Supplementary material 1

Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies

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eMethods

Search key

(cannab* or marijuana or THC or CBD) and (systematic or meta-analy*)

Transformation of effect sizes

When possible, effect sizes have been converted to eOR, to provide a common effect size with an unique scale[1]. The eOR for binary outcomes were considered equal to original metric eg, hazard ratio, risk ratio, odds ratio, as the re-calculation of an OR would have required the original 2x2 table, which was not available in individual studies. For continuous outcomes, limited to Hedge's g, standardized mean difference, and Cohen's d, we performed a transformation to a logOR based on the assumption that an underlying continuous variable produces a logistic distribution of equal standard deviation in the two intervention groups. In order to improve communication of clinical value of findings, we have made the eOR greater than 1 for clinically harmful associations. For instance, an association with increased risk of psychosis has an eOR=1.71, 95%CI=1.47-2.00, while an association with less seizures has an eOR=0.59, 95%CI=0.38-0.92.

Credibility of observational evidence

Credibility of results of meta-analyses of observational studies were graded into convincing (class I), highly suggestive (class I), suggestive (class III), weak (class IV), and no evidence, according to following criteria previously implemented in numerous umbrella reviews[2–10]. For class I, all criteria below had to be met i) more than 1000 cases, ii) significant summary associations (p<10-6) per random-effects calculations, iii) no evidence of small-study effects, iv) no evidence of excess of significance bias, v) prediction intervals not including the null value, vi) largest study nominally significant (p<0.05), vii) not large heterogeneity (i.e., I2< 50%). For class II, i) more than 1000 cases, ii) significant summary associations (p<10-6) per random-effects calculation, iii) largest study nominally significant (p<0.05). For class III, i) more than 1000 cases, ii) significant summary associations (p<10-3) per random-effects calculations. For class IV, i) all other associations with p < 0.05. No evidence was defined when p > 0.05.

Certainty of evidence from randomized controlled trials

We classified evidence from meta-analyses of RCTs using the GRADE framework, which allows to classify certainty of evidence as high, moderate, low, or very low. As recommended by GRADE, level of evidence was determined by risk of bias, inconsistency, indirectness, imprecision, publication bias[11].

The following criteria were used:

i) for risk of bias, no downgrade if >75% RCTs had low risk of bias, one downgrade if <75% had low risk of bias, two downgrades if <50% have low risk of bias

ii) for inconsistency, no downgrade if I2 <75%, one downgrade if >75%, two downgrades if more than 90%

iii) for indirectness, we downgraded one or two levels if one or two or more of the following conditions applied: meta-analyses were mixing clinical and non-clinical populations, or cannabinoids with other interventions, or where mixing active, inactive, and placebo control groups.

iv) for imprecision, no downgrade if sample size >200, one downgrade 100-199, two downgrades 1-99 or the 95% CI of summary estimate had overlap with the effect size threshold of clinical importance, which we defined as interval of 0.9 to 1.1

v) for publication bias no downgrade if publication bias is undetected by tests or the reviewers say that they did a systematic search of multiple databases and did not restrict their search language, one dowgrade if publication bias is strongly suspected by tests or the reviewers say that did not perform a systematic search of multiple databases and restricted their search language

Evidence could be upgraded according to the following rules[12]. Upgrade of one level is possible with large effect size (i.e. risk ratio <0.5 or >2.0, or standardized mean difference >0.8, based on direct evidence with no

plausible or possible confounders). Upgrade of two levels is possible with very large effect size (i.e. risk ratio <0.2 or >5.0, or standardized mean difference >1.2, based on direct evidence without risk of bias or imprecision).

Starting from high, level of evidence was downgraded to moderate with one or two downgrades, to low with three or four downgrades, and to very low with five or six downgrades.

Protocol amendments

The following amendments to the original protocol have been implemented:

We did not conduct fixed effect model meta-analyses, and only conducted random effects meta-analyses, as we did not believe the assumption for using fixed effect meta-analysis applies to the included meta-analyses. We do not believe only one true effect size exists for such an heterogeneous population (human population) and exposure (i.e. different types of cannabis).

We originally planned to also include Mendelian randomization studies. For feasibility considerations related with the amount of information reported in this work, we will report findings from Mendelian randomization studies in a separate publication.

The PRIOR checklist was published after we prepared our protocol. We believe the PRIOR checklist better applies to this umbrella review than an adapted PRISMA checklist, and we have now used that instead.

We did not conduct all pre-planned sensitivity analyses, for the following reasons:

Based on quality of meta-analyses: because individual studies and not meta-analyses are the unit of analyses;

Age group: because meta-analyses were already focusing on one age group only, and if not, individual studies were mixing age groups;

Follow-up duration: because this information was seldomly reported

Year of data collection: because splitting dates by decade left only one study per decade, precluding any meta-analysis

Sample size: because sample size is already accounted for in the overall credibility assessment criteria

Study population: because meta-analyses were already organized by population

Type of cannabinoid and cannabis: because we already divided recreational cannabis from medical cannabis or cannabis-based medicines splitting observational and interventional evidence, and because cannabidiol and THC were already separated in meta-analyses.

Amount of cannabis, since this information was not reported

We conducted the following sensitivity analyses to all classes of observational evidence:

Removing the >1,000 cases criterion

We conducted the following sensitivity analyses only to class I and II observational evidence:

Adjusted studies only

Cohort studies only

Supplementary table 1. PRIOR checklist[13]

Section Topic	#	Item	Locationreported
TITLE			
Title	1	Identify the report as an overview of reviews.	Pg 1
ABSTRACT			
Abstract	2	Provide a comprehensive and accurate summary of the purpose, methods, and results of theoverview of reviews.	Pg 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for conducting the overview of reviews in the context of existingknowledge.	Pg 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) addressed by the overview of reviews.	Pg 6
METHODS			
Eligibility criteria	5a	Specify the inclusion and exclusion criteria for the overview of reviews. If supplemental primarystudies were included, this should be stated, with a rationale.	Pg 6
	5b	Specify the definition of 'systematic review' as used in the inclusion criteria for the overview of reviews.	NA
Informationsources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searchedor consulted to identify systematic reviews and supplemental primary studies (if included). Specify the date when each source was last searched or consulted.	Protocol, pg 6, eMethods
Search strategy	7	Present the full search strategies for all databases, registers and websites, such that they could be reproduced. Describe any search filters and limits applied.	eMethods
Selection process	8a	Describe the methods used to decide whether a systematic review or supplemental primary study(if included) met the inclusion criteria of the overview of reviews.	Pg 6
	8b	Describe how overlap in the populations, interventions, comparators, and/or outcomes ofsystematic reviews was identified and managed during study selection.	Pg 6
Data collection process	9a	Describe the methods used to collect data from reports.	Pg 6-7
	9b	If applicable, describe the methods used to identify and manage primary study overlap at the level of the comparison and outcome during data collection. For each outcome, specify the method usedto illustrate and/or quantify the degree of primary study overlap across systematic reviews.	NA
	9c	If applicable, specify the methods used to manage discrepant data across systematic reviews during data collection.	NA
Data items	10	List and define all variables and outcomes for which data were sought. Describe any assumptions made and/or measures taken to identify and clarify missing or unclear information.	Pg 6-7
Risk of bias assessment	11a	Describe the methods used to *assess* risk of bias or methodological quality of the includedsystematic reviews.	Pg 7-8, Protocol, eMethods
	11b	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* the riskof bias of the primary studies included in the systematic reviews. Provide a justification for instances where flawed, incomplete, or missing assessments are identified but not re-assessed.	Pg 6-7

	11c	Describe the methods used to *assess* the risk of bias of supplemental primary studies (if included).	NA
Synthesismethods	12a	Describe the methods used to summarize or synthesize results and provide a rationale for the choice(s).	Pg 7-8
	12b	Describe any methods used to explore possible causes of heterogeneity among results.	Pg 7-8, Protocol, eMethods
	12c	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg 7-8, Protocol, eMethods
Reporting bias assessment	13	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* the risk of bias due to missing results in a summary or synthesis (arising from reporting biases at the levelsof the systematic reviews, primary studies, and supplemental primary studies, if included).	Pg 7-8, Protocol, eMethods
Certainty assessment	14	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* certainty(or confidence) in the body of evidence for an outcome.	Pg 7-8, Protocol, eMethods
RESULTS			
Systematic review and supplemental primary study selection	15a	Describe the results of the search and selection process, including the number of records screened, assessed for eligibility, and included in the overview of reviews, ideally with a flow diagram.	Figure 1, Pg 8
	15b	Provide a list of studies that might appear to meet the inclusion criteria, but were excluded, withthe main reason for exclusion.	Appendix

Section Topic	**#**	**Item**	**Location reported**
Characteristics of systematic reviews and supplemental primary studies	16	Cite each included systematic review and supplemental primary study (if included) and present its characteristics.	Table 1
Primary studyoverlap	17	Describe the extent of primary study overlap across the included systematic reviews.	NA
Risk of bias in systematic reviews, primarystudies, and supplemental primary studies	18a	Present assessments of risk of bias or methodological quality for each included systematic review.	Pg 8-10, Tables, appendix
	18b	Present assessments (*collected* from systematic reviews or *assessed* anew) of the risk of bias of the primary studies included in the systematic reviews.	NA
	18c	Present assessments of the risk of bias of supplemental primary studies (if included).	NA
Summary orsynthesis ofresults	19a	For all outcomes, summarize the evidence from the systematic reviews and supplemental primary studies (if included). If meta-analyses were done, present for each the summary estimate and its precision and measures of statistical heterogeneity. If comparing groups, describe the direction ofthe effect.	Pg 8-11, Tables, appendix
	19b	If meta-analyses were done, present results of all investigations of possible causes of heterogeneity.	Pg 8-11, Tables, appendix
	19c	If meta-analyses were done, present results of all sensitivity analyses conducted to assess the robustness of synthesized results.	Pg 8-11, Tables, appendix

Reporting biases	20	Present assessments (*collected* from systematic reviews and/or *assessed* a new) of the risk of bias due to missing primary studies, analyses, or results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included) for each summary or synthesis assessed.	Pg 8-11, Tables, appendix
Certainty of evidence	21	Present assessments (*collected* or *assessed* anew) of certainty (or confidence) in the body of evidence for each outcome.	Pg 8-11, Tables, appendix
DISCUSSION			
Discussion	22a	Summarize the main findings, including any discrepancies in findings across the includedsystematic reviews and supplemental primary studies (if included).	Pg 11-15
	22b	Provide a general interpretation of the results in the context of other evidence.	Pg 11-15
	22c	Discuss any limitations of the evidence from systematic reviews, their primary studies, and supplemental primary studies (if included) included in the overview of reviews. Discuss any limitations of the overview of reviews methods used.	Pg 14-15
	22d	Discuss implications for practice, policy, and future research (both systematic reviews and primary research). Consider the relevance of the findings to the end users of the overview ofreviews, e.g., healthcare providers, policymakers, patients, among others.	Pg 14-15
OTHER INFORMATION			
Registration and protocol	23a	Provide registration information for the overview of reviews, including register name andregistration number, or state that the overview of reviews was not registered.	Pg 6
	23b	Indicate where the overview of reviews protocol can be accessed, or state that a protocol was not prepared.	Pg 6
	23c	Describe and explain any amendments to information provided at registration or in the protocol. Indicate the stage of the overview of reviews at which amendments were made.	Appendix
Support	24	Describe sources of financial or non-financial support for the overview of reviews, and the role of the funders or sponsors in the overview of reviews.	Pg 15-16
Competing interests	25	Declare any competing interests of the overview of reviews' authors.	Pg 15-16
Author information	26a	Provide contact information for the corresponding author.	Pg 1
	26b	Describe the contributions of individual authors and identify the guarantor of the overview of reviews.	Pg 15-16
Availability ofdata and othermaterials	27	Report which of the following are available, where they can be found, and under which conditions they may be accessed: template data collection forms; data collected from included systematic reviews and supplemental primary studies; analytic code; any other materials used in the overviewof reviews.	Pg 16

Supplementary table 2. PRISMA 2020 abstract checklist adapted for umbrella reviews[14]

PRISMA v1.0 for Abstracts checklist*			
Section and topic	**Item #**	**Checklist item**	**Reported?**
Title			
Title	1	Identify the report as a UR.	y
Background			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the UR addresses.	y
Methods			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the UR.	y
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	y
Quality	5	Specify the methods used to assess quality in the included reviews/meta-analyses.	y
Synthesis of results	6	Specify the methods used to present and synthesise results, including exploring biases.	y
Results			
Included studies	7	Give the total number of included comparisons, reviews, studies, and describe reviews' quality	y
Synthesis of results	8	Present results for main outcomes or of most credible evidence, preferably indicating the number of included studies and participants for each. If meta-analysis wasdone, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	y
Discussion			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the UR (e.g. review quality, inconsistency and imprecision).	y
Interpretation	10	Provide a general interpretation of the results and important implications.	y
Other			
Funding	11	Specify the primary source of funding for the UR.	y
Registration	12	Provide the register name and registration number.	y

Supplementary table 3. Studies excluded, with reason for exclusion.

Author, year	**Reason for exclusion**
Abrams, 2018[15]	No meta-analysis
Addington, 2014[16]	No meta-analysis
Alharbi, 2016[17]	No meta-analysis
Al-Kahlil, 2015[18]	Not largest
Allan, 2018[19]	Not largest meta-analysis
Allen, 2018[20]	No cannabis/cannabinoid related outcome
Alshaarawy, 2015[21]	No meta-analysis
Anand, 2009[22]	No meta-analysis
Ananth, 2018[23]	No meta-analysis
Andrade, 2016[24]	No meta-analysis
Andrade, 2016[25]	No meta-analysis
Andrzejewski, 2016[26]	No meta-analysis
Angarita, 2016[27]	No meta-analysis
Antonsdottir, 2015[28]	No meta-analysis
Aryana, 2007[29]	No meta-analysis
Ashton, 2005[30]	No meta-analysis
Ashton, 2007[31]	No meta-analysis
Attal, 2015[32]	No meta-analysis
Badowski, 2014[33]	No meta-analysis
Badowski, 2017[34]	No meta-analysis
Bagot, 2015[35]	No meta-analysis
Bagshaw, 2002[36]	No meta-analysis
Bahji, 2016[37]	No meta-analysis
Bahji, 2021[38]	No outcome of interest
Baker, 2010[39]	No meta-analysis
Baldacchino, 2012[40]	No meta-analysis
Baldinger, 2012[41]	No meta-analysis
Bally, 2014[42]	No meta-analysis

Bao, 2014[43]	No meta-analysis
Barbetta, 2017[44]	No meta-analysis
Barkin, 2016[45]	No meta-analysis
Barkin, 2017[46]	No meta-analysis
Baron, 2015[47]	No meta-analysis
Barthelemy, 2016[48]	No meta-analysis
Batalla, 2013[49]	No meta-analysis
Batalla, 2014[50]	No meta-analysis
Batet Sanchez, 2016[51]	No meta-analysis
Beaulieu, 2002[52]	No meta-analysis
Beaulieu, 2007[53]	No meta-analysis
Behm, 2018[54]	No meta-analysis
Belbasis, 2018[55]	No meta-analysis
Ben Amar, 2006[56]	No meta-analysis
Ben Amar, 2007[57]	No meta-analysis
Beneria, 2021[58]	No cannabis exposure
Benze, 2012[59]	No meta-analysis
Berthet, 2016[60]	No meta-analysis
Bertolin-Guillen, 2008[61]	No meta-analysis
Bhandari, 2016[62]	No meta-analsysis
Bhattacharyya, 2009[63]	No meta-analsysis
Bifulco, 2006[64]	No meta-analsysis
Birdsall, 2016[65]	No meta-analsysis
Blake, 2017[66]	No meta-analsysis
Blessing, 2015[67]	No meta-analsysis
Blest-Hopley, 2018[68]	Duplicated
Blest-Hopley, 2018[69]	Duplicated
Blumenthal, 2016[70]	No meta-analsysis
Bogaty, 2018[71]	Duplicated
Bogaty, 2018[71]	Duplicated

Bonnet, 2015[72]	No meta-analsysis
Borgan, 2019[73]	No meta-analsysis
Bosnjak, 2021	No meta-analysis
Bossong, 2014[74]	No meta-analsysis
Bowen, 2018[75]	No meta-analsysis
Boychuk, 2015[76]	No meta-analsysis
Brafford May, 2016[77]	No meta-analysis
Braum, 2017[78]	No meta-analsysis
Braun, 2016[79]	No meta-analsysis
Bravo-Soto, 2017[80]	No meta-analsysis
Breet, 2018[81]	No meta-analsysis
Brents, 2016[82]	No meta-analsysis
Broyd, 2016[83]	No meta-analsysis
Buadze, 2012[84]	No meta-analsysis
Budney, 2002[85]	No meta-analsysis
Budney, 2004[86]	No meta-analsysis
Bugra, 2012[87]	No English language
Burns, 2006[88]	No meta-analsysis
Burns, 2016[89]	No meta-analsysis
Busch, 2014[90]	No meta-analsysis
Butler, 2009[91]	No meta-analsysis
Cabeza, 2017[92]	No meta-analsysis
Cadet, 2014[93]	No meta-analsysis
Cadet, 2016[94]	No meta-analsysis
Cairns, 2016[95]	No meta-analsysis
Calabria, 2010[96]	No meta-analsysis
Calandre, 2015[97]	No meta-analsysis
Campbell, 1999[98]	No meta-analsysis
Campbell, 2001[99]	No meta-analsysis
Campillo, 2009[100]	No meta-analsysis

Cancino Botello, 2016[101]	No meta-analsysis
Caplan, 1990[102]	No meta-analsysis
Carrigan, 2016[103]	No meta-analsysis
Cascini, 2012[104]	No meta-analsysis
Castaneto, 2014[105]	No meta-analysis
Castle, 1996[106]	No meta-analysis
Chatkin, 2019[107]	No meta-analysis
Chisini 2019[108]	Cross-sectional
Chisini,2019[108]	Duplicated
Chiurchiù, 2015[109]	No meta-analysis
Cinti, 2009[110]	No meta-analysis
Claflin, 2018[111]	No meta-analysis
Clark, 2005[112]	No meta-analysis
Cohen, 2008[113]	No meta-analysis
Cohen, 2018[114]	Duplicated
Cohen, 2018[114]	No meta-analysis
Colizzi, 2018[115]	No meta-analysis
Collo, 2014[116]	No meta-analysis
Compton, 2007[117]	No meta-analysis
Contreras, 2017[118]	No meta-analysis
Contreras, 2018[119]	No meta-analysis
Cookey, 2014[120]	No meta-analysis
Cooper, 2016[121]	No meta-analysis
Copeland, 2016[122]	No meta-analysis
Correa, 2005[123]	No meta-analysis
Costa, 2007[124]	No meta-analysis
Costa, 2016[125]	No meta-analysis
Cottencin, 2014[126]	No meta-analysis
Courts, 2016[127]	No meta-analysis
Crean, 2011[128]	No meta-analysis

Crippa, 2009[129]	No meta-analysis
Crippa, 2012[130]	No meta-analysis
Crippa, 2015[131]	No meta-analysis
Croxford, 2003[132]	No meta-analysis
Croxford, 2005[133]	No meta-analysis
Cuba, 2017[134]	No meta-analysis
Curtis, 2009[135]	No meta-analysis
Darkovska-Serafimovska, 2018[136]	No meta-analysis
Das, 2015[137]	No meta-analysis
De Almeida Pereira, 2018[138]	No meta-analysis
De Irala, 2005[139]	No meta-analysis
De Tommaso, 2017[140]	No meta-analysis
De Vita, 2018[141]	Duplicated
Degenhardt, 2003[142]	No meta-analysis
Degenhardt, 2008[143]	No meta-analysis
Dekker, 2009[144]	No meta-analysis
Delisi, 2008[145]	No meta-analysis
Denier, 2012[146]	No meta-analysis
Deshpande, 2015[147]	No meta-analysis
Deyniecki, 2015[148]	No meta-analysis
Dimitrios, 2021[149]	No meta-analysis
Di Forti, 2007[150]	No meta-analysis
Doggui, 2021[151]	Cross-sectional
Dos Santos, 2015[152]	No meta-analysis
Dosenovic, 2017[153]	No meta-analysis
Douet, 2017[154]	No meta-analysis
Du Plessis, 2015[155]	No meta-analysis
Eisentstein, 2015[156]	No meta-analysis
Elliott, 2019[157]	Duplicated
Esmaeelzadeh, 2018[158]	Not largest meta-analysis

Elowe, 2016[159]	No meta-analysis
England, 2015[160]	Not human report
Farquhar-Smith, 2009[161]	No meta-analysis
Farzaei, 2016[162]	No meta-analysis
Farzaei, 2016[163]	No meta-analysis
Farzaei, 2017[164]	No meta-analysis
Fattore, 2016[165]	No meta-analysis
Fergusson, 2015[166]	No meta-analysis
Fernandez-Ruiz, 2004[167]	No meta-analysis
Fernandez-Ruiz, 2005[168]	No meta-analysis
Fernandez-Ruiz, 2015[169]	No meta-analysis
Ferraro, 2009[170]	No meta-analysis
Fife, 2015[171]	No meta-analysis
Fijal, 2016[172]	No meta-analysis
Filloux, 2015[173]	No meta-analysis
Fine, 2014[174]	No meta-analysis
Fisher, 2021[175]	Not largest meta-analysis
Fitzcharles, 2016[176]	No meta-analysis
Fitzcharles, 2016[177]	No meta-analysis
Fitzcharles, 2016[178]	No meta-analysis
Fitzcharles, 2016[179]	No meta-analysis
Fletcher, 2022	No meta-analysis
Fleury, 2016[180]	No cannabis/cannabinoid related outcome
Fowler, 2003[181]	No meta-analysis
Freeman, 2021	No meta-analysis
Frisher, 2009[182]	No meta-analysis
Gaffari, 2014[183]	No meta-analysis
Gandhi, 2017[184]	No meta-analysis
Garay, 2015[185]	No meta-analysis
Garay, 2016[186]	No meta-analysis

Garcia, 2015[187]	No meta-analysis
Garcia, 2016[188]	No meta-analysis
Gates, 2014[189]	No meta-analysis
Giacoppo, 2017[190]	No meta-analysis
Gloss, 2014[191]	No meta-analysis
Gobbi, 2019[192]	Not largest meta-analysis
Godin, 2022[193]	No meta-analysis
Godsey, 2016[194]	No meta-analysis
Goldchluk, 2008[195]	No meta-analysis
Gomez Ochoa, 2021[196]	No meta-analysis
Gonzalez, 2007[197]	No meta-analysis
Gorey, 2019[198]	No meta-analysis
Gorman, 2002[199]	Cross-sectional
Gravas, 2016[200]	No meta-analysis
Gruber, 1996[201]	No meta-analysis
Grundy, 2001[202]	No meta-analysis
Guinguis, 2017[203]	No meta-analysis
Gully, 2017[204]	No meta-analysis
Gunn, 2015[205]	No meta-analysis
Gurney, 2014[206]	No meta-analysis
Haffar, 2018[207]	No meta-analysis
Hall, 2000[208]	No meta-analysis
Hall, 2005[209]	No meta-analysis
Hall, 2006[210]	No meta-analysis
Hammond, 2021[211]	Not largest meta-analysis
Harrison, 2015[212]	No cannabis/cannabinoids related outcome
Hasenoehrl, 2017[213]	No meta-analysis
Hashibe, 2005[214]	No meta-analysis
Hauser, 2017[215]	No meta-analysis
Hauser, 2018[216]	No meta-analysis

