The effects of cannabis intoxication on motor vehicle collision revisited and revised

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Ethics approval not required.

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Abstract

Aims: To determine whether and to what extent acute cannabis intoxication increases motor vehicle crash risk.

Design: Study 1 replicates two published meta-analyses, correcting for methodological shortcomings. Study 2 is an updated meta-analysis using 28 estimates from 21 observational studies. These included studies from three earlier reviews, supplemented by results from structured search in Web of Science and Google Scholar, supplemented by the personal libraries of the research team. Risk estimates were combined using random effects models and meta-regression techniques.

Setting: Study 1 replicates the analysis of Asbridge et al, based on 9 studies from 5 countries - published 1982-2007, and Li et al, based on 9 studies from 6 countries - published 2001-10. Study 2 involves studies from 13 countries published in the period 1982-2015.

Participants: In Study 1, total counts extracted totalled 50 877 (27 967 cases, 22 910 controls) for Asbridge et al and 93 229 (4 236 cases and 88 993 controls) for Li et al. Study 2 used confounder-adjusted estimates where available (combined sample size of 222 511) and crude counts from the remainder (17 228 total counts), giving a combined sample count of 239 739.

Measures: Odds-ratios were used from case-control studies and adjusted odds-ratio analogues from culpability studies. The impact of the substantial variation in confounder adjustment was explored in subsample analyses.

Findings: Study 1 substantially revises previous risk estimates downwards, with both the originally reported point estimates lying outside the revised confidence interval . Revised estimates were similar to those of Study 2, which found cannabis-impaired driving associated with a statistically significant risk increase of low-to-moderate magnitude (random effects model odds ratio 1.36 (1.15-1.61), meta-regression odds ratio 1.22 (1.1-1.36)). Subsample analyses found higher odds-ratio estimates for case control studies, low study quality, limited control of confounders, medium quality use data, and not controlling for alcohol intoxication.

Conclusions: Acute cannabis intoxication is associated with a statistically significant increase in crash risk. The increase is of low to medium magnitude. Remaining selection effects in the studies used may limit causal interpretation of the pooled estimates.

Introduction

The raised traffic crash risks of cannabis-impaired drivers has received increasing attention from researchers and policy makers following legislative changes for medical and recreational cannabis, particularly in US states. Researchers have highlighted cannabis-impaired driving as one the three "primary reasons for concern about legalized cannabis" [1], and the current consensus, as summarized in a recent narrative review of cannabis research, holds that the evidence "suggests strongly" that cannabis-impaired driving increases the crash risk 2-3 times [2].

The evidence for this claim includes both laboratory and epidemiological research. Experimental studies find evidence of dose-related impairment on a number of driving-relevant abilities, with a typical duration of 3-4 hours following intake through smoking [3,4], but also find that cannabis users tend to be aware of, and to some extent compensate for, these impairments when driving. Overall, the external validity of these studies remains unclear, necessitating the use of observational epidemiological studies to assess the net traffic risk of cannabis intoxication. This requires the use of

meta-analytic techniques that pool evidence from different studies, since individual studies tend to be small and find strongly differing risk estimates. The most widely referenced meta-reviews are both from 2012, and report summary odds-ratios from pooled studies of 1.92 and 2.66 [5,6], each based on a set of nine estimates.

The present meta-review was motivated by two concerns: One, we suspected that methodological issues, particularly relating to established confounders, were insufficiently addressed in the earlier meta-analyses. For this reason, we replicated the analyses of Asbridge et al [5] and Li et al [6], correcting for a set of identified methodological issues (Study 1). Second, the evidence base has grown rapidly in recent years as a result of increased research attention. To address this, we performed an updated and more comprehensive meta-analysis that identified a total of 26 estimates from 21 studies (Study 2).

Study 1: A critique and re-analysis of previous meta-analyses

Study selection and comparability

Meta-analyses are meaningful to the extent that the underlying studies can yield comparable estimates of the effect of interest.

 In Li et al [6], study selection criteria are unclear and hard to rationalize. The pooled studies report qualitatively different types of associations: Self-reported crashes in some past period for cannabis ever-users vs never-users [7,8], self-reported crashes in a past period for those with self-reported intoxicated driving episodes in the past vs. those without [9,10], and acute intoxication amongst crash involved and other motorists [11–15]. In addition to the difference in outcome measures, this means that habitual cannabis users who do not drive while intoxicated are placed in the exposed counts extracted from some studies and the control counts extracted from others. The review does not discuss how these differences affect the interpretation of the pooled estimate.

