REVIEW

# Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use

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### Abstract

***Issues.*** *To conduct a comprehensive search of the peer-reviewed literature to assess risk of cannabis-related mortality.* ***Approach.*** *Systematic peer-reviewed literature searches were conducted in Medline, EMBASE and PsycINFO to identify data on mortality associated with cannabis use. Search strings for* cannabis *and* mortality *were used. Searches were limited to human subjects and the publication timeframe of January 1990 to January 2008. Reference lists of review articles and of specific studies deemed important by colleagues were searched to identify additional studies. A list of the selected articles was emailed to experts in the field asking for comment on completeness.* ***Key Findings.*** *There is insufficient evidence, particularly because of the low number of studies, to assess whether the all-cause mortality rate is elevated among cannabis users in the general population. Case–control studies suggest that some adverse health outcomes may be elevated among heavy cannabis users, namely, fatal motor vehicle accidents, and possibly respiratory and brain cancers. The evidence is as yet unclear as to whether regular cannabis use increases the risk of suicide.* ***Conclusions.*** *There is a need for long-term cohort studies that follow cannabis using individuals into old age, when the likelihood of any detrimental effects of cannabis use are more likely to emerge among those who persist in using cannabis into middle age and older. Case–control studies of cannabis use and various causes of mortality are also needed.* [Calabria B, Degenhardt L, Hall W, Lynskey M. 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]

**Key words:** review, cannabis, drug, mortality, risk.

## Introduction

Cannabis is a generic term for preparations (e.g. marijuana, hashish and hash oil) derived from the *Cannabis sativa* plant. 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 between its use and mortality [2,3]. Other illicit drug use and associated mortality is more frequently investigated, especially opioid overdose deaths. Because cannabis use is not reported to cause fatal overdoses, its impact on mortality has rarely been explored.

This paper is a result of continuing work by the mental disorders and illicit drug use work group for the Global Burden of Disease (GBD) study that commenced in 2007 (for more information see *Acknowledgements* or visit http://www.gbd.unsw.edu.au). In this paper we summarise the results of a systematic review of the literature on mortality among people who use cannabis. We also consider the risks in users compared with non-users, for outcomes that are often fatal (identified by the search strategy): culpable driving associated with fatal motor vehicle accidents, various cancers, and suicide ideation, attempt or completion.

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## Method

### Identifying studies

The search strategy was consistent with the methodology recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [4]. In consultation with a qualified librarian, three electronic databases were chosen: Medline, EMBASE and PsycINFO to provide the most complete coverage of the peer-reviewed literature. Search strings, tailored to each database were devised for *cannabis*, *mortality*, *cohort* and *drug use* (see Appendix A for search strings). Varied search strategies were carried out using these search strings, limited to human subjects and the publication timeframe of January 1990 to January 2008 (see Appendix B for varied search combinations). The terms *cannabis* and *mortality* were chosen. Using only these search strings identified a manageable number of articles for examination within the allotted time. References for the identified articles were compiled in EndNote X® (Thomson Reuters, New York, NY, USA), and duplicates were deleted. The reference lists of review articles and important articles identified by colleagues were hand-searched to identify additional studies.

Abstracts of all identified articles were read and the list culled according to predetermined criteria. Excluded articles were moved to Endnote libraries labelled to represent the exclusion criteria.

### Included studies

Included studies were studies with a focus on mortality associated with cannabis use or dependence. General population studies within the timeframe of January 1990 to January 2008 were of most interest.

### Excluded studies

Articles were excluded if they were not focused on cannabis or mortality, for example if cannabis was grouped with other drug types for analysis or the focus of the article was on injury. Review articles and case series were excluded. When several articles were published on the same cohort of people the most recent or most relevant results were included.

### Expert input

Louisa Degenhardt reviewed the initial list post-cull. A reference list of the selected articles was emailed to experts in the field (see *Acknowledgements*) and asked to comment on the completeness. The eleven members of the mental disorders and illicit drug use expert group and corresponding members also reviewed the list.

### Data extraction

The next stage was data extraction that aimed to obtain information about study design and participants as recommend by the STROBE guidelines [5,6], which are parallel to the CONSORT guidelines for reporting of randomised trials [7].

A Microsoft Excel® (Microsoft, Redmond, WA, USA) spreadsheet was used to record article information, the specific location of the study, as well as the country and region, according to GBD provisions (see Appendix C for country and region list). Study type and sample characteristics were also noted, as was: diagnostic criteria, cause of death and measures of association between cannabis use and mortality. A random sample of extractions was cross-checked for consistency.

### Quality score

The quality index was developed for use across all parameters in the GBD study. It was modeled from one developed by John McGrath and Sukanta Saha [8,9] and derived via the 'Delphi method' with discussion, final agreement and approval from the members of the exert group (see Appendix D for quality index criteria). Descriptions of items on the quality index are shown in Table 1. Scores range from zero to 15. Highest scores are achieved by general population cohort studies with age- and sex-disaggregated estimates. The quality index score for each study was recorded in the Microsoft Excel® spreadsheet.

