Supplementary Appendix 1: Search strategy

1. Exp Cannabinoids/
2. Exp Cannabis/
3. Cannab* or Marijuana or Marinol or Dronabinol or Nabilone or Levonantradol or Tetrahydrocannabinol or Cesamet or Delta-9-THC or Delta-9-Tetrahydrocannabinol or Nabiximols or Sativex or Cannabidiol.mp.
4. Exp medical marijuana/
5. 'Medicinal marijuana' or 'medical marijuana'.mp.
6. 'Medicinal cannabis' or 'medical cannabis'.mp.
7. Or/1-6
8. meta analysis.pt.
9. (meta-analys* or meta analys* or metaanalys*).tw,sh.
10. exp meta-analysis as topic/
11. exp meta-analysis/
12. (systematic* adj5 review*).tw,sh.
13. (systematic* adj5 overview*).tw,sh.
14. (quantitativ* adj5 review*).tw,sh.
15. (quantitativ* adj5 overview*).tw,sh.
16. (quantitativ* adj5 synthesis*).tw,sh.
17. (methodologic* adj5 review*).tw,sh.
18. (methodologic* adj5 overview*).tw,sh.
19. (integrative research review* or research integration).tw.
20. Cochrane.ti.
21. Or/8-20
22. (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
23. side effect$.ti,ab.
24. 3 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
25. (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
26. (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
27. (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
28. (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
29. (adrs or ades).ti,ab.
30. drug safety.ti,ab.
31. (drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.
32. tolerability.ti,ab.
33. (harm or harms or harmful).ti,ab.
34. product surveillance, postmarketing/
35. adverse drug reaction reporting systems/
36. exp Drug Hypersensitivity/
37. iatrogenic disease/
38. exp drug toxicity/
39. Abnormalities, Drug-Induced/
40. treatment emergent.ti,ab.
41. drug toxicity.ti,ab.
42. (iatrogenic or iatrogenesis).ti,ab.
43. complication$.ti.
44. toxicity.ti.
45. safety.ti.
46. safe.ti.
47. abus*.ti,ab. OR addict*.ti,ab. OR dependen*.ti,ab.
48. behav*.ti,ab. OR psycho*.ti,ab. OR psychiatry*.ti,ab. OR mental.ti,ab. OR mania.ti,ab. OR depress*.ti,ab. OR suicide*.ti,ab. OR cogniti*.ti,ab. OR impair*.ti,ab. OR intoxicat*.ti,ab.
49. morbidity.ti,ab. OR mortality.ti,ab. OR overdos*.ti,ab. OR poison*.ti,ab. OR death.ti,ab.
50. blood pressure.ti,ab. OR cardiac.ti,ab. OR cardiovascular.ti,ab. OR coronary.ti,ab.
51. cancer.ti,ab. OR carcinogenic*.ti,ab. OR teratogenic*.ti,ab. OR pregnancy.ti,ab. OR prenatal.ti,ab. OR perinatal.ti,ab. OR neonatal.ti,ab.

52. lung*.ti,ab. OR pulmonary.ti,ab. OR respiratory.ti,ab. OR immun*.ti,ab. OR endocrin*.ti,ab.
53. motor vehicle*.ti,ab. OR car accident*.ti,ab. OR accident*.ti,ab. OR collision*.ti,ab. OR injur*.ti,ab.
54. Or/22-53
55. 7 AND 21 AND 54