The study selection criteria in Asbridge et al [5] are clearly stated: studies on the association between acute intoxication and traffic crashes resulting in serious injuries or fatalities. To avoid confounding from alcohol, counts are extracted from "no-alcohol" subsamples of the underlying studies.

While the research question in the studies pooled by Asbridge et al are similar, the studies pooled use two distinct methodological approaches that yield incompatible estimators: culpability studies and case-control studies. A case-control study compares the ratio of intoxicated to non-intoxicated drivers amongst those involved in crashes to the same ratio amongst those not involved in crashes. This estimates the increased crash risk associated with acute use. A culpability study uses data on crash-involved drivers only, and compares the ratio of intoxicated to non-intoxicated drivers amongst those judged culpable for their crash to the same ratio amongst those not judged culpable. While this is commonly interpreted as an estimate of the increase in crash risk, it is actually an estimate of the increased risk of *culpable* accidents associated with acute use, which will necessarily be higher than the overall increase in crash risk.

To see this, note that the identifying assumption of culpability studies is "that drivers found non-culpable after a car crash represent a random sample of the general driving population » [16]. By this

assumption, the denominator in the odds-ratio estimator of case-control studies can be proxied by the intoxication odds of the non-culpable drivers, yielding the estimator:

$$\hat{\theta}_A = \frac{\left(culp_+ + nonculp_+\right)/\left(culp_- + nonculp_-\right)}{nonculp_+/nonculp_-}$$

This estimator can be compared to the one used in culpability studies

$$\hat{\theta}_B = \frac{culp_+/culp_-}{nonculp_+/nonculp_-}$$

A simple simulation exercise comparing these two estimators shows that the traditional culpability estimator is biased upwards relative to the underlying true value (see Figure 1). The explanation lies in the identifying assumption of culpability studies, which requires that non-culpable crashes were random and not due to intoxication. Consequently, an intoxicated driver would have the same number of non-culpable, but a raised number of culpable accidents, and the risk increase has to be multiplied by the baseline culpability share[1]. Actual baseline culpability rates in the culpability studies used in Asbridge et al. ranged from 42-76%.

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[1] For adjusted odds-ratios controlling for known confounders, we use $\hat{\theta}_A = \hat{\theta}_B \cdot culp + (1 - culp)$, where culp is the baseline culpability rate in non-intoxicated drivers. This correction fails to reduce the estimator's standard error appropriately, but is sufficient for our purposes.
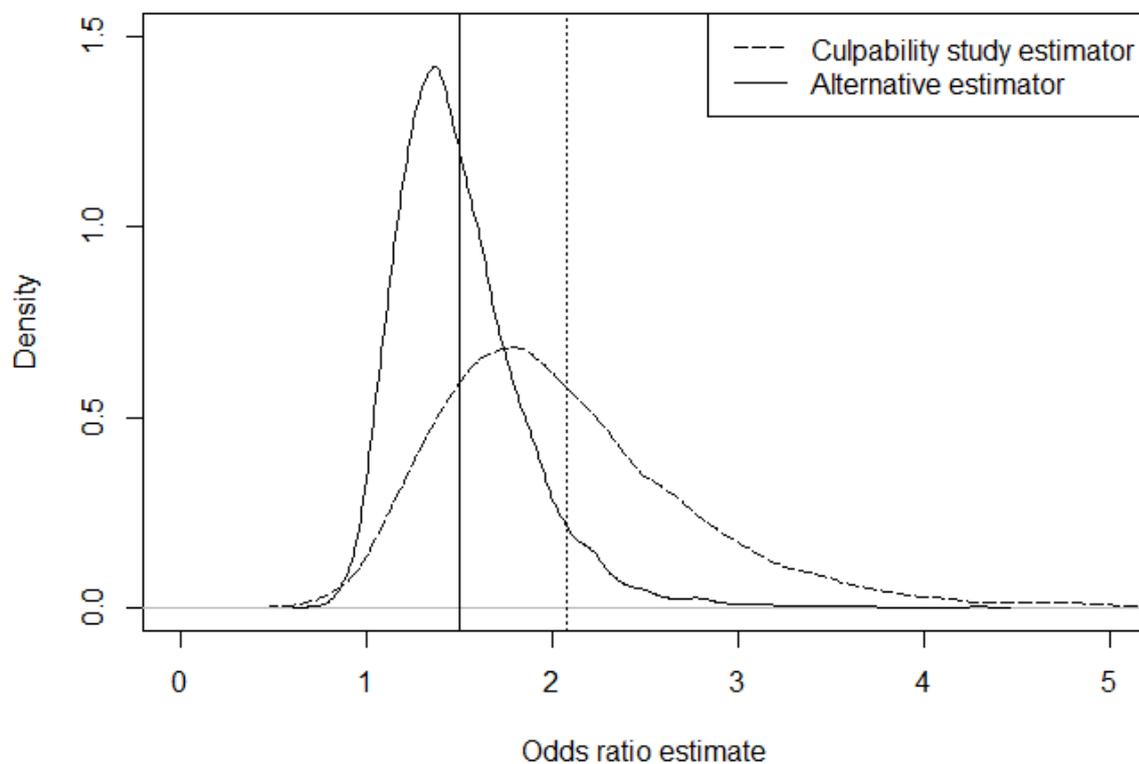
Figure 1 – Compared distributions of estimators from simulated culpability studies. Solid line shows underlying effect, dashed lines show mean value of estimators (line for Alternative estimator mean indistinguishable from solid due to overlap). Assumptions: DUIC and non-DUIC drivers have same risk of non-culpable crash, non-DUIC drivers have 50% culpability rate, DUIC doubles risk of culpable crash. Each simulated study had 500 participants drawn from a multinomial distribution, figure is based on 100 000 simulations. Laplace-correction applied to both estimators.

