Global Burden of Disease

Mental Disorders and Illicit Drug Use Expert Group

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Cannabis-related mortality

Illicit Drugs Discussion Paper No. 3

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CANNABIS-RELATED MORTALITY

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Overview and recommendations

- This discussion paper outlines the results of a comprehensive search of the peer-reviewed literature to identify studies investigating cannabis use and associated mortality.

- Findings from cohort studies indicate that cannabis use was not associated with significantly elevated total mortality in the general population, although it was in a population of individuals who had suffered myocardial infraction.

- Case control studies suggest that fatal motor vehicle accidents may be elevated in the general population.

- The evidence for respiratory cancers caused by cannabis use is not consistent.

- Several studies report an association between cannabis use and suicide but it is not conclusive that the relationship is causal.

- Therefore, increased mortality related to cannabis dependence will not be estimated for the Global Burden of Disease study.

- The Global Burden of Disease comparative risk assessment (CRA) for cannabis use will include cannabis dependence, fatal motor vehicle accidents, as well as schizophrenia (see discussion paper 2).

1. Introduction

Cannabis has a high prevalence of use in many developed societies [1] but there is a lack of good evidence from controlled epidemiological studies about the relationship of its use with mortality [2, 3]. Other illicit drug use and associated mortality is more frequently investigated, especially overdose deaths. Because cannabis use is not reported to cause fatal overdoses its impacts on mortality has rarely been explored.

In this paper we summarise the results of a systematic review of the literature on all-cause mortality among people who use cannabis. We also consider the risks in users compared to non-users, for outcomes that are often fatal: various cancers, culpable driving associated with fatal motor vehicle accidents, and suicide attempts/completion.

2. Method

2.1. Identifying studies

Systematic peer reviewed literature searches were conducted to identify population-level data focused on mortality associated with cannabis use. In consultation with a qualified librarian, three electronic databases were chosen: Medline, EMBASE and PsycINFO (see Appendix A). This combination provides the most complete coverage of the peer reviewed literature. Search strings, tailored to each database (including keywords, MeSH terms, EMTREE terms and explode terms) were devised for *cannabis*, *mortality*, *cohort* and *drug use* (see Appendix B). Varied search strategies were carried out using these search strings (see Appendix C), limited to human subjects and the publication timeframe of January 1990 to January 2008.

After assessing the number of articles identified by each search variation it was decided that only the terms *cannabis* and *mortality* would be used in the relevant search, as using only these search strings (and not limiting the search further by *cohort* and *drug use*) identified a manageable number of articles for examination. References for the articles that were identified from Medline, EMBASE and PsycINFO searches were compiled in EndNote X and duplicates were deleted. Grey literature was not reviewed for information on mortality associated with cannabis use or dependence. A direct link between cannabis and mortality is not commonly investigated and therefore underestimation is likely, if reported.

The reference lists of review articles and of specific studies deemed important by colleagues were also searched to identify additional studies that may not have been identified in the electronic database search.

2.2. Included studies

Included studies were studies with a focus on mortality associated with cannabis use or dependence.

2.3. Excluded studies

Articles were excluded if they were not focused on cannabis or mortality, for example grouped cannabis with other drug types for analysis or with a focus on use or injury and hospitalisation. Review articles were excluded (not raw data), as well as case studies. When several reports were published on the same study population only the most recent results were included.

A reference list of the selected articles was emailed to experts in the field with an explanation of the focus of the search strategy for this review. They were asked to comment on the completeness of the reference list.

2.4. Data extraction

An Excel spreadsheet recorded article information (authors, year of study, title, journal name, journal volume, pages). The specific location of the study was recorded, as well as the country and region (according to GBD provisions). Study type and sample characteristics were also noted (population, number of people in the sample, age, sex), as was: diagnostic criteria (was dependence diagnosed?), cause of death, and, measures of association between cannabis use and mortality (e.g. relative risk, odds ratio, hazard ratio).

2.5. Quality score

The quality of each study was also rated in the Excel spreadsheet, using the quality variables presented in Table 1. Quality variables were assigned scores that were summed to create a Quality Index score for each study. The Quality Index scores were used to rate the methodological quality of each included study.

Table 1. Variables that form the Quality Index

Quality variable	Explanation
1. Case ascertainment	Ascertainment of cases nationwide or regionally
2. Measurement instrument	Measurement instrument to determine cannabis use or dependence (i.e. self-report or toxicological screen)
3. Diagnostic criteria	Indicates whether cannabis dependence was diagnosed.
4. Estimate	Estimate presented (e.g. prevalence, incidence, mortality, relative risk, etc.)
5. Numerator and denominator presented?	Was the numerator and denominator presented for estimate of interest?
6. Numerator and denominator based on identical epochs and identical catchment areas?	Were the numerator and denominator based on identical epochs and identical catchment areas for estimate of interest?
7. Completeness of follow-up in cohort studies and response for cross-sectional studies	Captures response rates and attrition rates.
8. Representativeness of catchment area	Determines generalisability of the sample to the population
9. Age/sex specific values presented?	Identifies whether age and/or sex specific values were reported.
10. Quality of methods of reporting	To capture methods that were not reported on by other variables (free text)
11. Duration of follow-up	To obtain more information about follow-up periods and sample sizes when doing so (free text)

3. Results

The results of the search strategy and specific information about the reasoning and number of articles culled are shown in Figure 1.