Hedlund, 2014[217]	No meta-analysis
Hendren, 2015[218]	No meta-analysis
Henquet, 2005[219]	No meta-analysis
Hill, 2015[220]	No meta-analysis
Hill, 2017[221]	No meta-analysis
Hjorthoj, 2012[222]	No cannabis/cannabinoids related outcome
Hobbs, 2018[223]	No meta-analysis
Hoch, 2015[224]	No meta-analysis
Hoch, 2019[225]	Duplicated
Hoch, 2019[225]	No meta-analysis
Hohmann, 2014[226]	Duplicated
Hohmann, 2014[226]	No meta-analysis
Holitzki, 2017[227]	No meta-analysis
Horwood, 2010[228]	No meta-analysis
Hosseini, 2019[229]	No meta-analysis
Hostiuc, 2018[230]	Duplicated
Houze, 2017[231]	No meta-analysis
Houze, 2018[232]	No meta-analysis
Hoyte, 2012[233]	No meta-analysis
Huemer, 2015[234]	No meta-analysis
Huizink, 2014[235]	No meta-analysis
Hummel, 2013[236]	No meta-analysis
Humphreys, 2013[237]	No cannabis/cannabinoids related outcome
Hunt, 2018[238]	No meta-analysis
Hyman, 2009[239]	No meta-analysis
Iffland, 2017[240]	No meta-analysis
Irner, 2012[241]	No meta-analysis
Iskedjan, 2007[242]	Not largest meta-analysis
Iyalomhe, 2009[243]	No meta-analysis
Izzo, 2008[244]	No meta-analysis

Jacobson, 2019[245]	No meta-analysis
Jacques, 2014[246]	No meta-analysis
Jager, 2008[247]	No meta-analysis
James, 2013[248]	No meta-analysis
Jawahar, 2013[249]	Unclear included studies
Jensen, 2015[250]	No meta-analysis
Johns, 2001[251]	No meta-analysis
Jonsson, 2014[252]	No meta-analysis
Joshi, 2014[253]	No meta-analysis
Jouanjus, 2017[254]	No meta-analysis
Jung, 2016[255]	No meta-analysis
Jutras-Aswad, 2009[256]	No meta-analysis
Kafil, 2018[257]	No meta-analysis
Kafil, 2018[258]	No meta-analysis
Kahan, 2014[259]	No meta-analysis
Kanit, 2009[260]	No meta-analysis
Karila, 2014[261]	No meta-analysis
Karl, 2017[262]	No meta-analysis
Katchan, 2016[263]	No meta-analysis
Katona, 2015[264]	No meta-analysis
Katzberg, 2015[265]	No meta-analysis
Keating, 2017[266]	No meta-analysis
Kedzior, 2014[267]	Not largest meta-analysis
Keen, 2019[268]	No meta-analysis
Kennedy, 2017[269]	No meta-analysis
Kerbage, 2015[270]	No meta-analysis
Khan, 2017[271]	No meta-analysis
Khoury, 2019[272]	No meta-analysis
Kilcher, 2017[273]	No meta-analysis
Kluger, 2015[274]	No meta-analysis

Koek, 2016[275]	No meta-analysis
Kokona, 2017[276]	No meta-analysis
Koppel, 2014[277]	No meta-analysis
Koppel, 2015[278]	No meta-analysis
Korantzopoulos, 2007[279]	No meta-analysis
Kosiba, 2019[280]	Cross-sectional
Koskinen, 2010[281]	No cannabis/cannabinoids related outcome
Kreitzer, 2009[282]	No meta-analysis
Krishnan, 2009[283]	No meta-analysis
Kristanc, 2016[284]	No meta-analysis
Ksir, 2016[285]	No meta-analysis
Kucerova, 2014[286]	No meta-analysis
Kuczkowski, 2004[287]	No meta-analysis
Kumar, 2016[288]	No meta-analysis
La Porta, 2014[289]	No meta-analysis
Lago, 2007[290]	No meta-analysis
Lakhan, 2009[291]	No meta-analysis
Lamy, 2015[292]	No meta-analysis
Langhorst, 2015[293]	No meta-analysis
Lanza, 2017[294]	No meta-analysis
Large, 2012[295]	No meta-analysis
Lattanzi, 2018[296]	Duplicated
Laviolette, 2006[297]	No meta-analysis
Le Bec, 2009[298]	No meta-analysis
Lee, 2011[299]	Duplicated
Lee, 2011[299]	No cannabis/cannabinoids related outcome
Lee, 2018[300]	No meta-analysis
Levine, 2017[301]	No meta-analysis
Li, 2012[302]	Not largest meta-analysis
Lim, 2017[303]	No meta-analysis

Linszen, 2007[304]	No meta-analysis
Lisowska, 2017[305]	No meta-analysis
Liu, 2016[306]	No meta-analysis
Lochte, 2017[307]	No meta-analysis
Loeber, 1999[308]	No meta-analysis
Loeberg, 2009[309]	No meta-analysis
Lorenzetti, 2013[310]	No meta-analysis
Lorenzetti, 2014[311]	No meta-analysis
Lorenzetti, 2016[312]	No meta-analysis
Lorenzetti, 2017[313]	No meta-analysis
Lorenzetti, 2019[314]	Duplicated
Lotsch, 2018[315]	No meta-analysis
Lubman, 2015[316]	No meta-analysis
Lutge, 2013[317]	No meta-analysis
Lynch, 2011[318]	No meta-analysis
Lynch, 2015[319]	No meta-analysis
Lynch, 2016[320]	No meta-analysis
Maccarrone, 2005[321]	No meta-analysis
MacDonald, 2010[322]	No meta-analysis
Macdonald, 2016[323]	No meta-analysis
Machado-Rocha, 2008[324]	Not largest meta-analysis
Macleod, 2004[325]	No meta-analysis
Macleod, 2006[326]	No meta-analysis
Malchow, 2013[327]	No meta-analysis
Maldonado, 2003[328]	No meta-analysis
Mammen, 2018[329]	Duplicated
Mammen, 2018[330]	No meta-analysis
Mandelbaum, 2017[331]	No meta-analysis
Maniglio, 2015[332]	No meta-analysis
Marangoni, 2016[333]	No meta-analysis

Marconi, 2016[334]	Not largest meta-analysis
Martinasek, 2016[335]	No meta-analysis
Martinotti, 2017[336]	No meta-analysis
Martin-Sanchez, 2009[337]	Not largest meta-analysis
Martin-Santos, 2010[338]	No meta-analysis
Massi, 2013[339]	No meta-analysis
Mather, 2005[340]	No meta-analysis
Matheson, 2014[341]	No meta-analysis
Maule, 2015[342]	No meta-analysis
McCartney, 2022[343]	No outcome of interest
McElroy, 2015[344]	No meta-analysis
McKenna, 2014[345]	No meta-analysis
McLachlan, 2015[346]	No meta-analysis
McLaren, 2010[347]	No meta-analysis
McLoughlin, 2014[348]	No meta-analysis
Mechoulam, 2002[349]	No meta-analysis
Mendiguren, 2018[350]	Not human report
Meng, 2017[351]	Not largest meta-analysis
Merlin, 2016[352]	No meta-analysis
Merlob, 2017[353]	No meta-analysis
Metz, 2015[354]	No meta-analysis
Mhera, 2006[355]	No meta-analysis
Mheta, 2016[356]	No meta-analysis
Milano, 2019[357]	No meta-analysis
Minozzi, 2009[358]	No meta-analysis
Moore, 2007[359]	Not largest meta-analysis
More, 2015[360]	No meta-analysis
Morena, 2014[361]	No meta-analysis
Moulin, 2014[362]	No meta-analysis
Mu, 2017[363]	No meta-analysis

Mucke, 2016[364]	Duplicated
Mucke, 2018[365]	Duplicated
Muller, 2013[366]	No meta-analysis
Murillo-Rodriguez, 2014[367]	No meta-analysis
Myles, 2016[368]	No meta-analysis
Nader, 2018[369]	No meta-analysis
Navarri, 2022[370]	Cross-sectional
Neale, 2017[371]	No meta-analysis
Neasta, 2014[372]	No meta-analysis
Ng, 2017[373]	No meta-analysis
Niaz, 2017[374]	No meta-analysis
Nielsen, 2017[375]	Not human report
Nielsen, 2018[376]	No meta-analysis
Niesink, 2013[377]	No meta-analysis
Norton, 2017[378]	No meta-analysis
Nsuala, 2015[379]	No meta-analysis
Nucci, 2008[380]	No meta-analysis
Nugent, 2017[381]	No meta-analysis
Nunez, 2017[382]	No meta-analysis
O'Connel, 2017[383]	No meta-analysis
O'Neil, 2017[384]	No meta-analysis
O'Tuathaigh, 2014[385]	No meta-analysis
Ojo, 2018[386]	No cannabis/cannabinoid related outcome
Onaivi, 2009[387]	No meta-analysis
Orsolini, 2017[388]	No meta-analysis
Osazuwa-Peters, 2016[389]	No meta-analysis
Osborne, 2017[390]	No meta-analysis
Oxentine, 2017[391]	No meta-analysis
Pacheco, 2018[392]	No meta-analysis
Palleria, 2018[393]	No meta-analysis

Pamplona, 2018[394]	Duplicated
Panza, 2015[395]	No meta-analysis
Papanti, 2013[396]	No meta-analysis
Papathansoupolos, 2008[397]	No meta-analysis
Parak, 2013[398]	No meta-analysis
Park, 2004[399]	No meta-analysis
Parmar, 2016[400]	No meta-analysis
Pattij, 2008[401]	No meta-analysis
Pena, 2017[402]	No meta-analysis
Pena, 2018[403]	No meta-analysis
Pertwee, 2007[404]	No meta-analysis
Perucca, 2017[405]	No meta-analysis
Peters, 2012[406]	No meta-analysis
Phillips, 2016[407]	No cannabis/cannabinoid related outcome
Pidgeon, 2013[408]	No meta-analysis
Pisani, 2021[409]	No meta-analysis
Pisanti, 2009[410]	No meta-analysis
Pisanti, 2017[411]	No meta-analysis
Porsteinsson, 2017[412]	No meta-analysis
Poupon, 2015[413]	No meta-analysis
Prud'homme, 2015[414]	No meta-analysis
Pusjpa-Rajan, 2015[415]	No meta-analysis
Qin, 2020[416]	No cannabis exposure
Quickfall, 2006[417]	No meta-analysis
Qureshi, 2018[418]	No meta-analysis
Rabgay, 2020[419]	Not largest meta-analysis
Rabinak, 2014[420]	No meta-analysis
Radhakrishnan, 2014[421]	No meta-analysis
Ragazzi, 2018[422]	No meta-analysis
Ragen, 2015[423]	No meta-analysis

Rai, 2017[424]	No meta-analysis
Rai, 2017[425]	No meta-analysis
Ramkellawan, 2016[426]	No meta-analysis
Ramo, 2012[427]	No meta-analysis
Ramsay Wan, 2018[428]	No meta-analysis
Ranganathan, 2006[429]	No meta-analysis
Raphael, 2005[430]	No meta-analysis
Ravi, 2018[431]	No meta-analysis
Reece, 2009[432]	No meta-analysis
Reisfield, 2009[433]	No meta-analysis
Renard, 2014[434]	No meta-analysis
Reuter, 2016[435]	No meta-analysis
Ribeiro, 2016[436]	No meta-analysis
Ribeiro, 2016[437]	No meta-analysis
Richardson, 2016[438]	No meta-analysis
Rivera-Olmos, 2016[439]	No meta-analysis
Robson, 2001[440]	No meta-analysis
Rocco, 2018[441]	No meta-analysis
Rocha, 2014[442]	No meta-analysis
Rock, 2016[443]	No meta-analysis
Rodriguez, 2018[444]	Duplicated
Rogeberg, 2018[445]	No meta-analysis
Rogeberg, 2019[446]	Duplicated
Rogers, 2017[447]	No meta-analysis
Rohleder, 2016[448]	No meta-analysis
Romero-Sandoval, 2015[449]	No meta-analysis
Romero-Sandoval, 2017[450]	No meta-analysis
Rong, 2018[451]	No meta-analysis
Rosenberg, 2015[452]	No meta-analysis
Rothbart, 2014[453]	No meta-analysis

Rothman, 2015[454]	No meta-analysis
Rubino, 2015[455]	No meta-analysis
Ruisch, 2018[456]	Duplicated
Russel, 2018[457]	No meta-analysis
Sami, 2015[458]	No meta-analysis
Santana, 2015[459]	No meta-analysis
Sarfaraz, 2008[460]	No meta-analysis
Sarne, 2005[461]	No meta-analysis
Schneider, 2008[462]	No meta-analysis
Schreck, 2018[463]	No meta-analysis
Schubart, 2014[464]	No meta-analysis
Schussel, 2018[465]	No meta-analysis
Schussel, 2018[466]	No meta-analysis
Schwartz, 1997[467]	No meta-analysis
Scott, 2018[468]	Duplicated
Sellers, 2017[469]	No meta-analysis
Semple, 2005[470]	Not largest meta-analysis
Serafini, 2012[471]	No meta-analysis
Shahpiri, 2016[472]	No meta-analysis
Sharapova, 2018[473]	No meta-analysis
Sharma, 2015[474]	No meta-analysis
Shorter, 2015[475]	No meta-analysis
Shrivastava, 2015[476]	No meta-analysis
Silva, 2015[477]	No meta-analysis
Silveira, 2017[478]	Not human report
Simons-Linares, 2017[479]	No meta-analysis
Sims, 2018[480]	No meta-analysis
Skalski, 2017[481]	No meta-analysis
Snedecor, 2013[482]	No meta-analysis
Snedecor, 2014[483]	No meta-analysis

Soares, 2017[484]	No meta-analysis
Soler, 2013[485]	No meta-analysis
Soliman, 2021[486]	Not in humans
Solowij, 2008[487]	No meta-analysis
Spadaru, 2017	No meta-analysis
Stanley, 2014[488]	No meta-analysis
Steenkamp, 2017[489]	No meta-analysis
Stern, 2018[490]	No meta-analysis
Stevens, 2017[491]	No meta-analysis
Sticht, 2015[492]	No meta-analysis
Stockings, 2018[493]	Duplicated
Stout, 2014[494]	No meta-analysis
Suarez-Pinilla, 2014[495]	No meta-analysis
Sznitzman, 2015[496]	No meta-analysis
Tafelski, 2016[497]	No meta-analysis
Tahamtan, 2016[498]	No meta-analysis
Tait, 2016[499]	No meta-analysis
Talamo, 2006[500]	No cannabis/cannabinoid related outcome
Tandon, 2017[501]	No meta-analysis
Tateo, 2017[502]	No meta-analysis
Termine, 2013[503]	No meta-analysis
Tetrault, 2007[504]	No meta-analysis
Thornicroft, 1990[505]	No meta-analysis
Tomassini, 2013[506]	No meta-analysis
Tournebize, 2015[507]	Duplicated
Tournebize, 2017[508]	No meta-analysis
Trescot, 2006[509]	No meta-analysis
Trinh, 2018[510]	No meta-analysis
Trojano, 2015[511]	No meta-analysis
Tsang, 2016[512]	No meta-analysis

Tuca, 2013[513]	No meta-analysis
Turcotte, 2016[514]	No meta-analysis
Turgeman, 2017[515]	No meta-analysis
Turna, 2017[516]	No meta-analysis
Turna, 2019[517]	No meta-analysis
Turner, 2014[518]	No meta-analysis
Twomey, 2017[519]	Not largest meta-analysis
Urbi, 2019[520]	Not human report
van den Beuken-van Everdingen, 2017[521]	No meta-analysis
Van den Elsen, 2014[522]	No meta-analysis
Van der Meer, 2012[523]	Duplicated
Van Winkel, 2014[524]	No meta-analysis
VanderVeen, 2016[525]	No cannabis/cannabinoid related outcome
Vassoler, 2014[526]	No meta-analysis
Vaucher, 2018[527]	Duplicated
Velasco, 2015[528]	No meta-analysis
Velayudhan, 2014[529]	No meta-analysis
Verdejo-Garcia, 2007[530]	No meta-analysis
Verdoux, 2004[531]	No meta-analysis
Vermersch, 2015[532]	No meta-analysis
Verrotti, 2016[533]	No meta-analysis
Versteeg, 2008[534]	No meta-analysis
Verweij, 2010[535]	No cannabis/cannabinoid related outcome
Verweij, 2013[536]	No meta-analysis
Vilain, 2013[537]	No meta-analysis
Viteri, 2014[538]	No meta-analysis
Volkow, 2016[539]	No meta-analysis
Voth, 1997[540]	No meta-analysis
Vyas, 2018[541]	No meta-analysis
Wade, 2010[542]	Not largest meta-analysis

Walit, 2016[543]	No meta-analysis
Walker, 2005[544]	No meta-analysis
Walsh, 2017[545]	No meta-analysis
Walter, 2004[546]	No meta-analysis
Watson, 2000[547]	No meta-analysis
Weier, 2017[548]	No meta-analysis
Weinstein, 2017[549]	No meta-analysis
Weiss, 2017[550]	No meta-analysis
Welsh, 2017[551]	No meta-analysis
Werneck, 2018[552]	No meta-analysis
Wijayendran, 2018[553]	No meta-analysis
Wilkinson, 2016[554]	No meta-analysis
Wilson, 2022	Cross-sectional
Wisdon, 2011[555]	No meta-analysis
Witkin, 2005[556]	No meta-analysis
Wolff, 2017[557]	No meta-analysis
Wong, 2017[558]	Duplicated
Wrege, 2014[559]	No meta-analysis
Wright, 2007[560]	No meta-analysis
Yadav, 2014[561]	No meta-analysis
Yadav, 2014[562]	No meta-analysis
Yalcin, 2014[563]	No meta-analysis
Yanes, 2018[564]	No meta-analysis
Yap, 2015[565]	No meta-analysis
Yarnell, 2015[566]	No meta-analysis
Youssef, 2017[567]	Not largest meta-analysis
Yucel, 2012[568]	Duplicated
Yucel, 2012[568]	Not largest meta-analysis
Yurcheshen, 2015[569]	No meta-analysis
Zammit, 2008[570]	No meta-analysis

Zarifi, 2017[571]	No meta-analysis
Zettl, 2016[572]	No meta-analysis
Zhang, 2015[573]	No meta-analysis
Zhang, 2018[574]	No meta-analysis
Zhang, 2018[575]	No meta-analysis
Zilverstand, 2018[576]	No meta-analysis
Zlebnik, 2016[577]	No meta-analysis
Zuardi, 2008[578]	No meta-analysis
Alayash, 2021[579]	Mendelian randomization study
Baumeister, 2021[580]	Mendelian randomization study
Jefsen, 2021[581]	Mendelian randomization study
Johnson, 2021[582]	Mendelian randomization study
Gage, 2017[583]	Mendelian randomization study
Mahedy, 2021[584]	Mendelian randomization study
Soler, 2019[585]	Mendelian randomization study
Orri, 2021[586]	Mendelian randomization study
Vaucher, 2017[527]	Mendelian randomization study
Verweij, 2018[587]	Mendelian randomization study
Zhao, 2021[588]	Mendelian randomization study

eTable 4. Finding across meta-analyses of randomized controlled trials using cannabis and cannabinoids across different populations