## Results

### Study identification and selection

Nineteen papers were included in this review: two dealing with all-cause mortality, four with motor vehicle accidents, nine with cancer and four with suicidal behaviours (see Appendix E for flow chart of search strategy and culling process).

### Assessment of cannabis use

Reports of exposure to cannabis varied across these nineteen studies. This variation in reporting prevented systematic comparisons across studies. This paper compares 'heavy' use, constituting heavy (>50 times, >10 joint-years), weekly, and highest reports of detection of Delta-9-tetrahydrocannabinol (THC), and 'light' use representing ever use, less than weekly, and any detection of THC.

**Table 1.** *Variables that form the quality index*

| Quality variable | Explanation |
| --- | --- |
| Case ascertainment | Ascertainment of subjects nationwide or regionally (high score for national sample) |
| Measurement instrument | Measurement instrument to determine cannabis use or dependence (i.e. self-report or toxicological screen) (high score for standardised diagnosis tool used) |
| Diagnostic criteria | Indicates whether cannabis dependence was diagnosed (higher score for dependence data than use data) |
| Estimate | Estimate presented (e.g. prevalence, incidence, mortality, relative risk, etc.) (higher score for estimate presented than detection of drug use) |
| Numerator and denominator presented? | Was the numerator and denominator presented for estimate of interest? (high score if numerator and denominator presented for each estimate) |
| 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? (high score if numerator and denominator presented from the same time and place) |
| Completeness of follow up in cohort studies and response for cross-sectional studies | Captures response rates (high score for response rates >80%, moderate score for 60%–79%, low score for <60%) |
| Representativeness of catchment area | Determines generalisability of the sample to the population (high score for representative sample) |
| Age/sex-specific values presented? | Identifies whether age- and/or sex-specific values were reported (high score for age- and sex-specific estimates, moderate score for only age- or sex-specific estimates) |
| Quality of methods of reporting | To capture methods that were not reported on by other variables (free text to record additional information) |
| Duration of follow up | To obtain more information about follow-up periods and sample sizes when doing so (free text to record additional information) |

### Risk assessments

*All-cause mortality.* There have been two prospective epidemiological cohort studies published on mortality among cannabis users (see Figure 1 and Table 2). 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 times by age 18 years compared with non-users [10]. However, the association between mortality and cannabis use disappeared after multivariate statistical adjustment for alcohol and other drug use. Unfortunately this is the most recent publication, to the knowledge of the authors, reporting on this cohort with a focus on cannabis use and mortality. It would be beneficial to have more recently published results that would have a longer follow-up period, possible yielding stronger associations of cannabis use and mortality.

Sidney *et al.* [11] 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 years. Current cannabis use by male people had a small association with premature mortality [relative risk (RR) = 1.3, 95% confidence interval (CI) = 1.1, 1.6)] that was 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 only modestly increased the risk of premature mortality.

The limited available evidence does not indicate an increased risk of mortality for cannabis users in the general population. Overall, there are too few studies to draw clear conclusions about the relationship between cannabis use and all-cause mortality.

*Motor vehicle accidents.* Cannabis produces dose-related impairments in cognitive and behavioural functions that may potentially impair driving an automobile or operating machinery [12]. These impairments are larger and more persistent in difficult tasks involving sustained attention [12]. A possible adverse consequence of acute cannabis use therefore is a motor vehicle accident if an individual drives while intoxicated [13,14].