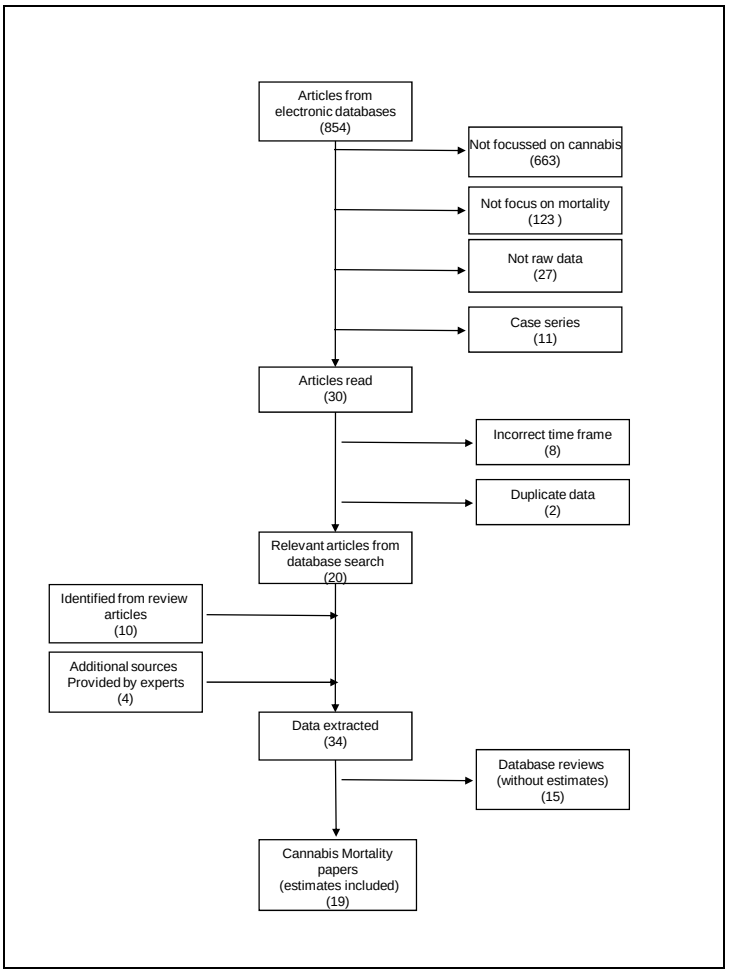


Figure 1. Flowchart of search strategy to identify articles reporting on mortality associated with cannabis use

The electronic database search recovered 854 (98%) articles for potential inclusion in the systematic review. Ten additional articles (1%) were identified from reference lists of review articles and articles of interest identified by experts. Overall, 864 abstracts were reviewed. Only 30 possibly relevant articles (4%) remained from the electronic database search after articles were excluded that: did not focus on cannabis (76%), or

mortality associated with cannabis (14%), did not present primary research (not raw data) (3%), or was a case study (1%).

The revised list of recovered references, including those identified from reference lists of review articles and articles of interest identified by colleagues, was reviewed by experts in the field (see acknowledgements) for comment on the completeness of the reference list. Four additional articles (< 1%) were added by experts, including three articles that were published after the database search was conducted.

Forty-four articles (5%) were read, with further exclusions for data recorded prior to 1990 (1%) and data reported from the same sample population as a more recent article (duplicate data: < 1%). Data was extracted from remaining thirty-four articles (4%). Database reviews (2%), were excluded from the results of this review since no estimates were reported.

Articles written in languages other than English were identified as part of the systematic review. Most had English abstracts that provided sufficient information to indicate that they did not meet the inclusion criteria. Information from English titles was used to exclude most of those without English abstracts. Three remaining articles were translated. Data were extracted from one French article which was not included in this review because it did not report estimates of association.

Nineteen papers (2%) remained and were included in this review: three dealing with all-cause mortality; four with motor vehicle accidents; nine with cancer; and three with suicide.

3.1. All-cause mortality

There are two prospective epidemiological studies of mortality among cannabis users. A Swedish study of mortality over 15 years among male military conscripts found an increased risk of premature death among men who had smoked cannabis 50 or more times by age 18 when compare to non-users [4]. Violent and accidental deaths were the major contributor to this excess. However, the association between mortality and cannabis use disappeared after multivariate statistical adjustment for alcohol and other drug use.

Sidney et al [5] reported a 10-year study of mortality in cannabis users among 65,171 members of the Kaiser Permanente Medical Care Program aged between 15 and 49. The sample comprised 38% who had never used cannabis, 20% who had used less than six times, 20% who were former users, and 22% who were current cannabis users. Regular cannabis use had a small association with premature mortality (RR = 1.3, 95% CI=1.11, 1.59) that thought to be explained by increased AIDS deaths in men, probably because cannabis use was a marker for male homosexual behaviour in this cohort. It is too early to conclude that cannabis use does not increase mortality because the average age at follow-up was only 43 years, and cigarette smoking and alcohol use were only modestly associated with premature mortality. For this reason, we have not included any estimate of cannabis' effects on overall premature mortality.

Recently, Mukamal et al. [6] investigated increased risk of mortality for cannabis users in a sample of adults hospitalised for myocardial infraction (N=1913). In this specific population increased risk of mortality was found for those who had ever-used marijuana (N=52), compared to those who had never-used marijuana (HR = 1.3). Heavy marijuana use increased the risk of mortality (HR = 4.2). It was also reported that those who had ever-used marijuana had increased non-cardiovascular mortality compared to never-users but cardiovascular mortality was not elevated. The latter is a puzzling finding that may reflect the small sample size and limited statistical power of the study.

As shown in Figure 2, "heavy" and "light" use of cannabis are marginally associated with total mortality (Study 2, RR#1 and RR#3) in men. However, as Table 2 indicates;

these results may be confounded by homosexuality. Figure 2 also shows an increased risk of mortality for those who have been hospitalised for myocardial infraction and ever-used cannabis (Study 3, HR#1) or who use cannabis at least weekly (Study 3, HR#3). Therefore, the limited available evidence does not indicate an increased risk of mortality for cannabis users in the general population but it may increase risk in vulnerable populations such as those with coronary heart disease. Overall, there are too few studies to draw clear conclusions about the relationship between cannabis use and all cause mortality.