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Mixed conditions																		
CBM																		
Aviram, 2017	Mixed conditions (A)	CBM	Psychological adverse events	27	2113	RR	3.07 (1.79, 5.26)	<0.005	0.00/ 0.00	V	V	V	V	V	+	H	L	3.07 (1.79, 5.26)
Aviram, 2017	Mixed conditions (A)	CBM	Vision related adverse events	15	753	RR	3.00 (1.79, 5.03)	<0.005	16.73/ 0.16	V	V	V	V	V	+	H	L	3.00 (1.79, 5.03)
Aviram, 2017	Mixed conditions (A)	CBM	CNS adverse events	40	2934	RR	2.84 (2.16, 3.73)	<0.005	0.00/ 0.00	V	V	V	V	V	+	H	L	2.84 (2.16, 3.73)
Allan, 2018	Mixed conditions (A)	CBM	Nausea/vomit reduction	7	663	RR	3.29 (2.03, 5.30)	<0.005	40.35/ 0.16	V	V	↓	V	V	+	M	H	0.30 (0.19, 0.49)
Amato, 2017	Mixed conditions (A)	CBM	Application site discomfort	3	347	RR	1.15 (0.68, 1.96)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	1.15 (0.68, 1.96)
Aviram, 2017	Mixed conditions (A)	CBM	Cardiac adverse events	10	845	RR	1.50 (0.77, 2.93)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	L	1.50 (0.77, 2.93)
Amato, 2017	Mixed conditions (A)	CBM	Feeling high	8	442	RR	2.82 (1.15, 6.94)	0.01<p< 0.05	54.75/ 0.66	V	V	↓↓	V	V	x	M	H	2.82 (1.15, 6.94)
Aviram, 2017	Mixed conditions (A)	CBM	Gastrointestinal adverse events	42	3299	RR	1.87 (1.44, 2.43)	<0.005	0.00/ 0.00	V	V	V	↓	V	x	M	L	1.87 (1.44, 2.43)
Amato, 2017	Mixed conditions (A)	CBM	Gastrointestinal disorder (non-serious)	10	1909	RR	1.34 (1.02, 1.76)	0.01<p< 0.05	0.00/ 0.00	V	V	↓↓	V	V	x	M	H	1.34 (1.02, 1.76)
Amato, 2017	Mixed conditions (A)	CBM	General psychiatric disorder	3	764	RR	3.00 (1.60, 5.64)	<0.005	1.38/ 0.01	V	V	↓↓	V	V	x	M	H	3.00 (1.60, 5.64)
Amato, 2017	Mixed conditions (A)	CBM	Headache	10	1776	RR	0.97 (0.71, 1.34)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	0.97 (0.71, 1.34)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Amato, 2017	Mixed conditions (A)	CBM	Musculoskeletal and connective disorder	4	1103	RR	1.19 (0.81, 1.74)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	1.19 (0.81, 1.74)
Aviram, 2017	Mixed conditions (A)	CBM	Musculoskeletal adverse events	10	561	d	0.35 (-0.04, 0.73)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	L	1.88 (0.94, 3.78)
Aviram, 2017	Mixed conditions (A)	CBM	Pain reduction	41	2559	d	-0.40 (-0.58, -0.21)	<0.005	77.84/ 0.25	V	↓	V	↓	V	x	M	L	0.48 (0.35, 0.68)
Allan, 2018	Mixed conditions (A)	CBM	Pain reduction, response (30% reduction)	15	2674	RR	1.30 (1.11, 1.54)	0.005<p <0.01	29.53/ 0.03	V	V	↓	V	↓	x	M	H	0.77 (0.65, 0.91)
Amato, 2017	Mixed conditions (A)	CBM	Pain, pain intensity	2	142	d	-0.62 (-1.00, -0.24)	<0.005	19.04/ 0.01	↓	V	↓	V	V	x	M	H	0.32 (0.16, 0.65)
Amato, 2017	Mixed conditions (A)	CBM	Quality of sleep	2	676	MD	0.40 (-0.30, 1.09)	>0.05	0.78/ NA	V	V	↓↓	V	V	x	M	H	NA
Amato, 2017	Mixed conditions (A)	CBM	Renal urinary disorder	7	1779	RR	1.15 (0.72, 1.84)	>0.05	0.28/ NA	V	V	↓↓	V	V	x	M	H	1.15 (0.72, 1.84
Amato, 2017	Mixed conditions (A)	CBM	Respiratory disorder	3	493	RR	0.84 (0.45, 1.57)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	0.84 (0.45, 1.57)
Allan, 2018	Mixed conditions (A)	CBM	Spasticity reduction, positive global impression of change	4	1066	RR	1.48 (1.04, 2.11)	0.01<p< 0.05	72.78/ 0.09	V	V	↓	V	↓	x	M	H	0.67 (0.47, 0.96)
Amato, 2017	Mixed conditions (A)	CBM	Spasticity reduction	5	1216	MD	-0.10 (-0.27, 0.07)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	NA
Amato, 2017	Mixed conditions (A)	CBM	Weakness	4	804	RR	1.30 (0.96, 1.75)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	1.30 (0.96, 1.75)
Amato, 2017	Mixed conditions (A)	CBM	Acceptability	3	176	RR	0.29 (0.06, 1.38)	>0.05	0.00/ NA	↓	V	↓↓	V	V	x	L	H	0.29 (0.06, 1.38)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Velayudan, 2021	Mixed conditions(A)	THC	All withdrawals, thc:cbd studies	26	2850	IRR	1.40 (1.08, 1.80)	0.01<p< 0.05	32.40/ NA	V	V	↓↓	V	↓	x	L	L	1.40 (1.08, 1.80)
Velayudan, 2021	Mixed conditions(A)	THC, Cannabinoids	All-cause AE, thc studies	30	2627	IRR	1.42 (1.12, 1.79)	0.01<p< 0.05	86.50/ NA	V	↓	↓↓	V	↓	x	L	L	1.42 (1.12, 1.79)
Whiting, 2015	Mixed conditions (NR)	CBM	Anxiety	12	1242	OR	1.98 (0.73, 5.35)	>0.05	54.00/ NA	V	V	↓↓	V	↓	x	L	H	1.98 (0.73, 5.35)
Whiting, 2015	Mixed conditions (NR)	CBM	Any adverse event	29	3458	OR	3.03 (2.42, 3.79)	<0.005	30.98/ 0.10	V	V	↓↓	↓	V	x	L	H	3.03 (2.42, 3.79)
Whiting, 2015	Mixed conditions (NR)	CBM	Asthenia	15	1717	OR	2.03 (1.35, 3.06)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.03 (1.35, 3.06)
Whiting, 2015	Mixed conditions (NR)	CBM	Balance	6	920	OR	2.62 (1.12, 6.13)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.62 (1.12, 6.13)
Whiting, 2015	Mixed conditions (NR)	CBM	Blood and lymphatic system disorder	3	543	OR	1.42 (0.20, 10.25)	>0.05	18.00/ NA	V	V	↓↓	V	↓	x	L	H	1.42 (0.20, 10.25)
Whiting, 2015	Mixed conditions (NR)	CBM	Cardiac disorders	7	833	OR	1.42 (0.58, 3.48)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.42 (0.58, 3.48)
Whiting, 2015	Mixed conditions (NR)	CBM	Confusion	13	1160	OR	4.03 (2.05, 7.97)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	4.03 (2.05, 7.97)
Whiting, 2015	Mixed conditions (NR)	CBM	Death	5	929	OR	1.01 (0.51, 2.00)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.01 (0.51, 2.00)
Velayudhan, 2021	Mixed conditions(A)	THC	Death	30	2627	IRR	1.09 (0.75, 1.59)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	L	1.09 (0.75, 1.59)
Whiting, 2015	Mixed conditions (NR)	CBM	Depression	15	2353	OR	1.32 (0.87, 2.01)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.32 (0.87, 2.01)
Amato, 2017	Mixed conditions (A)	CBM	Dissociation	2	499	RR	3.34(0.89, 12.42)	>0.05	21.49/ 0.36	↓	V	↓↓	V	V	x	L	H	3.34(0.89, 12.42)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Amato, 2017	Mixed conditions (A)	CBM	Disturbance in attention	4	754	RR	6.72 (1.78, 25.34)	0.005<p <0.01	1.50/ 0.03	↓	V	↓↓	V	V	x	L	H	6.72 (1.78, 25.34)
Whiting, 2015	Mixed conditions (NR)	CBM	Diarrhoea	17	2077	OR	1.65 (1.04, 2.62)	0.01<p< 0.05	15.00/ NA	V	V	↓↓	V	↓	x	L	H	1.65 (1.04, 2.62)
Whiting, 2015	Mixed conditions (NR)	CBM	Disorientation	12	1736	OR	5.41 (2.61, 11.19)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	5.41 (2.61, 11.19)
Whiting, 2015	Mixed conditions (NR)	CBM	Dizziness	41	4243	OR	5.09 (4.10, 6.32)	0.01<p< 0.05	18.00/ NA	V	V	↓↓	V	↓	x	L	H	5.09 (4.10, 6.32)
Whiting, 2015	Mixed conditions (NR)	CBM	Drowsiness	18	1272	OR	3.68 (2.24, 6.01)	0.01<p< 0.05	44.00/ NA	V	V	↓↓	V	↓	x	L	H	3.68 (2.24, 6.01)
Whiting, 2015	Mixed conditions (NR)	CBM	Dry mouth	36	4181	OR	3.50 (2.58, 4.75)	0.01<p< 0.05	28.00/ NA	V	V	↓↓	V	↓	x	L	H	3.50 (2.58, 4.75)
Amato, 2017	Mixed conditions (A)	CBM	Dysgeusia	3	774	RR	5.11 (1.75, 14.93)	<0.005	3.88/ 0.04	V	V	↓↓	↓	V	x	L	H	5.11 (1.75, 14.93)
Whiting, 2015	Mixed conditions (NR)	CBM	Dyspnoea	4	375	OR	0.83 (0.26, 2.63)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.83 (0.26, 2.63)
Whiting, 2015	Mixed conditions (NR)	CBM	Ear labyrinth disorders	3	922	OR	2.72 (1.55, 4.75)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.72 (1.55, 4.75)
Whiting, 2015	Mixed conditions (NR)	CBM	Euphoria	27	2420	OR	4.08 (2.18, 7.64)	0.01<p< 0.05	49.00/ NA	V	V	↓↓	V	↓	x	L	H	4.08 (2.18, 7.64)
Whiting, 2015	Mixed conditions (NR)	CBM	Fatigue	20	2717	OR	2.00 (1.54, 2.62)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.00 (1.54, 2.62)
Whiting, 2015	Mixed conditions (NR)	CBM	General disorders and administration-site conditions (non-serious)	6	1280	OR	1.78 (1.34, 2.36)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.78 (1.34, 2.36)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Whiting, 2015	Mixed conditions (NR)	CBM	Hallucination	10	898	OR	2.19 (1.02, 4.68)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.19 (1.02, 4.68)
Watanabe, 2021	Mixed conditions (NR)	CBM	Hypotension	9	656	RR	3.18 (1.05, 9.56)	0.01<p< 0.05	35.50/ 0.06	V	V	↓↓	↓↓	V	x	L	L	3.18 (1.05, 9.56)
Aviram, 2017	Mixed conditions (A)	CBM	Hearing related adverse events	9	386	RR	3.53 (1.58, 7.89)	<0.005	12.34/ 0.18	↓	V	V	↓	↓	x	L	L	3.53 (1.58, 7.89)
Amato, 2017	Mixed conditions (A)	CBM	Mouth ulceration	3	347	RR	2.00 (0.42, 9.51)	>0.05	0.00/ NA	↓	V	↓↓	V	V	x	L	H	2.00 (0.42, 9.51)
Whiting, 2015	Mixed conditions (NR)	CBM	Infections and infestations	7	1681	OR	1.13 (0.87, 1.46)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.13 (0.87, 1.46)
Whiting, 2015	Mixed conditions (NR)	CBM	Injury, poisoning and procedural complications	3	543	OR	1.18 (0.48, 2.93)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.18 (0.48, 2.93)
Whiting, 2015	Mixed conditions (NR)	CBM	Investigations	2	427	OR	1.55 (0.36, 6.71)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.55 (0.36, 6.71)
Whiting, 2015	Mixed conditions (NR)	CBM	Mental status change	3	106	OR	2.49 (0.49,12.64)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	2.49 (0.49, 12.64)
Whiting, 2015	Mixed conditions (NR)	CBM	Metabolism and nutrition disorders (non-serious)	2	427	OR	2.37 (1.00, 5.61)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.37 (1.00, 5.61)
Whiting, 2015	Mixed conditions (NR)	CBM	Musculoskeletal, connective tissue, bone disorder	7	1310	OR	1.32 (0.75, 2.32)	>0.05	34.00/ NA	V	V	↓↓	V	↓	x	L	H	1.32 (0.75, 2.32)
Amato, 2017	Mixed conditions (A)	CBM	Nausea	11	1926	RR	1.96 (1.49, 2.58)	<0.005	0.00/ 0.00	V	V	↓↓	V	↓	x	L	H	1.96 (1.49, 2.58)
Whiting, 2015	Mixed conditions (NR)	CBM, THC/CBD	Nausea	30	3579	OR	2.08 (1.63, 2.65)	0.01<p< 0.05	0.00/ 0.00	V	V	↓↓	V	↓	x	L	H	0.48 (0.38, 0.61)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Amato, 2017	Mixed conditions (A)	CBM	Nausea, absence	3	313	RR	2.73 (0.90, 8.27)	>0.05	88.95/ 0.84	V	↓	↓↓	↓	V	x	L	H	0.37 (0.12, 1.11)
Allan, 2018	Mixed conditions (A)	CBM	Nausea/ vomiting reduction, response	14	1260	RR	1.73 (1.17, 2.55)	0.005<p <0.01	70.82/ 0.22	V	V	↓	↓	↓	x	L	H	0.58 (0.39, 0.85)
Amato, 2017	Mixed conditions (A)	CBM	Nausea/vomit absence	2	176	RR	3.68 (0.11, 22.40)	>0.05	0.84/ NA	↓	V	↓↓	V	V	x	L	H	0.27 (0.02, 3.88)
Whiting, 2015	Mixed conditions (NR)	CBM, THC/CBD	Nausea/vomit complete	3	102	OR	2.84 (1.12, 7.22)	0.01<p< 0.05	18.70/ 0.14	↓	V	↓↓	↓	V	x	L	H	0.35 (0.14, 0.89)
Whiting, 2015	Mixed conditions (NR)	CBM	Neoplasms, benign, malignant, and unspecified	2	427	OR	0.99 (0.47, 2.08)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.99 (0.47, 2.08)
Whiting, 2015	Mixed conditions (NR)	CBM	Nervous system disorder (non-serious)	10	1521	OR	3.17 (2.20, 4.58)	0.01<p< 0.05	46.00/ NA	V	V	↓↓	V	↓	x	L	H	3.17 (2.20, 4.58)
Whiting, 2015	Mixed conditions (NR)	Nabiximols, THC	Pain reduction	8	1370	OR	1.41 (0.99, 2.00)	>0.05	47.60/ NA	V	V	↓↓	V	↓	x	L	H	0.71 (0.50, 1.01)
Amato, 2017	Mixed conditions (A)	CBM	Pain, minimum score	2	78	d	-0.36 (-0.80, 0.09)	>0.05	0.00/ NA	↓↓	V	↓↓	V	V	x	L	H	NA
Whiting, 2015	Mixed conditions (NR)	CBM	Paranoia	4	492	OR	2.05(0.42, 10.10)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.05(0.42, 10.10)
Whiting, 2015	Mixed conditions (NR)	CBM	Psychiatric disorders (non-serious)	8	1672	OR	3.10 (1.81, 5.29)	0.01<p< 0.05	55.00/ NA	V	V	↓↓	V	↓	x	L	H	3.10 (1.81, 5.29)
Whiting, 2015	Mixed conditions (NR)	CBM	Renal and urinary disorder (non-serious)	3	470	OR	2.45 (2.27, 2.65)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	2.45 (2.27, 2.65)
Whiting, 2015	Mixed conditions (NR)	CBM	Respiratory, thoracic, mediastinal disorder	5	851	OR	0.80 (0.46, 1.39)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.80 (0.46, 1.39)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Whiting, 2015	Mixed conditions (NR)	CBM	Serious adverse events	34	3248	OR	1.41 (1.04, 1.92)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.41 (1.04, 1.92)
Velayudhan, 2021	Mixed conditions(A)	THC	Serious adverse events	27	2082	IRR	1.08 (0.80, 1.46)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	L	1.08 (0.80, 1.46)
Whiting, 2015	Mixed conditions (NR)	CBM	Skin and subcutaneous tissue	3	405	OR	0.85 (0.34, 2.13)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.85 (0.34, 2.13)
Whiting, 2015	Mixed conditions (NR)	CBM	Somnolence	26	3168	OR	2.83 (2.05, 3.91)	0.01<p< 0.05	27.00/ NA	V	V	↓↓	V	↓	x	L	H	2.83 (2.05, 3.91)
Whiting, 2015	Mixed conditions (NR)	Nabiximols, dronabinol THC/CBD	Spasticity reduction	6	1134	MD	-0.12(-0.24,0.01)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	NA
Velayudhan, 2021	Mixed conditions(A)	THC	Tolerability	27	3330	IRR	1.18 (0.89, 1.57)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	L	1.18 (0.89, 1.57)
Velayudan, 2021	Mixed conditions(A)	THC	Treatment related AE, thc:cbd studies	9	1113	IRR	1.70 (1.24, 2.33)	0.01<p< 0.05	85.20/ NA	V	↓	↓↓	V	↓	x	L	L	1.70 (1.24, 2.33)
Velayudan, 2021	Mixed conditions(A)	THC, Cannabinoids	Treatment related AE, thc studies	9	391	IRR	1.60 (1.26, 2.04)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	L	1.60 (1.26, 2.04)
Whiting, 2015	Mixed conditions (NR)	CBM	Vomiting	17	2191	OR	1.67 (1.13, 2.47)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.67 (1.13, 2.47)
Amato, 2017	Mixed conditions (A)	CBM	Vomiting absence	3	140	RR	1.85 (0.14, 24.19)	>0.05	0.71/ NA	↓	V	↓↓	V	V	x	L	H	0.54 (0.04, 7.10)
Amato, 2017	Mixed conditions (A)	CBM	Vertigo	4	957	RR	3.35 (1.44, 7.77)	<0.005	32.64/ 0.23	↓	V	↓↓	V	V	x	L	H	3.35 (1.44, 7.77)
Amato, 2017	Mixed conditions (A)	CBM	Vision blurred	4	1063	RR	2.29 (0.70, 7.43)	>0.05	30.91/ 0.49	↓	V	↓↓	V	V	x	L	H	2.29 (0.70, 7.43)
Whiting, 2015	Mixed conditions (NR)	CBM	Withdrawal due to adverse events	23	2755	OR	2.94 (2.18, 3.96)	0.01<p< 0.05	2.00/	V	V	↓↓	V	↓	x	L	H	2.94 (2.18, 3.96)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									NA									
Velayudan, 2021	Mixed conditions(A)	THC	All-cause AE, thc:cbd studies	16	2254	IRR	1.58 (1.26, 1.98)	0.01<p< 0.05	92.20/ NA	V	↓↓	↓↓	V	↓	x	VL	L	1.58 (1.26, 1.98)
Wang, 2008	Mixed conditions (A)	Cannabis	Non serious adverse events	26	4198	RR	1.86 (1.56, 2.21)	<0.005	86.66/ 0.14	V	↓	↓↓	↓↓	V	x	VL	L	1.86 (1.56, 2.21)
Watanabe, 2021	Mixed conditions (NR)	CBM	Orthostatic hypotension	10	384	RR	3.27 (1.85, 5.78)	<0.005	6.94/ 0.06	V	V	↓↓	↓↓	↓	x	VL	L	3.27 (1.85, 5.78)
Whiting, 2015	Mixed conditions (NR)	CBM	Psychosis	2	37	OR	1.09(0.07, 16.35)	>0.05	25.00/ NA	↓↓	V	↓↓	V	↓	x	VL	H	1.09(0.07, 16.35)
Whiting, 2015	Mixed conditions (NR)	CBM	Seizures	2	42	OR	0.91(0.05, 15.66)	>0.05	0.00/ NA	↓↓	V	↓↓	V	↓	x	VL	H	0.91(0.05, 15.66)
Whiting, 2015	Mixed conditions (NR)	Nabiximols, THC	Sleep disturbances	3	602	MD	-0.23 (-0.60, 0.14)	>0.05	79.51/ 0.06	V	↓	↓↓	↓	↓	x	VL	H	NA
Whiting, 2015	Mixed conditions (NR)	Nabiximols, THC	Sleep quality	8	1415	MD	-0.28 (-1.88, 1.31)	>0.05	96.18/ 3.91	V	↓↓	↓↓	↓	V	x	VL	H	NA
Watanabe, 2021	Mixed conditions (NR)	CBM	Syncope	3	128	RR	1.18 (0.25, 5.59)	>0.05	0.00/ NA	↓	V	↓↓	↓↓	↓	x	VL	L	1.18 (0.25, 5.59)
Watanabe, 2021	Mixed conditions (NR)	CBM	Tachycardia	12	492	RR	1.94 (0.81, 4.64)	>0.05	48.06/ NA	V	V	↓↓	↓↓	↓	x	VL	L	1.94 (0.81, 4.64)
CBD																		
Treves, 2021	Mixed conditions (C)	CBD	50% seizure reduction	2	1026	RR	1.70 (1.09, 2.65)	0.01<p< 0.05	3.83/ 0.01	V	V	V	V	V	x	H	H	0.59 (0.38, 0.92)
Treves, 2021	Mixed conditions (C)	CBD	Reported seizure events	3	318	RR	0.59 (0.36, 0.96)	0.01<p< 0.05	23.21/ 0.05	V	V	V	V	V	x	H	H	0.59 (0.36, 0.96)
Chesney, 2020	Mixed conditions (C, A)	CBD	Pneumonia	3	516	OR	5.37 (1.95, 24.94)	0.01<p< 0.05	1.36/	↓↓	V	V	V	V	x	M	H	5.37 (1.95, 24.94)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									0.03									
Chesney, 2020	Mixed conditions (C, A)	CBD	Somnolence	5	570	OR	2.97 (1.92, 6.11)	<0.005	31.35/ 0.21	↓	V	V	V	V	x	M	H	2.97 (1.92, 6.11)
Treves, 2021	Mixed conditions (C)	CBD	Gastrointestinal hyperactivity events	3	352	RR	2.30 (1.28, 4.13)	<0.005	30.26/ 0.08	↓	V	V	V	V	+	M	H	2.30 (1.28, 4.13)
Chesney, 2020	Mixed conditions (C, A)	CBD	Tolerability	5	570	OR	3.66 (1.04, 12.95)	0.01<p< 0.05	22.80/ 0.47	↓↓	V	V	V	V	x	M	H	3.66 (1.04, 12.95)
Chesney, 2020	Mixed conditions (C, A)	CBD	Acceptability	6	521	OR	1.30 (0.45, 3.76)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.30 (0.45, 3.76)
Chesney, 2020	Mixed conditions (C, A)	CBD	Adverse event - Any	10	775	OR	1.55 (1.03, 2.33)	0.01<p< 0.05	22.0/ NA	V	V	↓↓	↓	↓	x	L	H	1.55 (1.03, 2.33)
Chesney, 2020	Mixed conditions (C, A)	CBD	Adverse event - Decreased appetite	7	606	OR	3.56 (1.94, 6.53)	<0.005	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	3.56 (1.94, 6.53)
Chesney, 2020	Mixed conditions (C, A)	CBD	Adverse event - Diarrhoea	9	734	OR	2.61 (1.46, 4.67)	<0.005	15.00/ NA	V	V	↓↓	↓	↓	x	L	H	2.61 (1.46, 4.67)
Chesney, 2020	Mixed conditions (C, A)	CBD	Adverse event - Sedation	4	266	OR	4.21 (1.18, 15.01)	0.01<p< 0.05	0.00/ 0.00	V	V	↓↓	↓	↓	x	L	H	4.21 (1.18, 15.01)
Chesney, 2020	Mixed conditions (C, A)	CBD	Adverse event - Somnolence	7	682	OR	2.23 (1.07, 4.64)	0.01<p< 0.05	37.00/ NA	V	V	↓↓	↓	↓	x	L	H	2.23 (1.07, 4.64)
Chesney, 2020	Mixed conditions (C, A)	CBD	Constipation	3	230	OR	0.74 (0.18, 3.08)	>0.05	15.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.74 (0.18, 3.08)
Chesney, 2020	Mixed conditions (C, A)	CBD	Convulsion	4	550	OR	1.54 (0.38, 6.33)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.65 (0.16, 2.65)
Chesney, 2020	Mixed conditions (C, A)	CBD	Cough	5	377	OR	0.69 (0.16, 2.92)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.69 (0.16, 2.92)
Velayudhan, 2021	Mixed conditions(A)	THC, CBD	Death	26	3622	IRR	1.14 (0.89, 1.46)	>0.05	0.00/	V	V	↓↓	V	↓	x	L	L	1.14 (0.89, 1.46)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									NA									
Treves, 2021	Mixed conditions (C)	CBM, CBD	Decreased appetite	5	642	RR	2.10 (0.96, 4.62)	>0.05	22.00/ NA	↓	V	↓↓	V	↓	x	L	H	2.10 (0.96, 4.62)
Chesney, 2020	Mixed conditions (C, A)	CBD	Fatigue	8	646	OR	1.27 (0.45, 3.36)	>0.05	44.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.27 (0.45, 3.36)
Treves, 2021	Mixed conditions (C)	CBM, THC/CBD	Gastrointestinal hyperactivity events	5	706	RR	1.63 (0.96, 2.76)	>0.05	62.00/ NA	V	V	↓↓	V	↓	x	L	H	1.63 (0.96, 2.76)
Treves, 2021	Mixed conditions (C)	CBD:THC mixed	Gastrointestinal hyperactivity events	2	354	RR	1.04 (0.63, 173)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.04 (0.63, 173)
Chesney, 2020	Mixed conditions (C, A)	CBD	Headache	9	734	OR	0.92 (0.45, 1.86)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.92 (0.45, 1.86)
Chesney, 2020	Mixed conditions (C, A)	CBD	Insomnia	4	364	OR	1.14 (0.35, 3.77)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.14 (0.35, 3.77)
Chesney, 2020	Mixed conditions (C, A)	CBD	Nasopharyngitis	6	455	OR	1.19 (0.55, 2.57)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.19 (0.55, 2.57)
Chesney, 2020	Mixed conditions (C, A)	CBD	Pyrexia	4	550	OR	1.16 (0.60, 2.25)	>0.05	24.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.16 (0.60, 2.25)
Treves, 2021	Mixed conditions (C)	CBD:THC mixed	Reported seizure events	2	144	RR	1.35 (0.46, 4.03)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	1.35 (0.46, 4.03)
Treves, 2021	Mixed conditions (C)	CBM, THC/CBD	Reported seizure events	5	706	RR	0.71 (0.41, 1.25)	>0.05	24.00/ NA	V	V	↓↓	V	↓	x	L	H	0.71 (0.41, 1.25)
Treves, 2021	Mixed conditions (C)	CBM, THC/CBD	Serious adverse events	6	744	RR	1.63 (0.80, 3.29)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	1.63 (0.80, 3.29)
Velayudhan, 2021	Mixed conditions(A)	THC, CBD	All cause serious adverse events	26	3803	IRR	1.17 (0.99, 1.39)	>0.05	7.00/ NA	V	V	↓↓	V	↓	x	L	L	1.17 (0.99, 1.39)
Velayudhan, 2021	Mixed conditions(A)	THC, CBD	Treatment related serious adverse events	21	2627	IRR	1.19 (0.88, 1.62)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	L	1.19 (0.88, 1.62)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Chesney, 2020	Mixed conditions (C, A)	CBD	Status epilepticus	4	550	OR	1.36 (0.54, 3.41)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.36 (0.54, 3.41)
Chesney, 2020	Mixed conditions (C, A)	CBD	Upper respiratory tract infections	5	575	OR	0.92 (0.51, 1.67)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.92 (0.51, 1.67)
Chesney, 2020	Mixed conditions (C, A)	CBD	Vomiting	7	622	OR	0.93 (0.54, 1.60)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.93 (0.54, 1.60)
Chesney, 2020	Mixed conditions (C, A)	CBD	Withdrawal - Adverse events	7	683	OR	2.65 (1.04, 6.80)	0.01<p< 0.05	0.00/ 0.00	V	V	↓↓	↓	↓	x	L	H	2.65 (1.04, 6.80)
Chesney, 2020	Mixed conditions (C, A)	CBD	Withdrawal - Any reason	11	779	OR	2.61 (1.38, 4.96)	<0.005	0.00/ 0.00	V	V	↓↓	↓	↓	x	L	H	2.61 (1.38, 4.96)
Chesney, 2020	Mixed conditions (C, A)	CBD	Irritability	3	379	OR	2.84 (0.80, 10.03)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	2.84 (0.80, 10.03)
Chesney, 2020	Mixed conditions (C, A)	CBD	Rash	6	315	OR	2.33 (0.70, 7.76)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	2.33 (0.70, 7.76)
Chesney, 2020	Mixed conditions (C, A)	CBD	Serious adverse event - Pneumonia	3	516	OR	5.37 (1.17, 24.65)	0.01<p< 0.05	0.00/ NA	↓↓	V	↓↓	↓	↓	x	VL	H	5.37 (1.17, 24.65)
Chesney, 2020	Mixed conditions (C, A)	CBD	Abdominal pain	4	103	OR	1.14 (0.25, 5.16)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	1.14 (0.25, 5.16)
Chesney, 2020	Mixed conditions (C, A)	CBD	Abnormal liver test	4	199	OR	3.41 (0.73, 15.88)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	3.41 (0.73, 15.88)
Chesney, 2020	Mixed conditions (C, A)	CBD	Dizziness	5	137	OR	0.44 (0.12, 1.58)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	0.44 (0.12, 1.58)
Chesney, 2020	Mixed conditions (C, A)	CBD	Gastrointestinal	3	153	OR	1.78 (0.34, 9.36)	>0.05	72.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	1.78 (0.34, 9.36)
Chesney, 2020	Mixed conditions (C, A)	CBD	Nausea	5	184	OR	1.74 (0.49, 6.13)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	1.74 (0.49, 6.13)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Chesney, 2020	Mixed conditions (C, A)	CBD	Nervous system disorder	2	112	OR	2.00 (0.10, 38.36)	>0.05	81.00/ NA	↓	↓	↓↓	↓	↓	x	VL	H	2.00 (0.10, 38.36)
Chesney, 2020	Mixed conditions (C, A)	CBD	Lethargy	4	390	OR	1.42 (0.45, 4.50)	>0.05	21.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	1.42 (0.45, 4.50)
Chesney, 2020	Mixed conditions (C, A)	CBD	Serious adverse event - Any	7	710	OR	2.30 (1.18, 4.48)	0.01<p< 0.05	16.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	2.30 (1.18, 4.48)
Chesney, 2020	Mixed conditions (C, A)	CBD	Nasal congestion	3	216	OR	0.89 (0.09, 8.97)	>0.05	55.00/ NA	↓	V	↓↓	↓	↓	x	VL	H	0.89 (0.09, 8.97)
Chronic pain conditions																		
Stockings, 2018	Mixed conditions (chronic pain, non-cancer, A)	CBM	Pain 30% reduction	9	1734	OR	1.70 (1.08, 2.68)	0.01<p< 0.05	66.31/ 0.28	V	V	V	V	V	x	H	M	0.59 (0.37, 0.93)
Wang, 2021	Mixed conditions (chronic pain, A)	CBM or cannabinoids	Pain relief	4	1359	MD	-0.09 (-0.30, 0.10)	>0.05	40.19/ 0.02	V	V	V	V	V	x	H	H	NA
Wong, 2020	Mixed conditions (chronic pain, non-cancer, A)	Cannabinoids (oromucosal)	Analgesic efficacy	14	1767	MD	-0.44 (-0.67, -0.21)	<0.005	48.18/ 0.08	V	V	↓↓	V	V	x	M	L	NA, beneficial
Wong, 2020	Mixed conditions (chronic MS neuropathic pain, A)	Cannabinoids	Analgesic efficacy	11	1258	MD	-0.67 (-0.97, -0.37)	<0.005	49.57/ 0.11	V	V	↓↓	V	V	x	M	L	NA, beneficial
Wong, 2020	Mixed conditions (chronic pain, non-cancer, A)	Cannabinoids	Analgesic efficacy	38	3382	MD	-0.63 (-0.82, -0.44)	<0.005	64.55/ 0.19	V	V	↓↓	V	V	x	M	L	NA, beneficial
Wong, 2020	Mixed conditions (chronic pain, non-cancer, A)	Cannabinoids (oral)	Analgesic efficacy	11	735	MD	-0.75 (-1.14, -0.35)	<0.005	57.59/ 0.23	V	V	↓↓	V	V	x	M	L	NA, beneficial
Wong, 2020	Mixed conditions (chronic non-cancer non-neuropathic pain, A)	Cannabinoids	Analgesic efficacy	8	729	MD	-0.61 (-1.01, -0.22)	<0.005	62.64/ 0.18	V	V	↓↓	V	V	x	M	L	NA, beneficial
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Pain 50% reduction	9	1001	RD	0.06 (-0.01, 0.12)	>0.05	65.77/ 0.01	V	V	↓↓	V	V	x	M	H	NA