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% [13]. However, studies of the effects of cannabis on driving under more realistic conditions on roads have found much more modest impairments [15,16].
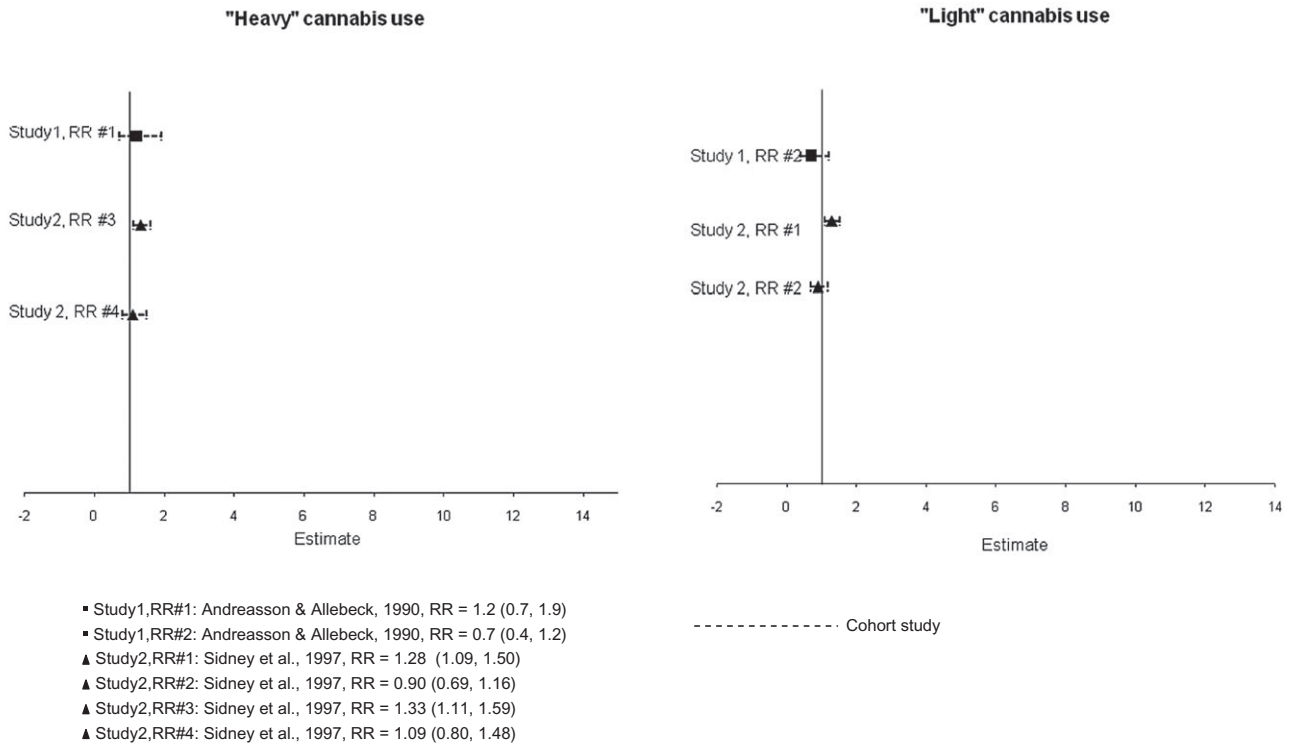
"Heavy" cannabis use

"Light" cannabis use



- Study1,RR#1: Andreasson & Allebeck, 1990, RR = 1.2 (0.7, 1.9)
- Study1,RR#2: Andreasson & Allebeck, 1990, RR = 0.7 (0.4, 1.2)
- ▲ Study2,RR#1: Sidney et al., 1997, RR = 1.28 (1.09, 1.50)
- ▲ Study2,RR#2: Sidney et al., 1997, RR = 0.90 (0.69, 1.16)
- ▲ Study2,RR#3: Sidney et al., 1997, RR = 1.33 (1.11, 1.59)
- ▲ Study2,RR#4: Sidney et al., 1997, RR = 1.09 (0.80, 1.48)

- - - - - - - - - - - - Cohort study

**Figure 1.** *Associations between 'heavy' and 'light' cannabis use and mortality. RR: relative risk.*

This is probably because cannabis intoxication results in an increased awareness of impairments, and there may be less inclination to take risks than when intoxicated with alcohol [16].

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 [13,17]. Blows *et al.* [18] found a 10-fold increase in culpable driving for those who reported cannabis use 3 h prior to a motor vehicle accident resulting in hospitalisation of the driver or their passenger. This association disappeared when 'risky behaviours', including blood alcohol concentration, were controlled for.

Only modest associations have been found by three case–control studies comparing detection of THC with drug- and alcohol-free drivers [19]; when focusing on drivers who had higher levels of THC detected ($\geq 5$ ng mL$^{-1}$), the risk of culpable driving was increased [20,21]. 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 2 and Table 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. Efird *et al.* [22]

reported an increased risk of developing a brain tumour when marijuana was smoked at least once a month (RR = 2.8, 95% CI = 1.3, 6.2). The second study reported no increase in overall cancer rates among cannabis users (although there were slightly increased rates of prostate and cervical cancer) [23].

Case–control studies have also investigated the risk of cancer among cannabis users. Most have found no association between cannabis use and cancer [24–27]. However, in New Zealand an increased risk of lung cancer for heavy use has been identified, with an 8% increase in risk for each joint-year of use [28]. Furthermore, in a sample of men only, a significant trend was found between increasing joint-years of marijuana use and bladder cancer [29]. Finally, Zhang *et al.* [30] reported a marginally increased risk of head and neck cancer for those who had ever used marijuana compared with those who had never used marijuana (odds ratio = 2.6, 95% CI = 1.1, 6.6). No association was found when frequency of use was investigated; however, low power because of the small sample size may have impacted on this result.

Figure 3 and Table 4 show inconsistent evidence across cancer types for 'heavy' and 'light' cannabis use. One study did not determine whether cannabis use referred to ever use or current use [27], thus was omitted from Figure 3.