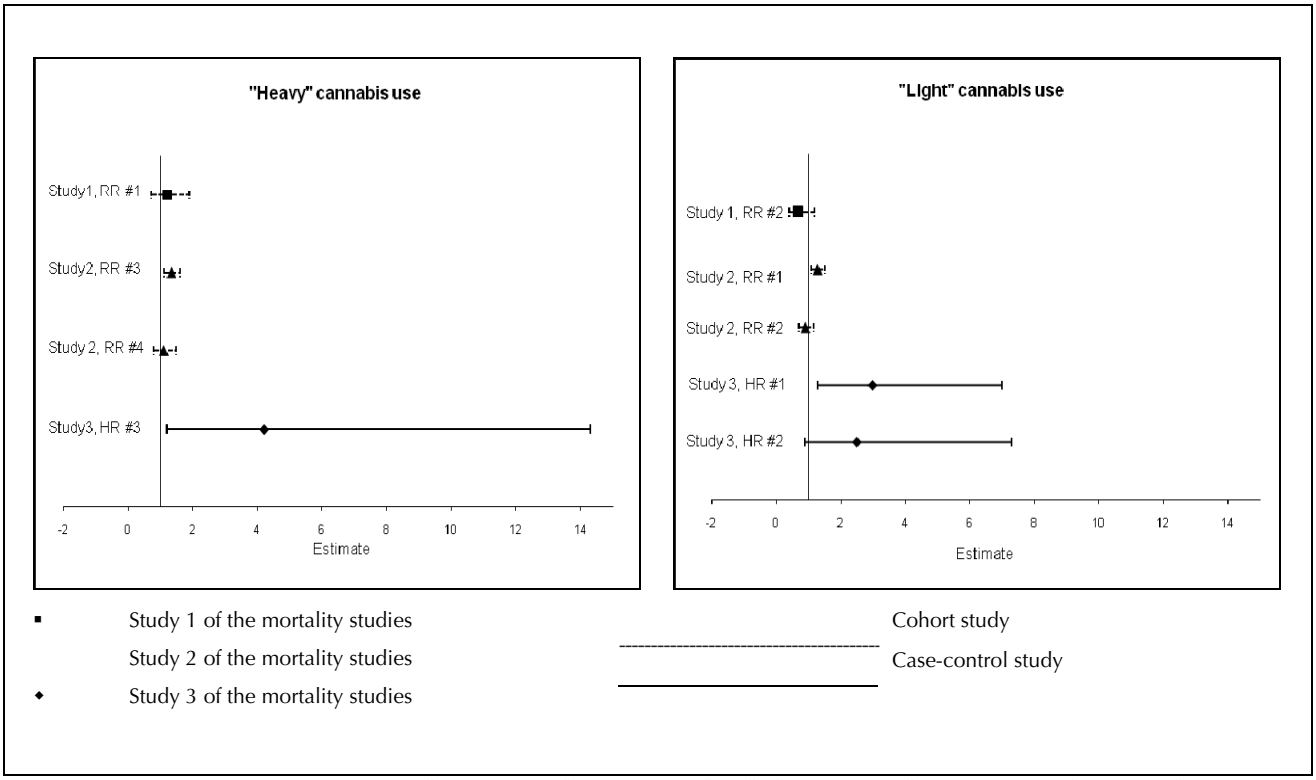


Figure 2. Associations between "heavy" and "light" cannabis use and mortality

Table 2. Studies investigating cannabis use as a risk factor for all-cause mortality

Study	Country	Study type	Year	Quality score	N (mean person years follow-up)	Sample	Adjusted estimate (95% CI)	Comments
1.	Sweden	Cohort	1990	8	45540 (15)	Swedish conscripts	RR = 1.2[a] (0.7, 1.9)	No increased risk of all-cause mortality for high levels of marijuana use (>50 times) compared to non-users.
							RR = 0.7[a] (0.4, 1.2)	Less than 50 times marijuana use was not associated with increased all-cause mortality.
								Relative risk may be underestimated as conscripts were asked non-anonymously about drug use.
2.	USA	Cohort	1991	7	65171 (10)	People enrolled in a medical care program	RR = 1.28[b] (1.09, 1.50)	Men: ever-use of marijuana was associated with increased risk of all-cause mortality, (homosexuality could confound these results as men also had an increased risk of AIDS mortality and were more likely to be single. Analysis with homosexuality as a covariate was not possible).
							RR = 0.90[b] (0.69, 1.16)	Women: No increased risk of all-cause mortality for ever-used compared to non-use.
							RR = 1.33[b] (1.11, 1.59)	Men: Current marijuana use was associated with sig increased risk of all-cause mortality (homosexuality could confound these results as men also had an increased risk of AIDS mortality and were more likely to be single. Analysis with homosexuality as a covariate was not possible).
							RR = 1.09[b] (0.80, 1.48)	Women: No increased risk of all-cause mortality for current use of marijuana compared to non-use.
3.	USA	Case-control	~1997	10	52 cases; 1861 controls	Adults hospitalised for myocardial infarction	HR = 3.0[c] (1.3, 7.0)	Increased risk of all-cause mortality for ever-used marijuana compared to never-used marijuana.
							HR = 2.5[c] (0.9, 7.3)	No increased risk for less than weekly marijuana use compared to non-use.
							HR = 4.2[c] (1.2, 14.3)	Increased risk for at least weekly marijuana use compared to non-use.
							HR = 1.9[d] (0.6, 6.3)	No increased risk for ever-used marijuana compared to non-use for cardiovascular mortality*.
							HR = 4.9[d] (1.6, 14.7)	Increased risk for ever-used marijuana compared to non-use for non-cardiovascular mortality*.