Data-extraction

We re-extracted counts from the individual studies used in Asbridge et al and Li et al. In some cases, the extracted numbers could not be inferred from or control-checked using the underlying studies and the original study authors were contacted directly.

For Asbridge et al, this resulted in substantial changes (>10%) of extracted OR estimates for four of the nine studies used, all of which were adjusted downwards. For Blows et al [12], Asbridge et al misinterpreted a published table. Accurate counts of cannabis-only and non-intoxicated case and controls had to be requested from the authors of the underlying study, yielding an OR estimate of 2.6 rather than the 7.2 extracted by Asbridge . For Terhune [17], Asbridge et al included the "partly culpable" as culpable – while excluding the same group when extracting counts from Drummer [18]. Excluding them in both cases reduced the Terhune OR from 4.4 to 1.7[2]. The remaining two substantial adjustments were smaller, causing a roughly 20% reduction in the extracted OR [19,20]. In addition, the re-extracted counts caused the total counts extracted from studies to change substantially (>10%) for three studies, with two total counts declining [12,17] and one increasing [20].

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[2] Including the contributory cases would have reduced the OR from Drummer from 3.25 to 3.

In Li et al, substantial (>10%) changes in OR was found only for one study [7], where the correct OR was 1.4 rather than the 2.4 extracted by Li et al. No studies saw substantial changes in total counts after re-extraction of data.