Supplementary Appendix 2: Excluded articles at full text screening stage

First author year	Reason for exclusion	Citation
Alharbi 2016	Not a systematic review	Addict Disord Their Treatment 2016;15:190–200
Allan 2018	Not a systematic review	Can Fam Physician 2018;64:e78-94.
Andrade 2008	Not a systematic review	Psicologia em Estudo, Maringá, v. 13, n. 3, p. 567-573, jul./set. 2008
Arnone 2006	Not a review of harms (Measures of structural damage in corpus callosum)	Neuropsychobiology 2006;54:107–113 DOI: 10.1159/000096992
Batalla 2013	Not a review of harms (Brain structure and function)	PLoS ONE 8(2): e55821. doi:10.1371/journal.pone.0055821
Batalla 2014	Not a review of harms (Brain structure and function)	Curr Pharm Des. 2014;20(13):2168-85.
Blavos 2017	Not a systematic review	A Critical Review of the Literature, American Journal of Health Education, 48:3, 167-184, DOI: 10.1080/19325037.2017.1292878
Bondallaz 2017	Not a systematic review	Percy Bondallaz, Bernard Favrat, Ha¨ıthem Chtioui, Eleonora Fornari, Philippe Maeder, Christian Giroud, Cannabis and its effects on driving skills, Forensic Science International http://dx.doi.org/10.1016/j.forsciint.2016.09.007
Bugra 2012	Not a systematic review	Fortschr Neurol Psychiatr. 2012 Nov;80(11):635-43
Carbuto 2012	Animal subjects	Psychopharmacology (2012) 219:885–896 DOI 10.1007/s00213-011-2417-y
Cohen 2018	Not a systematic review	Brain Sci. 2018, 8, 40; doi:10.3390/brainsci8030040
Colizzi 2016	Not a review of harms (Glutamate levels and and release) & included animals	Neuroscience and Biobehavioral Reviews 64 (2016) 359–381
Cookey 2014	Not a review of harms (White matter tissue, disruption)	Schizophrenia Research 156 (2014) 137–142. http://dx.doi.org/10.1016/j.schres.2014.04.026
Degenhardt 2008	Not a systematic review	Lancet 2009; 374: 1383–91
deIrala 2005	Not a systematic review	Med Sci Monit, 2005; 11(12): RA355-358. PMID: 16319805
Drummer 2019	Not a systematic review	Forensic Science International 298 (2019) 298–306. https://doi.org/10.1016/j.forsciint.2019.03.007
Gage 2016	Not a systematic review	Biological Psychiatry April 1, 2016; 79:549–556. http://dx.doi.org/10.1016/j.biopsych.2015.08.001
Garfield 2014	Not a review of harms (Anhedonia)	Aust N Z J Psychiatry. 2014 Jan;48(1):36-51
Gates 2014	Not a review of harms (Sleep quality)	Sleep Medicine Reviews 18 (2014) 477e487
GomezOchoa 2017	Not in English	Neurologia. 2017 Dec 22. pii: S0213-4853(17)30362-6
Hackam 2015	Not a systematic review	Stroke. 2015;46:852-856. DOI: 10.1161/STROKEAHA.115.008680
Hoch 2015	Not a systematic review	Dtsch Arztebl Int 2015; 112: 271–8. DOI: 10.3238/arztebl.2015.0271
Imtiaz 2016	Not a systematic review	Addiction, 111, 653–662. doi:10.1111/add.13237
James 2013	Not a review of harms (Brain structure and function, brain activity)	Psychiatry Research: Neuroimaging 214 (2013) 181–189. http://dx.doi.org/10.1016/j.pscychresns.2013.07.012
Kose 2018	Not a systematic review	Psychiatry and Clinical. Psychopharmacology, 28:1, 1-3, DOI:10.1080/24750573.2018.1403671
LeBec 2009	Not in English	Encephale. 2009 Sep;35(4):377-85
Lindsey 2012	Not a systematic review	The American Journal of Drug and Alcohol Abuse, 2012; 38(4): 334–343. DOI: 10.3109/00952990.2011.643997
Lorenzetti 2010	Not a review of harms (Brain changes in hippocamus, amygdala)	Substance Use & Misuse, 45:11, 1787-1808, DOI: 10.3109/10826084.2010.482443

Malchow 2013	Not a review of harms (Brain morphology in pts with schizophrenia), pts with schizophrenia	Eur Arch Psychiatry Clin Neurosci (2013) 263:3–13. DOI 10.1007/s00406-012-0346-3
Martin-Santos 2010	Not a review of harms (Brain structure and functioning (blood flow relations to impairments), changes in volume)	Psychological Medicine (2010), 40, 383–398. doi:10.1017/S0033291709990729
Mcloughlin 2014	Not a review of harms	Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD004837. DOI: 10.1002/14651858.CD004837.pub3
Memedovich 2018	Not a systematic review	CMAJ Open 2018. DOI:10.9778/cmajo.20180023
Minozzi 2010	Not a systematic review	Drug and Alcohol Review (May 2010), 29, 304–317. DOI: 10.1111/j.1465-3362.2009.00132.x
Mishra 2017	Not a systematic review	Medicine (2017) 96:19(e6917)
Nugent 2017	Review of harms in context of efficacy	Ann Intern Med. 2017;167:319-331. doi:10.7326/M17-0155
Osazuwa-Peters 2016	Not a systematic review	J Evid Base Dent Pract 2016: [127-129] 1532-338. http://dx.doi.org/10.1016/ j.jebdp.2016.06.004
Park 2018	Review of harms in context of efficacy	Ann Intern Med. 2017 Sep 5;167(5):319-331.
Quickfall 2006	Not a review of harms (Brain structure, functioning (global cortical activity))	The Journal of Neuropsychiatry and Clinical Neurosciences 2006; 18:318–332
Rapp 2012	Not a review of harms (Brain structure (decreased activity globally))	Current Pharmaceutical Design, 2012, 18, 5070-5080
Reece 2009	Not a systematic review	Clinical Toxicology (2009) 47, 517–524. DOI: 10.1080/15563650903074507 LCLT
Rey 2004	Not a systematic review	J Am Acad Child Adolesc. Psychiatry, 43:10. DOI: 10.1097/01.chi.0000135623.12843.60
Richards 2019	Not a systematic review	Society for Academic Emergency Medicine. doi: 10.1111/acem.13756
Rochetti 2013	Not a review of harms (Brain structure (whole brain volume))	Psychiatry and Clinical Neurosciences 2013; 67: 483–492. doi:10.1111/pcn.12085
Ruiz-Veguilla 2012	Association of psychosis and neurological fn (Neurological soft signs (sensory integration, motor coordination, motor sequencing))	Current Pharmaceutical Design, 2012, 18, 5156-5164
Sami 2015	Not a review of harms (Dopamine functioning)	European Neuropsychopharmacology (2015) 25, 1201–1224. http://dx.doi.org/10.1016/j.euroneuro.2015.03.011 0924-977X
Santos 2013	Not a systematic review	Aten Primaria. 2013;45(Espec Cong 1):59-131
Schoeler 2014	Not a review of harms (Relapse of cannabis use)	Schizophrenia Research Volume 153, Supplement 1, April 2014, Page S235
Schreck 2018	Summarized cases of CHS but no comparison to other populations	Drug and Alcohol Dependence 182 (2018) 27–32. https://doi.org/10.1016/j.drugalcdep.2017.09.038
Schwitzer 2015	Not a review of harms (Visual processing (disturbances, foveal glare, retinal processing, activation visual cortex))	Eur Neuropsychopharmacol. 2015 Jan;25(1):100-12
Simons-Linares 2017	Not a systematic review	Gastroenterology, Volume 152, Issue 5, S293