**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 | 45 540 (16) | 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 with 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 | 65 171 (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, 1.17) | Women: no increased risk of all-cause mortality for ever use compared with non-use |
| | | | | | | | RR = 1.33[b] (1.12, 1.59) | Men: current marijuana use was associated with significant 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 with non-use |

1. Andreasson and Allebeck (1990) [10]; 2. Sidney *et al.* (1997) [11]. [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. Only seven deaths among marijuana users (cases) and 310 deaths among non-users (controls), so insufficient numbers to evaluate and compare cardiovascular and non-cardiovascular mortality. CI, confidence interval; RR, relative risk.
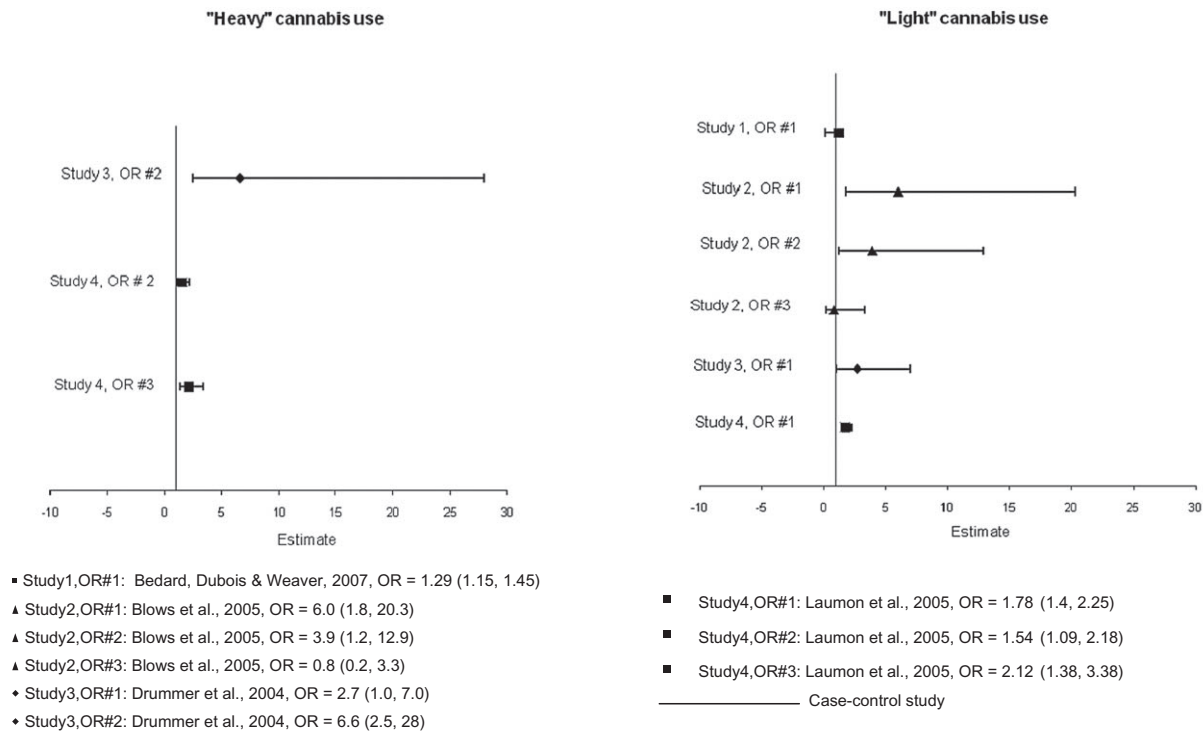
"Heavy" cannabis use

"Light" cannabis use



- ■ Study1,OR#1: Bedard, Dubois & Weaver, 2007, OR = 1.29 (1.15, 1.45)
- ▲ Study2,OR#1: Blows et al., 2005, OR = 6.0 (1.8, 20.3)
- ▲ Study2,OR#2: Blows et al., 2005, OR = 3.9 (1.2, 12.9)
- ▲ Study2,OR#3: Blows et al., 2005, OR = 0.8 (0.2, 3.3)
- ◆ Study3,OR#1: Drummer et al., 2004, OR = 2.7 (1.0, 7.0)
- ◆ Study3,OR#2: Drummer et al., 2004, OR = 6.6 (2.5, 28)

- ■ Study4,OR#1: Laumon et al., 2005, OR = 1.78 (1.4, 2.25)
- ■ Study4,OR#2: Laumon et al., 2005, OR = 1.54 (1.09, 2.18)
- ■ Study4,OR#3: Laumon et al., 2005, OR = 2.12 (1.38, 3.38)
- —————— Case-control study

**Figure 2.** *Associations between 'heavy' and 'light' cannabis use and fatal motor vehicle accidents. OR, odds ratio.*

*Suicidal behaviour.* The final area of research was on cannabis use as a risk factor for suicide ideation, attempt and completion. Inclusion of research on suicide ideation and attempt in addition to suicide completion is as a result of the scarcity of research on completed suicide. Literature suggests that suicidal behaviours occur together as part of a process [31], therefore investigating risk factors for suicide ideation and attempt will also in fact identify risk factors for suicide completion (see Table 5).