Sparse data bias in odds-ratios

The odds-ratio estimator has a known upward bias when cells have small counts [21–23]. A resampling analysis examined the impact of this for the two meta-reviews. From each study, the (corrected) counts were taken to accurately characterize the underlying case and control populations, and new case and control samples were drawn 10 000 times from this population, each with the same sample size as the original study. Taking the mean of all finite estimates, the results indicate that sparse data bias is an issue with a third of the studies used in Asbridge et al and one in Li et al (Figure 2): Samples of the size used in these studies would be expected to overestimate the underlying risks. Repeating the exercise with Laplace correction of the resampled OR estimates, i.e., adding 1 to each cell count and rescaling all cells proportionately to keep total sample size fixed, largely removed the bias.
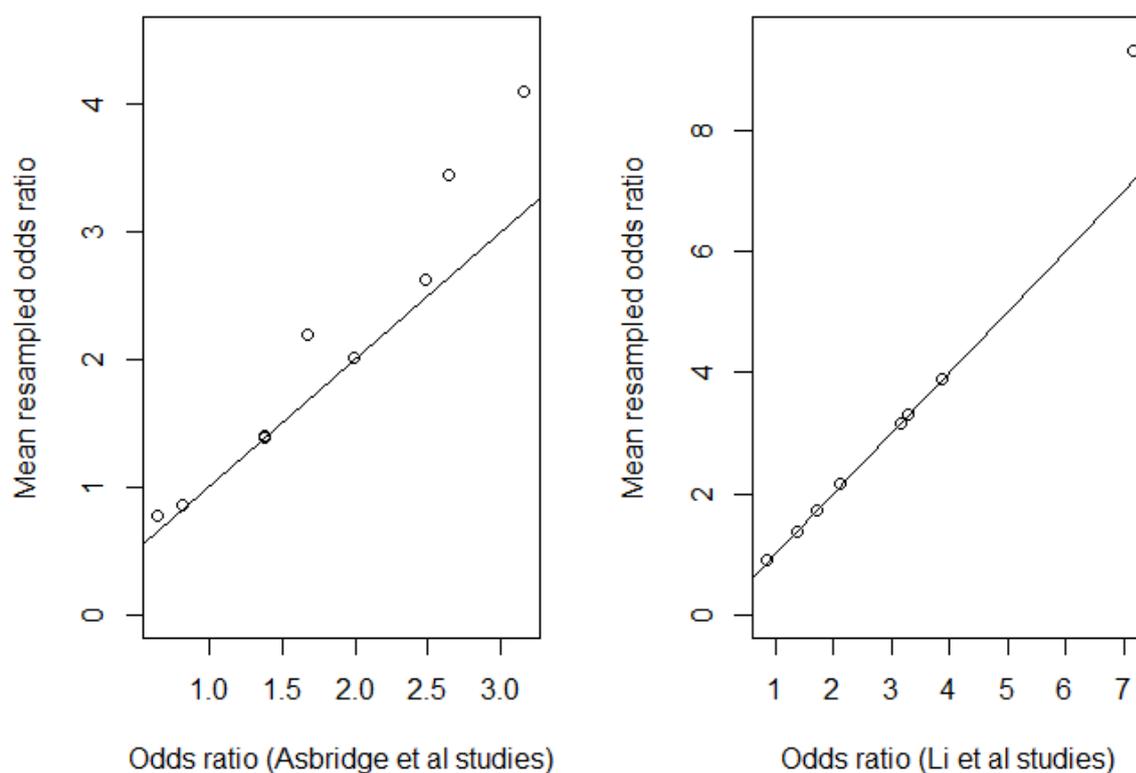
Figure 2 – **Indications of sparse data bias in studies used by Asbridge et al and Li et al. The plots compare the odds ratios calculated from (corrected) counts with means of 10 000 simulated studies of the same size, resampled from the same case and control counts.**

Known and observable confounders

Using cannabis and driving under the influence are behaviours that are more common among young adults and males, groups with higher crash risks irrespective of use. Estimated odds-ratios typically