Sneider 2013	Not a review of harms (Levels of brain chemicals (N-acetyl aspartate, choline), GABA levels)	J Addict Res Ther. 2013 Apr 24; Suppl 4: 010.
Szoke 2014	Not a review of harms (Schizotypal traits)	Psychiatry Research, http://dx.doi.org/10.1016/j.psychres. 2014.05.008
Underner 2018	Not in English	Rev Pneumol Clin (2018), https://doi.org/10.1016/j.pneumo.2018.06.003
Wrege 2014	Not a review of harms (Impulsivity, neuroimaging (prefrontal blood flow, brain metabolism, prefrontal volume))	Current Pharmaceutical Design, 2014, 20, 2126-2137, 1873-4286/14
Zarifi 2017	Not a systematic review	Perm J 2017;21:16-160. https://doi.org/10.7812/TPP/16-160
Zhang 2015	Not a systematic review	Oncotarget, Vol. 7, No. 40

Supplementary Appendix 3: List of included reviews with citations

Author year	Title of Review	Citation
Akram 2019	What are the psychological effects of using synthetic cannabinoids? A systematic review	Journal of Psychopharmacology 2019, Vol. 33(3) 271–283
Asbridge 2012	Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis	BMJ 2012;344:e536–e536.
Barkin 2016	Cannabis-Induced Acute Pancreatitis A Systematic Review	Pancreas 2017;46:1035–1038.
Ben Amar 2007	Cannabis and Psychosis: What is the Link?	Journal of Psychoactive Drugs; Jun 2007; 39, 2;
Bennett 2008	The statistical association between drug misuse and crime: A meta-analysis	Aggress Violent Behav 2008;13:107–118.
Blithikioti 2019	Cerebellar alterations in cannabis users: A systematic review	Addiction Biology. 2019;1–17.
Bogaty 2018	Meta-analysis of neurocognition in young psychosis patients with current cannabis use	J Psychiatr Res 2018;99:22–32.
Borges 2016	A literature review and meta-analyses of cannabis use and suicidality	J Affect Disord 2016;195:63–74
Breet 2018	Substance use and suicidal ideation and behaviour in low- and middle-income countries: a systematic review	Breet et al. BMC Public Health (2018) 18:549
Broyd 2016	Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review	Biological Psychiatry April 1, 2016; 79:557–567
Burns 2012	Cannabis use and Duration of Untreated Psychosis: A Systematic Review and Meta-Analysis	Current Pharmaceutical Design, 2012, 18, 5093-5104
Calabria 2010	Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use	Drug Alcohol Rev 2010;29:318–330.
Conner 2016	Maternal Marijuana Use and Adverse Neonatal Outcomes A Systematic Review and Meta-analysis	Obstet Gynecol 2016;128:713–723.
Coughlin 2006	Arterial Consequences of Recreational Drug Use	Eur J Vasc Endovasc Surg 2006;32:389–396.
Courts 2016	Signs and symptoms associated with synthetic cannabinoid toxicity: systematic review	Australasian Psychiatry 2016, Vol 24(6) 598–601
deCarvalho 2015	Head and neck cancer among marijuana users: A meta-analysis of matched case–control studies	Arch Oral Biol 2015;60:1750–1755.
Dellazizzo 2019	Cannabis use and violence in patients with severe mental illnesses: A meta-analytical investigation	Psychiatry Res 2019;274:42–48.
Elvik 2013	Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies	Accid Anal Prev 2013;60:254–267.
English 1997	Maternal cannabis use and birth weight: a meta-analysis	Addiction (1997) 92 (11), 1553-1560
Esmaeelzadeh 2018	Examining the Association and Directionality between Mental Health Disorders and Substance Use among Adolescents and Young Adults in the U.S. and Canada—A Systematic Review and Meta-Analysis	J Clin Med 2018;7:543
Foglia 2017	Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis	Psychol Med 2017;47:1691–1705.
Ganzer 2016	Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults	Neuropsychol Rev 2016;26:186–222.
Ghasemiesfe 2018	Marijuana Use, Respiratory Symptoms, and Pulmonary Function A Systematic Review and Meta-analysis	Ann Intern Med 2018;169:106.
Ghasemiesfe 2019	Association Between Marijuana Use and Risk of Cancer A Systematic Review and Meta-analysis	JAMA Network Open. 2019;2(11):e1916318.
Gibbs 2015	Cannabis use and mania symptoms: A systematic review and meta-analysis	J Affect Disord 2015;171:39–47
Gobbi 2019	Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood A Systematic Review and Meta-analysis	JAMA Psychiatry 2019;76:426.
Gonzalez 2002	Nonacute (Residual) Neuropsychological Effects of Cannabis Use: A Qualitative Analysis and Systematic Review	J Clin Pharmacol 2002;42:48S-57S