Three studies found an increased risk of suicide was associated with cannabis use (two cohort and one case–control). Neither DSM-III-R cannabis abuse nor dependence was associated with medically serious suicide attempt, defined as requiring hospitalisation for more than 24 h and fulfilling one of three treatment options (specialised unit treatment, surgery under general anaesthesia or other medical treatment as specified in the article) [32].

Significant associations were found in three studies. Ever use of cannabis was found to be associated with increased risk of completed suicide (study 2) [33]. In a school sample, early onset cannabis use marginally increased the risk of suicide attempt (study 3) [34]. These findings were significant, but of uncertain interpretation because potential confounding variables that are strongly related to suicide were not controlled for (namely, depression and alcohol use). Fergusson *et al.* found significant associations between annual cannabis use and suicide ideation and attempt when controlling for fixed and time-dynamic factors (study 4) [35]. These results were omitted from Figure 4 as adjusted hazard or odds ratios were not reported.

## Discussion and conclusions

### Discussion

This study was the first systematic review of mortality related to cannabis use. Systematic peer-reviewed literature searches were conducted to identify data focused on mortality associated with cannabis use. Nineteen articles were included in this review: only two dealt with all-cause mortality, four with motor vehicle accidents, nine with cancer and four with suicide.

At present there is insufficient evidence to assess whether the all-cause mortality rate is elevated among cannabis users in the general population. Recently, Mukamal *et al.* [36] investigated increased risk of mortality for cannabis users in a sample of adults hospitalised for myocardial infarction (N = 1913) using a case–control design. In this population increased risk of mortality was found for those who had ever used

**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 | 32 543 | 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 | 1 159 | Cars involved in a fatal motor vehicle accident or accident that required hospitalisation | OR = 6.0[b] (1.8, 20.3) | Self-reported cannabis use (any dose) in the 3 h prior to the accident was associated with sixfold 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 | 3 398 | 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 with drug- and alcohol-free drivers |
| | | | | | | | OR = 6.6[e] (2.5, 28) | Cannabis use (THC detection ≥5 ng mL$^{-1}$ only) was positively associated with culpable driving, compared with drug- and alcohol-free drivers |
| 4. | France | Case–control | 2001–2003 | 8 | 10 748 | 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 ≥1 ng mL$^{-1}$) 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 1–2 ng mL$^{-1}$, had a weaker association with culpable driving than cannabis use, THC ≥5 ng mL$^{-1}$ |

1. Bedard *et al.* (2007) [19]; 2. Blows *et al.* (2005) [18]; 3. Drummer *et al.* (2004) [20]; 4. Laumon *et al.* (2005) [21]. [a] Adjusted for age, sex and previous driving record. [b] Adjusted for age and sex. [c] Adjusted for age, sex, ethnicity, driving exposure, time of day and number of passengers. [d] Adjusted for age, sex, ethnicity, driving exposure, age of vehicle, time of day, number of passengers, blood alcohol concentration, 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. CI, confidence interval; OR, odds ratio.
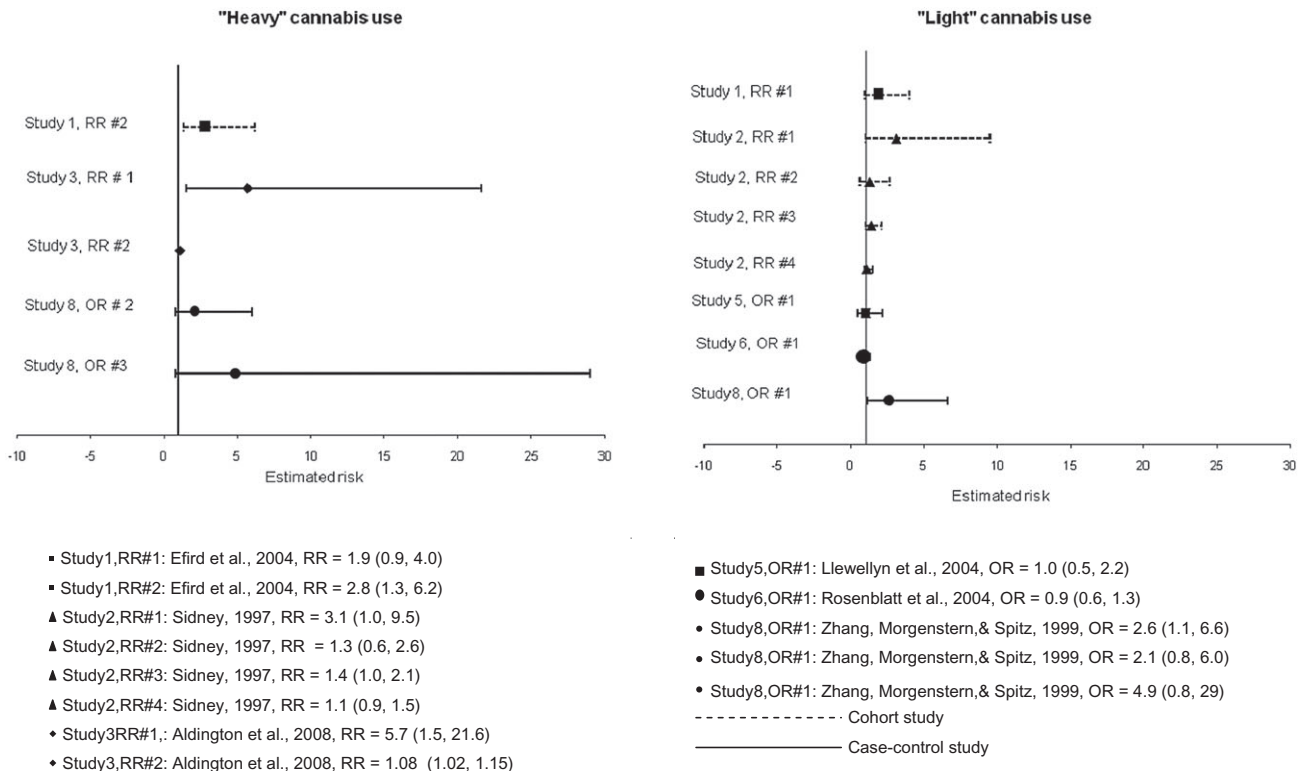
"Heavy" cannabis use

