Additional file 1 (Supplementary Appendix)

Kedzior K, Laeber L: **A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies.** *BMC Psychiatry* 2014.

Contents

The mathematical approach to meta-analysis in this document is based on Borenstein *et al.*, 2009 [1].

Computation of odds ratio (*OR*) and its 95% confidence interval (*95%CI*)

The odds ratios (*OR*) were not reported in some studies and were computed according to the following formulae based on the number of cases (letters A-D) in the following groups ('cannabis user' or 'cannabis user with cannabis use disorder (CUD)', 'non-user' or 'no CUD', 'anxiety' or 'anxiety+depression', 'no anxiety' or 'no diagnosis') below [1, Table 5.1, p. 33]:

	ANXIETY (or ANXIETY+DEPRESSION)	NO ANXIETY (or NO DIAGNOSIS)
CANNABIS USER (or CUD)	A	B
NON-USER (or NO CUD)	C	D

The *OR* for anxiety (vs. no anxiety) in cannabis users (vs. non-users or CUD vs. no CUD) was computed as follows [1, p. 36]:

$$OR = \frac{A/B}{C/D}$$

The *OR* for cannabis use (vs. no use or CUD vs. no CUD) in anxiety (vs. no anxiety) was computed as follows:

$$OR = \frac{A/C}{B/D} = \frac{A/B}{C/D}$$

The formulae indicate that both *ORs* are equivalent.

Since the *OR* is limited on its lower end (it cannot be negative) but can take on any positive value, its distribution is skewed [2]. Thus, to maintain symmetry and obtain an approximately normal distribution, the *95%CI* was computed based on the log (natural logarithmic, *ln*) scale using the values from the contingency table above as follows [2]:

$$LogOR = ln(OR)$$

$$\text{LogLower } (ln \text{ lower bound } 95\%CI) = LogOR - (1.96 \times SE_{LogOR})$$

$$\text{LogUpper } (ln \text{ upper bound } 95\%CI) = LogOR + (1.96 \times SE_{LogOR})$$

$$SE_{LogOR} = \sqrt{V_{LogOR}}$$

$$V_{LogOR} = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$$

In the final step the LogLower and LogUpper were converted back (antiloged) into *OR* scale as follows [2]:

$$\text{Lower } (95\%CI) = e^{LogLower}$$

$$\text{Upper } (95\%CI) = e^{LogUpper}$$

Computation of standardised mean difference (Cohen's *d*) and its conversion to *OR*

Some studies reported the severity of anxiety scores based on standardised scales in user and non-user (or CUD and no CUD) groups. Based on mean (*M*), standard deviation (*SD)* of scores and group size (*N)* in each group the standardised mean difference (Cohen's *d*) and its variance (V_d) were computed in these studies as follows [1, p. 26-27]:

$$d = \frac{M_{User} - M_{Non-user}}{SD_{pooled}}$$

$$SD_{pooled} = \sqrt{\frac{(N_{User} - 1)SD_{User}^{\ 2} + (N_{Non-user} - 1)SD_{Non-user}^{\ 2}}{N_{User} + N_{Non-user} - 2}}$$

$$V_d = \frac{N_{User} + N_{Non-user}}{N_{User} N_{Non-user}} + \frac{d^2}{2(N_{User} + N_{Non-user})}$$

The *d* and V_d were converted into the log *OR* scale as follows [1, p. 47]:

$$LogOR = d \times \frac{\pi}{\sqrt{3}}$$

$$V_{LogOR} = V_d \times \frac{\pi^2}{3}$$

$$SE_{LogOR} = \sqrt{V_{LogOR}}$$

Finally, the log *95%CI* (LogLower and LogUpper) was computed and all log values were antiloged as follows [2]:

$$\text{LogLower} = LogOR - (1.96 \times SE_{LogOR})$$

$$\text{LogUpper} = LogOR + (1.96 \times SE_{LogOR})$$

$$OR = e^{LogOR}$$

$$\text{Lower } (95\%CI) = e^{LogLower}$$

$$\text{Upper } (95\%CI) = e^{LogUpper}$$

Combining of data in independent groups to compute *Cohen's d*

One study reported the severity of anxiety scores separately for boys and girls in non-user, user and user with CUD groups. Thus, the mean (*M*) and the standard deviation (*SD*) of scores for boys and girls had to be combined into a single score in each group (non-user, user and user with CUD).