Grant 2003	Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study	J Int Neuropsychol Soc 2003;9:679–689.
Grotenhermen 2010	Cannabis-associated arteritis	Vasa 2010;39:43–53.
Gunn 2016	Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis	BMJ Open 2016;6:e009986.
Gurney 2015	Cannabis exposure and risk of testicular cancer: a systematic review and metaanalysis	BMC Cancer 2015;15:897.
Haden 2017	MDMB-CHMICA: Availability, Patterns of Use, and Toxicity Associated With This Novel Psychoactive Substance	Substance Use & Misuse, 52:2, 223-232
Hashibe 2005	Epidemiologic review of marijuana use and cancer risk	Alcohol 2005;35:265–275.
Hartman 2013	Cannabis Effects on Driving Skills	Clinical Chemistry 59:3 478–492 (2013)
Hobbs 2018	Spicing it up - synthetic cannabinoid receptor agonists and psychosis – a systematic review	European Neuropsychopharmacology 28 (2018) 1289–1304
Hostiuc 2018	The Association of Unfavorable Traffic Events and Cannabis Usage: A Meta-Analysis	Front Pharmacol 2018;9:99.
Huang 2015	An Epidemiologic Review of Marijuana and Cancer: An Update	Cancer Epidemiol Biomarkers Prev 2015;24:15–31.
Johnson 2017	Marijuana use and physical dating violence among adolescents and emerging adults: A systematic review and meta-analysis	Drug Alcohol Depend 2017;174:47–57.
Jouanjus 2017	What is the Current Knowledge About the Cardiovascular Risk for Users of Cannabis-Based Products? A Systematic Review	Curr Atheroscler Rep 2017;19:26.
Kedzior 2014	A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies	BMC Psychiatry 2014;14:136.
Korantzopoulos 2008	Atrial fibrillation and marijuana smoking	Int J Clin Pract 2007;62:308–313.
Kraan 2015	Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis	Psychol Med 2016;46:673–681.
Large 2011	Cannabis Use and Earlier Onset of Psychosis	Arch Gen Psychiatry/Vol 68 (No. 6), June 2011
Lev-Ran 2014	The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies	Psychol Med 2014;44:797–810.
Li 2012	Marijuana Use and Motor Vehicle Crashes	Epidemiol Rev 2012;34:65–72.
Macleod 2004	Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies	Lancet 2004; 363: 1579–88
Mammen 2018	Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies	J Clin Psychiatry. 2018;79(4):17r11839
Mansoor 2017	Systematic review of nephrotoxicity of drugs of abuse, 2005–2016	Mansoor et al. BMC Nephrology (2017) 18:379
Marconi 2016	Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis	Schizophr Bull 2016;42:1262–1269.
Martinasek 2016	A Systematic Review of the Respiratory Effects of Inhalational Marijuana	Respir Care 2016;61:1543–1551.
McLaren 2010	Assessing evidence for a causal link between cannabis and psychosis: A review of cohort studies	International Journal of Drug Policy 21 (2010) 10–19
Mehra 2006	The Association Between Marijuana Smoking and Lung Cancer A Systematic Review	Arch Intern Med 2006;166:1359.
Moore 2007	Cannabis use and risk of psychotic or aff ective mental health outcomes: a systematic review	Lancet 2007; 370: 319–28

Myles 2012	The Association between Cannabis Use and Earlier Age at Onset of Schizophrenia and other Psychoses: Meta-analysis of Possible Confounding Factors	Current Pharmaceutical Design, 2012, 18, 5055-5069
Myles 2016	Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use	Australian & New Zealand Journal of Psychiatry 2016, Vol. 50(3) 208–219
Oomen 2018	The acute effects of cannabis on human executive function	Behavioural Pharmacology 2018, 29:605–616
Peters 2012	Clinical correlates of co-occurring cannabis and tobacco use: a systematic review	Addiction 2012;107:1404–1417
Platt 2019	The effects of licit and illicit recreational drugs on prospective memory: a meta-analytic review	Psychopharmacology (Berl) 2019;236:1131–1143.
Rabin 2011	The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis	Schizophr Res 2011;128:111–116.
Ragazzi 2018	Cannabis use as a risk factor for psychotic-like experiences: A systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences	Early Intervention in Psychiatry. 2018;1–11
Rajanahally 2019	The relationship between cannabis and male infertility, sexual health, and neoplasm: a systematic review	Andrology 2019;7:139–147.
Ravi 2018	Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes A Systematic Review	Ann Intern Med 2018;168:187
Rogeberg 2019	A meta-analysis of the crash risk of cannabis-positive drivers in culpability studies—Avoiding interpretational bias	Accid Anal Prev 2019;123:69–78.
Schoeler 2016a	The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis	Psychol Med 2016;46:177–188.
Schoeler 2016b	Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis	Lancet Psychiatry 2016 http://dx.doi.org/10.1016/ S2215-0366(15)00363-6
Schreiner 2012	Residual Effects of Cannabis Use on Neurocognitive Performance After Prolonged Abstinence: A Meta-Analysis	Exp Clin Psychopharmacol 2012;20:420–429.
Scott 2018	Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults A Systematic Review and Meta-analysis	JAMA Psychiatry. 2018;75(6):585-595
Semple 2005	Cannabis as a risk factor for psychosis: systematic review	Journal of Psychopharmacology 19(2) (2005) 187–194
Sharapova 2018	Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: A systematic review	Paediatr Perinat Epidemiol. 2018;32:512–532
Skalski 2015	The impact of marijuana use on memory in HIV-infected patients: a comprehensive review of the HIV and marijuana literatures	Curr Drug Abuse Rev. 2017 ; 9(2): 126–141
Smith 2014	Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis	Drug Alcohol Depend 2014;145:1–33.
Tait 2016	A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment	CLINICAL TOXICOLOGY, 2016 VOL. 54, NO. 1, 1–13
Tan 2006	Bullous disease of the lung and cannabis smoking: insufficient evidence for a causative link	J R Soc Med 2006;99:77–80
Tetrault 2007	Effects of Marijuana Smoking on Pulmonary Function and Respiratory Complications	Arch Intern Med 2007;167:221.
Tournebize 2017	Acute effects of synthetic cannabinoids: Update 2015	SUBSTANCE ABUSE 2017, VOL. 38, NO. 3, 344–366
Van der meer 2012	Cannabis Use in Patients at Clinical High Risk of Psychosis: Impact on Prodromal Symptoms and Transition to Psychosis	Current Pharmaceutical Design, 2012, 18, 5036-5044
Wang 2008	Adverse effects of medical cannabinoids: a systematic review	Can Med Assoc J 2008;178:1669–1678.
Williams-Ross 2007	Consequences of prenatal toxin exposure for mental health in children and adolescents A systematic review	Eur Child Adolesc Psychiatry (2007) 16:243–253
Zammit 2008	Effects of cannabis use on outcomes of psychotic disorders: systematic review	BJP 2008, 193:357-363.