Note. CI: confidence interval; HR: hazard ratio; RR: relative risk
* only 7 deaths among marijuana users (cases) and 310 deaths among non-users (controls), so insufficient numbers to evaluate and compare cardiovascular and non-cardiovascular mortality.
a. adjusting for contact with police or juvenile authorities, run away from home, school adjustment, smoking, solvents abuse, alcohol consumption, psychiatric diagnosis at conscription, other drug abuse, intravenous drug abuse. **b.** adjusted for age, race, education, marital status, obesity, tobacco smoking, and alcohol use. **c.** for age, sex, body mass index, marital status, race, income, education, physical activity, current smoking, former smoking, tea intake, usual and binge alcohol intake, medical history, receipt of thrombolytic therapy and medication use. **d.** adjusted for age and sex.
1. Andreasson & Allebeck, 1990. **2.** Sidney et al., 1997. **3.** Mukamal et al., 2008.

3.2. Motor vehicle accidents

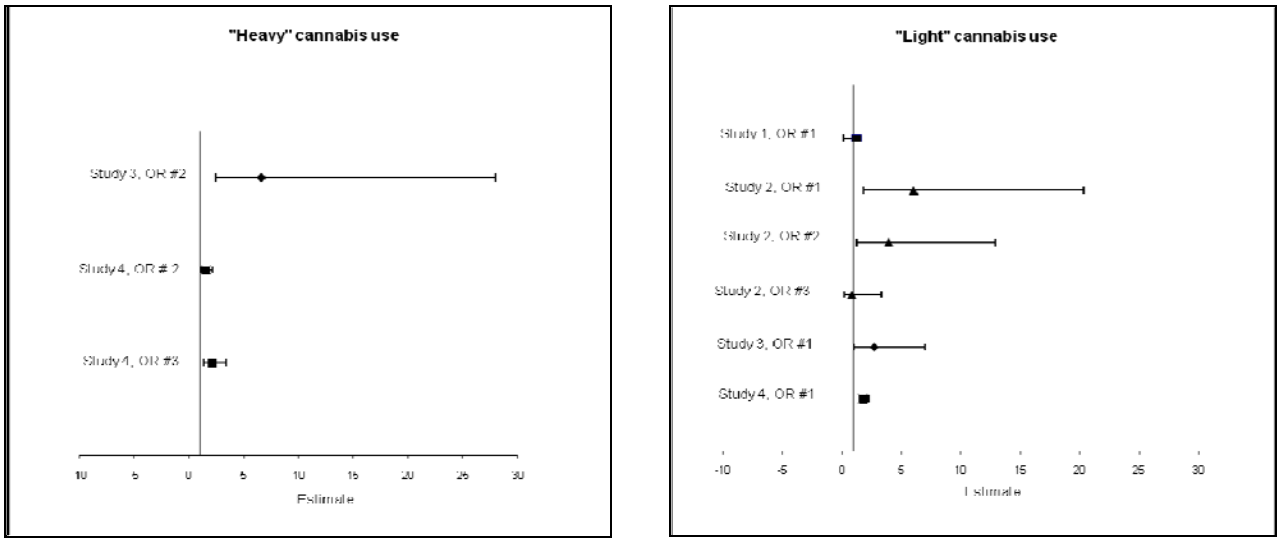
Cannabis produces dose-related impairments in cognitive and behavioural functions that may potentially impair driving an automobile or operating machinery [7]. These impairments are larger and more persistent in difficult tasks involving sustained attention [7]. A documented possible consequence of acute cannabis use is a motor vehicle accident if a user drives while intoxicated [8].

The effects of recreational doses of cannabis on driving performance in laboratory simulators and standardised driving courses have been reported as similar to blood alcohol concentrations, between 0.07% and 0.10% [8]. However, studies of the effects of cannabis on driving under more realistic conditions on roads have found much more modest impairments [9, 10]. This is probably because cannabis users are more aware of their impairment and less inclined to take risks than alcohol users [10].

Epidemiological studies of motor vehicle accidents have produced equivocal results because most drivers who have cannabinoids in their blood also have high blood alcohol levels [8, 11]. Blows and colleagues [13] found a ten-fold increase in culpable driving for those who reported cannabis use three hours prior to a motor vehicle accident resulting in hopsitalisation of the driver or their passenger. This association disappeared when 'risky behaviours', including blood alcohol concentration, were controlled for. Also included as 'risky behaviours', were travelling speed and seat belt use, which may have also contributed to the severity of the accident and were possibly encouraged by cannabis and alcohol intoxication.

Two studies with reasonable numbers of persons who have *only* used cannabis have not found clear evidence of increased culpability in these drivers [12]. Only modest associations have been found by three case-control studies comparing detection of THC with drug and alcohol free drivers [13], when focusing on drivers who had higher levels of THC detected (≥5ng/ml), the risk of culpable driving was increased [14, 15].

Studies show that heavy cannabis use is associated with greater risk of culpable driving than light cannabis use, with a dose response effect, as shown in Figure 3.



- Study 1 of the MVA studies
- Study 2 of the MVA studies
- Study 3 of the MVA studies
- Study 4 of the MVA studies

Case-control study

Figure 3. Associations between "heavy" and "light" cannabis use and fatal motor vehicle accidents

Table 3. Studies investigating cannabis use as a risk factor for fatal motor vehicle accident

