45,087 adult Swedish conscripts who were followed retrospectively over a 35-year period.. The authors found an increased risk of depression, HR 1.5, 95% CI: 1.0-2.2, associated with their highest category of marijuana use (greater than fifty times). However, this increased risk disappeared when they adjusted for prior personality disorders, IQ, risky alcohol use, socioeconomic status, tobacco use, other illicit drug use, childhood behavioral disturbances, and childhood rearing in an urban environment. This data was not included in the meta-analysis due to its heterogeneity. The authors found no association between frequency of marijuana use and depression.

The remaining 7 observational studies were either of fair to poor quality. These studies were also mixed with respect to their conclusions.

Moore et al.'s[30] systematic review was a high quality review according to AMSTAR criteria (See Appendix IV). Their conclusion was that based on the low quality and inconsistent available data, there was insufficient evidence to draw a relationship between marijuana use and depression.

**Conclusion**

The totality of evidence describing the relationship between marijuana and depression is not strong enough to claim that marijuana use is associated with depression. There is some evidence that suggests this relationship, but it is of low to very low quality. Moreover, if there is significant association between the two that has not been defined by the observational studies in the literature, there is no strong evidence to support a causal relationship. Any magnitude of effect between marijuana and depression is clinically insignificant. There does not appear to be a dose response. There is no evidence evaluated in this review to support a claim that the relationship exists across cultures.

There are, however, several limitations to this study. One of the major challenges is that the studies included do not include a uniform measure of depression, for example major depression. It is possible that marijuana use is associated with the symptom of depression but not major depression. This study did not address that question. Another challenge is that the study did not examine whether depression leads to marijuana use. There may be a strong association consistent with the notion that individuals may use marijuana in attempts to self-medicate. Studies were excluded if they were non-English studies. There may be a cultural component to depression that this study did not address.

Lastly, data from both high and low quality studies were pooled together. One concern is that the results might be different if just the data from high quality studies was used. This is unlikely as both groups of studies had similar results.

**Future Directions**

Randomized controlled trials are lacking in this topic. Unfortunately, due to the tenuous legal status of marijuana in the United States it may be difficult for some time to legally carry out these trials. It would be useful in that time frame to develop prospective observational trials that specifically measured major depressive disorder as defined by the Diagnostic and Statistical Manual V.[31] These studies must include groups that did not have any baseline major depressive disorder and ideally no baseline marijuana use. Incidence of major depression in the group that started using marijuana or had marijuana use at baseline would be compared over time to the incidence in non-users. In addition, it would be quite meaningful to include individuals in non-English speaking countries including those in the continents of Africa, Asia, and South America as a positive correlation between marijuana and depression in these settings would provide further support to the argument for causality and a negative correlation would support the opposite argument.

**Conflicts of Interest**

There are no conflicts of interest to report, including but not limited to financial.

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**Appendix I**

**Included Studies**

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## Appendix III

***Newcastle-Ottawa Scale (N-O-S)*** for observational studies (e.g., cohort studies and case control studies)

*The Newcastle-Ottawa Scale includes 3 categories, with a maximum of 9 points, based on:*

**Selection** ***(maximum of 4 points)***

1) Representativeness of the exposed cohort (one point)
2) Selection of the non exposed cohort (one point)
3) Ascertainment of exposure (one point)
4) Demonstration that outcome of interest was not present at start of study (one point)

**Comparability** ***(maximum of 2 points)***

1) Comparability of cohorts on the basis of the design or analysis
    a) Study controls for age (one point)
    b) Study controls for any additional factor (one point)

**Outcome** ***(maximum of 3 points)***

1) Assessment of outcome (one point)
2) Was follow-up long enough for outcomes to occur (one point)
3) Adequacy of follow up of cohorts (one point)