The total sample size per group (N_{1+2}) was the sum of N_1 (number of boys) and N_2 (number of girls) in that group. The combined mean severity of anxiety score for boys (M_1) and girls (M_2) in each group (M_{1+2}) was computed as follows [1, p. 222]:

$$M_{1+2} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

The combined standard deviation of the mean severity of anxiety scores for boys (SD_1) and girls (SD_2) in each group (SD_{1+2}) was computed as follows [1, p. 222]:

$$SD_{1+2} = \sqrt{\frac{(N_1 - 1)SD_1^{\,2} + (N_2 - 1)SD_2^{\,2} + \frac{N_1 N_2}{N_1 + N_2}(M_1 - M_2)^2}{N_1 + N_2 - 1}}$$

Based on the single *M*, *SD*, and *N* values per group, the standardised mean difference, Cohen's *d*, was computed for the difference between users – non-users and CUD – non-users as explained under subsection 2 of this document.

Combining *OR* from studies with dependent data (using the same cases/data sets)

If the same cases were used in different studies or same studies provided two estimates of *ORs* based on the same cases then a mean of such *ORs* and its variance were computed. Because the same cases were used it was assumed that the *ORs* were dependent and thus the correlation between them is r=1. This approach is conservative in that it overestimates the variance of the mean *OR* and thus increases the length of the *95%CI* [1, p. 232]. The two *ORs* and their *95%CIs* were first converted into a log scale as follows [1, p. 36, 3]:

$$LogOR_1 = ln(OR_1)$$

$$LogOR_2 = ln(OR_2)$$

$$\text{LogLower}_1 = ln(\text{lower bound } 95\%\ CI_1)$$

$$\text{LogUpper}_1 = ln(\text{upper bound } 95\%\ CI_1)$$

$$\text{LogLower}_2 = ln(\text{lower bound } 95\%\ CI_2)$$

$$\text{LogUpper}_2 = ln(\text{upper bound } 95\%\ CI_2)$$

Then, an arithmetic mean ($LogOR_{combined}$) of $LogOR_1$ and $LogOR_2$ was computed. Next, the variance of each *OR* was computed separately as follows [3]:

$$SE_{LogOR1} = [(\text{LogUpper}_1 - \text{LogLower}_1)/2]/1.96$$

$$V_{LogOR1} = (SE_{LogOR1})^2$$

$$SE_{LogOR2} = [(\text{LogUpper}_2 - \text{LogLower}_2)/2]/1.96$$

$$V_{LogOR2} = (SE_{LogOR2})^2$$

The two individual estimates of variance (V_{LogOR1} and V_{LogOR2}) for both *ORs* were combined into one variance estimate ($V_{LogORcombined}$) using r=1 as follows [1, p. 228]:

$$V_{LogORcombined} = \frac{V_{LogOR1} + V_{LogOR2} + 2r\sqrt{V_{LogOR1}}\sqrt{V_{LogOR2}}}{4}$$

$$SE_{LogORcombined} = \sqrt{V_{LogORcombined}}$$

Finally, the log *95%CI* of $LogOR_{combined}$ ($LogLower_{combined}$ and $LogUpper_{combined}$) was computed and all log values were antiloged as follows [2]:

$$\text{LogLower}_{\text{combined}} = LogOR_{combined} - (1.96 \times SE_{LogORcombined})$$

$$\text{LogUpper}_{\text{combined}} = LogOR_{combined} + (1.96 \times SE_{LogORcombined})$$

$$OR_{combined} = e^{LogORcombined}$$

$$\text{Lower } (95\%CI_{combined}) = e^{LogLowercombined}$$

$$\text{Upper } (95\%CI_{combined}) = e^{LogUppercombined}$$

Random-effects meta-analysis of *OR* (binary) data

All computations were done by converting each study's *OR* and its *95%CI* into the log scale [1, p. 36, 3]:

$$LogOR = ln(OR)$$

$$\text{LogLower} = ln(\text{lower bound } 95\%\ CI)$$

$$\text{LogUpper} = ln(\text{upper bound } 95\%\ CI)$$

Next, the within-study variance for each study was computed as follows [3]:

$$SE_{LogOR} = [(\text{LogUpper} - \text{LogLower})/2]/1.96$$

$$V_{LogOR}\ (\text{within-study variance}) = (SE_{LogOR})^2$$

The weight of each study (W_{LogOR}) was computed according to the random-effects model as follows [1, Chapter 12]:

$$W_{LogOR} = \frac{1}{V_{LogOR} + T^2},$$

where V_{LogOR} is the within-study variance of *LogOR* and T^2 is the between-study variance which was computed according to the method of moments also known as the DerSimonian and Laird method [4] and using $df=k-1$ (k=number of studies) as follows:

$$T^2 = \frac{Q - df}{C}$$

$$C = \sum \frac{1}{V_{LogOR}} - \frac{\sum \left(\frac{1}{V_{LogOR}}\right)^2}{\sum \frac{1}{V_{LogOR}}}$$

$$Q = \sum \frac{LogOR^2}{V_{LogOR}} - \frac{\left(\sum \frac{LogOR}{V_{LogOR}}\right)^2}{\sum \frac{1}{V_{LogOR}}}$$

The overall mean weighted effect size (M_{LogOR}) of all studies and its variance (V_{MLogOR}) were computed as follows:

$$M_{LogOR} = \frac{\sum W_{LogOR} \times LogOR}{\sum W_{LogOR}}$$

$$V_{M_{LogOR}} = \frac{1}{\sum W_{LogOR}}$$

$$SE_{M_{LogOR}} = \sqrt{V_{M_{LogOR}}}$$

The lower and upper bounds of the log *95% CI* of M_{LogOR} ($LogLower_{MLogOR}$ and $LogUpper_{MLogOR}$) were computed as follows:

$$\text{LogLower}_{MLogOR} = LogOR_{MLogOR} - (1.96 \times SE_{MLogOR})$$

$$\text{LogUpper}_{MLogOR} = LogOR_{MLogOR} + (1.96 \times SE_{MLogOR})$$

Next, the *z*-score for M_{LogOR} was computed to test the null-hypothesis that $M_{LogOR}=1$ (meaning that there is no association between anxiety and cannabis use/CUD) according to the following formula:

$$Z = \frac{M_{LogOR}}{SE_{MLogOR}}$$

In the final step of the analysis the overall mean weighted effect size (M_{LogOR}) and its *95%CI* were antiloged as follows [1, p. 97]:

$$M_{LogOR} = e^{MLogOR}$$

$$\text{Lower } (95\%CI_{MLogOR}) = e^{LogLowerMLogOR}$$

$$\text{Upper } (95\%CI_{MLogOR}) = e^{LogUpperMLogOR}$$

Publication bias analyses in Comprehensive Meta-Analysis (CMA) software

Publication bias refers to an overestimation of the overall mean weighted effect size in meta-analysis due to inclusion of studies based on large sample sizes and/or large effect sizes [1, Chapter 30]. Such studies are more likely to be published and thus are easier to locate during a systematic search than studies based on smaller samples and/or small (often not statistically significant) effect sizes that are either not published at all or published in smaller (often non-English language) journals that are not included in major databases [1, Chapter 30].

Publication bias in the current study was assessed using methods available in the Comprehensive Meta-Analysis (CMA) software, version 2.2 (Biostat Inc., Englewood, NJ, USA). The theoretical number of null-studies (with *OR*=1) required to remove the statistical significance of the overall mean weighted *OR* in meta-analysis was computed using Rosenthal's Fail-Safe *N* [5]. The smaller the Fail-Safe *N*, the more likely it is that publication bias is present in meta-analysis.

Publication bias can also be assessed visually using a funnel plot of *LogOR* vs. *SEM* [6]. According to the funnel plot, the distribution of all effect sizes around the overall mean weighted *LogOR* should resemble a symmetrical funnel. Since the Y-axis is reversed (smaller *SEM* values on top, larger on the bottom of the plot), it was expected that larger studies with smaller variability would be found towards the top of the plot, close to and on both sides of the overall mean weighted *LogOR*. The small studies with larger variability would be found towards the bottom of the plot and they would spread wider away from and on both sides of the overall mean weighted *LogOR.* Such symmetrical funnel plot would indicate that some studies in the current meta-analysis show that anxiety and cannabis use/CUD are positively associated while others show either no association or a negative association. Any deviation

from such symmetry towards the right or the left of the overall mean weighted *LogOR* would indicate presence of publication bias in the current analysis.