decline substantially after adjustments for such factors. Despite this, both meta-reviews used case and control counts from individual studies rather than adjusted estimates, although Asbridge et al avoid confounding from alcohol by using "no-alcohol" subsamples. The choice not to use adjusted risks systematically and substantially raises risk estimates, as can be seen by plotting the counts-based odds ratios against the adjusted estimates from the underlying studies where both are available (Figure 3).
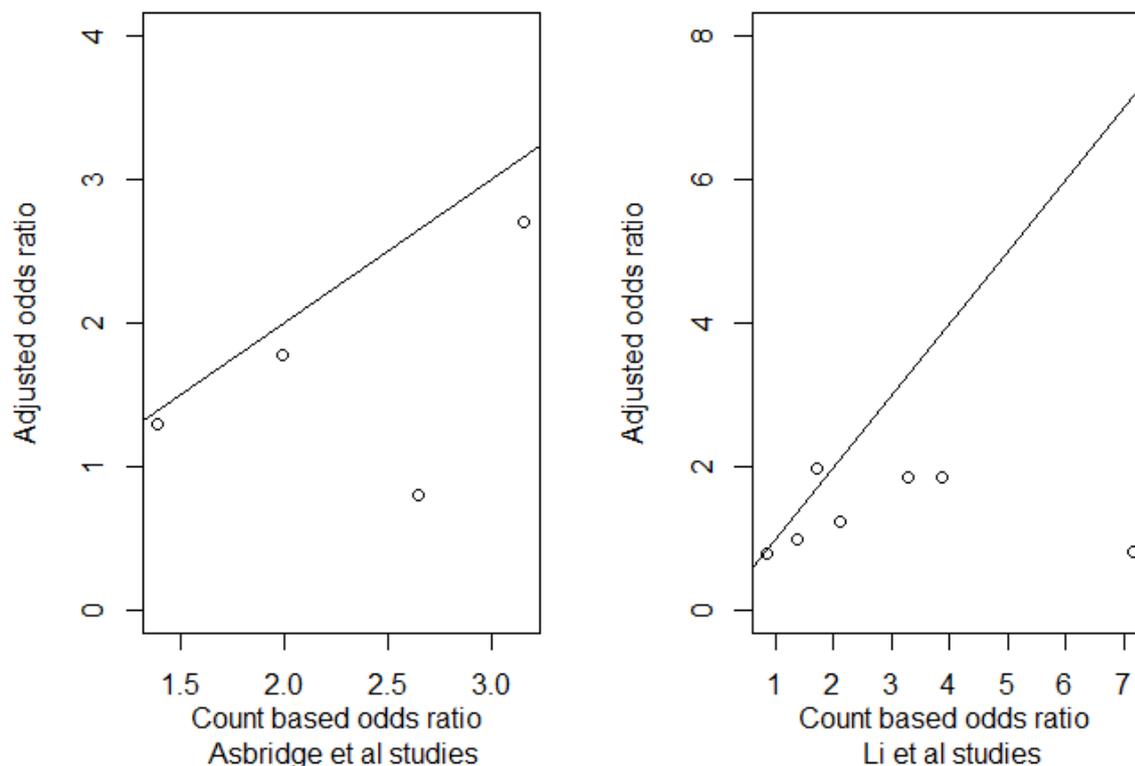
Figure 3 – Crude odds based on corrected counts versus adjusted odds reported in the original studies (for studies where confounder adjusted estimates were reported). Note: For Gerberich [8], used in Li et al, adjusted estimates were reported for men (OR=1.96) and women (OR=1.23) separately. The estimate for men was chosen as they were 72% of the current users in the sample.

Overall impact of methodological issues on pooled estimates

Correcting for the methodological issues noted substantially and systematically revises the pooled estimates downwards (Figure 4)[3]. All pooled analyses use the DerSimonian-Laird Random Effects estimate, using the metafor R-package [24]. Note that the originally reported pooled estimates of both meta-analyses are outside the 95% confidence bands of the revised pooled estimates. For Li et al, however, the main shortcoming remains the lack of clear study selection criteria which gives the resulting pooled estimate no meaningful interpretation.

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[3] For the pooled estimates based on adjusted odds-ratios sparse data bias could not be corrected for.
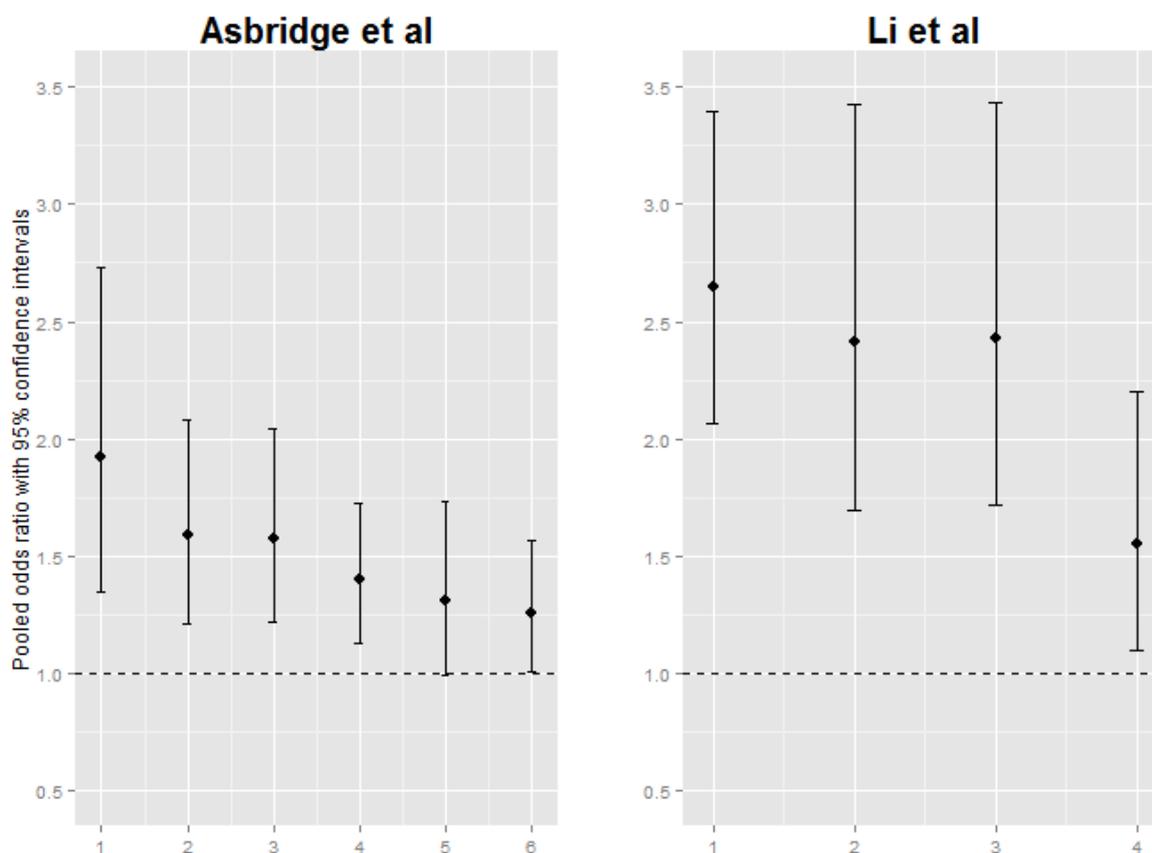
Figure 4 – Pooled estimates after adjustments. Left panel displays results for Asbridge et al (1: Reported counts, 2: Corrected counts, 3: As 2 + Laplace correction, 4: As 3 + adjusted culpability estimator, 5: Adjusted estimates from underlying studies, 6: As 5 + adjusted culpability estimator). Right panel displays results for Li (1: Reported counts, 2: Corrected counts, 3: As 2 + Laplace correction, 4: Adjusted estimates from underlying studies)