Study	Country	Study type	Year	Quality score	N	Sample	Adjusted estimate (95% CI)	Comments
1.	USA	Case-control	1993-2003	7	32543	Fatally injured drivers	OR = 1.29[a] (1.15, 1.45)	Cannabis use (THC detection, no alcohol detection) associated with higher risk of unsafe driving than non-use.
2.	New Zealand	Case-control	1998-1999	9	1159	Cars involved in a fatal motor vehicle accident or accident that required hospitalisation and controls	OR = 6.0[b] (1.8, 20.3)	Self-reported cannabis use (any dose) in the three hours prior to the accident was associated with six fold increased risk of car crash injury.
							OR = 3.9[c] (1.2, 12.9)	Decreased association when controlling for additional confounding variables
							OR = 0.8[d] (0.2, 3.3)	Association not significant when controlling for risky behaviours
3.	Australia	Case-control	1990-1999	6	3398	Fatally injured drivers	OR = 2.7[e] (1.0, 7.0)	Cannabis use (THC detection only) was positively associated with culpable driving for all drivers, compared to drug and alcohol free drivers.
							OR = 6.6[e] (2.5, 28)	Cannabis use (THC detection ≥5ng/ml only) was positively associated with culpable driving, compared to drug and alcohol free drivers.
4.	France	Case-control	2001-2003	8	10748	Fatally injured people from motor vehicle accident with known drug and alcohol concentration in their blood	OR = 1.78[f] (1.4, 2.25)	Cannabis use found at any dose (THC detected threshold ≥1ng/ml) associated with culpable driving.
							OR = 1.54[f] (1.09, 2.18) OR = 2.12[f] (1.38, 3.38)	Dose response effect was identified as cannabis use, THC 1-2ng/ml, had a weaker association with culpable driving than cannabis use, THC ≥5ng/ml.

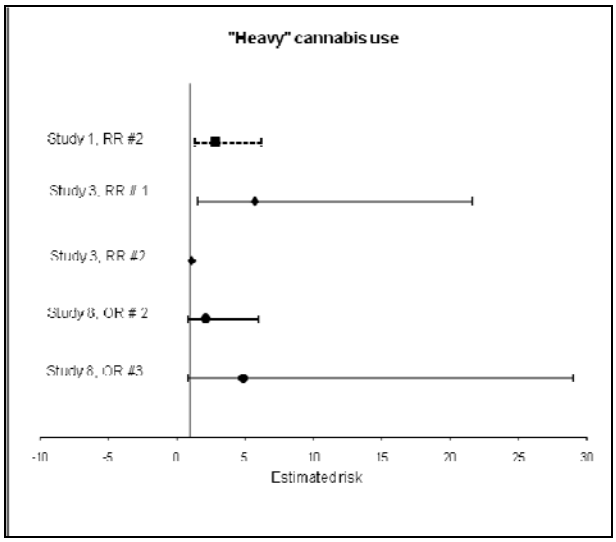
Note. CI: confidence interval; OR: odds ratio; RR: relative risk
a. adjusted for age, sex and previous driving record. **b.** adjusted for age and sex. **c.** adjusted for age, sex, ethnicity, driving exposure, age of vehicle, time of day and number of passengers. **d.** adjusted for age, sex, ethnicity, driving exposure, age of vehicle, time of day, number of passengers, BAC, seat-belt use and travelling speed. **e.** adjusted for blood alcohol concentration, drug type, gender, age, type of accident (single or multiple vehicle), location of crash, year of crash. **f.** adjusted for blood concentration of THC, blood concentration of alcohol, age, vehicle type, time of crash.
1. Bedard, Dubois & Weaver, 2007. **2.** Blows et al., 2005. **3.** Drummer et al., 2004. **4.** Laumon et al., 2005.

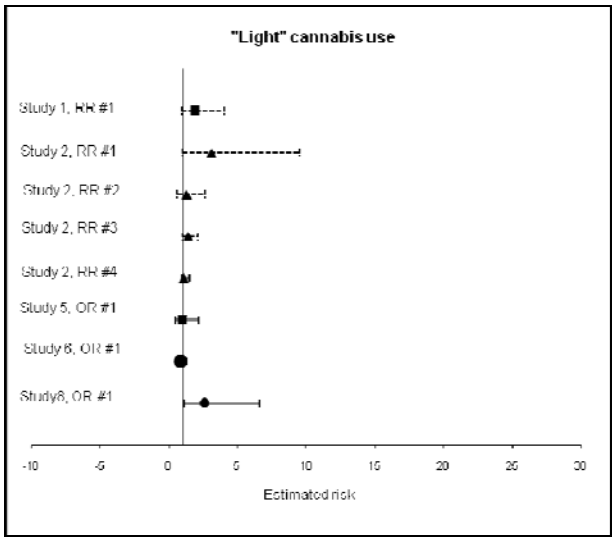
3.3. Cancer

We have been able to identify two cohort studies that have examined the effects of regular, prolonged cannabis use on risks of cancer. One of these reported no increase in overall cancer rates among cannabis users (although there were slightly increased rates of prostate and cervical cancer) [16]. The second study by Enfird and colleagues [17] reported an increased risk of developing a brain tumour when marijuana was smoked at least once a month (RR = 2.8).

Case-control studies have also investigated the risk of cancer among cannabis users. Most have found no association between cannabis use and cancer [18-21]. However, in New Zealand an increased risk of lung cancer for heavy use has been identified, which an 8% increase in risk for each joint-year of use [22]. Furthermore, in a sample of men only, a significant trend was found between increasing joint-years of marijuana use and bladder cancer [23]. Finally, Zhang et al. [24] reported a marginally increased risk of head and neck cancer for those who had ever-used marijuana compared to those who had never-used marijuana (OR = 1.1). It did not find any association when frequency of use was investigated.

Figure 3 shows inconsistent evidence across cancer types for "heavy" and "light" cannabis use. "Heavy" use is associated with increased risk of brain tumour (use at least once a month) and lung cancer (>10 joint years of use). One study did not determine whether cannabis use referred to ever-use or current-use [21], thus was omitted from Figure 4. When confounding factors were controlled for "light" use did not increase the risk of cancer.