## APPENDIX IV

## A measurement tool to assess systematic reviews (AMSTAR)

| | |
|---|---|
| **1. Was *a priori* design provided?** The research question and inclusion criteria should be established before the conduct of the review. | □ Yes □ No ☑ Can't answer □ Not applicable |
| **2. Was there duplicate study selection and data extraction?** There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **3. Was a comprehensive literature search performed?** At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?** The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **5. Was a list of studies (included and excluded) provided?** A list of included and excluded studies should be provided. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **6. Were the characteristics of the included studies provided?** In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. | □ Yes ☑ No □ Can't answer □ Not applicable |
| **7. Was the scientific quality of the included studies assessed and documented?** A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **8. Was the scientific quality of the included studies used appropriately in formulating conclusions?** The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. | ☑ Yes □ No □ Can't answer □ Not applicable |
| **9. Were the methods used to combine the findings of studies appropriate?** For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi squared test for homogeneity, $I^2$). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?). | ☑ Yes □ No □ Can't answer □ Not applicable |
| **10. Was the likelihood of publication bias assessed?** An assessment of publication bias | ☑ Yes □ No □ Can't |

| | |
|---|---|
| should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). | answer □ Not applicable |
| **11. Was the conflict of interest included?** Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. | ☑ Yes □ No □ Can't answer □ Not applicable |
| | **Total = 9** |

| **AMSTAR Scale** [32] | |
|---|---|
| **8 – 11** | **High Quality** |
| **4 – 7** | **Moderate Quality** |
| **0 – 3** | **Low Quality** |

## APPENDIX V

### Risk of Bias Table[26]

| Study | Development of control group (selection of control from a unique population) | Differential surveillance for exposed vs. unexposed group | Failure to control for confounding factors | Incomplete follow-up | Prognostic Imbalance |
|---|---|---|---|---|---|
| *Bovasso et al., 2001* | *Low risk of bias.* The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no difference between measurements of outcomes in the exposed and unexposed group | *Low risk of bias*. The study adjusted for gender, age, marital status, race, highest level of education at baseline, and income | *High risk of bias*. 298 participants (11.3%) refused to participate in the follow-up, and 415 participants (15.7%) were unable to be located. Given the low number of individuals who were cannabis smokers without depression at baseline (n=15), those any individual cannabis smokers without depression in the lost to follow up group may have affected the conclusions. The authors describe those that were lost as different from the retained group. | *Unclear risk of bias.* The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Brook et al., 1998* | *Low risk of bias. The control cohort and the exposed cohort were taken from the same population.* | *Low risk of bias*. There was no difference between measurements of outcomes in the exposed and unexposed group | *Unclear risk of bias.* The authors adjust for gender and age but not other potentially significant covariates including socioeconomic status or psychiatric comorbidity. | *Low risk of bias*. The authors clearly described those lost to follow up and measured differences between the groups concluding there were no significant differences. | *Unclear risk of bias*. The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Brook et al., 2002* | *Low risk of bias. The control cohort and the exposed cohort were taken from the same* | *Low risk of bias*. There was no difference between measurements of outcomes in the | *Low risk of bias.* The authors adjust for demographics as well as psychiatric comorbidity. | *Low risk of bias*. The authors describe a 2% attrition rate between analysis dates | *Unclear risk of bias*. The authors do not report other prognosticators of depression such as family history of |

| | | | | | |
|---|---|---|---|---|---|
| | *population.* | exposed and unexposed group | | | depression, or serious illness such as diabetes or HIV. |
| *Degenhardt et al., 2013* | *Low risk of bias*. The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias*. There was no difference between measurements of outcomes in the exposed and unexposed group | *Low risk of bias.* The study adjusted for depression/anxiety at the onset of the study as well as illicit drug use and alcohol use | *Unclear risk of bias.* Of the 1727 that had participated by the second wave 339 were lost to follow-up. The authors do not give detailed sociodemographc data on those lost to follow-up. | *Unclear risk of bias.* The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Fergusson et al., 2002* | *Low risk of bias*. The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no differential surveillance between the groups | *Low risk of bias.* The authors do report adjusting for "fixed" confounders but are not clear about what those confounders are | *Unclear risk of bias.* The authors were able to follow up with 89-96% of the participants depending on the survey year | *Unclear risk of bias.* The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. There is however, conceivably a low risk of bias given the large sample size. Nevertheless, an unclear risk is assessed to error on the side of caution. |
| *Harder et al. 2006* | *Low risk of bias*. The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias*. There was no differential surveillance between the groups | *Low risk of bias.* The authors adjusted for a large number of potential confounders in their analysis included age, race, gender, history of | *High risk of bias.* The authors do not provide characteristics of those lost to follow up | *Unclear risk of bias.* The authors do not report other prognosticators of depression such as family history of depression, or serious illness |