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Andreae, 2015	Pain, chronic neuropathic (Ado, A)	Cannabis (inhaled)	Pain reduction	9	520	OR	3.14 (1.90, 5.18)	<0.005	3.24/ 0.02	V	V	↓	↓	V	x	M	L	0.32 (0.19, 0.52)
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Pain reduction, response (30% reduction)	11	1586	RD	0.09 (0.03, 0.15)	0.005<p <0.01	36.19/ 0.00	V	V	↓↓	V	V	x	M	H	NA, beneficial
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Patient global impression much/very much improved	6	1090	RD	0.10 (-0.00, 0.19)	>0.05	72.64/ 0.01	V	V	↓↓	V	V	x	M	H	NA
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Psychological distress	10	751	d	-0.31 (-0.61, -0.01)	0.01<p< 0.05	66.91/ 0.14	V	V	↓↓	V	V	x	M	H	1.76 (1.03, 3.05)
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Withdrawals due to adverse events	16	1778	RD	0.04 (0.02, 0.07)	<0.005	25.84/ 0.00	V	V	↓↓	V	V	x	M	H	NA, harmful
Stockings, 2018	Mixed conditions (chronic pain, non-cancer, A)	CBM	Pain, change in pain scores	34	3866	d	-0.17 (-0.28, -0.05)	<0.005	62.20/ 0.06	V	V	↓↓	V	V	x	M	H	0.73 (0.60, 0.90)
Wong, 2020	Mixed conditions (chronic pain, non-cancer, A)	Cannabinoids (inhaled)	Analgesic efficacy	8	468	MD	-1.06 (-1.56, -0.55)	<0.005	79.76/ 0.39	V	↓	↓↓	V	↓	x	L	L	NA, beneficial
Wong, 2020	Mixed conditions ((chronic neuropathic pain, A)	Cannabinoids	Analgesic efficacy	25	2060	MD	-0.74 (-0.94, -0.54)	<0.005	52.74/ 0.12	V	V	↓↓	V	↓	x	L	L	NA, beneficial
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Any adverse event	7	1356	RD	0.20 (0.10, 0.30)	<0.005	79.71/	V	↓	↓↓	V	↓	x	L	H	NA, harmful
Spanagel, 2021	Mixed conditions (chronic, neuropathic pain, A)	CBM, THC/CBD	Appetite decrease	9	948	OR	0.70 (0.42, 1.17)	>0.05	18.00/ NA	V	V	↓↓	↓	↓	x	L	H	0.70 (0.42, 1.17)
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Health related quality of life	9	1284	d	0.02 (-0.10, 0.30)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.96 (0.67, 1.39)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Sainsbury, 2021	Mixed conditions (chronic, neuropathic pain, A)	THC/CBD	Pain intensity, 30% reduction from baseline	2	371	RR	1.75 (1.16, 2.65)	<0.005	0.00/ 0.00	V	V	↓↓	↓	V	x	L	L	0.57 (0.38, 0.86)
Sainsbury, 2021	Mixed conditions (chronic, neuropathic pain, A)	THC	Pain intensity, 30% reduction from baseline	6	213	RR	1.98 (1.48, 2.62)	<0.005	29.26/ 0.04	V	V	↓↓	↓	V	x	L	L	0.51 (0.38, 0.67)
Sainsbury, 2021	Mixed conditions (chronic neuropathic pain, A)	CBM, THC/CBD	Pain intensity, change from baseline	6	196	MD	-8.67 (-11.50, -5.84)	<0.005	15.60/ 2.04	↓	V	↓↓	↓	V	x	L	L	NA, beneficial
Wang, 2021	Mixed conditions (chronic pain, A)	CBM	Pain relief	27	3939	MD	-0.98 (-1.47, -0.49)	<0.005	94.12/ 1.44	V	↓↓	V	V	↓	x	L	H	NA, beneficial
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Pain, mean intensity	17	1837	d	-0.35 (-0.60, -0.09)	0.005<p <0.01	83.90/ 0.22	V	↓	↓↓	V	V	x	L	H	0.53 (0.33, 0.84)
Mucke, 2018	Mixed conditions (chronic cancer neuropathic pain, A)	CBM	Serious adverse events	11	968	RD	0.06 (0.01, 0.10)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	NA, harmful
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Serious adverse events	13	1876	RD	0.01 (-0.01, 0.03)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	NA
Spanagel, 2021	Mixed conditions (chronic, neuropathic pain, A)	THC	Sleep decrease	13	1100	OR	1.12 (0.79, 1.57)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	1.12 (0.79, 1.57)
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Specific adverse effects NCS	11	1305	RD	0.38 (0.17, 0.58)	<0.005	94.35/ NA	V	↓↓	↓↓	V	V	x	L	H	NA, harmful
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Specific adverse effects psychiatric disorder	11	1314	RD	0.10 (0.06, 0.16)	<0.005	55.05/ 0.01	V	V	↓↓	V	↓	x	L	H	NA, harmful
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Withdrawals due to lack of efficacy	9	1576	RD	0.00 (-0.02, 0.01)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	NA
Allende-Salazar, 2017	Mixed conditions (chronic non-cancer pain)(A)	CBM	Pain reduction, response (30% reduction)	15	1788	RR	1.27 (1.12, 1.44)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	V	x	L	L	0.79 (0.69, 0.89)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Gazendam, 2020	Surgery (A)	CBM	Pain score	6	678	MD	-0.90 (-1.69, -0.10)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	↓	x	VL	L	NA, beneficial
Sainsbury, 2021	Mixed conditions (chronic, neuropathic pain, A)	CBM, THC/CBD	Pain, difference in post-treatment	2	77	MD	1.00 (-19.14, 21.15)	>0.05	NR/ NA	↓	↓	↓↓	↓	↓	x	VL	L	NA
Mucke, 2018	Mixed conditions (chronic neuropathic pain, A)	CBM	Sleep problems	11	1386	d	-0.44 (-0.83, -0.05)	0.01<p< 0.05	93.03/ 0.39	V	↓↓	↓↓	V	↓	x	VL	H	2.22 (1.09, 4.49)
Epilepsy																		
Elliott, 2018	Epilepsy (C)	CBD	Diarrhoea	3	516	RR	2.25 (1.33, 3.81)	<0.005	12.17/ 0.03	V	V	V	V	V	+	H	M	2.25 (1.33, 3.81)
Elliott, 2018	Epilepsy (C)	CBD	Sleep disruption	3	516	MD	-0.29 (-0.88, 0.30)	>0.05	23.44/ 0.06	V	V	V	V	V	x	H	M	NA
Elliott, 2018	Epilepsy (C)	CBD	Seizures, frequency reduction	3	516	Median	-20.18 (-27.40, -12.96)	<0.005	0.03/ 0.01	↓↓	V	V	V	V	x	M	M	NA, beneficial
Elliott, 2018	Epilepsy (C)	CBD	Tonic-clonic seizure reduction	3	321	Median	-26.67 (-39.04, -14.30)	<0.005	7.95/ 9.56	↓↓	V	V	V	V	x	M	M	NA, beneficial
Stockings, 2018	Epilepsy (any age)	CBD	Any adverse event	5	531	RR	1.24 (1.13, 1.36)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	1.24 (1.13, 1.36)
Lattanzi, 2018	Treatment-resistant Dravet syndrome, Lennox-Gastaut (C)	CBD	Any adverse event	2	396	OR	1.23 (1.10, 1.37)	<0.005	0.00/ 0.00	V	V	V	V	↓	x	M	H	1.23 (1.10, 1.37)
Lattanzi, 2018	TR epilepsy (Ado, A)	CBD	Any seizure frequency	3	516	MD	19.94 (11.79, 28.08)	<0.005	0.06/ 0.03	↓	V	V	V	V	x	M	H	NA, beneficial
Lattanzi, 2018	TR epilepsy (Ado, A)	CBD	Convulsive seizure frequency	3	516	MD	20.54 (12.56, 28.52)	<0.005	0.46/ 0.24	↓	V	V	V	V	x	M	H	NA, beneficial