- Study 1 of the cancer studies
- Study 2 of the cancer studies
- Study 3 of the cancer studies
- Study 5 of the cancer studies
- Study 6 of the cancer studies
- Study 8 of the cancer studies

Cohort study

Case-control study

Figure 4. Associations between "heavy" and "light" cannabis use and cancer

Table 4. Studies investigating cannabis use as a risk factor for cancer

Study	Country	Study type	Year	Quality score	N (mean person years follow up)	Cancer diagnosis	Adjusted estimate (95% CI)	Comments
1.	USA	Cohort	1998	9	133811 (12.2)	Malignant primary adult-onset glioma (brain tumour)	RR = 1.9[a] (0.9, 4.0)	No increased risk of brain tumour for ever-smoked marijuana compared to never-smoked marijuana.
							RR = 2.8[a] (1.3, 6.2)	Increased risk for marijuana smoked at least once a month compared to never-smoked marijuana.
2.	USA	Cohort	1993	7	64855 (6.9)	Prostate cancer	RR = 3.1[b] (1.0, 9.5)	Males: Marginal increased risk of prostate cancer for ever-used marijuana compared to never-used marijuana in non-smokers of tobacco.
							RR = 1.3[c] (0.6, 2.6)	But no increased risk found when investigating all men and controlling for tobacco smoking, as well as other variables.
						Cervix cancer	RR = 1.4[b] (1.0, 2.1)	Women: Marginal increased risk of cervix cancer for ever-used marijuana compared to never-used marijuana in non-smokers of tobacco.
							RR = 1.1[c] (0.9, 1.5)	But no increased risk found when investigating all women and controlling for tobacco smoking, as well as other variables.
						Tobacco related, lung, colorectal, melanoma, breast	*see article for NS results reported for males and females for each cancer type*	No significant increased risk of tobacco related, lung, colorectal, melanoma or breast cancer for ever-used marijuana compared to non-users or experimental (< 7 times of use) marijuana.
3.	New Zealand	Case-control	2001-2005	9	403	Lung cancer	RR = 5.7[d] (1.5, 21.6)	Increased risk of lung caner for highest marijuana use (>10 joint yrs) compared to non-use.
							RR = 1.08[d] (1.02, 1.15)	Joint-years used as a continuous variable indicated a significant risk of 8% with each joint year of use.
4.	USA	Case-control	Not reported	7	156	Transitional cell carcinoma of the bladder	NR[e] *P* trend = 0.01	Men: After adjustment, increasing joint-years of marijuana smoking was associated with transitional cell carcinoma (no women in the sample).
5.	UK	Case-control	1990-1997	8	323	Oral squarmous cell carcinoma	OR = 1.0[f] (0.5, 2.2)	No association found between smoking marijuana and oral squarmous cell carcinoma. Sample age range only reached 45 years (young sample may explain NS finding).

Study	Country	Study type	Year	Quality score	N (mean person years follow up)	Cancer diagnosis	Adjusted estimate (95% CI)	Comments
6.	USA	Case-control	1985-1995	7	1022	Oral squarmous cell carcinoma	OR = 0.9[g] (0.6, 1.3)	No association found between ever-used marijuana and oral squarmous cell carcinoma (compared to never-used). May have under-recruited cases that used/reported marijuana use.*
7.	Morocco	Case-control	1996-1998	7	353	Incident cases of lung cancer	OR = 1.93[h] (0.57, 6.58) OR = 1.05[h] (0.28, 3.85)	No increased risk of lung cancer for use of hashish only or snuff (tobacco) only, compared to non-users.*
							OR = 6.67[h] (1.65, 26.90)	Increased risk of lung cancer for use of hashish and snuff (tobacco) compared to non-users.
8.	USA	Case-control	1992-1994	7	349	Head or neck cancer	OR = 2.6[i] (1.1, 6.6)	Increased risk for head or neck cancer for ever-used marijuana compared to never-used marijuana.
							OR = 2.1[i] (0.8, 6.0)	No increased risk for smoking marijuana once a day compared to non-use.
							OR = 4.9[i] (0.8, 29)	No increased risk for smoking marijuana more than once a day compared to non-use.
							OR = 1.9[i] (0.6, 5.9)	No increased risk for smoking marijuana for 1-5 years compared to never-used.
							OR = 4.3[i] (0.99, 19)	No increased risk for smoking marijuana for more than 5 years compared to never-used.
9.	USA	Case-control	1999-2004	7	2252	Lung or upper aerodigestive tract cancer	*see article for NS results reported for each cancer type*	No association found between marijuana use and lung or upper aerodigestive tract cancer, when adjusted for covariates.

Note. CI: confidence interval; NR: not reported; NS: not significant; OR: odds ratio; RR: relative risk
*Study does not indicate if measuring ever-use or past-year use, or current use.
a. adjusted for tobacco smoking, sex, race, alcohol education and coffee (from baseline questionnaire). **B.** adjusted for age, race, education and alcohol use. **c.** adjusted for age, race, education, alcohol use and tobacco smoking. **d.** adjusting for age, sex, ethnicity, pack-yrs of cigarette smoking and family history of lung cancer. **e.** adjusting for potential risk factors associated with transitional cell carcinoma (not specified) **f.** adjusted for alcohol and tobacco use. **g.** adjusted for sex, education, birth year, alcohol consumption, cigarette smoking, and study (first or second).
h. adjusted for tobacco smoking, history of bronchitis, passive smoking, occupational exposure, cooking and heat source, lighting source, ventilation of kitchen. **i.** adjusted for age, gender, race, education, heavy alcohol drinking, tobacco smoking, and passive smoking.
1. Efird et al., 2004. **2.** Sidney, 1997. **3.** Aldington et al., 2008. **4.** Chacko et al., 2006. **5.** Llewellyn et al., 2004. **6.** Rosenblatt et al., 2004. **7.** Sasco et al., 2002. **8.** Zhang, Morgenstern,& Spitz, 1999. **9.** Hashibe et al., 2006.

3.4. Suicide

The final area of research with focus on cannabis as a risk factor is that of suicide ideation, attempt or completion. The results of two case-control studies and one cohort study are shown in Table 5.