Because a visual inspection of the funnel plot is subjective, the Duval and Tweedie's Trim-and-Fill analysis [7] was used to test for symmetry in such plot using mathematical assumptions of symmetry. Specifically, first the extreme studies from one side of the plot are removed ('trimmed') until the plot becomes symmetrical. This procedure adjusts the overall mean weighted *LogOR.* Then, the studies are added ('filled') back onto the plot and a mirror image of each one is produced and added to the opposite side of the plot to maintain symmetry. This procedure corrects the variance of the new estimate of the overall mean weighted *LogOR.* Publication bias is present if mostly the smaller studies towards the bottom of the plot are missing from the analysis and the adjusted overall mean weighted effect size differs from the original overall mean weighted effect size (for example, the effect size changes direction and/or its *95%CI* overlaps with the line of no effect following the adjustment for missing studies).

Finally, the results of two more methods were inspected in the current analysis. However, both methods are unreliable because they are based on the standard null-hypothesis testing and have low power (and thus high Type II error) if the number of studies in the analysis is low. Specifically, the Begg and Mazumdar Rank Order Correlation (Kendall's *tau b*) was used to investigate the relationship between the standardised effect sizes vs. *SEM* in each study [8] and the Egger's regression [9] was used to predict the standardised effect size with 1/*SEM*. Publication bias is present if smaller studies differ systematically (significantly) from the larger studies. In this case, either the correlation is statistically significant and/or the intercept of the regression line significantly deviates from zero causing the asymmetry of the funnel plot [9].

Table S1. Exclusion criteria applied to *N*=267 studies

Titles and abstracts of *N*=267 studies assessed for relevance (by LTL and KKK); *N*=218 excluded

Exclusion criteria:

- *N*=164 Irrelevant title/abstract
- *N*=28 Review/comment/no original data
- *N*=2 Healthy controls missing
- *N*=22 Non-users missing
- *N*=2 Unpublished thesis

Note. From the *N*=267 studies on the association between cannabis use and anxiety disorders, *N*=256 were located based on the electronic searches and *N*=11 from the hand search. A complete list of *N*=218 excluded studies and the individual reasons of exclusion are available upon request from the authors.