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Decreased appetite	4	550	RR	3.69 (2.02, 6.72)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	H	3.69 (2.02, 6.72)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Diarrhoea	4	516	RR	2.25 (1.38, 3.68)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	H	2.25 (1.38, 3.68)
Elliott, 2018	Epilepsy (C)	CBD	Gastrointestinal adverse events	4	550	RR	1.54 (0.92, 2.58)	>0.05	52.00/ NA	V	V	↓↓	V	V	x	M	H	1.54 (0.92, 2.58)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Global impression change	4	510	RR	1.57 (1.30, 1.91)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	H	0.64 (0.52, 0.77)
Lattanzi, 2020	Dravet syndrome (C)	CBD	Global impression change	2	202	RR	1.51 (1.21, 1.89)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	CL	0.66 (0.53, 0.83)
Stockings, 2018	Epilepsy (any age)	CBD	Quality of life	2	274	RR	1.73 (1.33, 2.26)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	V	x	M	M	0.58 (0.44, 0.75)
Elliott, 2018	Epilepsy (C)	CBD	Quality of life	3	516	MD	0.60 (-2.60, 3.90)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	NA
De Carvalho, 2020	Treatment-resistant epilepsy (C, A)	CBD	Seizure reduction	6	892	OR	3.08 (2.22, 4.27)	<0.005	9.95/ 0.02	V	V	↓	V	V	x	M	H	0.33 (0.23, 0.45)
Stockings, 2018	Epilepsy (any age)	CBD	Seizure, 50% or greater reduction	2	291	RR	1.74 (1.24, 2.30)	0.01<p< 0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	0.57 (0.42, 0.78)
Lattanzi, 2020	Dravet syndrome, Lennox-Gastaut (C)	CBD	Seizure, 50% reduction	8	714	RR	1.87 (1.39, 2.52)	<0.005	28.84/ 0.05	V	V	V	↓	V	x	M	M	0.53 (0.39, 0.72)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	50% seizure reduction	2	291	RR	1.75 (1.23, 2.48)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	CL	0.58 (0.40, 0.81)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Seizure, 50% reduction in drop seizures	2	396	OR	2.13 (1.44, 3.17)	<0.005	16.78/ 0.01	V	V	V	V	↓	x	M	H	0.47 (0.31, 0.70)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Serious adverse events	4	550	RR	2.61 (1.52, 4.47)	<0.005	0.01/	V	V	↓↓	V	V	x	M	H	2.61 (1.52, 4.47)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									NA									
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Somnolence	4	550	RR	2.75 (1.69, 4.48)	<0.005	0.23/ NA	V	V	↓↓	V	V	x	M	H	2.75 (1.69, 4.48)
Elliott, 2018	Epilepsy (C)	CBD	Status epilepticus	3	516	RR	1.39 (0.55, 3.47)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	H	1.39 (0.55, 3.47)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Treatment-related adverse event	4	550	RR	2.16 (1.71, 2.73)	<0.005	0.00/ NA	V	V	↓↓	V	V	x	M	H	2.16 (1.71, 2.73)
Lattanzi , 2018	Epilepsy, all-types seizures	CBD	Upper respiratory infection	4	516	RR	0.96 (0.56, 1.64)	>0.05	0.09/ NA	V	V	↓↓	V	V	x	M	H	1.04 (0.61, 1.78)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Vomiting	4	550	RR	0.92 (0.56, 1.51)	>0.05	0.33/ NA	V	V	↓↓	V	V	x	M	H	1.09 (0.66, 1.79)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Pyrexia	4	550	RR	1.11 (0.69, 1.78)	>0.05	0.23/ NA	V	V	↓↓	V	V	x	M	H	1.11 (0.69, 1.78)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Acceptability	2	396	RR	5.42 (1.10, 26.76)	0.01<p< 0.05	40.87/ 0.56	↓↓	V	V	V	↓	+	L	M	5.42 (1.10, 26.76)
Lattanzi, 2018	Treatment-resistant Dravet syndrome, Lennox-Gastaut (C)	CBD	Seizure, change in baseline seizures frequency	3	516	MD	17.41 (0.95, 33.88)	0.01<p< 0.05	44.55/ 5.92	↓↓	V	V	V	↓	x	L	H	NA, beneficial
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Tolerability	2	396	RR	6.60 (1.38, 31.42)	0.01<p< 0.05	14.12/ 0.18	↓↓	V	V	V	↓	+	L	M	6.60 (1.38, 31.42)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Fatigue	3	325	RR	1.45 (0.20, 10.57)	>0.05	0.74/ NA	↓	V	↓↓	V	V	x	L	H	1.45 (0.20, 10.57)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Increased aminotransferases	4	550	RR	11.88 (3.77, 37.44)	<0.005	0.00/ NA	↓	V	↓↓	V	V	x	L	M	11.88 (3.77, 37.44)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Sedation	4	205	RR	4.88 (0.92, 25.93)	>0.05	0.00/ NA	↓	V	↓↓	V	V	x	L	H	4.88 (0.92, 25.93)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Stockings, 2018	Epilepsy (any age)	CBD	Seizure, complete freedom	3	306	RR	6.17 (1.50, 25.32)	0.01<p< 0.05	0.00/ NA	↓	V	↓↓	V	V	x	L	H	0.16 (0.04, 0.67)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Treatment-related serious adverse event	4	550	RR	6.93 (1.92, 24.92)	<0.005	0.00/ NA	↓	V	↓↓	V	V	x	L	M	6.93 (1.92, 24.92)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Decreased appetite	2	396	RR	3.21 (1.56, 6.60)	<0.005	NA/ NA	V	↓↓	↓↓	V	V	x	L	M	3.21 (1.56, 6.60)
Lattanzi, 2018	Treatment-resistant Dravet syndrome, Lennox-Gastaut (C)	CBD	Diarrhoea	2	396	RR	1.93 (1.05, 3.52)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	V	x	L	M	1.93 (1.05, 3.52)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Pyrexia	2	396	RR	0.93 (0.54, 1.61)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	M	0.93 (0.54, 1.61)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Somnolence	2	396	RR	2.56 (1.35, 4.83)	<0.005	NA/ NA	V	↓↓	↓↓	V	V	x	L	M	2.56 (1.35, 4.83)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Upper respiratory infections	2	396	RR	0.86 (0.46, 1.59)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	M	0.86 (0.46, 1.59)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Vomiting	2	396	RR	0.71 (0.41, 1.24)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	M	0.71 (0.41, 1.24)
Elliott, 2018	Epilepsy (C)	CBD	Vomiting	4	550	RR	1.00 (0.92, 1.96)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	H	1.00 (0.92, 1.96)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Withdrawal for any reason	4	NA	RR	3.54 (1.55, 8.12)	<0.005	0.00/ NA	↓↓	V	↓↓	V	V	x	L	M	3.54 (1.55, 8.12)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Seizure, 50% reduction in any seizures	1	171	RR	1.76 (1.07, 2.88)	0.01<p< 0.05	NA/ NA	↓	↓↓	↓↓	V	V	x	VL	H	0.57 (0.35, 0.93)
Lattanzi, 2018	Lennox-gastaut syndrome (C)	CBD	Seizure, 50% reduction in non-drop seizures	1	156	RR	1.62 (1.09, 2.43)	0.01<p< 0.05	NA/ NA	↓	↓↓	↓↓	V	V	x	VL	H	0.62 (0.41, 0.92)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Lattanzi, 2018	Epilepsy, all-types seizures	CBD	Withdrawal due to adverse events	4	NR	RR	5.59 (1.67, 16.73)	<0.005	NA/ NA	↓↓	↓↓	↓↓	V	V	x	VL	M	5.59 (1.67, 16.73)
General population																		
Hindley, 2020	General population (A)	Cannabis	Positive symptom	15	324	d	0.91 (0.67, 1.15)	<0.005	67.79/ 0.14	V	V	V	V	↓	+	H	H	5.21 (3.36, 8.01)
Hindley, 2020	General population (A)	Cannabis	Total psychiatric symptoms	10	196	d	1.11 (0.92, 1.29)	<0.005	2.96/ 0.00	↓	V	V	V	V	+	H	H	7.49 (5.31, 10.42)
Hindley, 2020	General population (A)	Cannabis	Negative symptom severity	13	267	d	0.79 (0.58, 0.99)	<0.005	50.50/ 0.07	V	V	V	V	↓	x	M	H	4.19 (2.88, 6.05)
McCartney, 2021	General population (A)	THC	Conflict control	27	805	d	-0.34 (-0.42, -0.25)	<0.005	58.40/ NA	V	V	↓↓	V	V	x	M	L	1.85 (1.59, 2.16)
McCartney, 2021	General population (A)	THC	Divided attention	22	486	d	-0.28 (-0.36, -0.20)	<0.005	14.20/ NA	V	V	↓↓	V	V	x	M	L	1.66 (1.43, 1.92)
McCartney, 2021	General population (A)	THC	Fine motor function	12	310	d	-0.36 (-0.60, -0.12)	<0.005	61.90/ NA	V	V	↓↓	V	V	x	M	L	1.92 (1.24, 2.96)
McCartney, 2021	General population (A)	THC	Fluid intelligence	10	346	d	-0.37 (-0.46, -0.27)	<0.005	16.60/ NA	V	V	↓↓	V	V	x	M	L	1.95 (1.64, 2.32)
McCartney, 2021	General population (A)	THC	Information processing	13	290	d	-0.38 (-0.55, -0.21)	<0.005	23.80/ NA	V	V	↓↓	V	V	x	M	L	1.99 (1.46, 2.71)
McCartney, 2021	General population (A)	THC	Lateral control	16	378	d	-0.24 (-0.41, -0.08)	<0.005	35.70/ NA	V	V	↓↓	V	V	x	M	L	1.54 (1.14, 2.08)
McCartney, 2021	General population (A)	THC	Reaction time cognitive domain	24	647	d	-0.28 (-0.43, -0.13)	<0.005	53.30/ NA	V	V	↓↓	V	V	x	M	L	1.66 (1.26, 2.19)
McCartney, 2021	General population (A)	THC	Standard deviation of lane position	15	353	d	-0.29 (-0.47, -0.11)	<0.005	32.30/ NA	V	V	↓↓	V	V	x	M	L	1.69 (1.22, 2.34)
McCartney, 2021	General population (A)	THC	Sustained attention	16	524	d	-0.23 (-0.37, -0.10)	<0.005	20.30/	V	V	↓↓	V	V	x	M	L	1.52 (1.19, 1.94)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									NA									
McCartney, 2021	General population (A)	THC	Tracking performance	27	606	d	-0.42 (-0.58, -0.25)	<0.005	64.8/ NA	V	V	↓↓	V	V	x	M	L	2.14 (1.59, 2.88)
McCartney, 2021	General population (A)	THC	Working memory	36	800	d	-0.36 (-0.52, -0.20)	<0.005	69.60/ NA	V	V	↓↓	V	V	x	M	L	1.92 (1.44, 2.56)
Hindley, 2020	General population (A)	Cannabis	General psychiatric symptom severity	9	162	d	1.29 (0.42, 2.17)	<0.005	94.59/ 1.59	↓	↓↓	V	V	↓	x	L	H	10.50 (2.15, 51.32)
McCartney, 2021	General population (A)	THC	Car following headway	8	124	d	-0.03 (-0.32, 0.27)	>0.05	44.40/ NA	↓	V	↓↓	V	V	x	L	L	1.05 (0.62, 1.80)
McCartney, 2021	General population (A)	THC	Car following headway variability	8	124	d	-0.24 (-0.58, 0.11)	>0.05	37.10/ NA	↓	V	↓↓	V	V	x	L	L	1.54 (0.83, 2.83)
McCartney, 2021	General population (A)	THC	Reaction time car driving	8	124	d	-0.47 (-0.70, -0.23)	<0.005	15.70/ NA	↓	V	↓↓	V	V	x	L	L	2.34 (1.53, 3.58)
McCartney, 2021	General population (A)	THC	Sensory discrimination	5	67	d	0.09 (-0.08, 0.25)	>0.05	0.00/ NA	↓↓	V	↓↓	V	V	x	L	L	0.85 (0.63, 1.15)
McCartney, 2021	General population (A)	THC	Speed variability	10	112	d	-0.16 (-0.35, 0.02)	>0.05	0.70/ NA	↓	V	↓↓	V	V	x	L	L	1.34 (0.96, 1.87)
McCartney, 2021	General population (A)	THC	Time perception	6	150	d	-0.05 (-0.30, 0.20)	>0.05	54.40/ NA	↓	V	↓↓	V	V	x	L	L	1.10 (0.69, 1.72)
Sultan, 2017	General population (A)	CBD, acute	Heart rate change	7	NR	MD	-1.25 (-3.02, 0.51)	>0.05	0.00/ NA	↓↓	V	↓↓	V	↓	x	VL	M	NA
Sultan, 2017	General population (A)	CBD, chronic	Heart rate change	5	NR	MD	0.32 (-4.16, 4.80)	>0.05	64.00/ NA	↓↓	V	↓↓	V	↓	x	VL	M	NA
Multiple sclerosis																		
Torres-Moreno, 2018	Multiple sclerosis (A)	CBM	Pain reduction	12	2692	d	-0.19 (-0.34, -0.03)	0.01<p<0.05	61.44/ 0.04	V	V	↓↓	V	V	x	M	H	0.71 (0.53, 0.94)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Torres-Moreno, 2018	Multiple sclerosis (A)	CBM	Spasticity (subjective)	12	2909	d	-0.25 (-0.37, -0.12)	<0.005	58.92/ 0.03	V	V	↓↓	V	V	x	M	H	0.63 (0.51, 0.80)
Da Rovare, 2017	Multiple sclerosis, paraplegia (spasticity, A)	Cannabinoids	Dizziness	14	2763	RR	3.45 (2.72, 4.37)	<0.005	20.62/ 0.04	V	V	↓↓	V	V	x	M	M	3.45 (2.72, 4.37)
Da Rovare, 2017	Multiple sclerosis, paraplegia (spasticity, A)	Cannabinoids	Dry mouth	10	2390	RR	2.82 (2.06, 3.85)	<0.005	0.00/ 0.00	V	V	↓↓	V	V	x	M	M	2.82 (2.06, 3.85)
Da Rovare, 2017	Multiple sclerosis, paraplegia (spasticity, A)	Cannabinoids	Nausea	11	1797	RR	2.24 (1.61, 3.12)	<0.005	0.00/ 0.00	V	V	↓↓	V	V	x	M	M	2.24 (1.61, 3.12)
Da Rovare, 2017	Multiple sclerosis, paraplegia (spasticity, A)	Cannabinoids	Somnolence	11	1911	RR	2.90 (1.98, 4.23)	<0.005	0.00/ 0.00	V	V	↓↓	V	V	x	M	M	2.90 (1.98, 4.23)
Meza, 2017	Multiple sclerosis (A)	CBM	Any adverse event	4	1985	RR	1.18 (1.10, 1.27)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	V	x	L	L	1.18 (1.10, 1.27)
Torres-Moreno, 2018	Multiple sclerosis (A)	CBM	Bladder dysfunction	8	2208	d	-0.14 (-0.24, -0.03)	0.005<p <0.01	28.78/ 0.01	V	V	↓↓	V	↓	x	L	H	0.77 (0.64, 0.94)
Torres-Moreno, 2018	Multiple sclerosis (A)	CBM	Spasticity	12	1962	d	-0.09 (-0.38, 0.00)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.85 (0.60, 1.20)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Daily activities	2	180	d	0.01 (-1.21, 1.24)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	M	0.98 (0.11, 9.02)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Headache	12	2597	RR	1.10 (0.79, 1.54)	>0.05	7.00/ NA	V	V	↓↓	V	↓	x	L	M	1.10 (0.79, 1.54)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Motricity	4	399	d	0.34 (-0.6, 1.27)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	M	0.54 (0.10, 2.93)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Pain reduction	2	665	d	-0.02 (-0.39, 0.35)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	M	0.96 (0.49, 1.88)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Spasticity reduction	7	550	d	0.36 (-0.17, 0.88)	>0.05	88.00/ NA	V	↓	↓↓	V	↓	x	L	M	0.52 (0.20, 1.35)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Spasticity reduction, frequency	6	520	d	0.04 (-0.15, 0.22)	>0.05	2.00/ NA	V	V	↓↓	V	↓	x	L	M	0.93 (0.66, 1.30)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Spasticity reduction, severity	3	142	d	-0.14 (-0.63, 0.36)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	M	0.77 (0.32, 1.90)
da Rovare, 2017	Multiple sclerosis or paraplegia (spasticity, A)	Cannabinoids	Cognitive overall	3	107	d	0.55 (-3.33, 4.43)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	VL	M	2.70 (0.00, 33035.62)
Fu, 2018	Multiple sclerosis (A)	CBM	Non serious adverse events	10	NR	OR	2.77 (1.22, 6.55)	0.01<p< 0.05	NA/ NA	↓↓	↓↓	↓↓	V	V	x	VL	CL	2.77 (1.22, 6.55)
Cancer																		
Hauser, 2019	Cancer (A)	CBM	Daily break-through opioid dosage	4	971	d	-0.11(-0.25, 0.02)	>0.05	7.09/ 0.01	V	V	↓↓	V	V	x	M	H	0.82 (0.64, 1.05)
Hauser , 2019	Cancer (A)	CBM	Gastrointestinal disorder adverse events	7	1330	RD	0.09 (0.01, 0.17)	0.01<p< 0.05	61.66/ 0.01	V	V	↓↓	V	V	x	M	H	NA, harmful
Hauser , 2019	Cancer (A)	CBM	Nervous system disorder adverse events	7	1330	RD	0.10 (0.04, 0.16)	<0.005	49.53/ 0.00	V	V	↓↓	V	V	x	M	H	NA, harmful
Hauser, 2019	Cancer (A)	CBM	Pain 30% reduction	7	1333	RD	0.03 (-0.03, 0.09)	>0.05	24.93/ 0.01	V	V	↓↓	V	V	x	M	H	NA
Hauser, 2019	Cancer (A)	CBM	Pain 50% reduction	7	1333	RD	0.00 (-0.03, 0.04)	>0.05	12.32 70.00	V	V	↓↓	V	V	x	M	H	NA
Hauser, 2019	Cancer (A)	CBM	Pain intensity	7	1331	d	-0.12 (-0.28,0.03)	>0.05	40.70/ 0.02	V	V	↓↓	V	V	x	M	H	0.81 (0.61, 1.06)
Hauser, 2019	Cancer (A)	CBM	Psychiatric disorder	7	1330	RD	0.01 (-0.01, 0.03)	>0.05	31.42/ 0.00	V	V	↓↓	V	V	x	M	H	NA

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Hauser , 2019	Cancer (A)	CBM	Serious adverse events	7	1330	RD	1.03 (0.70, 1.35)	<0.005	29.38/ 0.05	V	V	↓↓	V	V	x	M	H	NA, harmful
Hauser, 2019	Cancer (A)	CBM	Tolerability	7	1332	RD	0.04 (-0.00, 0.09)	>0.05	27.16/ 0.01	V	V	↓↓	V	V	x	M	H	NA
Noori, 2021	Cancer pain on opioids	CBM	Nausea	4	1334	RR	1.43 (1.03, 1.96)	0.01<p< 0.05	3.25/ 0.00	V	V	↓↓	V	V	x	M	L	1.43 (1.03, 1.96)
Noori, 2021	Cancer pain on opioids	CBM	Sleep disturbances	8	2437	MD	-0.23 (-0.46, -0.01)	0.01<p< 0.05	35.24/ 0.04	V	V	↓↓	V	V	x	M	L	NA, beneficial
Noori, 2021	Cancer pain on opioids	CBM	Pain relief	8	2437	MD	-0.18 (-0.38, 0.02)	>0.05	28.10/ NA	V	V	↓↓	V	V	x	M	L	NA
Noori, 2021	Cancer pain on opioids	CBM	Vomiting	4	1334	RR	1.50 (0.99, 2.27)	>0.05	5.89/0. 01	V	V	↓↓	V	V	x	M	L	1.50 (0.99, 2.27)
Noori, 2021	Cancer pain on opioids	CBM	Constipation	3	1157	RR	0.85 (0.54, 1.35)	>0.05	0.00/ NA	V	V	↓↓	V	V	x	M	L	0.85 (0.54, 1.35)
Hauser, 2019	Cancer (A)	CBM	Daily maintenance opioid dosage	4	970	d	0.09 (-0.11,0.31)	>0.05	55.65/ 0.02	V	V	↓↓	V	↓	x	L	H	1.18 (0.81, 1.72)
Hauser, 2019	Cancer (A)	CBM	Global impression to be much/very much improved	2	710	RD	0.06 (-0.00, 0.12)	>0.05	0.00/ 0.00	V	V	↓↓	V	↓	x	L	H	NA
Hauser, 2019	Cancer (A)	CBM	Sleep problems	3	971	d	0.04 (-0.09, 0.17)	>0.05	0.01/ NA	V	V	↓↓	↓	↓	x	L	H	1.08 (0.85, 2.45)
Lobos Urbina, 2016	Cancer (A)	Cannabinoids	Any adverse event	29	290	OR	3.03 (2.42, 3.80)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	V	x	L	L	3.03 (2.42, 3.80)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Dizziness	9	743	RR	3.32 (1.91, 5.79)	<0.005	70.71/ 0.33	V	V	↓↓	↓	↓	x	L	H	3.32 (1.91, 5.79)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Euphoria	4	358	RR	8.80 (1.82, 42.51)	0.005<p <0.01	13.00/ 0.33	V	V	↓↓	↓↓	V	x	L	H	8.80 (1.82, 42.51)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs other antiemetic drugs	Feeling high	5	419	RR	5.98 (3.03, 11.78)	<0.005	19.44/ 0.12	V	V	↓↓	↓↓	V	x	L	H	5.98 (3.03, 11.78)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs placebo	Feeling high	3	137	RR	31.10 (6.36, 152.05)	<0.005	0.16/ 0.00	↓	V	↓↓	↓	V	x	L	H	31.10 (6.36, 152.05)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs other antiemetic drugs	Nausea/vomit absence	2	302	RR	17.98 (2.44, 132.44)	<0.005	0.00/ 0.00	V	V	↓↓	↓↓	V	x	L	H	0.06 (0.01, 0.41)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs placebo	Nausea/vomit absence	3	288	RR	2.94 (1.42, 6.08)	<0.005	40.80/ 0.17	V	V	↓↓	↓	V	x	L	H	0.34 (0.16, 0.70)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs placebo	Participant preference	2	856	RR	4.78 (1.79, 12.66)	<0.005	66.32/ 0.35	V	V	↓↓	↓	↓	x	L	H	0.21 (0.08, 0.55)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Sedation	11	1055	RR	1.34 (1.10, 1.63)	<0.005	48.36/ 0.04	V	V	↓↓	↓↓	V	x	L	H	1.34 (1.10, 1.63)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs placebo	Withdrawal due to adverse event	2	276	RR	7.06 (1.78, 27.94)	0.005<p <0.01	8.73/ 0.13	V	V	↓↓	↓	V	x	L	H	7.06 (1.78, 27.94)
Mucke, 2018	Cancer, HIV (A)	CBM	Weight change	3	192	d	0.60 (0.18, 1.02)	<0.005	32.33/ 0.05	↓	V	↓↓	↓	V	x	L	H	2.97 (1.40, 6.40)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Depression	3	317	RR	0.81 (0.51, 1.28)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.81 (0.51, 1.28)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Hallucinations	2	144	RR	5.39 (0.66, 43.68)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	5.39 (0.66, 43.68)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs prochlorperazine	Nausea/vomit absence	4	409	RR	2.00 (0.74, 5.38)	>0.05	60.00/ NA	V	V	↓↓	V	↓	x	L	H	0.50 (0.18, 1.35)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs other antiemetic agent	Nausea/vomit absence	2	116	RR	1.10 (0.70, 1.72)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	0.91 (0.58, 1.43)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Sedation	2	139	RR	4.47 (0.35, 57.81)	>0.05	0.72/	↓	V	↓↓	V	↓	x	L	H	4.47 (0.35, 57.81)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
									NA									
Smith, 2015	Cancer (chemotherapy, A)	CBM	Vomiting absence	4	209	RR	1.11 (0.86, 1.44)	>0.05	0.00/ NA	V	V	↓↓	V	↓	x	L	H	0.90 (0.69, 1.66)
Smith, 2015	Cancer (chemotherapy, A)	Dronabinol	Nausea absence	2	117	RR	2.38 (0.21, 26.91)	>0.05	0.68/ NA	↓	V	↓↓	V	↓	x	L	H	0.42 (0.04, 4.75)
Smith, 2015	Cancer (chemotherapy, A)	Dronabinol	Nausea/vomit absence	3	188	RR	1.44 (0.62, 3.31)	>0.05	0.52/ NA	↓	V	↓↓	V	↓	x	L	H	0.69 (0.30, 1.60)
Smith, 2015	Cancer (chemotherapy, A)	Dronabinol	Vomiting absence	2	116	RR	1.05 (0.64, 1.71)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	0.95 (0.58, 1.56)
Smith, 2015	Cancer (chemotherapy, A)	Nabilone	Nausea absence	3	141	RR	1.41 (0.33, 6.03)	>0.05	0.53/ NA	↓	V	↓↓	V	↓	x	L	H	0.71 (0.17, 3.03)
Noori, 2021	Cancer pain on opioids	CBM	Pain reduction	5	1180	MD	-3.43 (-12.66, 5.80)	>0.05	40.10/ NA	↓	V	↓↓	V	V	x	L	L	NA
Mucke, 2018	Cancer, HIV (A)	CBM	Dizziness	8	823	RD	0.03 (-0.02, 0.08)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	NA
Mucke, 2018	Cancer, HIV (A)	CBM	Mental health symptoms	9	799	RD	0.01 (-0.02, 0.04)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	NA
Mucke, 2018	Cancer, HIV (A)	CBM	Nausea/vomit reduction	3	307	d	0.20 (-0.03, 0.44)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	0.70 (0.46, 1.07)
Mucke, 2018	Cancer, HIV (A)	CBM	Pain 30% reduction	5	537	RD	0.07 (-0.01, 0.16)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	NA
Mucke, 2018	Cancer, HIV (A)	CBM	Quality of life	6	570	d	0.00 (-0.19, 0.18)	>0.05	0.00/ NA	V	V	↓↓	↓	V	x	L	H	1.00 (0.72, 1.40)
Mucke, 2018	Cancer, HIV (A)	CBM	Sleeping disorder	3	198	d	-0.09 (-0.62, 0.43)	>0.05	0.63/ NA	↓	V	↓↓	↓	V	x	L	H	0.85 (0.33, 2.20)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Smith, 2015	Cancer (chemotherapy, A)	Nabilone	Vomiting absence	2	93	RR	1.55 (0.39, 6.24)	>0.05	0.35/ NA	↓↓	V	↓↓	V	↓	x	VL	H	0.64 (0.16, 2.58)
Smith, 2015	Cancer (chemotherapy, A)	Nabilone, dronabinol	Vomiting absence	3	136	RR	2.53 (0.78, 8.17)	>0.05	83.63 70.85	↓	↓	↓↓	↓	V	x	VL	H	0.40 (0.12, 1.28)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs other antiemetic drugs	Participant preference	9	799	RR	2.80 (1.71, 4.58)	<0.005	76.85/ 0.40	V	↓	↓↓	↓↓	V	x	VL	H	0.36 (0.22, 0.58)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs other antiemetic drugs	Withdrawal due to adverse event	6	740	RR	3.93 (1.29, 11.97)	0.01<p< 0.05	20.01/ 0.40	V	V	↓↓	↓↓	↓	x	VL	H	3.93 (1.29, 11.97)
Simon. 2022	Cancer with cachexia (A)	Cannabinoids	Appetite	4	297	d	-0.02 (-1.22, 1.18)	>0.05	63.00/ NA	↓	V	↓↓	↓	↓	x	VL	L	1.04 (0.12, 9.09)
Morales, 2017	Cancer (chemotherapy, A)	Cannabinoids	Any adverse event	3	176	RR	1.92 (1.26, 2.91)	0.01<p< 0.05	NA/ NA	↓	↓↓	↓↓	V	V	x	VL	L	0.52 (0.34, 0.79)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Dysphoria	3	192	RR	7.16 (1.27, 40.37)	0.01<p< 0.05	4.33/ 0.10	↓	V	↓↓	↓↓	V	x	VL	H	7.16 (1.27, 40.37)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Dysphoria	2	96	RR	9.00(0.50,160 .59)	>0.05	NA/ NA	↓	↓↓	↓↓	V	↓	x	VL	H	9.00 (0.50,160.59)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Hypotension, postural	6	413	RR	2.40 (0.88, 6.53)	>0.05	0.60/ NA	↓	V	↓↓	V	↓	x	VL	H	2.40 (0.88, 6.53)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs placebo	Nausea absence	2	96	RR	2.00 (0.19, 20.97)	>0.05	NA/ NA	↓	↓↓	↓↓	V	↓	x	VL	H	0.50 (0.05, 5.25)
Smith, 2015	Cancer (chemotherapy, A)	CBM vs prochlorperazine	Nausea absence	5	258	RR	1.46 (0.67, 3.15)	>0.05	0.58/ NA	↓	V	↓↓	V	↓	x	VL	H	0.68 (0.32, 1.48)
Smith, 2015	Cancer (chemotherapy, A)	CBM	Withdrawal due to lack of efficacy	2	118	RR	0.97 (0.04, 20.93)	>0.05	0.76/ NA	↓	V	↓↓	↓	↓	x	VL	H	0.97 (0.04, 20.93)
Smith, 2015	Cancer (chemotherapy, A)	CBM plus other	Tolerability	2	105	RR	6.97 (0.88, 55.19)	>0.05	0.00/	↓	V	↓↓	↓	↓	x	VL	H	6.97 (0.88, 55.19)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
		antiemetic agent							NA									
Smith, 2015	Cancer (chemotherapy, A)	CBM plus other antiemetic agent	Vomiting absence	2	89	RR	1.47 (0.69, 3.13)	>0.05	NA/ NA	↓	↓↓	↓	↓	↓	x	VL	H	0.68 (0.32, 1.45)
Mucke, 2018	Cancer, HIV (A)	CBM	Appetite	5	517	d	0.65 (-0.82, 2.12)	>0.05	0.97/ NA	↓	V	↓↓	↓	V	x	VL	H	0.31 (0.02, 4.41)
Mental disorders																		
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Acceptability	15	2299	OR	1.51 (0.96, 2.36)	>0.05	0.42/ NA	V	V	↓↓	↓	↓	x	L	H	1.51 (0.96, 2.36)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Adverse events	2	385	OR	1.32 (0.79, 2.20)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.32 (0.79, 2.20)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Adverse events, all-cause	10	1495	OR	1.98 (1.20, 3.28)	0.005<p <0.01	59.51/ 0.32	V	V	↓↓	↓	V	x	L	H	1.98 (1.20, 3.28)
Black, 2019	Psychiatric disorders (A)	THC/ CBD	Anxiety symptoms	7	252	d	-0.26 (-0.54,0.02)	>0.05	76.13/ 0.09	V	↓	↓↓	↓	V	x	L	H	0.63 (0.38, 1.04)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Cognitive function	3	150	d	-0.01 (-0.33, 0.32)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	H	1.02 (0.56, 1.83)
Black , 2019	Psychiatric disorders (A)	Cannabinoids	Depressive symptoms	12	1656	d	-0.04 (-0.20,0.10)	>0.05	67.28/ 0.04	V	V	↓↓	↓	↓	x	L	H	0.93 (0.71, 1.22)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Emotional functioning	2	122	d	0.10 (-0.49, 0.69)	>0.05	0.57/ NA	↓	V	↓↓	V	↓	x	L	H	0.83 (0.29, 2.43)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Negative symptoms	2	122	d	0.08 (-0.27, 0.44)	>0.05	0.94/ 0.00	↓	V	↓↓	↓	V	x	L	H	1.16 (0.61, 2.19)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Positive symptoms	2	122	d	-0.16 (-0.68,0.35)	>0.05	46.94/ 0.07	↓	V	↓↓	↓	V	x	L	H	0.75 (0.32, 1.77)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Serious adverse events	4	954	OR	1.29 (0.94, 1.77)	>0.05	0.00/ NA	V	V	↓↓	↓	↓	x	L	H	1.29 (0.94, 1.77)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Total symptoms	2	122	d	0.05 (-0.50, 0.60)	>0.05	52.03/ 0.09	↓	V	↓↓	↓	V	x	L	H	1.09 (0.40, 2.96)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Withdrawals due to adverse events	11	1621	OR	2.78 (1.59, 4.86)	<0.005	21.42/ 0.17	V	V	↓↓	↓	V	x	L	H	2.78 (1.59, 4.86)
Kopelli, 2020	Schizophrenia (A)	CBD	Cognition	2	121	d	0.09 (-0.27, 0.45)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	L	L	1.18 (0.61, 2.26)
Zhang, 2021	Schizophrenia (A)	CBD	Schizophrenia, PANSS positive symptoms	2	122	MD	-1.61 (-2.68, -0.55)	0.005<p <0.01	31.45/ 0.21	↓	V	↓↓	↓	V	x	L	L	NA, beneficial
Black, 2019	Psychiatric disorders (A)	CBD	Anxiety symptoms	2	44	d	-0.87 (-1.96,0.21)	>0.05	83.44/ 0.52	↓↓	↓	↓↓	↓	↓	x	VL	H	0.21 (0.03, 1.47)
Bahji, 2020	Anxiety (A)	Cannabinoids	Anxiety symptoms, reduction	6	80	d	-1.76 (-2.46, -1.06)	<0.005	58.04/ 0.44	↓↓	V	↓↓	V	↓	x	VL	H	0.04 (0.01, 0.15)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Global functioning	2	41	d	-0.84 (-2.10, 0.42)	>0.05	0.68/ NA	↓↓	V	↓↓	V	↓	x	VL	H	4.57 (0.47, 44.74)
Black., 2019	Psychiatric disorders (A)	Cannabinoids	Tic or Tourette symptoms	2	41	d	-0.46 (-1.28,0.35)	>0.05	65.66/ 0.25	↓↓	V	↓↓	↓	↓	x	VL	H	0.43 (0.10, 1.90)
Black, 2019	Psychiatric disorders (A)	Cannabinoids	Tolerability	2	252	OR	0.56 (0.18, 1.76)	>0.05	3.70/ 0.04	↓	V	↓↓	↓↓	V	x	VL	H	1.78 (0.57, 5.58)
Kopelli, 2020	Schizophrenia (A)	CBD	Schizophrenia symptoms	2	122	d	-1.07 (-2.64, 0.49)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	L	0.14 (0.01, 2.45)
Zhang, 2021	Schizophrenia (A)	CBD	Schizophrenia, PANSS general scores	2	122	MD	-0.91 (-2.78, 0.96)	>0.05	0.00/ NA	↓	V	↓↓	↓	↓	x	VL	L	NA