Three studies investigated cannabis use as a risk factor of suicide (ideation, attempt or completion). Two studies found an increased risk of suicide was associated with cannabis use (one cohort and one case-control). Neither DSM-III-R cannabis abuse or dependence was associated with medically serious suicide attempt, that is defined as requiring hospitalisation for more than 24-hours and fulfilling one of three treatment options (specialised unit treatment, surgery under general anaesthesia, or other medical treatment as specified in the article) [25]. Significant associations were found in two studies. Ever-use of cannabis was found to be associated with increased risk of completed suicide (Study 2) [26]. In a school sample, early onset cannabis use marginally increased the risk of suicide attempt (Study 3) [27]. These findings were significant but of uncertain interpretation because confounds variables with strong relationship with suicide were not controlled for (namely, depression, or alcohol).

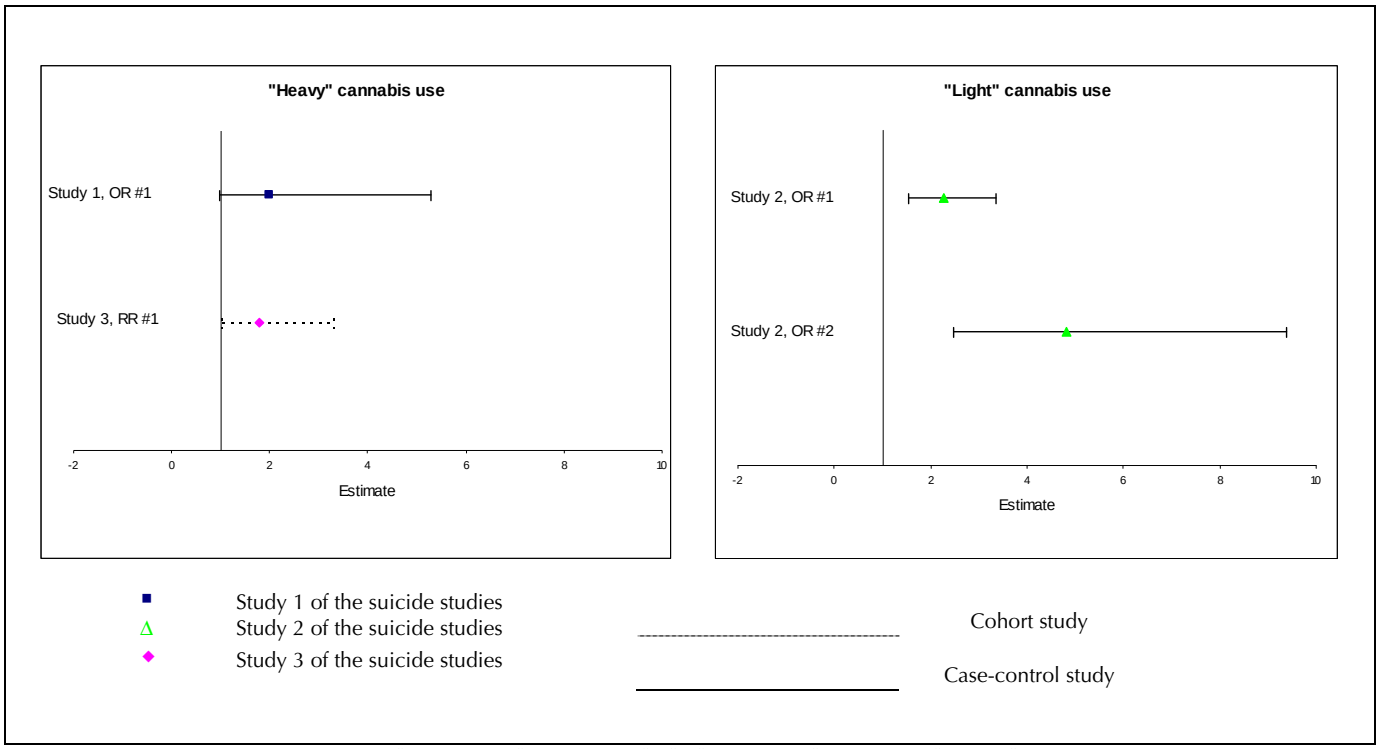


Figure 5. Associations between "heavy" and "light" cannabis use and suicide

Table 5. Studies investigating cannabis use as a risk factor for suicide

Study	Country	Study type	Year	Quality score	N (mean person years follow up)	Sample	Adjusted estimate (95% CI)	Comments
1.	New Zealand	Case control	1991-1994	9	1330	General hospital admissions for medically serious suicide attempt	OR = 2.0[a] (0.97, 5.3)	Cannabis abuse/dependence not found to be a risk factor for medically serious suicide attempt (compared to no suicide attempt).
2.	United States of America	Case control	1993	9	22957	All Current Mortality Sample (CMS) death certificates	OR = 2.28[b] (1.54, 3.37)	Males: Marijuana use was found to be associated with increased a risk of suicide.
							OR = 4.82[b] (2.47, 9.39)	Females: Marijuana use was found to be associated with increased a risk of suicide.
3.	United States of America	Cohort	1989-2002	7	NR (15)	School sample	RR = 1.8[c] (1.0, 3.3)	Early onset cannabis use marginally increased the risk of suicide attempt, compared to those who did not report early onset cannabis use.

Note. NS: not significant; NR: not reported; RR: relative risk; OR: odds ratio; CI: confidence interval
a. adjusted for lack of formal education qualifications, low socioeconomic status, childhood sexual abuse, parental alcohol problems, mood disorder in prior month, substance disorder (mood or drug other than cannabis) in prior month, antisocial disorder in lifetime. **b.** adjusting for age, race, education, and living arrangements. **c.** sex, race, cohort, free lunch, intervention status, MDD, early onset cannabis use (time dependent), level of early aggression, drug using and drug deviant peers, parental psychiatric disturbance.
1. Beautrais, Joyce, & Mulder, 1999. **2.** Kung, Pearson & Liu, 2003. **3.** Wilcox & Anthony, 2004.