"Light" cannabis use

- Study1,RR#1: Efird et al., 2004, RR = 1.9 (0.9, 4.0)
- Study1,RR#2: Efird et al., 2004, RR = 2.8 (1.3, 6.2)
- Study2,RR#1: Sidney, 1997, RR = 3.1 (1.0, 9.5)
- Study2,RR#2: Sidney, 1997, RR  = 1.3 (0.6, 2.6)
- Study2,RR#3: Sidney, 1997, RR = 1.4 (1.0, 2.1)
- Study2,RR#4: Sidney, 1997, RR = 1.1 (0.9, 1.5)
- Study3RR#1,: Aldington et al., 2008, RR = 5.7 (1.5, 21.6)
- Study3,RR#2: Aldington et al., 2008, RR = 1.08  (1.02, 1.15)

- Study5,OR#1: Llewellyn et al., 2004, OR = 1.0 (0.5, 2.2)
- Study6,OR#1: Rosenblatt et al., 2004, OR = 0.9 (0.6, 1.3)
- Study8,OR#1: Zhang, Morgenstern,& Spitz, 1999, OR = 2.6 (1.1, 6.6)
- Study8,OR#1: Zhang, Morgenstern,& Spitz, 1999, OR = 2.1 (0.8, 6.0)
- Study8,OR#1: Zhang, Morgenstern,& Spitz, 1999, OR = 4.9 (0.8, 29)
- - - - - - - - - - - - -  Cohort study
——————————————  Case-control study

**Figure 3.** *Associations between 'heavy' and 'light' cannabis use and cancer. OR, odds ratio; RR: relative risk.*

marijuana (N = 52), compared with those who had never used marijuana [hazard ratio (HR) = 3.0, 95% CI = 1.3, 7.0). Heavy marijuana use increased the risk of mortality (HR = 4.2, 95% CI = 1.2, 14.3). Those who had ever used marijuana had increased non-cardiovascular mortality compared with never-users, including fatal motor vehicle accident, AIDS and lung cancer, but their cardiovascular mortality was not elevated. The latter finding may reflect the small sample size and limited statistical power of the study, or other correlates of cannabis use (e.g. increased risk taking, alcohol and tobacco use) that result in mortality. These results indicate that cannabis use may increase the risk of mortality in vulnerable populations.

Case–control studies suggest that some outcomes may be elevated among 'heavy' cannabis users, namely, respiratory and brain cancers and responsibility in fatal motor vehicle accidents. The evidence is as yet unclear as to whether cannabis use increases the risk of suicide as most studies did not control for potential confounding variables that are strongly related to suicide (namely, depression and alcohol use). Fergusson *et al.* [35] controlled fixed and time-dynamic factors and found a significant association between annual cannabis use and suicide ideation and attempt. This study is a start, but more studies with significant findings,

which control for confounding variables, are required for clarity of whether cannabis use as a risk factor for suicide.

Dose–response effects were also identified. Laumon *et al.* [21] identified a dose–response effect for amount of THC detected and driving culpably. Furthermore, when joint-years was analysed as a continuous variable by Aldington *et al.* [28] a significant risk of eight percent was found with each joint-year of use. These findings indicate that future research should focus not only on frequency of use, but also on quantity and duration of continued use of cannabis to assess whether risks increase when greater amounts are used for longer periods of time.

The focus of this review has been mortality as a result of cannabis use. Indirect effects of cannabis use and associated mortality may also exist, such as the argument that cannabis use may be associated with other illicit drug use [37,38] of which mortality is directly associated [39]. This discussion is beyond the scope of this review.