Supplementary Appendix 4. Reviews (with no meta-analysis) of mental health harms associated with natural cannabis

Author	# of Included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results
Mental health outcomes						
Ben Amar 2007	9 - Longitudinal	105,628	General population aged 14-40	NR	no details provided	Cannabis use may increase risk for developing psychosis, or psychotic like symptoms but causality unclear.
Breet 2018	10 - Cohort	NR	Populations in low and middle-income countries	NR	Scottish Intercollegiate Guidelines Network checklist	Cannabis use may possibly increase risk of suicidal ideation behaviour, with greater risks for males.
Calabria 2010	3 – cohort (2), case-control (1)	25,552+	General population	NR	"McGrath-Saha Quality Index" score	Having ever used cannabis was associated with increased risk of completed suicide in one study. In another school sample, early onset cannabis use marginally increased the risk of suicide attempt. Findings significant but of uncertain interpretation due to confounding variables (alcohol and depression) not being controlled for.
Mammen 2018	12 – observational cohort (9), secondary analysis interventions (3)	11,959	Adults with mood or anxiety disorder at baseline, taking cannabis	Self-report through clinical interviews	Newcastle-Ottawa quality scale	Recent cannabis use (past month) was associated with negative course, outcomes and symptom severity of PTSD. Some evidence for any level of baseline cannabis use or sustained use over time associated with greater PTSD symptom severity at follow-up compared to abstinence. Stopping use of cannabis associated with less severe symptoms, and greater symptom improvement from treatment. Some evidence for cannabis use and association with greater symptom severity, number of symptoms and less occurrence of symptomatic remission for mania and depression compared to non-users. No evidence for cannabis being associated with symptoms of panic or social phobia.
McLaren 2010	10 - Cohort	110,538	General population	Self-report	predefined study quality inclusion criteria	Early and frequent cannabis use associated with developing psychosis. Most associations became non-significant after adjustment for confounders. Review authors unable to comment on whether cannabis use causes psychosis that would have otherwise not occurred.
Ragazzi 2018	19 - cross-sectional (17), prospective cohort (2)	39,779	Patients with PLEs in community	Self-report clinical interview	checklist of Strengthening the Report of Observational Studies (STROBE)	Cannabis use associated with psychotic like events (PLEs), which may be associated with a higher risk of developing schizophrenia. A dose-response relationship was found with higher probability of developing PLEs with increasing cannabis use, particularly among youth.
van der Meer 2012	11 - Case-control	715	Patients at clinical high risk of psychosis	Self-report clinical interview	no details provided	No association between cannabis use and transition to psychosis but may provoke and enhance subclinical psychotic symptoms in high risk individuals.
Zammit 2008	13- longitudinal cohort	Not reported	General population	Self-report	meta-analysis of observational studies in epidemiology (MOOSE) guidelines	Cannabis use consistently associated with increased rates of relapse or rehospitalisation and decreased treatment adherence. Inconsistent evidence for greater symptom severity, negative outcomes of reduced quality of life, productivity or more continuous illness course in cannabis-users.
Cognitive outcomes						
Blithikioti 2019	24 - NR	248	Adult or adolescent cannabis users	Self-report	no details provided	Acute or chronic cannabis not shown to have behavioral effect on auditory or visual attention tasks. Acute and residual effects of cannabis use associated with deficits in working memory and