4. Discussion and conclusions

At present there is insufficient evidence to suggest that the all-cause mortality rate is elevated among cannabis users in the general population. Case control studies suggest that responsibility of fatal motor vehicle accidents may be elevated among heavy cannabis users. The evidence for cannabis use as a risk factor for cancer is inconsistent. The evidence is as yet unclear as to whether cannabis use increases the risk of suicide. Finally, ever-use of cannabis is not reportedly associated with mortality, which is not surprising as individuals reporting ever-use of cannabis could vary in usage from once to heavy consistent use.

There is a need for long-term cohort studies that follow individuals into old age, when the likelihood of detrimental effects of cannabis use are more likely to emerge among those who persist in using cannabis into middle age and older.

Limitations:

Very few studies have been done and the largest cohort studies have typically had a low prevalence of regular cannabis use and not followed samples long enough to detect increases in mortality from cancers and cardiovascular disease. Moreover, these used diverse exposure and outcome measures.

Well designed case control studies are needed to identify potential causes of premature death that may be elevated in regular cannabis users that will warrant closer study in longitudinal studies. The latter may become easier to undertake as an ageing cohort of regular cannabis users reach middle age and older when deaths from chronic disease will increase.

Inconsistencies in defining “heavy” or “light” use make comparison across studies problematic. These recommendations and conclusions are supported by other recent reviews [28].

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Appendix A: Database information

Database	Information
Medline	Compiled by the U.S. National Library of Medicine (NLM) and published on the Web by Community of Science, MEDLINE® is the world's most comprehensive source of life sciences and biomedical bibliographic information. It contains nearly eleven million records from over 7,300 different publications from 1965 to November 16, 2005. *(Source: http://medline.cos.com/docs/abmedl.shtml)*
EMBASE	EMBASE is a biomedical and pharmacological database. The EMBASE journal collection is international with over 5,000 biomedical journals from 70 countries. EMBASE contains over 11 million records from 1974 to present. EMBASE features comprehensive coverage of: • Drug Research, Pharmacology, Pharmacy, Pharmacoeconomics, Pharmaceutics and Toxicology • Human Medicine (Clinical and Experimental) • Basic Biological Research • Health Policy and Management • Public, Occupational and Environmental Health • Substance Dependence and Abuse • Psychiatry • Forensic Science • Biomedical Engineering and Instrumentation *(Source: http://www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/523328/description#description)*
PsychINFO	PsycINFO is an abstract database of psychological literature from the 1800s to the present. More than 2.4 million records as of January 2008, including journals, books and dissertations. Over 2150 journal titles covered, 98% peer-reviewed; aso books and dissertations. *(Source: http://www.apa.org/psycinfo/)*

Appendix B: Search strings for literature searches

Database	Search group	Search terms
Medline*	Cannabis	Cannabis OR cannabin$ OR marijuana OR bhang OR ganga OR hashish OR hemp or cannabis indica OR cannabis sativa or hemp plant or marihuana **Exp cannabis/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp SUDDEN DEATH/ or exp Mortality/ or exp Hospitalization/ or exp Fatal Outcome/**
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up" **exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/**
	Drug Use	drug abuse$ OR drug use$ OR drug misuse$ OR drug dependenc$ OR substance abuse$ OR substance use$ OR substance misuse$ OR substance dependenc$ OR addict$ **Exp Substance-related disorders/**
EMBASE#	Cannabis	Cannabis OR cannabin$ OR marijuana OR bhang OR ganga OR hashish OR hemp or cannabis indica OR cannabis sativa or hemp plant or marihuana **Exp cannabis addiction/ or exp cannabis smoking/ or exp cannabis/ or exp cannabis derivative/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp ACCIDENTAL DEATH/ or exp SUDDEN DEATH/ or exp Fatality/ or exp Mortality/ or exp Hospitalization/**
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up" **exp COHORT ANALYSIS/ or exp LONGITUDINAL STUDY/ or exp PROSPECTIVE STUDY/ or exp Follow Up/**
	Drug Use	Drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$ **exp substance abuse/ or exp drug abuse/ or exp analgesic agent abuse/ or exp drug abuse pattern/ or exp drug misuse/ or exp drug traffic/ or exp multiple drug abuse/ or exp addiction/ or exp drug dependence/ or exp cocaine dependence/ or narcotic dependence/ or exp heroin dependence/ or exp morphine addiction/ or exp opiate addiction/**
PsychINFO^	Cannabis	Cannabis or cannabin$ or marijuana or bhang or ganga or hashish or hemp or cannabis indica or cannabis sativa or hemp plant or marihuana **exp CANNABIS/ or exp MARIJUANA USAGE/ or exp MARIJUANA/**
	Mortality	Mortal$ or fatal$ or death$ **exp "DEATH AND DYING"/ or exp Mortality/ or exp Hospitalization**
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up" **Exp age differences/ or exp cohort analysis/ or exp human sex differences**
	Drug Use	Drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$ **Exp drug abuse/ or exp drug addiction/ or exp addiction/ or exp drug usage**

* 'key-words' in lowercase, 'MeSH' terms in **bold**

'key-words' in lowercase, 'EMTREE' terms in bold

^ 'key words' in lowercase, explode terms in bold

Appendix C: Number of articles identified from cannabis mortality search combinations

	Search terms		Database		
			Medline	EMBASE	PsycINFO
1.	Cannabis	+ mortality	520	911	124
2.	Cannabis	+ mortality + cohort	129	161	30
3.	Cannabis	+ mortality + drug use	334	546	96
4.	Cannabis	+ mortality + cohort + drug use	105	120	24