| | | | | | |
|---|---|---|---|---|---|
| | | | depression, alcohol use, among many others. | | such as diabetes or HIV. |
| *Harder et al., 2008* | *Low risk of bias.* The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias*. There was no differential surveillance between the groups | *Low risk of bias.* The confounders included for adjustment were demographic, socioeconomic status, other drug use, childhood disturbances of psychological well-being, parental monitoring, and behavioral inter-vention status variables. | *Unclear risk of bias.* The study was retrospective. | *Unclear risk of Bias*. The authors do not report other prognosticator s of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Marique-Garcia et al., 2012* | *Low risk of bias.* The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias*. There was no differential surveillance between the groups | *Low risk of bias*. The covariates included for adjustment were history of personality disorder, IQ, use of other drugs, socioeconomic status, risky alcohol use, "disturbed" childhood behavior, smoking, social adjustment, urban upbringing. | *Low risk of bias.* The authors clearly describe those who were lost to follow-up. 8.7% of original 45087 were lost over a more than 30 year period | *Unclear risk of bias.* The authors do not report other prognosticator s of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Paton et al., 1977*[19] | *Low risk of bias.* The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no differential surveillance between the groups | *High risk of bias* There was no adjustment for covariates | High risk of bias The authors describe a loss to follow-up of 52% and do not characterize those who are lost to follow-up | *Unclear risk of bias*. The authors do not report other prognosticator s of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Pedersen et al., 2008* | *Low risk of bias.* The | *Low risk of bias.* There | *Low risk of bias*. The covariates | *Low risk of bias*. The authors clearly describe | *Unclear risk of bias*. The |

| | | | | | |
|---|---|---|---|---|---|
| | control cohort and the exposed cohort were taken from the same population. | was no differential surveillance between the groups | included for adjustment were parental socioeconomic factors, "problematic family situation," parental support, grades, tobacco smoking, alcohol problems, parental divorce, early pubarche, and more. These covariates were included in 4 models of analysis. | those who were lost to follow-up. They had a 70% response at 4 years. Those that were lost were more likely to be male, with low grades, and urban residency - variables that were adjusted for. | authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *Repetto* | *Low risk of bias.* The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no difference between measurements of outcomes in the exposed and unexposed group | *High risk of bias* There was no adjustment for covariants | *High risk of bias*. The authors clearly describe those who were lost to follow-up. At the final wave of analysis 25.3% of the original cohort did not respond. Those individuals who remained were more likely to have a higher GPA, but were not different with respect to gender, baseline depression, or marijuana use | *Unclear risk of bias*. The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |
| *van Laar et al., 2007* | *Low risk of bias*. The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no differential surveillance between the groups | *Low risk of bias*. The covariates included for adjustment were age, gender, education, urbanicity, employment, partner status, neuroticism, parental psychiatric history, childhood trauma , lifetime alcohol use disorders, other substance use disorders, lifetime anxiety disorders , lifetime mood | *High risk of bias*. The authors report that 7076 individuals were interviewed at t0, 5618 at t1, and 4848 at t2, but do not give the characteristic of those lost to follow-up. | *Low risk of bias*. The authors include other prognosticators of depression, namely family history of depression |

| | | | | | |
|---|---|---|---|---|---|
| | | | disorders, and lifetime psychotic symptoms | | |
| *Windle et al., 2004* | *Low risk of bias*. The control cohort and the exposed cohort were taken from the same population. | *Low risk of bias.* There was no differential surveillance between the groups | *High risk of bias.* They authors measure correlations between several variables and marijuana use but do not adjust for them between cohorts. | *Low risk of bias*. The authors determined that attrition bias was minimal. | *Unclear risk of bias*. The authors do not report other prognosticators of depression such as family history of depression, or serious illness such as diabetes or HIV. |