						learning, less aware of mistakes and less sensitive to negative consequences of actions. Functional cerebellar alterations with deficits in decision making, memory and associative learning.
Broyd 2016	105 - NR	Not reported	General population	NR	no details provided	Acute exposure to cannabinoids impaired focused, divided and sustained attention in a dose-dependent manner. In infrequent users, smoked or vaporised cannabis impaired critical tracking, reaction time and motor control in a dose-dependent manner. Overall, subdomains of executive function were differentially affected. There were acute effects that impaired inhibition, but planning, problem solving, reasoning and interference control were inconsistently impaired. Acute and chronic exposure to cannabinoids impaired cognition, and domains of verbal learning, memory and attention.
Gonzalez 2002	40 - NR	Not reported	General population	Self-report	"minimal criteria" for quality assessment	Cannabis users experienced poorer performance most frequently for attention and working memory domains in 45% of studies. 38% of studies investigating motor performance and 35% of studies looking at forgetting reported significantly poorer performance for cannabis users, relative to non-using controls. Less than one third of studies concluded that there was a detrimental effect of cannabis when assessing the perceptual and motor domains (28%), abstraction/executive (27%), simple reaction time (27%), learning (7%) and verbal (7%) domains. Only 55% of studies in the review concluded that nonacute cannabis use was associated with poorer neuropsychological performance.
Oomen 2018	75 - NR	3,201	Cannabis users	Measured dose administered	no details provided	Working memory, reasoning and association are mildly affected after cannabis administration. Inhibition acutely impaired after cannabis administration, with strongest effects seen for pulmonary administration and dose-response effects for higher doses of THC. Cannabis use also results in acute impairment of executive function.
Skalski 2016	23 - Case-controlled, cross-sectional, longitudinal	2902	General population	Self-report	no details provided	Cannabis users demonstrated verbal memory deficits immediately, and up to 7 days after stopping cannabis compared to non-using controls. When investigating memory function, participants who began to use cannabis before age 18 experienced a broad decline in cognitive performance compared to those using cannabis after 18. Dose-response effects were observed with memory deficits correlating with longer duration and frequency of use, and greater memory impairment correlating with a higher number of total lifetime use.
Psychosocial outcomes						
Macleod 2004	48 - Observational	172,718	High school and general population adolescents	Self-report via standardized instrument	predefined study quality inclusion criteria	Cannabis use consistently associated with reduced educational attainment and the use of other drugs. There was an inconsistent association between cannabis and psychological problems and antisocial behaviours. However, the extent and strength of all associations was less than what is conventionally assumed. Overall, no strong evidence that use of cannabis has important implications for psychological or social health.

Supplementary Appendix 5. Reviews of general harms with cannabis

Author	Harm considered	# of Included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results
Barkin 2016	Pancreatitis	16 - Case control (15), prospective cohort(1)	26	Cannabis induced pancreatitis patients	Clinical history or urine screen	no details provided	Acute pancreatitis (AP) reported in 26 patients, with 18 patients (69.2%) where development of AP correlated with start and increase of cannabis use from baseline. Recurrent AP was reported in 15/26 (57.5%) cases and was related temporally to cannabis use, with resolution of AP following cessation. In a prospective study, cannabis alone was identified as the etiology in 13% of all cases in patients under 35 years of age. Cannabis was significantly more prevalent as an etiology in those aged under 25 compared to those over 25 (13% vs 1%, p<0.0001).
Calabria 2010	All-cause Mortality	2 - Cohort	110,711	Military conscripts and patients in medical care program	NR	"McGrath-Saha Quality Index" score	Review authors concluded that there were too few studies to draw clear conclusions about relationship between cannabis and morality. However, the limited evidence available does not indicate an increased risk of mortality for cannabis users in the general population.
Peters 2012	Psychosocial outcomes, tobacco use	15 – cross sectional survey/cohort, longitudinal cohort,	NR	General population	Self-report	no details provided	Cannabis use co-occurring with tobacco use associated with greater likelihood of cannabis use disorders, more psychosocial problems and poorer cannabis-cessation outcomes compared to cannabis only use.
Rajanahally 2017	Male infertility and sexual health	28 – cohort (13), observational (3), case-control (8), cross-sectional (1), RCT (1), meta-analysis (1), multiple (1),	2,039	Any adults using any form of Cannabis and reported vascular risk factors or outcome	NR	no details provided	Cannabis use has an overall negative impact on male fertility, with decreased sperm motility, morphology and count. No relationship found between long-term cannabis use and sex hormones.
Wang 2008	Adverse events, death	20 - RCTs, observational	NR	General population	Dose administered	"Jadad trial quality score" (for trials) and "Downs and Black checklist" (for observational studies)	In a meta-analysis of AEs, compared to placebo (non-users) there was a greater incidence of AEs with: medical cannabis (1.86 (1.57,2.21)), oromucosal-THC (1.88 (1.48,2.39)), and oral-THC (2.18 (1.59-2.99)). No significant associations were found for death rate and SAEs. Control: non-users.

Commented [MM1]: Confirm which stat was used

Supplementary Appendix 6. Reviews (with no meta-analysis) of physical health harms associated with inhaled natural cannabis