Table S2. Studies assessed in full length (*N*=49) and reasons for exclusion

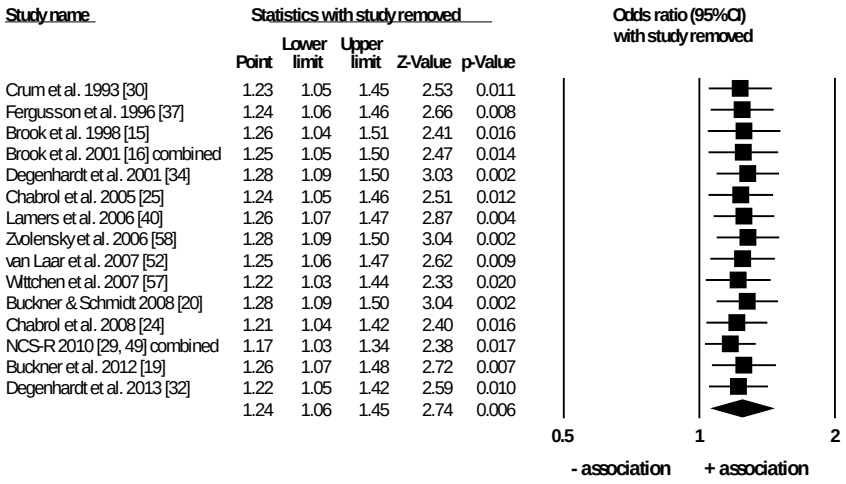
Citation	Search type	Included (+) Excluded (–)	Reason for exclusion or inclusion comments
[10]	Hand search	+	
[11]	Hand search	+	in Moore *et al.* 2007 [12]
[13]	Search 1-2	–	Inadequate data (*SD* values missing)
[14]	Search 1-2	–	No anxiety diagnosis (anxiety sensitivity, anxious arousal)
[15]	Hand search	+	
[16]	Search 1-2	+	in Moore *et al.* 2007 [12]
[17]	Search 1-2	–	Non-users missing
[18]	Search 1-2	–	Healthy non-users missing
[19]	Search 1-2	+	
[20]	Search 1-2	+	
[21]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[22]	Search 1-2	+	
[23]	Search 1-2	+	
[24]	Search 1-2	+	
[25]	Search 1-2	+	
[26]	Search 1-2	–	Same cases as in [25]
[27]	Search 1-2	+	Anxiety and depression
[28]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[29]	Search 1-2	+	
[30]	Hand search	+	in Moore *et al.* 2007 [12]
[31]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[32]	Search 1-2	+	
[33]	Search 1-2	–	Same cases as in [34]
[34]	Search 1-2	+	
[35]	Hand search	+	Anxiety and depression
[36]	Search 1-2	–	High comorbidity with other substances (seekers of treatment for cannabis withdrawal)
[37]	Hand search	+	in Moore *et al.* 2007 [12]
[38]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[39]	Search 1-2	+	Anxiety and depression
[40]	Search 1-2	+	
[41]	Search 1-2	+	
[42]	Search 1-2	–	No anxiety diagnosis (anxiety sensitivity)
[43]	Hand search	+	
[44]	Hand search	+	Anxiety and depression
[45]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[46]	Search 1-2	–	Cannabis vs. anxiety comparison not shown
[47]	Search 1-2	+	Anxiety and depression (in Moore *et al.* 2007 [12])
[48]	Search 1-2	–	High comorbidity with other substances (music festivals attendees)
[49]	Search 1-2	+	
[50]	Hand search	+	Anxiety and depression
[51]	Hand search	+	
[52]	Search 1-2	+	

[53]	Search 1-2	–	Cases in treatment for cannabis dependence
[54]	Search 1-2	–	Inadequate data (too few anxiety cases to compute *OR*)
[55]	Search 1-2	–	Inadequate data (*SD* values missing)
[56]	Hand search	+	NPMS study methods; unpublished results in Moore *et al.* 2007 [12]
[57]	Search 1-2	+	
[58]	Search 1-2	+	
[59]	Search 1-2	+	

Note: The *N*=49 studies included *N*=38 from the electronic searches and *N*=11 from the hand search. A total of *N*=31 studies were selected for the final meta-analysis. All studies in the table above were inspected in full-length and assessed by both authors.
Abbreviations: NPMS: the British National Psychiatric Morbidity Survey, UK; *OR*: odds ratio; *SD*: standard deviation

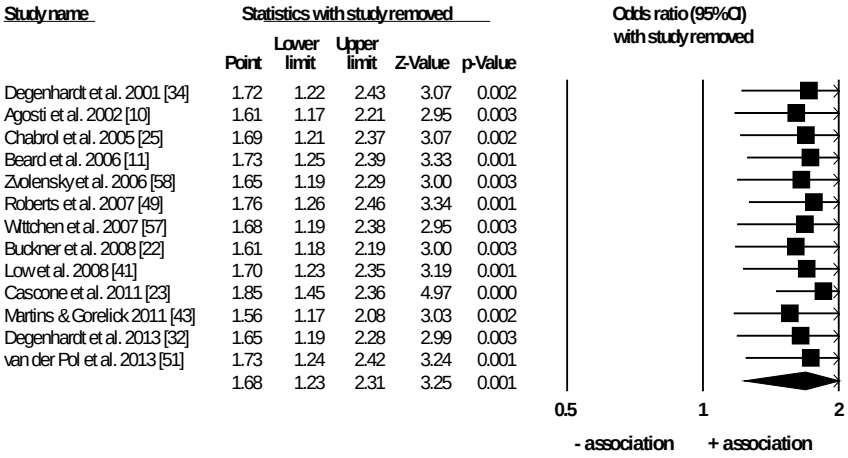
Figure S1. Random-effects one-study removed analysis

a) Anxiety vs. cannabis use (*N*=15)