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Zhang, 2021	Schizophrenia (A)	CBD	Schizophrenia, PANSS negative symptoms	2	122	MD	0.82 (-0.05, 1.69)	>0.05	45.00/ NA	↓	V	↓↓	↓	↓	x	VL	L	NA
Healthy subjects																		
De Vita, 2018	Experimental pain, healthy (A)	Cannabinoids	Pain threshold	18	467	d	0.17 (0.05, 0.29)	0.005<p <0.01	53.14/ 0.03	V	V	V	V	V	x	H	H	0.74 (0.59, 0.91)
De Vita, 2018	Experimental pain, healthy (A)	Cannabinoids	Pain unpleasantness	9	244	d	0.28 (0.07, 0.49)	0.005<p <0.01	62.44/ 0.06	V	V	V	V	V	x	H	H	0.60 (0.41, 0.88)
De Vita, 2018	Experimental pain, healthy (A)	Cannabinoids	Pain intensity	22	272	d	0.02 (NA, NA)	>0.05	53.00/ NA	V	V	↓↓	V	↓	x	L	H	0.96 (NA, NA)
Inflammatory bowel disease																		
Doeve, 2020	Inflammatory bowel disease (A)	Cannabinoids	Quality of life	5	2444	d	-0.60 (-0.84, -0.35)	<0.005	36.72/ 0.03	V	V	V	V	V	x	H	CL	0.34 (0.22, 0.53)
Doeve, 2020	Inflammatory bowel disease (A)	Cannabis	Post-treatment disease activity	4	128	d	0.61 (0.12, 1.09)	0.01<p< 0.05	44.50/ 0.11	↓	V	↓↓	V	V	x	L	CL	0.33 (0.14, 0.80)
Couch , 2018	Crohn's (A)	CBM	CDAI reduction	2	40	MD	-74.97 (-229.81, 79.87)	>0.05	75.00/ NA	↓↓	↓	↓↓	V	↓	x	VL	M	NA
Dementia, Alzheimer's and Parkinson's disease																		
Bahji, 2020	Dementia (elderlies)	Cannabinoids	Agitation	9	348	d	-0.89 (-1.97,0.17)	>0.05	94.65/ 2.26	V	↓↓	↓↓	↓	V	x	L	L	0.20 (0.03, 1.38)
Bahji, 2020	Dementia (elderlies)	Cannabinoids	CGI	9	208	d	-0.94 (-1.24, -0.64)	0.01<p< 0.05	0.70/ NA	V	V	↓↓	↓	↓	x	L	L	0.18 (0.11, 0.31)
Bahji, 2020	Dementia (elderlies)	Cannabinoids	MMSE	9	208	d	0.42 (0.07, 0.78)	0.01<p< 0.05	0.03/ NA	V	V	↓↓	↓	↓	x	L	L	0.47 (0.25, 0.89)
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	Adverse events	6	210	RR	1.26 (0.93, 1.71)	>0.05	NR /NA	V	↓↓	↓↓	V	V	x	L	H	1.26 (0.93, 1.71)

Author, year	Population	Cannabinoid	Outcome	k	N	Metric	ES (95% CI)	p	I^2/ tau2	Imprecision	Inconsistency	RoB	Indirectness	Publication bias	Upgrade	GRADE	Q	eOR (95% CI)
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	Agitation and aggression	7	251	d	-0.69 (-1.50, 0.13)	>0.05	0.86/ NA	↓	V	↓↓	V	V	x	L	H	0.29 (0.07, 1.25)
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	BMI	3	144	MD	0.05 (-0.15, 0.25)	>0.05	0.62/ NA	↓	V	↓↓	V	V	x	L	H	NA
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	Neuropsychiatric symptoms	6	229	MD	0.67 (-2.82, 4.16)	>0.05	0.00/ NA	↓	V	↓↓	V	V	x	L	H	NA
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	Sedation /Somnolence	4	244	RR	1.73 (1.02, 2.93)	0.01<p< 0.05	NA/ NA	V	↓↓	↓↓	V	V	x	L	H	1.73 (1.02, 2.93)
Ruthirakuhan, 2019	Alzheimer's disease (elderlies)	CBM	Tolerability	6	152	RR	1.31 (0.34, 5.13)	>0.05	NR/ NA	↓	↓↓	↓↓	V	V	x	VL	H	1.31 (0.34, 5.13)
Thanabalasingam, 2021	Parkinson's disease (A)	Cannabinoids	Motor function	3	68	MD	-0.21 (-4.15, 3.72)	>0.05	0.00/ NA	↓↓	V	↓↓	V	↓	x	VL	L	NA
Substance use disorder																		
McKee, 2021	Opioid use disorder (A)	CBM	CUD treatment	2	52	d	-1.28 (-1.89, -0.66)	<0.005	3.81/ 0.01	↓↓	V	↓↓	V	V	x	L	L	0.10 (0.03, 0.30)
Rodríguez, 2018	Cannabis use disorder	Nabiximols, dronabinol	Abstinence	4	388	RR	1.14 (0.56, 2.30)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	L	0.89 (0.43, 1.78)
Rodríguez, 2018	Cannabis use disorder	CBM	Adverse effects	4	388	RR	1.15 (0.90, 1.46)	>0.05	NR/ NA	V	↓↓	↓↓	V	V	x	L	L	1.15 (0.90, 1.46)
McKee, 2021	Opioid use disorder (A)	CBM	WDS	4	156	d	-0.21 (-0.52, 0.11)	>0.05	0.00/ NA	↓	V	↓↓	V	↓	x	L	L	0.68 (0.38, 1.21)
McKee, 2021	Opioid use disorder (A)	CBM	SOWS	2	81	d	-0.18 (-1.12, 0.76)	>0.05	69.00/ NA	↓↓	V	↓↓	V	↓	x	VL	L	0.72 (0.13, 3.96)

Legend. A, adults; BMI, body mass index; C, children; CBM, cannabis-based medications; CDAI, Crohn's disease activity index; CGI, clinical global impression; CI, confidence interval; CL, critically low; CNS, central nervous system; CUD, cannabis use disorder; ES, effect size; H, high; I^2, percentage of variation across effect sizes that is due to heterogeneity rather than change; tau2, tau-squared heterogeneity; IQ –intelligence quotient; K, number of studies for each factor; L, low; LS, largest study with significant effect; LBW– low birth weight; M, moderate; MD, mean difference; MMSE, Mini Mental State Examination; n , number of cases; N, total number of cohort per factor; N, no; NA, not assessable; NR, not reported; NP, not pertinent because the number of observed studies is less than the expected; OR, odds ratio; PANSS, positive and negative symptoms of schizophrenia; *Q, quality measured with AMSTAR 2; RR, risk ratio; sign., significant;*

eTable 5. Finding across meta-analyses of observational studies on health outcomes of cannabis use

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Pregnant women																
Marchand, 2022	Pregnancy (A)	Marijuana	Small for gestational age (unadjusted)	6	2078/22921 (9.1%)	RR	1.61 (1.41, 1.83)	1.61 (1.41, 1.83)	18.47/0.00	$4.1x10^{-13}$	Y	Y	N	N	I/I/NS*	L
Conner, 2016	Pregnancy (A)	Marijuana use	Low birth weight (unadjusted)	12	6204/57438 (10.8%)	RR	1.43 (1.27, 1.62)	1.43 (1.27, 1.62)	45.3/0.02	$5.8x10^{-9}$	Y	Y	N	N	I/I/NS*	M
Conner, 2016	Pregnancy (A)	Marijuana use	Pre-term delivery (unadjusted)	14	8060/81326 (9.9%)	RR	1.32 (1.14, 1.54)	1.32 (1.14, 1.54)	64.7/0.04	$2.7x10^{-4}$	N	Y	N	N	III/III	M
Marchand, 2022	Pregnancy (A)	Marijuana	Neonatal intensive care unit admission (unadjusted)	6	1315/18615 (7.1%)	RR	1.41 (1.15, 1.71)	1.41 (1.15, 1.71)	23.13/0.01	$7.2x10^{-4}$	Y	Y	N	Y	III/III	L
Marchand, 2022	Pregnancy (A)	Marijuana	Mean birth weight (unadjusted)	10	NR/18415 (NA)	MD	NA, harmful	-112.3 (-167.2, -57.4)	70.18/0.47	$1.0x10^{-4}$	N	Y	N	N	IV/III	L
Conner, 2016	Pregnancy (A)	Marijuana use	Abruption (unadjusted)	5	NR/22425 (NA)	OR	1.60 (1.28, 2.00)	1.60 (1.28, 2.00)	0.00/NA	<0.05	NA	NA	NA	NA	IV/IV	M
Conner, 2016	Pregnancy (A)	Marijuana use	Low Apgar score (unadjusted)	6	NR/24295 (NA)	RR	1.26 (1.07,1.49)	1.26 (1.07, 1.49)	0.00/NA	0.05	NA	NA	NA	NA	IV/IV	M
Conner, 2016	Pregnancy (A)	Marijuana use	Stillbirth (unadjusted)	2	NR/13892 (NA)	OR	1.74 (1.03,2.93)	1.74 (1.03, 2.93)	0.16/NA	<0.05	NA	NA	NA	NA	IV/IV	M
Conner, 2016	Pregnancy (A)	Marijuana use	Abruption (adjusted)	2	NR/NR (NA)	OR	1.35 (0.45, 3.96)	1.35 (0.45, 3.96)	0.00/NA	>0.05	NA	NA	N	NA	NS	M
Conner, 2016	Pregnancy (A)	Marijuana use	Gestational age (unadjusted)	6	NR/NR (NA)	MD	NA (NA	-0.10(-0.50,0.30)	0.91/NA	>0.05	NA	NA	NA	NA	NS	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Conner, 2016	Pregnancy (A)	Marijuana use	Low birth weight (adjusted)	4	NR/29773 (NA)	RR	1.15 (0.91, 1.45)	1.15 (0.91, 1.45)	43.59/ 0.02	>0.05	N	N	N	N	NS	M
Conner, 2016	Pregnancy (A)	Marijuana use	Non-intensive care unit (unadjusted)	5	6965/57684 (12.1%)	RR	1.41 (0.99, 2.00)	1.41 (0.99, 2.00)	0.90/NA	>0.05	NA	NA	NA	NA	NS	M
Conner, 2016	Pregnancy (A)	Marijuana use	Perinatal death (unadjusted)	3	272/22243 (1.2%)	RR	1.09 (0.62,1.91)	1.09 (0.62,1.91)	0.00/NA	>0.05	NA	NA	NA	NA	NS	M
Conner, 2016	Pregnancy (A)	Marijuana use	Pre-term delivery (adjusted)	4	NR/35139 (NA)	RR	1.16 (0.75, 1.79)	1.16 (0.75, 1.79)	82.62/ 0.15	>0.05	N	N	N	Y	NS	M
Conner, 2016	Pregnancy (A)	Marijuana use	SAB (unadjusted)	2	1003/3336 (30.1%)	OR	1.10 (0.84,1.44)	1.10 (0.84, 1.44)	0.00/NA	>0.05	NA	NA	NA	NA	NS	M
Gunn, 2016	Pregnancy (A)	Cannabis use	Head circumference	6	NR/2515 (NA)	MD	NA (NA)	-0.31 (-0.75, 0.13)	97.00/NA	>0.05	NA	NA	NA	NA	NS	M
Gunn, 2016	Pregnancy (A)	Cannabis use	Maternal anaemia (NR)	6	NR/9868 (NA)	OR	1.20 (0.85, 1.70)	1.20 (0.85, 1.70)	23.06/ 0.04	>0.05	N	Y	N	N	NS	M
Gunn, 2016	Pregnancy (A)	Cannabis use	Neonatal length (NR)	6	NR/2515 (NA)	MD	NA (NA)	-0.10 (-0.65,0.45)	59.00/NA	>0.05	NA	NA	NA	NA	NS	M
Ruisch, 2018	Pregnant women (A)	Cannabis use	Offspring conduct problem (NR)	3	NR/1263 (NA)	OR	1.29 (0.93, 1.80)	1.29 (0.93, 1.80)	0.00/NA	>0.05	NA	NA	Y	NA	NS	M
General population																
Kiburi, 2021	General population (Ado)	Cannabis	Psychosis (NR)	18	2512/67684 (3.7%)	RR	1.71 (1.47, 2.00)	1.71 (1.47, 2.00)	68.8/0.06	$8.4x10^{-12}$	N	Y	N	Y	II/II/I+	H
Borges, 2016	General population (Ado, A)	Cannabis heavy use	Suicide attempt (adjusted)	12	1066/21956 (4.9%)	OR	3.20 (1.72, 5.94)	3.20 (1.72, 5.94)	92.1/0.97	$2.3x10^{-4}$	N	N	N	Y	III/ III	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Moore, 2007	General population (Ado, A)	Cannabis most frequent use	Psychotic symptoms (adjusted)	6	1465/59671 (2.4%)	OR	2.18 (1.45, 3.27)	2.18 (1.45, 3.27)	67.5/0.15	$2.0x10^{-4}$	N	Y	N	N	III/ III	M
Sultan, 2018	General population (A)	THC	Heart rate change (unadjusted)	13	NR/150 (NA)	MD	NA, harmful	1.07 (0.73, 1.40)	1.19/0.00	$3.3x10^{-10}$	Y	Y	Y	Y	IV/II	M
Gibbs, 2015	General population (A)	Cannabis use	Mania symptoms (adjusted)	2	NR/5520 (NA)	OR	3.00 (1.73, 5.23)	3.00 (1.73, 5.23)	9.83/0.02	$9.2x10^{-5}$	NA	Y	NA	N	IV/ III	M
Gurney, 2015	General population (A <50)	Cannabis > 10 years use	Testicular cancer non seminoma (NR)	3	719/2138 (33.6%)	OR	2.39 (1.47, 3.86)	2.39 (1.47, 3.86)	6.65/0.01	$4.0x10^{-4}$	N	Y	N	N	IV/ III	M
Gurney, 2015	General population (A <50)	Cannabis current use	Testicular cancer non seminoma (NR)	2	532/1803 (29.5%)	OR	2.20 (1.57, 3.07)	2.20 (1.57, 3.07)	10.06/0.01	$3.8x10^{-6}$	NA	Y	NA	N	IV/ III	M
Gurney, 2015	General population (A <50)	Cannabis weekly use	Testicular cancer non seminoma (NR)	3	719/2138 (33.6%)	OR	2.82 (1.77, 4.48)	2.82 (1.77, 4.48)	24.68/0.04	$1.1x10^{-5}$	N	Y	N	N	IV/ III	M
Lorenzetti, 2019	General population (Ado, A)	Cannabis regular use	Medial orbitofrontal cortex volume (NR)	6	NR/356 (NA)	SMD	1.72 (1.29, 2.30)	0.30 (0.14, 0.46)	56.15/0.02	$2.2x10^{-4}$	N	Y	N	Y	IV/ III	H
Lorenzetti, 2019	General population (Ado, A)	Cannabis regular use	Total orbitofrontal cortex volume (NR)	7	NR/472 (NA)	SMD	1.63 (1.31, 2.03)	0.27 (0.15, 0.39)	42.60/0.01	$1.7x10^{-5}$	Y	Y	N	N	IV/ III	H
Moore, 2007	General population (Ado, A)	Cannabis use	Depression (adjusted)	11	NR/17628 (NA)	OR	1.21 (1.11, 1.31)	1.21 (1.11, 1.31)	0.00/0.00	$4.6x10^{-6}$	Y	Y	N	N	IV/ III	M
Johnson, 2017	General population (Ado, A)	Cannabis use	Physical dating violence perpetuation (adjusted)	13	NR/17356 (NA)	OR	1.45 (1.19, 1.77)	1.45 (1.19,1.77)	75.49/0.09	$7.7x10^{-4}$	N	Y	N	N	IV/ III	H
Gurney, 2015	General population (A <50, case-control)	Cannabis, current use	Any testicular cancer (adjusted)	2	NR/2138 (NA)	OR	1.62 (1.13, 2.32)	1.62 (1.13, 2.32)	0.00/NA	0.05	NA	NA	NA	NA	IV/IV	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Gurney, 2015	General population (A <50, case-control)	Cannabis, at least weekly use	Any testicular cancer (adjusted)	3	NR/2138 (NA)	OR	1.92 (1.35, 2.72)	1.92 (1.35, 2.72)	0.00/NA	0.05	NA	NA	NA	NA	IV/IV	M
Gurney, 2015	General population (A <50, case-control)	Cannabis, >=10 years	Any testicular cancer (adjusted)	3	NR/2138 (NA)	OR	1.50 (1.08, 2.09)	1.50 (1.08, 2.09)	0.00/NA	0.05	NA	NA	NA	NA	IV/IV	M
Ghasemiesfe, 2019	General population (A)	Marijuana, >10y	Non-seminoma testicular cancer (adjusted)	3	160/782 (20.5%)	OR	1.84 (1.22, 2.76)	1.84 (1.22, 2.76)	8.93/NA	0.003	N	Y	N	N	IV/IV	H
Ghasemiesfe, 2019	General population (A)	Marijuana, >10y	TGCT (adjusted)	3	357/1049 (34.1%)	OR	1.36 (1.02, 1.82)	1.36 (1.02, 1.82)	1.95/NA	0.035	N	Y	N	N	IV/IV	H
Grant, 2002	General population (A)	Cannabis	Residual forgetting/retrieval (NR)	6	NR/516 (NA)	d	1.63 (1.07, 2.43)	-0.27 (-0.49,-0.04)	NR/NA	<0.05	NA	NA	NA	NA	IV/IV	M
Grant, 2002	General population (A)	Cannabis	Residual learning (NR)	12	NR/888 (NA)	d	1.55 (1.11, 2.10)	-0.24 (-0.41,-0.06)	NR/NA	0.02	NA	NA	NA	NA	IV/IV	M
Szoke, 2014	General population (A)	Cannabis	Schizotypy measure (NR)	10	NR/5187 (NA)	d	1.46 (1.29, 1.69)	0.21 (0.14, 0.29)	0.00/NA	<0.05	NA	NA	N	NA	IV/IV	M
Johnson, 2017	General population (Ado and young A)	Cannabis use	Physical dating violence victimization (adjusted)	6	NR/23456 (NA)	OR	1.44 (1.08, 1.92)	1.44 (1.08, 1.92)	54.86/0.06	0.011	N	Y	N	N	IV/IV	H
Escelsior, 2020	General population (Ado, A)	Cannabinoids	Self-injurious behaviours (unadjusted)	9	NR/19321 (NA)	OR	1.64 (1.16, 2.32)	1.64 (1.16, 2.32)	53.88/NA	$4.6x10^{-3}$	N	N	Y	N	IV/IV	L
Scott, 2018	General population (Ado, A)	Cannabis	Abstraction/shifting (NR)	47	NR/8727 (NA)	d	1.72 (1.44, 2.06)	-0.30 (-0.40,-0.20)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H
Scott, 2018	General population (Ado, A)	Cannabis	Attention (NR)	53	NR/8727 (NA)	d	1.46 (1.24, 1.75)	-0.21 (-0.31, -0.12)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Scott, 2018	General population (Ado, A)	Cannabis	Delayed memory (NR)	62	NR/8727 (NA)	d	1.60 (1.34, 1.89)	-0.26 (-0.35,-0.16)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H
Scott, 2018	General population (Ado, A)	Cannabis	Inhibition memory (NR)	30	NR/8727 (NA)	d	1.57 (1.26, 1.99)	-0.25 (-0.38,-0.13)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H
Scott, 2018	General population (Ado, A)	Cannabis	Learning (NR)	60	NR/8727 (NA)	d	1.82 (1.54, 2.14)	-0.33 (-0.42,-0.24)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H
Blest, 2018	General population (Ado, A)	Cannabis	Left cuneus extending to ipsilateral superior, middle, and inferior occipital gyri (NR)	22	NR/755 (NA)	SDM-Z	NA	-1.66 (NA, NA)	NR/NA	$9.5x10^{-5}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado)	Cannabis (ACU vs NU)	Left inferior parietal lobule extending to ipsilateral superior parietal gyrus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.12 (NA, NA)	NR/NA	$1.38x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis (CCU vs ACU)	Left inferior parietal lobule extending to ipsilateral superior parietal gyrus (NR)	22	NR/459 (NA)	SDM-Z	NA	1.03 (NA, NA)	NR/NA	$1.97x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Left lingual gyrus extending to ipsilateral middle and superior occipital gyrus (NR)	22	NR/459 (NA)	SDM-Z	NA	1.23 (NA, NA)	NR/NA	$5.60x10^{-4}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Left medial frontal gyrus extending bilaterally (NR)	22	NR/755 (NA)	SDM-Z	NA	1.62 (NA, NA)	NR/NA	$1.41x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado)	Cannabis (ACU vs NU)	Left middle frontal gyrus extending to ipsilateral superior frontal gyrus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.12 (NA, NA)	NR/NA	$1.38x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis (CCU vs ACU)	Left middle frontal gyrus extending to ipsilateral superior frontal gyrus (NR)	22	NR/459 (NA)	SDM-Z	NA	1.02 (NA, NA)	NR/NA	$2.16x10^{-3}$	NA	NA	N	NA	IV/IV	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Chisini, 2019	General population (Ado, A)	Cannabis	Periodontitis (adjusted)	4	NR/4328 (NA)	PR	NA	1.18 (1.01, 1.38)	72.51/0.02	0.038	N	Y	Y	N	IV/IV	L
Blest, 2018	General population (Ado, A)	Cannabis	Precuneus extending to ipsilateral postcentral and superior parietal gyri (NR)	22	NR/459 (NA)	SDM-Z	NA	1.22 (NA, NA)	NR/NA	$5.84x10^{-4}$	NA	NA	N	NA	IV/IV	M
Myles, 2012	General population (Ado, A)	Cannabis	Psychosis, age of onset (NR)	46	NR/8914 (NA)	d	2.07 (1.76, 2.43)	-0.40 (-0.49, -0.31)	73.00/NA	<0.001	NA	NA	Y	NA	IV/IV	M
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual abstraction (NR)	33	NR/1849 (NA)	d	1.46 (1.09, 1.99)	-0.21 (-0.38, -0.05)	0.31/NA	<0.05	NA	NA	NA	NA	IV/IV	CL
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual attention (NR)	33	NR/1849 (NA)	d	1.92 (1.34, 2.76)	-0.36 (-0.56, -0.16)	0.54/NA	0.001	NA	NA	NA	NA	IV/IV	CL
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual learning (NR)	33	NR/1849 (NA)	d	1.89 (1.31, 2.71)	-0.35 (-0.55, -0.15)	49.03/NA	0.02	NA	NA	NA	NA	IV/IV	CL
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual memory (NR)	33	NR/1849 (NA)	d	1.57 (1.04, 2.35)	-0.25 (-0.47, -0.02)	0.69/NA	<0.001	NA	NA	NA	NA	IV/IV	CL
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual motor speed (NR)	33	NR/1849 (NA)	d	1.85 (1.22, 2.81)	-0.34 (-0.57, -0.11)	2.49/NA	<0.05	NA	NA	NA	NA	IV/IV	CL
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual verbal/language (NR)	33	NR/1849 (NA)	d	1.52 (1.00, 2.34)	-0.23 (-0.47, -0.00)	53.77/NA	0.02	NA	NA	NA	NA	IV/IV	CL
Blest, 2018	General population (Ado, A)	Cannabis	Right inferior frontal gyrus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.11 (NA, NA)	NR/NA	$1.51x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right inferior parietal lobule extending to ipsilateral inferior parietal, superior parietal and angular gyri (NR)	22	NR/459 (NA)	SDM-Z	NA	1.24 (NA, NA)	NR/NA	$5.01x10^{-4}$	NA	NA	N	NA	IV/IV	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Blest, 2018	General population (Ado, A)	Cannabis	Right inferior parietal lobule extending to ipsilateral superior parietal and angular gyri (NR)	5	NR/204 (NA)	SDM-Z	NA	1.55 (NA, NA)	NR/NA	$1.36x10^{-4}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right insula extending to ipsilateral inferior frontal gyrus (NR)	22	NR/755 (NA)	SDM-Z	NA	1.94 (NA, NA)	NR/NA	$1.26x10^{-4}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right middle frontal gyrus extending to ipsilateral inferior frontal gyrus (NR)	4	NR/755 (NA)	SDM-Z	NA	1.06 (NA, NA)	NR/NA	$7.34x10^{-4}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right middle frontal gyrus extending to ipsilateral superior frontal gyrus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.16 (NA, NA)	NR/NA	$1.02x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right middle occipital gyrus	4	NR/755 (NA)	SDM-Z	NA	1.21 (NA, NA)	NR/NA	$3.45x10^{-4}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right middle occipital gyrus extending to ipsilateral superior occipital gyrus and cuneus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.12 (NA, NA)	NR/NA	$1.38x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right precentral gyrus (NR)	22	NR/755 (NA)	SDM-Z	NA	-1.29 (NA, NA)	NR/NA	$1.31x10^{-3}$	NA	NA	N	NA	IV/IV	M
Blest, 2018	General population (Ado, A)	Cannabis	Right precuneus extending to ipsilateral superior parietal gyrus (NR)	5	NR/204 (NA)	SDM-Z	NA	1.17 (NA, NA)	NR	$9.80x10^{-4}$	NA	NA	N	NA	IV/IV	M
Scott, 2018	General population (Ado, A)	Cannabis	Verbal/language (NR)	21	NR/NR (NA)	d	1.29 (1.02, 1.66)	-0.14 (-0.28, -0.01)	NR/NA	0.05	NA	NA	Y	NA	IV/IV	H
Scott, 2018	General population (Ado, A)	Cannabis	Working Memory (NR)	51	NR/8727 (NA)	d	1.49 (1.26, 1.79)	-0.22 (-0.32, -0.13)	NR/NA	<0.001	NA	NA	Y	NA	IV/IV	H