Author	# of Included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results
Pulmonary outcomes						
Martinasek 2016	48 - case-control, experimental, secondary data analyses of cohort studies, case reports.	NR	General population	NR	no details provided	In the literature, cases of lung bullae, COPD, emphysema, and lung hyperinflation identified in cannabis smokers. Some evidence for relationship between COPD and cannabis taken through inhalation. There is insufficient evidence for an association with airflow obstruction. For respiratory symptoms, cases of wheezing, dyspnea, phlegm production and chest tightness identified in cannabis smokers. Cases of pulmonary infections such as aspergillosis, legionnaires, tuberculosis and other opportunistic infections.
Mehra 2006	19 - case-control (6), prospective cohort (5), experimental (4), retrospective cohort (2), case-series (2)	345	Patients smoked Cannabis with premalignant or cancerous changes in lung	Self-report	predefined study quality inclusion criteria	Cannabis smoking associated with 3-fold increase in tar delivery to lungs compared with tobacco. 2 case-control studies of non-tobacco smoking cannabis smokers found more metaplastic cells, macrophages and columnar cells in sputum. 6 studies found precancerous findings, such as squamous cell metaplasia, and increased mitotic figures on bronchial biopsy.
Tan 2006	4 - Case Reports	10	Patients with lung bullae.	Self-report	no details provided	No evidence of lung bullae in a histopathological study of 241 known cannabis smokers.
Tetrault 2007	34 - Cross-sectional (15), Laboratory challenge (12), Observational-cohort (3), case series (3), case-control (1)	12,351	Patients with respiratory system symptoms/testing after Cannabis inhalation	NR	predefined study quality inclusion criteria	No consistent association between long-term cannabis smoking and pulmonary function testing through measures such as FEV1/FVC ratios or airway hyperactivity. There was an increased risk of cough, sputum production, and wheezing with long-term cannabis smoking, even after adjusting for concurrent tobacco smoking.
Cardiovascular outcomes						
Coughlin 2006	2- Case reports	NR	Patients with arteritis	NR	no details provided	In cannabis smokers, cases of arteritis known as Buerger's disease well reported, with young individuals presenting with symptoms of ischemia in extremities.
Grotenhermen 2010	15 - Case Reports	57	Cases of cannabis arteritis	NR	no details provided	Cannabis use was not associated with arteritis, due to concurrent tobacco use in a considerable number of cases, and attributed as the most likely contributing factor.
Jouanjus 2017	81 (case reports), 29 (observational studies), 3 (clinical trials) and 2 (observation studies)	116	Humans exposed to cannabis-based products, suffering from CV problems	NR	"CARE", "STROBE", and "CONSORT" statements	Tachycardia and hypertension were the most frequently reported harms in synthetic cannabinoid exposure. Non-significant associations were found for risk of stroke with past and current cannabis use after adjusting for tobacco use. Some evidence for increased risks of multifocal intracranial stenosis, acute ischemic stroke and hospitalization in cannabis users. Weak evidence for association of cannabis with exercise induced myocardial infarction. No significant associations were found between cannabis use and increased cardiovascular mortality. In 38 cases of Buerger's disease (arteritis), concomitant tobacco use was found to be the more likely precipitating factor.
Korantzopoulos 2008	6 - Case Reports	6	Cases of AF associated with Cannabis smoking	NR	no details provided	In the literature, there were 6 cases with onset of atrial-fibrillation in individuals without structural heart disease, recently after cannabis smoking.

Ravi 2018	24- prospective cohort (9), cross-sectional (7), retrospective cohort (3), case-control (2), experimental (1), case-crossover (1), RCT (1)	NR	Any adults using any form of Cannabis and reported vascular risk factors or outcome	Self-report	Cochrane Risk of Bias Tool (for trials); Newcastle-Ottawa Scale (for observational studies)	Insufficient evidence that cannabis use is associated with adverse cardiovascular outcomes, such as diabetes, hyperlipidemia, acute MI, stroke or cardiovascular morality. Dose-response effects were observed, with weekly or greater cannabis use associated with increased risk of cardiovascular mortality. There was inconsistent evidence for association between cannabis use and increased risk for all-cause mortality. No association between cumulative (> 5 years) lifetime cannabis use and cardiovascular mortality, stroke, coronary heart disease
Cancer						
Calabria 2010	9 – case-control (7), cohort (2)	203,524	General population	Self-report	"McGrath-Saha Quality Index" score	One study found showing increased risk of developing brain tumours when marijuana was smoked at least once a month. Most studies found no association between cannabis use and cancer. No evidence for increased rates of overall cancer, but inconsistent evidence for increased risks of prostate, head and neck, lung, bladder and cervical cancers.
Hashibe 2005	2 - Cohort	169,860	Cancer patients	Self-report/survey	no details provided	No increased risk of tobacco related cancers among cannabis smokers from cohort studies, but some associations found in case-control studies. Parental cannabis use during gestational period revealed association with increased risk of childhood cancers, but these results varied greatly and did not remain consistent across studies. Among non-tobacco smokers, those who had ever smoked cannabis had increased risks for prostate and cervical cancer. There were no cases of lung cancer identified among cannabis smokers. A moderately increased risk of malignant primary adult onset glioma for ever use cannabis smokers was identified. For head and neck cancers, ever use of cannabis was strongly associated with increased risks, however in most studies tobacco use was not adjusted for. No associations between ever use of cannabis and colorectal or penile cancer were found.
Huang 2015	34- Case-control (30), cohort (4)	12,674 cases, 72,540 controls	Cancer patients	Self-report/survey	no details provided	No overall associations or dose-response relationships between cannabis use and lung cancer. No overall associations with head and neck cancer but increased risks with dose-response effects for oropharyngeal cancer. Three studies showed a consistent increased risk for testicular cancer with even moderate frequency and duration of use, with dose-response effects seen for duration. Across 6 studies on childhood cancers, parental cannabis use during gestational period associated with childhood leukemia, astrocytoma and rhabdomyosarcoma. For neuroblastoma, a 4-fold increased risk was observed for first trimester cannabis use. Cannabis use was not associated with overall cancer risk or with tobacco-related cancers. In never-tobacco smokers, cannabis use was associated with increased risk of prostate and cervical cancer. Dose-response effects were not observed with cancer risk nor with specific cancer sites. No association of anal or penile cancer with cannabis use. One study identified increased risks of primary glioma. No associations were found for non-Hodgkin's lymphoma. One study found significant association for transitional cell carcinoma of bladder.
Maternal and foetal health						
Sharapova 2018	21- longitudinal cohort	NR	Children (1-11) *in utero* cannabis exposure	Self-report	Newcastle-Ottawa Scale	Several studies found statistically significant associations between prenatal cannabis exposure and both decreased and increased neuropsychological functions, while others found no significant associations. Specific effects of prenatal cannabis exposure remain unclear, but there were more instances of negative than positive associations among studies, indicating that cannabis may be harmful to child neuropsychological functioning. Some potential adverse effects of prenatal cannabis exposure on attention and perceptive