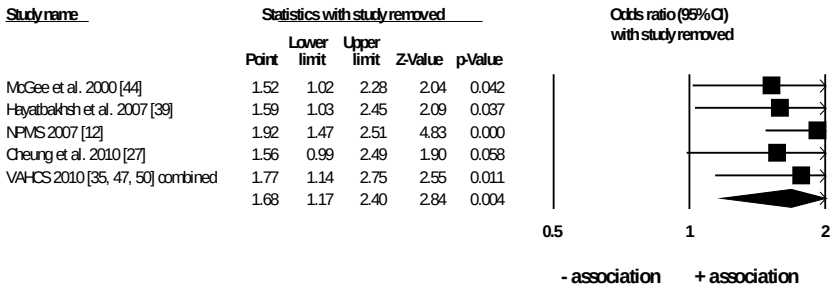
Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Crum et al. 1993 [30]	1.23	1.05	1.45	2.53	0.011
Fergusson et al. 1996 [37]	1.24	1.06	1.46	2.66	0.008
Brook et al. 1998 [15]	1.26	1.04	1.51	2.41	0.016
Brook et al. 2001 [16] combined	1.25	1.05	1.50	2.47	0.014
Degenhardt et al. 2001 [34]	1.28	1.09	1.50	3.03	0.002
Chabrol et al. 2005 [25]	1.24	1.05	1.46	2.51	0.012
Lamers et al. 2006 [40]	1.26	1.07	1.47	2.87	0.004
Zvolensky et al. 2006 [58]	1.28	1.09	1.50	3.04	0.002
van Laar et al. 2007 [52]	1.25	1.06	1.47	2.62	0.009
Wittchen et al. 2007 [57]	1.22	1.03	1.44	2.33	0.020
Buckner & Schmidt 2008 [20]	1.28	1.09	1.50	3.04	0.002
Chabrol et al. 2008 [24]	1.21	1.04	1.42	2.40	0.016
NCS-R 2010 [29, 49] combined	1.17	1.03	1.34	2.38	0.017
Buckner et al. 2012 [19]	1.26	1.07	1.48	2.72	0.007
Degenhardt et al. 2013 [32]	1.22	1.05	1.42	2.59	0.010
	1.24	1.06	1.45	2.74	0.006

b) Anxiety vs. cannabis use disorder (CUD; *N*=13)



Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Degenhardt et al. 2001 [34]	1.72	1.22	2.43	3.07	0.002
Agosti et al. 2002 [10]	1.61	1.17	2.21	2.95	0.003
Chabrol et al. 2005 [25]	1.69	1.21	2.37	3.07	0.002
Beard et al. 2006 [11]	1.73	1.25	2.39	3.33	0.001
Zvolensky et al. 2006 [58]	1.65	1.19	2.29	3.00	0.003
Roberts et al. 2007 [49]	1.76	1.26	2.46	3.34	0.001
Wittchen et al. 2007 [57]	1.68	1.19	2.38	2.95	0.003
Buckner et al. 2008 [22]	1.61	1.18	2.19	3.00	0.003
Low et al. 2008 [41]	1.70	1.23	2.35	3.19	0.001
Cascone et al. 2011 [23]	1.85	1.45	2.36	4.97	0.000
Martins & Gorelick 2011 [43]	1.56	1.17	2.08	3.03	0.002
Degenhardt et al. 2013 [32]	1.65	1.19	2.28	2.99	0.003
van der Pol et al. 2013 [51]	1.73	1.24	2.42	3.24	0.001
	1.68	1.23	2.31	3.25	0.001

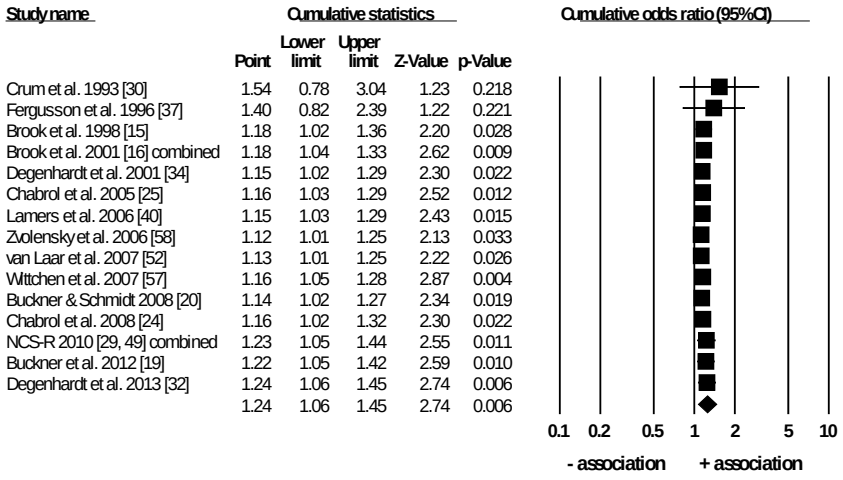
c) Anxiety+depression vs. cannabis use (*N*=5)