*Limitations*

Very few studies have been done focussing on cannabis use and mortality. The largest cohort studies have

**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 | 133 811 (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 with never-smoked marijuana |
|  |  |  |  |  |  |  | RR = 2.8[a] (1.3, 6.2) | Increased risk for marijuana smoked at least once a month compared with never-smoked marijuana |
| 2. | USA | Cohort | 1993 | 7 | 64 855 (6.9) | Prostate cancer | RR = 3.1[b] (1.0, 9.5) | Male: marginal increased risk of prostate cancer for ever-used marijuana compared with 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 with 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 |
| 3. | New Zealand | Case–control | 2001–2005 | 9 | 403 | Tobacco-related, lung, colorectal, melanoma, breast | See article for NS results reported for male and female people for each cancer type | No significant increased risk of tobacco-related, lung, colorectal, melanoma or breast cancer for ever-used marijuana compared with non-users or experimental (<7 times of use) marijuana |
|  |  |  |  |  |  | Lung cancer | RR = 5.7[d] (1.5, 21.6) | Increased risk of lung caner for highest marijuana use (>10 joint-years) compared with 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 squamous cell carcinoma | OR = 1.0[f] (0.5, 2.2) | No association found between smoking marijuana and oral squamous cell carcinoma |
|  |  |  |  |  |  |  |  | Sample age range only reached 45 years (young sample may explain NS finding) |
| 6. | USA | Case–control | 1985–1995 | 7 | 1022 | Oral squamous cell carcinoma | OR = 0.9[g] (0.6, 1.3) | No association found between ever-used marijuana and oral squamous cell carcinoma (compared with never-used) May have under-recruited cases that used/reported marijuana use[h] |
| 7. | Morocco | Case–control | 1996–1998 | 7 | 353 | Incident cases of lung cancer | OR = 1.93[i] (0.57, 6.58) OR = 1.05[i] (0.28, 3.85) | No increased risk of lung cancer for use of hashish only or snuff (tobacco) only, compared with non-users[h] |
|  |  |  |  |  |  |  | OR = 6.67[i] (1.65, 26.90) | Increased risk of lung cancer for use of hashish and snuff (tobacco) compared with 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 with never-used marijuana |
|  |  |  |  |  |  |  | OR = 2.1[i] (0.8, 6.0) | No increased risk for smoking marijuana once a day compared with non-use |
|  |  |  |  |  |  |  | OR = 4.9[i] (0.8, 29) | No increased risk for smoking marijuana more than once a day compared with non-use |
|  |  |  |  |  |  |  | OR = 1.9[i] (0.6, 5.9) | No increased risk for smoking marijuana for 1–5 years compared with never-used |
|  |  |  |  |  |  |  | OR = 4.3[i] (0.99, 19) | No increased risk for smoking marijuana for more than 5 years compared with 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 |

1. Efird *et al.* (2004) [22]; 2. Sidney *et al.* (1997) [23]; 3. Aldington *et al.* (2008) [28]; 4. Chacko *et al.* (2006) [29]; 5. Llewellyn *et al.* (2004) [25]; 6. Rosenblatt *et al.* (2004) [26]; 7. Sasco *et al.* (2002) [27]; 8. Zhang *et al.* (1999) [30]; 9. Hashibe *et al.* (2006) [24]. [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-years 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]Study does not indicate if measuring ever use or past-year use, or current use. [i]Adjusted for tobacco smoking, history of bronchitis, passive smoking, occupational exposure, cooking and heat source, lighting source, ventilation of kitchen. [j]Adjusted for age, gender, race, education, heavy alcohol drinking, tobacco smoking and passive smoking. CI, confidence interval; NR, not reported; NS, not significant; OR, odds ratio; RR, relative risk.

**Table 5.** *Studies investigating cannabis use as a risk factor 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 | 1 330 | 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 with no suicide attempt) |
| 2. | USA | Case–control | 1993 | 9 | 22 957 | All Current Mortality Sample (CMS) death certificates | $OR = 2.28^b$ (1.54, 3.37) | Male: marijuana use was found to be associated with an increased risk of suicide |
| | | | | | | | $OR = 4.82^b$ (2.47, 9.39) | Female: marijuana use was found to be associated with an increased risk of suicide |
| 3. | USA | 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 with those who did not report early onset cannabis use |
| 4. | Australia | Cohort | 1992–1998 | 7 | 1 265 (21) | Birth cohort | $B = 0.36^d$, $P < 0.001$ | Significant association between annual frequency of cannabis use and suicide ideation |
| | | | | | | | $B = 0.34^d$, $P < 0.05$ | Significant association between annual frequency of cannabis use and suicide attempt |