						abilities, cognitive function, memory, impulse control, IQ and reading comprehension in children aged >6 years.
Williams 2007	100 Various (SRs, prospective studies, longitudinal, epidemiological studies	NR	Children and adolescents with mental health concerns	NR	no details provided	Infants prenatally exposed to cannabis had negatively affected attention skills but not lower IQ as older children. No associations were found between prenatal cannabis exposure and ability to encode and retain items in memory. There were deficits in ability to maintain attention, which was consistent into adolescence. Infants also exhibited increased depressive symptoms from the ages of 10-12, along with poor attention skills, and future delinquency.

Abbreviations: COPD: chronic obstructive pulmonary disease. FEV1/FVC: Forced expiratory volume in one second/Forced Vital Capacity.

Supplementary Appendix 7. Reviews (with no meta-analysis) of harms associated with cannabinoids

Author	Harm considered	# of Included studies and designs	Participants (n)	Population	Assessment of administration	Assessment of study quality/risk of bias	Results
Akram 2019	Psychological	17 - experimental (1), cross-sectional (7), online surveys (5), Qualitative (4)	67,442	General population	Self-report, urine/blood	"QualSysts" criteria	Acute synthetic cannabinoid (SC) intoxication was found to potentially result in impaired motor functioning, attention and response inhibition. Internet surveys found significant impairments in working memory, inhibition and long-term memory compared to non-users.
Courts 2016	General	77 - Case reports	3,965	Patients presenting to ED with toxicity	NR	no details provided	AEs occurring from SC in >5% of individuals: tachycardia (30.2%), agitation (13.5%), drowsiness (12.3%), nausea/vomiting (8.2%), hallucinations (7.6%), irritability (7.2%), hypertension (6.4%), psychosis (6.0%) and delusions (5.6%).
Haden 2017	General	3 – Case reports (2), case series (1)	9 cases, 36 user reports (internet)	General population using MDMB-CHMICA	Self-report, blood samples	no details provided	In an analysis of 483 cases of intoxication from taking various cannabinoids – most common features in patients included aggression, euphoria, hallucinations, amnesia, loss of consciousness insomnia, anxiety, depression, seizures, dry mouth, red eyes, and increased blood pressure, temperature and heart rate. Two case reports of fatal intoxication after confirmed use of SC. From 36 individual user reports on Internet discussion, 31 (91.7%) reported AEs, with the most common including palpitations (30.6%), nausea and vomiting (25.0%), loss of consciousness (16.7%), chest pain (13.9%), anxiety (13.9%), visual (16.7%), auditory (5.6%) hallucinations reported.
Hobbs 2018	Psychiatric	24 - Case reports/series, Case-control, Cross-sectional, toxicology reviews	977+	Patients experiencing psychopathology with no previous history	Self-report, analytical (chromatography, urine)	no details provided	Individuals taking SC had higher levels of psychotic symptoms compared to natural cannabis and non-users. The most frequently seen symptoms in SC users were agitation, aggression, longer hospital admissions and more marked psychosis.
Mansoor 2017	Kidney damage	110 - Case Reports, Case Series	169	Population with AKI	NR	no details provided	There were case reports of cannabis causing acute tubular necrosis, acute interstitial nephritis, and occasionally rhabdomyolysis. Chronic cannabis use can lead to cannabinoid hyperemesis syndrome, extreme hypovolemia and severe prerenal azotemia.
Tait 2016	General	212- Letters, conference abstracts, papers (106), case-reports (77), case-series (29)	4,000	Presenting to ED	Self-report, analytical (chromatography)	no details provided	The risk of requiring medical attention following SC use was greater than that for natural cannabis use, with more significant and unique clinical effects. Generally, only supportive care was required and for a short duration. The most frequent symptoms were: tachycardia (39-77%), agitation (16-41%), nausea (13-94%). Fourth deaths involving SC use. Of ED presentations of

							SC toxicity, acute kidney injury (<1%), generalised tonic-clonic seizures (3.8%) nausea (13-94%).
Tournebize 2017	General	46- Case reports (29), case series (17)	114	Patients presenting to ED	Analytical (serum, urine)	no details provided	In a study of patients presenting to the ED, there were 25 deaths attributed to SC use. There were various neurological and neuromuscular effects identified, including: agitation (38%), somnolence (25%), vertigo (19%), paresthesias (16%), psychomotor retardation (8%), seizures (18%), aggression (12%), tachycardia (44%) and hypertension (41%), kidney damage (11%), emesis (41%), nausea (39%), abdominal pain (18%), diarrhea (12%), excessive thirst (10%), xerostomia (11%), cases of intractable nausea and emesis, mydriasis (20%), hyperglycemia (25%), hypokalemia (27%), ad leukocytosis (9%).