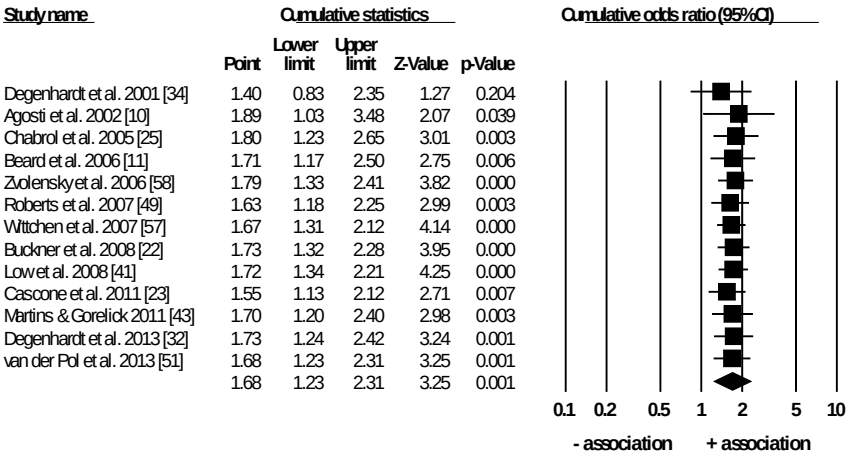
Note. 'Point' refers to the overall mean weighted effect size (*OR*) of all studies without the study in each row.

Figure S2. Random-effects cumulative analysis

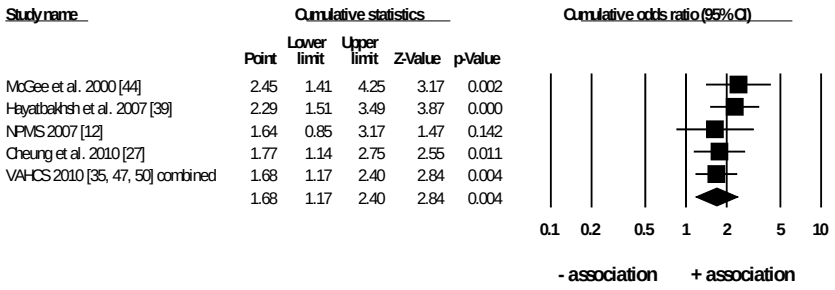
a) Anxiety vs. cannabis use (*N*=15)



b) Anxiety vs. cannabis use disorder (CUD; *N*=13)



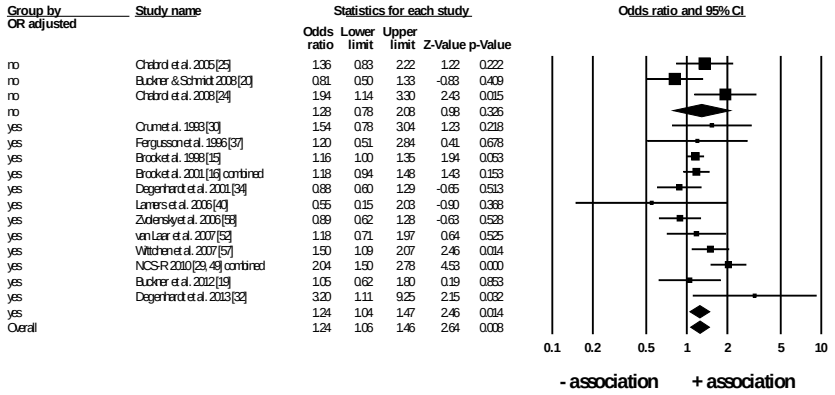
c) Anxiety+depression vs. cannabis use (*N*=5)