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Scott, 2018	General population (Ado, A)	Cannabis use	Cognitive specific, speed of processing (NR)	30	NR/8727 (NA)	d	1.60 (1.31, 1.99)	-0.26 (-0.38, -0.15)	NA/NA	<0.001	NA	NA	NA	NA	IV/IV	H
Schumacher, 2018	General population (Ado, A)	Cannabis use	Condom use (adjusted)	11	NR/4414 (NA)	OR	1.41 (1.13, 1.78)	0.71 (0.56, 0.89)	11.80/0.02	0.003	N	Y	N	N	IV/IV	M
Rocchetti, 2013	General population (Ado, A)	Cannabis use	Hippocampal volume (unadjusted)	12	NR/520 (NA)	d	2.30 (1.29, 4.04)	-0.46 (-0.77, -0.14)	68.40/0.21	0.005	N	Y	N	N	IV/IV	M
Moore, 2007	General population (Ado, A)	Cannabis use	Psychosis, symptoms (adjusted)	7	1490/61485 (2.4%)	OR	1.46 (1.09, 1.95)	1.46 (1.09, 1.95)	70.46/0.09	0.011	N	Y	N	N	IV/IV	M
Borges, 2016	General population (Ado, A)	Cannabis use	Suicide attempt (adjusted)	8	336/8681 (3.9%)	OR	2.14 (1.26,3.61)	2.14 (1.26, 3.61)	62.91/0.29	0.004	N	N	Y	N	IV/IV	M
Borges, 2016	General population (Ado, A)	Cannabis use	Suicide ideation (adjusted)	8	1737/24455 (7.1%)	OR	1.55 (1.09,2.20)	1.55 (1.09, 2.20)	93.44/0.17	0.015	N	N	Y	N	IV/IV	M
Lev-Ran, 2014	General population (Ado, A)	Cannabis use, heavy	Depression (adjusted)	8	NR/18983 (NA)	OR	1.61 (1.12, 2.31)	1.61 (1.12, 2.31)	63.59/0.15	0.009	N	Y	N	NA	IV/IV	H
Borges, 2016	General population (Ado, A)	Cannabis use, heavy	Suicide ideation (adjusted)	7	814/7759 (10.5%)	OR	2.54 (1.08, 5.95)	2.54 (1.08, 5.95)	92.59/1.12	0.032	N	N	N	Y	IV/IV	M
Borges, 2016	General population (Ado, A)	Cannabis use	Suicide death (adjusted)	5	2051/85742 (2.4%)	OR	2.53 (1.35, 4.75)	2.53 (1.35, 4.75)	86.89/0.42	0.004	N	N	Y	Y	IV/IV	M
Ghasemiesfe, 2018	General population (Ado, A)	Marijuana use	Cough (unadjusted)	2	153/1158 (13.2%)	RR	2.04 (1.02, 4.06)	2.04 (1.02, 4.06)	0.41/NA	0.043	NA	N	N	N	IV/IV	H
Ghasemiesfe, 2018	General population (Ado, A)	Marijuana use	Sputum production (unadjusted)	2	126/1234 (10.2%)	RR	3.78 (1.48,9.64)	3.78 (1.48, 9.64)	33.62/NA	0.006	NA	Y	N	N	IV/IV	H

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Hippocampus volume (NR)	16	NR/1063 (NA)	d	1.31 (1.04, 1.63)	0.15 (0.02, 0.27)	73.9/0.04	0.021	N	N	N	N	IV/IV	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Lateral orbitofrontal cortex volume (NR)	6	NR/356 (NA)	d	1.44 (1.09, 1.92)	0.20 (0.05, 0.36)	53.96/0.02	0.011	N	N	N	N	IV/IV	H
Gurney, 2015	General population (A <50, case-control)	Cannabis use, >= 10 year	Seminoma (NR)	3	NR/2138 (NA)	OR	1.04 (0.65, 1.64)	1.04 (0.65, 1.64)	0.00/NA	>0.05	NA	NA	NA	NA	NS	M
Gurney, 2015	General population (A <50, case-control)	Cannabis use, current	Seminoma (NR)	2	NR/2138 (NA)	OR	1.25 (0.78,1.96)	1.25 (0.78,1.96)	0.00/NA	>0.05	NA	NA	NA	NA	NS	M
Gurney, 2015	General population (A <50, case-control)	Cannabis use, weekly	Seminoma (NR)	3	NR/2138 (NA)	OR	1.27 (0.76,2.10)	1.27 (0.76, 2.10)	0.00/NA	>0.05	NA	NA	NA	NA	NS	M
Kamp, 2018	General population (A)	Cannabis use	Brain striatal dopaminergic function (NR)	5	NR/132 (NA)	d	1.13 (0.55, 2.34)	-0.07 (-0.47, 0.33)	26.24/ NA	>0.05	NA	NA	N	NA	NS	M
Grant, 2002	General population (A)	Cannabis use, chronic	Residual abstraction/executive (NR)	9	NR/820 (NA)	d	0.76 (0.54, 1.07)	-0.15 (-0.34, 0.04)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Grant, 2002	General population (A)	Cannabis use, chronic	Residual attention (NR)	12	NR/884 (NA)	d	0.82 (0.54, 1.24)	-0.11 (-0.34, 0.12)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Grant, 2002	General population (A)	Cannabis use, chronic	Residual motor (NR)	2	NR/69 (NA)	d	0.62 (0.18, 1.24)	-0.26 (-0.95, 0.44)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Grant, 2002	General population (A)	Cannabis use, chronic	Residual perceptual motor (NR)	8	NR/693 (NA)	d	0.89 (0.60, 1.31)	-0.07 (-0.28, 0.15)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Grant, 2002	General population (A)	Cannabis use, chronic	Residual reaction time (NR)	5	NR/526 (NA)	d	1.02 (0.67, 1.53)	0.01 (-0.22, 0.23)	NR/NA	>0.05	NA	NA	NA	NA	NS	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Grant, 2002	General population (A)	Cannabis use, chronic	Residual verbal/language (NR)	5	NR/468 (NA)	d	0.60 (0.32, 1.11)	-0.28(-0.62, 0.06)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Zhang, 2015	General population (A)	Cannabis use, habitual	Lung cancer (NR)	6	2159/3196	OR	0.95 (0.65,1.37)	0.95 (0.65, 1.37)	0.00/ NA	>0.05	NA	NA	NA	NA	NS	L
Ghasemiesfe, 2019	General population (A)	Marijuana, >10y	Seminoma (adjusted)	3	160/748 (21.4%)	OR	0.94 (0.59, 1.50)	0.94 (0.59, 1.50)	15.32/ 0.03	>0.05	N	N	N	N	NS	H
Ghasemiesfe, 2019	General population (A)	Marijuana, ever use	HNSCC (adjusted)	4	696/1976 (35.2%)	OR	1.27 (0.88, 1.85)	1.27 (0.88, 1.85)	50.27/ 0.07	>0.05	N	N	Y	Y	NS	H
Ghasemiesfe, 2019	General population (A)	Marijuana, ever use	Oral cancer (adjusted)	2	709/2357 (30.0%)	OR	1.21 (0.94,1.57)	1.21 (0.94,1.57)	43.29/ 0.02	>0.05	NA	Y	N	N	NS	H
Ghasemiesfe, 2019	General population (A)	Marijuana, ever use	TGCT (adjusted)	3	695/2112 (32.9%)	OR	1.11 (0.79, 1.56)	1.11 (0.79, 1.56)	55.98/ 0.05	>0.05	N	N	N	N	NS	H
Xue, 2021	General population (Ado, A)	Cannabis	Anxiety disorders/symptoms	7	NR/40553 (NA)	OR	1.31 (0.96, 1.78)	1.31 (0.96, 1.78)	70.58/ 0.10	>0.05	N	Y	N	N	NS	L
Scott, 2018	General population (Ado, A)	Cannabis	Motor speed (NR)	9	NR/NR (NA)	d	1.04 (0.77, 1.40)	-0.02 (-0.22, 0.18)	NR/NA	>0.05	NA	NA	Y	NA	NS	H
Schreiner, 2012	General population (Ado, A)	Cannabis	Residual simple reaction time (NR)	33	NR/775 (NA)	d	1.66 (0.82, 3.36)	0.28 (-0.11, 0.67)	63.98/NA	>0.05	NA	NA	NA	NA	NS	CL
Smith, 2014	General population (Ado, A)	Cannabis use	Behavioural inibition, go errors (NR)	2	NR/744 (NA)	d	0.81 (0.47, 1.86))	-0.12(-0.41,0.18)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Smith, 2014	General population (Ado, A)	Cannabis use	Behavioural inibition, GO RT (frequent-Go/rare-NoGo task, NR)	3	NR/744 (NA)	d	1.25 (0.77, 2.06)	0.13 (-0.15, 0.40)	NR/NA	>0.05	NA	NA	NA	NA	NS	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	Population	Cannabinoid specific exposure	Outcome	k	n/N (prevalence)	Metric	eOR (95% CI)	ES (95% CI)	I^2/ tau2	p	PI sign	LS sign	SSE	ESB	CE/CES	Q
Smith, 2014	General population (Ado, A)	Cannabis use	Behavioural inibition, GO RT (stop-signal task, NR)	3	NR/744 (NA)	d	1.20 (0.72, 2.00)	0.10 (-0.18, 0.39)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Smith, 2014	General population (Ado, A)	Cannabis use	Behavioural inibition, nogo errors (NR)	5	NR/744 (NA)	d	1.22 (0.81, 1.86)	0.11 (-0.12, 0.34)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Smith, 2014	General population (Ado, A)	Cannabis use	Behavioural inibition, SSRT (NR)	6	NR/744 (NA)	d	1.01 (0.66, 1.54)	0.01 (-0.23, 0.24)	NR/NA	>0.05	NA	NA	NA	NA	NS	M
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual abstraction/executive function after at least 25 days (NR)	13	NR/775 (NA)	d	0.83 (0.59, 1.19)	-0.10 (-0.29, 0.10)	0.00/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual attention effect after at least 25 d (NR)	13	NR/775 (NA)	d	0.69 (0.41, 1.18)	-0.20(-0.49, 0.09)	45.90/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual forgetting/retrieval effect after at least 25 d (NR)	13	NR/775 (NA)	d	0.76 (0.54, 1.08)	-0.15 (-0.34, 0.04)	20.02/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual learning effect after at least 25 days (NR)	13	NR/775 (NA)	d	0.75 (0.54, 1.03)	-0.16 (-0.33, 0.02)	0.00/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual motor effect after at least 25 d (NR)	13	NR/775 (NA)	d	0.71 (0.39, 1.30)	-0.19 (-0.53, 0.14)	0.00/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual perceptual-motor effect (NR)	33	NR/775 (NA)	d	1.04 (0.77, 1.40)	0.02 (-0.15, 0.18)	1.87/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual perceptual-motor effect after at least 25 d (NR)	13	NR/775 (NA)	d	1.18 (0.85, 1.63)	0.09 (-0.09, 0.27)	0.20/NA	>0.05	NA	NA	NA	NA	NS	CL
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual simple reaction time effect after at least 25 d (NR)	13	NR/775 (NA)	d	1.13 (0.69, 1.87)	0.07 (-0.21, 0.34)	0.00/NA	>0.05	NA	NA	NA	NA	NS	CL

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Schreiner, 2012	General population (Ado, A)	Cannabis use	Residual verbal/language effect after at least 25 d (NR)	13	NR/775 (NA)	d	0.83 (0.57, 1.22)	-0.10 (-0.31, 0.11)	0.00/NA	>0.05	NA	NA	NA	NA	NS	CL
Scott, 2018	General population (Ado, A)	Cannabis use	Visuospatial performance (NR)	15	NR/NR (NA)	d	1.07 (0.86, 1.34)	-0.04 (-0.16,0.08)	NR/ NA	>0.05	NA	NA	Y	NA	NS	H
Scott, 2018	General population (Ado, A)	Cannabis use, abstinent<72h	Overall cognition (NR)	69	NR/NR (NA)	d	NA	NR	NR/NA	>0.05	NA	NA	Y	NA	NS	H
Scott, 2018	General population (Ado, A)	Cannabis use, abstinent>72h	Overall cognition (NR)	15	NR/928 (NA)	d	1.15 (0.88, 1.52)	-0.08 (-0.23, 0.07)	NR/ NA	>0.05	NA	NA	Y	NA	NS	H
Scott, 2018	General population (Ado, A)	Cannabis use, current use	Overall cognition (NR)	69	NR/NR (NA)	d	NA (NA)	NR	NR/NA	>0.05	NA	NA	Y	NA	NS	H
Moore, 2007	General population (Ado, A)	Cannabis use, most frequent	Depression (adjusted)	8	760 /9010 (8.4%)	OR	1.47 (0.97, 2.21)	1.47 (0.97, 2.21)	68.78/ 0.19	>0.05	N	N	N	N	NS	M
Lorenzetti, 2019	General population (Ado, A)	Cannabis use, regular	Amygdala volume (NR)	8	NR/659 (NA)	d	1.04 (0.78, 1.38)	0.02 (-0.14, 0.18)	0.75/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Cannabis use, regular	Anterior cingulate cortex volume (NR)	3	NR/163 (NA)	d	0.95 (0.49, 1.82)	-0.03(-0.39, 0.33)	0.71/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Cannabis use, regular	Caudate volume (NR)	3	NR/435 (NA)	d	1.18 (0.74, 1.87)	0.09 (-0.17, 0.35)	0.85/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Cannabis use, regular	Cerebellum volume (NR)	5	NR/327 (NA)	d	3.36 (0.38, 29.24)	0.67 (-0.53, 1.87)	0.99/NA	>0.05	NA	NA	Y	NA	NS	H
de Carvalho, 2015	General population (Ado, A)	Marijuana use	Head and neck cancer (NR)	9	5082/11187 (45.4%)	OR	1.02 (0.91, 1.14)	1.02 (0.91, 1.14)	78.95/NA	>0.05	NA	NA	NA	NA	NS	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Intracranial volume (NR)	13	NR/992 (NA)	d	0.96 (0.75, 1.23)	-0.02(-0.16,0.12)	0.76/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Nucleus accumbens volume (NR)	3	NR/312 (NA)	d	0.76 (0.44, 1.31)	-0.15(-0.45, 0.15)	0.85/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Parietal cortex volume (NR)	2	NR/90 (NA)	d	1.06 (0.55, 2.03)	0.03 (-0.33, 0.39)	0.64/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Prefrontal cortex volume (NR)	3	NR/148 (NA)	d	1.10 (0.82, 1.46)	0.05 (-0.11,0.21)	0.00/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Putamen volume (NR)	3	NR/181 (NA)	d	0.87 (0.27, 2.75)	-0.08 (-0.72, 0.56)	0.94/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Striatum volume (NR)	2	NR/132 (NA)	d	0.24 (0.05, 1.28)	-0.79 (-1.72, 0.14)	0.07/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Total brain volume (NR)	8	NR/494 (NA)	d	0.91 (0.62, 1.35)	-0.05(-0.27, 0.17)	0.82/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Total grey matter (NR)	6	NR/358 (NA)	d	1.04 (0.85, 1.26)	0.02 (-0.09, 0.13)	0.11/NA	>0.05	NA	NA	Y	NA	NS	H
Lorenzetti, 2019	General population (Ado, A)	Regular cannabis use	Total white matter (NR)	6	NR/366 (NA)	d	1.04 (0.86, 1.24)	0.02 (-0.08, 0.12)	0.00/NA	>0.05	NA	NA	Y	NA	NS	H
Healthy cannabis users vs non users with cognitive outcomes																
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Prospective memory (NR)	5	NR/294 (NA)	d	3.43 (2.23, 5.28)	0.68 (0.44, 0.92)	92.51/0.06	1.9x10-8	N	Y	N	N	IV/ II	L