1. Beautrais *et al.* (1999) [32]; 2. Kung *et al.* (2003) [33]; 3. Wilcox and Anthony (2004) [34]; 4. Fergusson *et al.* (2002) [35]. [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] Adjusted for 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. [d] Adjusted for fixed effects and time–dynamic effects (adverse life events, deviant peer affiliations, alcohol abuse, age of leaving school, age of leaving home). CI, confidence interval; NR, not reported; OR, odds ratio; RR, relative risk.
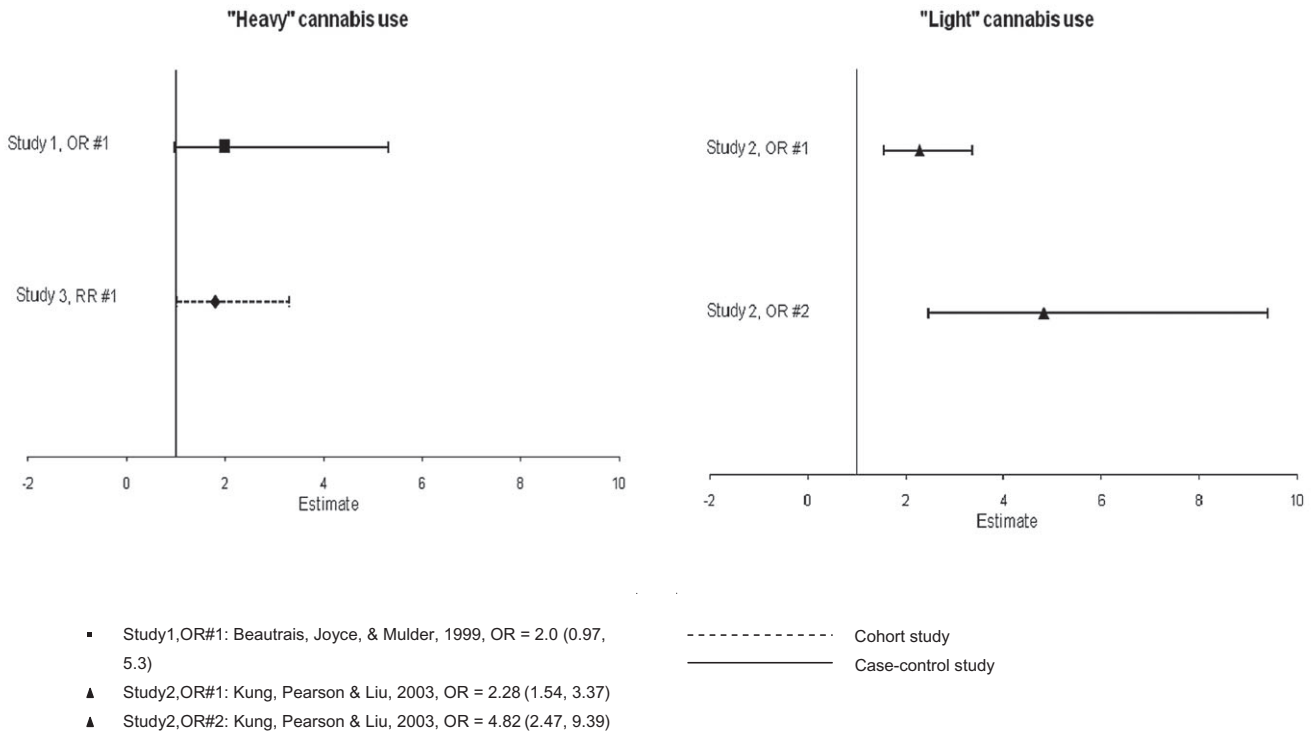
Figure 4. *Associations between 'heavy' and 'light' cannabis use and suicide.*

typically had a low prevalence of regular cannabis use and have not followed samples long enough to detect increases in mortality from cancers and coronary heart disease. Cohort studies with longer follow-up periods would expectantly strengthen the associations between cannabis use and mortality and thus are necessary before clearer conclusions can be made. Moreover, studies have used diverse exposure and outcome measures that make comparison across studies problematic.

Well-designed case–control studies are needed that strengthen the evidence base for outcomes that may be fatal for cannabis users compared with non-users and to identify other 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. These recommendations and conclusions are supported by other recent reviews [40].

### Conclusions

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

studies would greatly enrich the current research that points to negative outcomes associated with 'heavy' cannabis use, providing further evidence to inform those who use cannabis about possible adverse long-term effects.

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## Appendix A

*Search strings*

http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/
CannMortPaper/$file/GBD_Cann_A_MortPaper_
SearchStrings.pdf

## Appendix B

*Search combinations*

http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/
CannMortPaper/$file/GBD_Cann_B_MortPaper_
SearchCombinations.pdf

## Appendix C

*Global Burden of Disease study region and country list*

http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/
CannMortPaper/$file/GBD_Cann_C_MortPaper_
CountryList.pdf

## Appendix D

*Quality Index*

http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/
CannMortPaper/$file/GBD_Cann_D_MortPaper_
QualityIndex.pdf

## Appendix E

*Flowchart of search strategy and culling process*

http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/
CannMortPaper/$file/GBD_Cann_E_MortPaper_
Flowchart.pdf