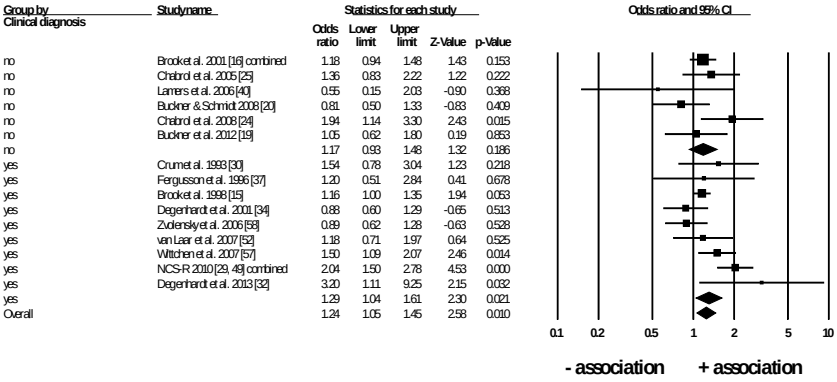
Note. 'Point' refers to the overall mean weighted effect size (*OR*) of all studies up to and including a study in that row.

Figure S3. Random-effects subgroup analyses

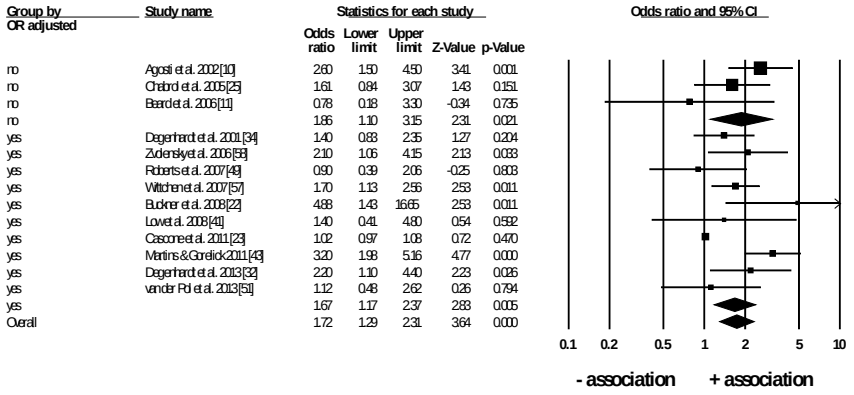
a) Anxiety vs. cannabis use (*N*=15)- comparing studies with *OR* adjusted for substance use/other illnesses/demographics vs. studies with unadjusted *OR*



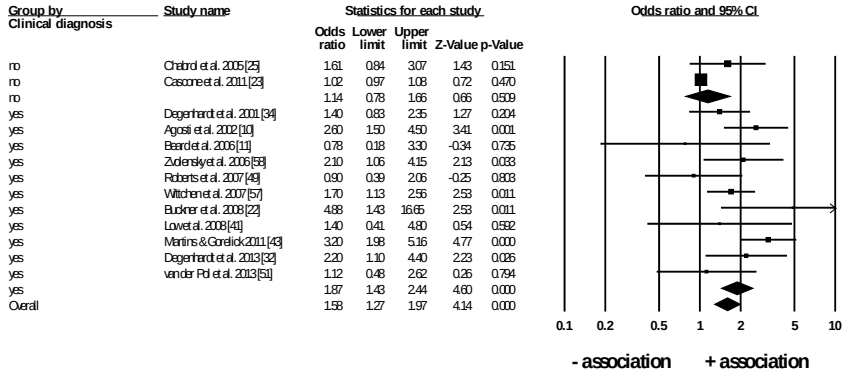
b) Anxiety vs. cannabis use (*N*=15)- comparing studies with vs. without clinical diagnoses of anxiety



c) Anxiety vs. cannabis use disorder (CUD; *N*=13)- comparing studies with *OR* adjusted for substance use/other illnesses/demographics vs. studies with unadjusted *OR*



d) Anxiety vs. cannabis use disorder (CUD; *N*=13)- clinical diagnoses



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