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Verbal delayed recall (NR)	38	NR/3368 (NA)	d	1.95 (1.63, 2.34)	0.37 (0.27, 0.47)	98.2/0.09	4.4x10-13	N	Y	Y	Y	IV/ II	L
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Verbal learning (NR)	41	NR/3085 (NA)	d	2.03 (1.72, 2.39)	0.39 (0.30, 0.48)	96.2/0.08	1.01x10-16	Y	Y	N	N	IV/ II	L
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Visual immediate recall (NR)	2	NR/89 (NA)	d	3.76 (2.64, 5.34)	-0.73 (-0.93, -0.54)	37.76/0.01	1.7x10-13	NA	Y	NA	N	IV/ II	L
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Working memory (NR)	39	NR/4550 (NA)	d	1.29 (1.14, 1.46)	0.14 (0.07, 0.21)	94.10/0.02	8.5x10-5	N	Y	N	N	IV/ III	L
Schoeler, 2016	Healthy subjects, (A)	Cannabis use	Verbal immediate recall (NR)	40	NR/3169 (NA)	d	2.10 (1.52, 2.97)	0.41 (0.23, 0.60)	99.60/0.36	1.6x10-5	N	Y	N	N	IV/ III	L
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Verbal recognition (NR)	21	NR/1485 (NA)	d	1.69 (1.36, 2.07)	0.29 (0.17, 0.40)	95.90/0.07	1.31x10-6	N	Y	N	N	IV/ III	L
Schoeler, 2016	Healthy subjects (A)	Cannabis use	Visual recognition (NR)	9	NR/485 (NA)	d	2.26 (1.20, 4.35)	0.45 (0.10, 0.81)	98.13/0.29	0.013	N	Y	N	N	IV/IV	L
Drivers and general population users vs non users with car outcomes																
Rogeberg, 2019	Drivers (A)	THC positive	Car crash (adjusted)	13	NR/78025 (NA)	RR	1.27 (1.21, 1.34)	1.27 (1.21. 1.34)	13.35/0.00	1.5x10-23	Y	Y	N	N	IV/ I	L
Rogeberg, 2019	Drivers (A)	THC positive	Car crash, culpability (adjusted)	13	NR/78025 (NA)	RR	1.53(1.39, 1.67)	1.53 (1.39, 1.67)	30.9/0.01	2.9x10-19	Y	Y	N	N	IV/ I	L
Hostiuc, 2018	General population (Ado, A)	Cannabis use	Car death after car crash (unadjusted)	5	NR/66705 (NA)	OR	1.72 (1.40, 2.10)	1.72 (1.40, 2.10)	71.49/0.03	1.2x10-7	N	Y	N	N	IV/ II	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Hostiuc, 2018	General population (Ado, A)	Cannabis use	Car unfavourable traffic events (unadjusted)	23	NR/245021 (NA)	OR	1.89 (1.58, 2.26)	1.89 (1.58, 2.26)	90.0/0.11	4.0x10-12	N	Y	Y	Y	IV/ II	M
Hostiuc, 2018	General population (Ado, A)	Cannabis use	Car collision (unadjusted)	6	NR/82875 (NA)	OR	1.91 (1.34, 2.72)	1.91 (1.34, 2.72)	82.31/0.14	3.0x10-4	N	Y	Y	Y	IV/ III	M
Hostiuc, 2018	General population (Ado, A)	Cannabis use	Car injury (unadjusted)	12	NR/95441 (NA)	OR	2.15 (1.42, 3.28)	2.15 (1.42, 3.28)	82.20/0.39	3.4x10-4	N	Y	N	N	IV/ III	M
Asbridge, 2012	General population (Ado)	THC	Car crash, deaths/injuries (adjusted)	7	2365/47641 (4.9%)	OR	1.63 (1.02, 2.60)	1.63 (1.02, 2.60)	88.66/0.28	0.039	N	Y	N	N	IV/IV	M
Psychosis and UHR																
Schoeler, 2016	Psychosis (A)	Cannabis use	Working memory (NR)	19	NR/2468 (NA)	d	1.44 (1.21, 1.71)	-0.20 (-0.30,-0.11)	97.10/0.03	$1.1x10^{-5}$	N	Y	N	N	IV/ III	L
Schoeler, 2016	Psychosis (A)	Cannabis continued use	Psychosis relapse (NR)	24	NR/16257 (NA)	d	1.88 (1.34, 2.71)	0.35 (0.16, 0.55)	92.27/0.19	$3.1x10^{-4}$	N	Y	N	N	IV/ III	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis current use	Premorbid IQ (unadjusted)	7	NR/515 (NA)	d	1.99 (1.34, 2.96)	-0.38 (-0.60, -0.16)	18.63/0.02	$5.0x10^{-4}$	N	Y	N	N	IV/ III	M
Foglia, 2017	Psychosis (Ado, A)	Cannabis current use vs none	Adherence to antipsychotic treatment (adjusted)	3	NR/259 (NA)	OR	5.78 (2.68, 12.46)	5.78 (2.68, 12.46)	14.61/0.07	$7.4x10^{-6}$	N	Y	N	N	IV/III	H
Foglia, 2017	Psychosis (Ado, A)	Cannabis use	Adherence to antipsychotic treatment (adjusted)	11	NR/3055 (NA)	OR	2.46 (1.97, 3.07)	2.46 (1.97, 3.07)	0.00/0.00	$2.2x10^{-15}$	Y	N	N	Y	IV/ III	H
Schoeler, 2016	Psychosis (A)	Cannabis use, continued	Psychosis, hospital length (NR)	5	NR/803 (NA)	d	1.89 (1.14, 3.13)	0.35 (0.07, 0.63)	58.44/0.06	0.013	N	N	N	N	IV/IV	M
Schoeler, 2016	Psychosis	Cannabis use, continued	Psychosis, positive symptoms (NR)	10	NR/1224 (NA)	d	1.31 (1.00, 1.72)	0.15 (0.00, 0.30)	24.70/0.01	0.049	N	N	N	N	IV/IV	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Schoeler, 2016	Psychosis	Cannabis use, continued	Psychosis, relapse (NR)	6	NR/884 (NA)	d	1.76 (1.09, 2.76)	0.31 (0.05, 0.56)	61.30/0.07	0.017	N	Y	N	Y	IV/IV	M
Schoeler, 2016	Psychosis	Cannabis use, discontinued	Psychosis, relapse (NR)	6	NR/884 (NA)	d	1.69 (1.11, 2.61)	0.29 (0.06, 0.53)	31.56/0.03	0.020	Y	Y	N	N	IV/IV	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis use	Verbal learning (NR)	8	NR/1153 (NA)	d	2.03 (1.82, 2.26)	-0.39(-0.45,-0.33)	89.0NA	<0.05	NA	NA	N	NA	IV/IV	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Working memory (verbal, unadjusted)	6	NR/703 (NA)	d	4.11 (1.06, 16.04)	-0.78 (-1.53, -0.03)	96.03/0.83	0.041	N	N	Y	N	IV/IV	M
Sabe, 2020	Schizophrenia (A)	Cannabis use	Negative symptoms (unadjusted)	7	NR/760 (NA)	d	1.89 (1.22, 2.97)	-0.35 (-0.60, -0.11)	47.95/0.05	0.005	N	N	N	N	IV/IV	H
Kraan, 2016	Ultra-high risk of psychosis (Ado, A)	Cannabis (abuse/dependence)	Psychosis (NR)	5	NR/1230 (NA)	OR	1.75 (1.14, 2.71)	1.75 (1.14, 2.71)	0.00/NA	0.011	NA	NA	Y	NA	IV/IV	H
Burns, 2012	First episode psychosis (Ado, A)	Cannabis use	Psychosis, duration untreated (NR)	9	447/1214 (36.8%)	d	1.22 (0.91, 1.66)	-0.11 (-0.28, 0.05)	58.28/ NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Attention (NR)	3	NR/318 (NA)	d	0.46 (0.01, 14.65)	-0.43 (-2.34, 1.48)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Executive function (NR)	6	NR/634 (NA)	d	2.86 (0.69, 11.78)	0.58 (-0.20, 1.36)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Premorbid IQ (NR)	4	NR/420 (NA)	d	2.03 (0.48, 8.50)	0.39 (-0.40, 1.18)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Overall cognition (NR)	7	NR/673 (NA)	d	0.89 (0.45, 1.78)	-0.06 (-0.44, 0.32)	NR/NA	>0.05	NA	NA	N	NA	NS	L

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Processing speed (NR)	2	NR/189 (NA)	d	2.61 (0.01, 1634.6)	0.53 (-3.03, 4.09)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Verbal memory and learning (NR)	5	NR/435 (NA)	d	0.95 (0.46, 1.93)	-0.03(-0.42, 0.36)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Visual memory (NR)	3	NR/228 (NA)	d	0.57 (0.08, 3.89)	-0.31(-1.37, 0.75)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Sánchez, 2019	First-episode psychosis (Ado, A)	Cannabis use	Working memory (NR)	6	NR/634 (NA)	d	0.79 (0.20, 3.14)	-0.13(-0.89, 0.63)	NR/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Verbal delayed recall (NR)	11	NR/1433 (NA)	d	0.77 (0.47, 1.26)	-0.14 (-0.41, 0.13)	72.0/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Verbal immediate recall (NR)	6	NR/1146 (NA)	d	1.24 (0.65, 2.36)	0.12 (-0.24, 0.48)	72.1/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Verbal learning (NR)	14	NR/2101 (NA)	d	1.22 (0.73, 2.03)	0.11 (-0.17, 0.39)	72.2/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Visual delayed recall (NR)	14	NR/783 (NA)	d	1.18 (0.83, 1.68)	0.09 (-0.11, 0.29)	72.3/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Visual immediate recall (NR)	19	NR/3164 (NA)	d	1.11 (0.93, 1.34)	0.06 (-0.04, 0.16)	72.4/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Visual learning (NR)	2	NR/143 (NA)	d	0.83 (0.46, 1.52)	-0.10 (-0.43, 0.23)	72.6/NA	>0.05	NA	NA	N	NA	NS	L
Schoeler, 2016	Psychosis (A)	Cannabis use	Visual working memory (NR)	7	NR/454 (NA)	d	0.96 (0.63, 1.47)	-0.02 (-0.26, 0.22)	72.7/NA	>0.05	NA	NA	N	NA	NS	L

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I²/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Schoeler, 2016	Psychosis (A)	Cannabis use, continued	Psychosis, functioning (NR)	9	NR/1198 (NA)	d	1.08 (0.75, 1.54)	0.04 (-0.16, 0.24)	56.27/ 0.05	>0.05	N	N	N	N	NS	M
Schoeler, 2016	Psychosis (A)	Cannabis use, continued	Psychosis, negative symptoms (NR)	10	NR/1202 (NA)	d	1.20 (0.82, 1.72)	-0.10 (-0.30, 0.11)	54.90/ 0.05	>0.05	N	Y	N	N	NS	M
Ruiz, 2012	Psychosis (Ado, A)	Cannabis use	Neurological soft signs (NR)	2	NR/142 (NA)	d	2.30 (0.89, 5.93)	0.46 (-0.06, 0.98)	55.00/ NA	>0.05	NA	NA	N	NA	NS	M
Foglia, 2017	Psychosis (Ado, A)	Cannabis use, current vs former	Adherence to antipsychotic treatment (NR)	4	NR/404 (NA)	OR	1.81 (0.25, 13.17)	1.81 (0.25, 13.17)	88.0/NA	>0.05	NA	NA	N	NA	NS	H
Foglia, 2017	Psychosis (Ado, A)	Cannabis use, former	Adherence to antipsychotic treatment (NR)	3	NR/259 (NA)	OR	1.12 (0.61, 2.06)	1.12 (0.61, 2.06)	0.00/NA	>0.05	NA	NA	N	NA	NS	H
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Cognitive flexibility (NR)	8	NR/1015 (NA)	d	1.41 (0.76, 2.63)	0.19 (-0.16, 0.54)	82.0/NA	>0.05	NA	NA	N	NA	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Conceptual set-shifting (NR)	8	NR/740 (NA)	d	1.78 (0.92, 3.45)	0.32 (-0.05, 0.67)	79.0/NA	>0.05	NA	NA	N	NA	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Current IQ (unadjusted)	6	NR/658 (NA)	d	1.34 (0.93, 1.92)	-0.16 (-0.36, 0.04)	37.99/ 0.02	>0.05	N	Y	N	N	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Motor inhibition (NR)	8	NR/781 (NA)	d	0.71 (0.48, 1.04)	-0.19(-0.40, 0.02)	34.0/NA	>0.05	NA	NA	N	NA	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Processing speed (NR)	10	NR/1823 (NA)	d	1.43 (0.92, 2.24)	0.20 (-0.05, 0.45)	79.0/NA	>0.05	NA	NA	N	NA	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Sustained attention (NR)	9	NR/771 (NA)	d	2.70 (0.56, 12.95)	0.55 (-0.32, 1.42)	94.0/NA	>0.05	NA	NA	N	NA	NS	M

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Verbal fluency (NR)	6	NR/736 (NA)	d	0.43 (0.11, 1.66)	-0.47(-1.22, 0.28)	34.0/NA	>0.05	NA	NA	N	NA	NS	M
Bogaty, 2018	Psychosis (Ado, A)	Cannabis, current use	Verbal memory (NR)	8	NR/1153 (NA)	d	0.79 (0.46, 1.34)	-0.13(-0.42, 0.16)	75.0/NA	>0.05	NA	NA	N	NA	NS	M
Rabin, 2011	Schizophrenia (A)	Cannabis use	Attention, selective, sustained and divided (NR)	6	NR/NR (NA)	d	1.88 (0.83, 4.25)	0.35 (-0.10, 0.80)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Executive abilities (NR)	7	NR/NR (NA)	d	1.29 (0.23, 7.32)	0.14 (-0.82, 1.10)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Language, receptive and expressive abilities (NR)	4	NR/NR (NA)	d	1.11 (0.39, 3.21)	0.06 (-0.52, 0.65)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Overall cognition and intelligence (NR)	4	NR/NR (NA)	d	2.38 (0.39, 14.56)	0.48 (-0.52, 1.48)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Retrieval and recognition (NR)	6	NR/NR (NA)	d	1.24 (0.21, 7.32)	0.12 (-0.86, 1.10)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Visuo-spatial abilities (NR)	3	NR/NR (NA)	d	1.82 (0.69, 4.74)	0.33 (-0.20, 0.86)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Rabin, 2011	Schizophrenia (A)	Cannabis use	Working memory and learning (NR)	5	NR/NR (NA)	d	1.14 (0.27, 4.70)	0.07 (-0.71, 0.86)	NR/NA	>0.05	NA	NA	NA	NA	NS	L
Kraan, 2016	Ultra-high risk of psychosis (Ado, A)	Cannabis use (lifetime)	Psychosis (NR)	7	NR/953 (NA)	OR	1.14 (0.86,1.52)	1.14 (0.86, 1.52)	0.00/NA	>0.05	NA	NA	Y	NA	NS	H
Frequent/dependent (adolescents) cannabis users																

Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Power, 2020	Frequent/dependent cannabis users (Ado)	Cannabis use	IQ decline (adjusted)	7	NR/5846 (NA)	d	1.29 (1.06, 1.55)	-0.14 (-0.24, -0.03)	50.26/0.01	0.010	N	Y	N	N	IV/IV	H
Power, 2020	Frequent/dependent cannabis users (Ado)	Cannabis use	Verbal IQ decline (adjusted)	4	NR/3672 (NA)	d	1.38 (1.16, 1.66)	-0.18 (-0.28, -0.08)	15.02/0.00	0.001	N	N	N	N	IV/IV	H
Power, 2020	Frequent/dependent cannabis users (Ado)	Cannabis use	Performance IQ (NR)	5	NR/2689 (NA)	d	1.00 (0.86, 1.16)	0.00 (-0.09, 0.08)	0.00/ NA	>0.05	NA	NA	NA	NA	NS	H
Insomnia																
Bhagavan, 2020	Insomnia (A)	Cannabinoids	Sleep quality/quantity (NR)	4	NR/352 (NA)	MD	NA, beneficial	1.95 (1.04, 2.87)	19.40/0.00	$3.0x10^{-5}$	N	Y	N	Y	IV/ III	H
Chronic pain population																
Noori, 2021	Chronic pain (A)	CBM	Pain relief (unadjusted)	6	NR/345 (NA)	MD	NA, beneficial	-3.00 (-4.60, -1.40)	96.28/3.82	$2.0x10^{-4}$	N	N	N	N	IV/III	L
Noori, 2021	Chronic pain (A)	CBM	Oral morphine equivalence dose reduction (NR)	8	NR/723 (NA)	MD	NA	-23.89 (-58.25, 10.47)	90.31/ 1.81	>0.05	N	Y	Y	N	NS	L
Mixed conditions																
Goldenberg, 2017	Mixed medical conditions (fibromyalgia, HIV, IBD, neuropatic pain) (A)	Nabiximol, nabilone, dronabinol cannabis extract, dexanabinol	Quality of life (NR)	20	NR/3902 (NA)	d	1.09 (0.54, 2.22)	0.05 (-0.34, 0.44)	NR/NA	>0.05	NA	NA	N	NA	NS	M
HCV+/- NAFDL population																
Farooqui, 2019	HCV+ NAFDL (A)	Marijuana use	Liver steatosis (adjusted)	4	NR/5962412 (NA)	OR	0.78 (0.71, 0.87)	0.78 (0.71, 0.87)	25.18/0.00	$3.31x10^{-6}$	Y	Y	Y	N	IV/ III	M

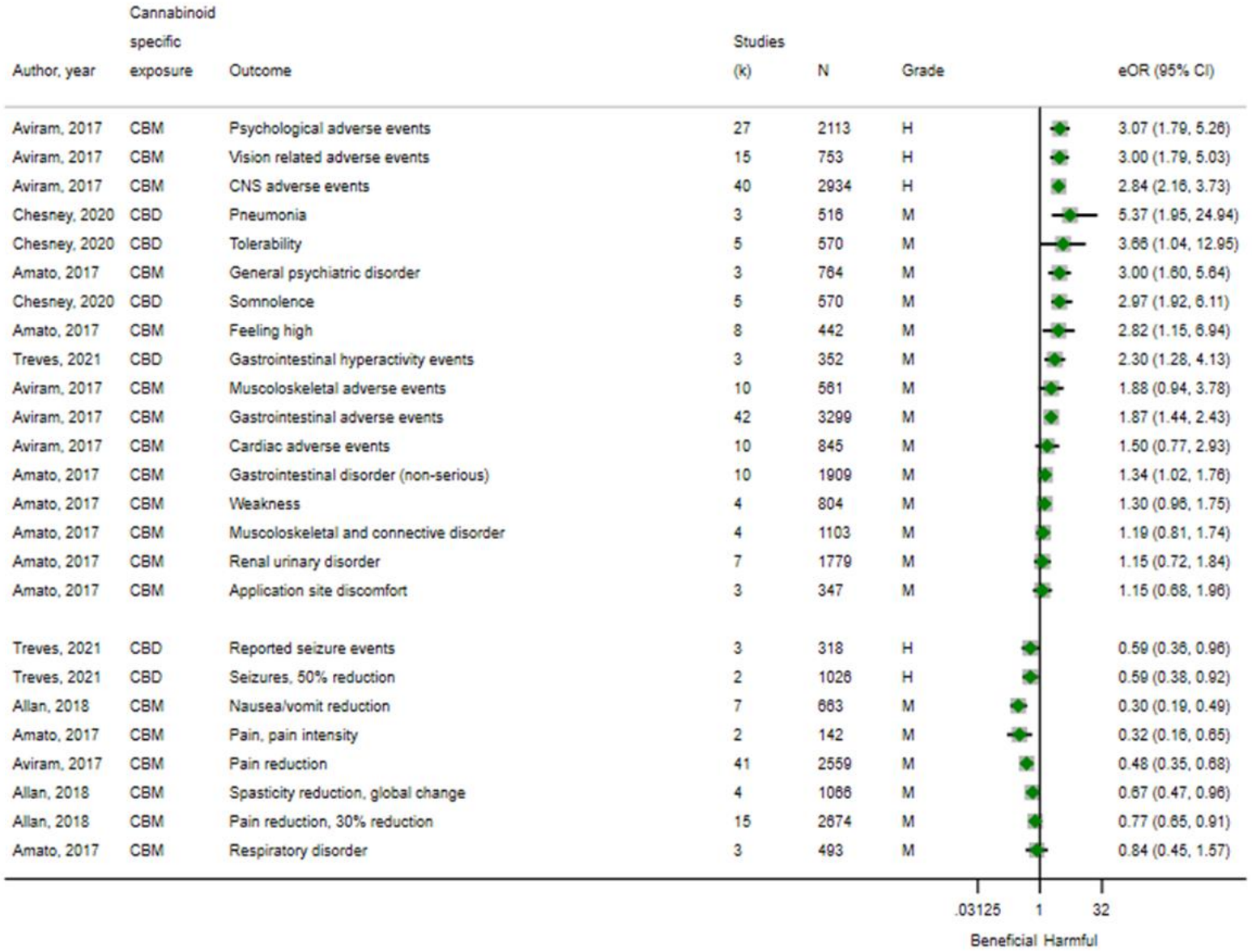
Source	Population	Cannabis	Outcome	Sample size		Effect size			Heterogeneity	Significance			Biases		Class and quality of evidence	
Author, year	**Population**	**Cannabinoid specific exposure**	**Outcome**	**k**	**n/N (prevalence)**	**Metric**	**eOR (95% CI)**	**ES (95% CI)**	**I^2/ tau2**	**p**	**PI sign**	**LS sign**	**SSE**	**ESB**	**CE/CES**	**Q**
Farooqui, 2018	HCV+ NAFDL (A)	Marijuana use	Liver fibrosis in coinfection HCV and HIV (NR)	2	NR/1265 (NA)	HR	1.00 (0.93,1.07)	1.00 (0.93,1.07)	0.00/ NA	>0.05	NA	NA	N	NA	NS	M
Farooqui, 2018	HCV+ NAFDL (A)	Marijuana use	Liver fibrosis in hepatitis C (NR)	4	NR/1166 (NA)	OR	1.96 (0.79, 4.93)	1.96 (0.79, 4.93)	77.00/ NA	>0.05	NA	NA	N	NA	NS	M
Wijarnpreecha, 2018	HCV (A)	Cannabis extract, oro-mucosal	Liver fibrosis (NR)	3	NR/898 (NA)	OR	1.77 (0.78, 4.02)	1.77 (0.78, 4.02)	75.00/ NA	>0.05	NA	NA	NA	NA	NS	H
Malignant CNS population																
Rodriguez, 2020	Malignant central nervous system tumors (A)	Cannabidiol	Survival (NR)	2	NR/44 (NA)	RR	0.46 (0.16,1.32)	0.46 (0.16,1.32)	0.00/NA	>0.05	NA	NA	N	NA	NS	L

*Legend. A, adults; Ado, adolescents; C, children; CE, class of evidence; CES, class of evidence after removing the n>1000 cases criterion, and where possible additional sensitivity analyses as specified; CBM, cannabis based medicine; CI, confidence interval; CL, critically low; ES, effect size; ESB, excess significance bias; H, high; I^2, percentage of variation across effect sizes that is due to heterogeneity rather than change; tau2, tau-squared heterogeneity; IQ, intelligence quotient; K, number of studies for each factor; L, low; LBW, low birth weight; LS, largest study with significant effect; M, moderate; n/N, number of cases/total number of cohort per factor; N, no; NA, not assessable; NR, not reported; OR, odds ratio; PI, prediction interval; Q, quality, AMSTAR 2; RR, risk ratio; SSE, small study effects; sign., significant; Y, yes; eOR>1 indicates "bad" outcome; *, not significant in adjusted analyses; +, class of evidence convincing in cohort studies*

Supplementary Table 6. Type of cannabis exposure across individual studies

See supplementary material 3.

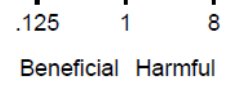
Supplementary figure 1. Moderate and high certainty evidence according to GRADE, from randomized controlled trials on outcomes of cannabis-based medications in persons with mixed conditions



Legend. Results are displayed in descending order of level of evidence, and magnitude of effect size; CBD, cannabidiol; CBM, cannabis-based medicines; CNS, central nervous system; eOR, equivalent odds ratio; H, high; M, moderate; N, sample size.

Supplementary figure 2. Moderate and high certainty evidence according to GRADE, from randomized controlled trials on outcomes of cannabis-based medications in the general population

Author, year	Cannabinoid specific exposure	Outcome	Studies (k)	N	Grade	eOR (95% CI)
Hindley, 2020	Cannabis	Total psychiatric symptoms	10	196	H	7.49 (5.31, 10.42)
Hindley, 2020	Cannabis	Positive symptom	15	324	H	5.21 (3.36, 8.01)
Hindley, 2020	Cannabis	Negative symptom severity	13	267	M	4.19 (2.88, 6.05)
McCartney, 2021	THC	Tracking performance	27	606	M	2.14 (1.59, 2.88)
McCartney, 2021	THC	Information processing	13	290	M	1.99 (1.46, 2.71)
McCartney, 2021	THC	Fluid intelligence	10	346	M	1.95 (1.64, 2.32)
McCartney, 2021	THC	Fine motor function	12	310	M	1.92 (1.24, 2.96)
McCartney, 2021	THC	Working memory	36	800	M	1.92 (1.44, 2.56)
McCartney, 2021	THC	Conflict control	27	805	M	1.85 (1.59, 2.16)
McCartney, 2021	THC	Standard deviation of lane position	15	353	M	1.69 (1.22, 2.34)
McCartney, 2021	THC	Divided attention	22	486	M	1.66 (1.43, 1.92)
McCartney, 2021	THC	Reaction time cognitive domain	24	647	M	1.66 (1.26, 2.19)
McCartney, 2021	THC	Lateral control	16	378	M	1.54 (1.14, 2.08)
McCartney, 2021	THC	Sustained attention	16	524	M	1.52 (1.19, 1.94)



Legend. Results are displayed in descending order of level of evidence, and magnitude of effect size; eOR, equivalent odds ratio; H, high; M, moderate; N, sample size.

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