Study 2: An updated meta-analysis of cannabis intoxication and traffic risks

Sources

We aimed to include studies using case-control or culpability methods to assess the effects of acute cannabis intoxication on the risks of traffic crashes involving motor vehicles. Studies from before 2011 were identified by pooling the studies identified in Asbridge et al, Li et al, and the cannabis-related studies included in a broader overview of studies on crashes and drugs [25]. Studies published since 2011 were identified using a structured search in Google Scholar and Web of Science.[4] The database was supplemented by reviews of the authors' personal research libraries. In cases with substantial overlap in the data employed, studies reporting estimates after adjustment for relevant confounders and studies with larger sample sizes were preferred (see supplementary material).

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[4](cannabis OR marihuana OR marijuana OR hash OR THC OR cannabinoids OR hashish OR ganja OR hemp OR pot) AND (car OR automobile OR vehicle OR traffic OR road) AND (accident* OR crash* OR collision* OR collide OR injury OR fatal*). The first 500 search results, April 5 2015, were assessed.

Data collection

One author (RE) extracted data from the recent and additional studies, adding these to a database containing extracted data from the studies used in the three earlier meta-reviews. Extracted information included study details (author, year, country, study design), measure of cannabis exposure, and multivariate associations between cannabis and outcomes. For studies without adjusted estimates, subsamples free of alcohol and other drugs were inferred when possible.The other author (OR) checked each result (odds ratios and standard errors) against the original studies, documenting the locations of the information as well as any inferences required (see supporting material).

Quality assessment for individual studies

Study quality was assessed in terms of four criteria [25]:

1. The quality of the information regarding the use of cannabis while driving
2. Specification of crash severity
3. Control for potential confounding factors
4. Test of the presence of a dose-response pattern in the relationship between the dose taken of cannabis and the increase in crash risk

Table 1 explains how the various characteristics of study quality were defined and measured.

Table 1: Quantitative assessment of study quality (from [25])

Study characteristic	Scores assigned	Maximum possible score
Measure of drug use	5 = laboratory analysis of blood samples for all subjects (cases and controls); 4 = laboratory analysis of samples of saliva or mix of blood and saliva; 3 = laboratory analysis of samples of urine or mix of urine and other body fluids; 2 = prescriptions; 1 = self report	5 (25 % of total score)
Specification of crash severity	2 = at least two levels of crash or injury severity included in the same study; 1 = crashes at a specific level of severity (fatal, injury, property damage) included; 0 = a mix of injury crashes and property damage crashes included	2 (10 % of total score)
Control for confounding factors	9 = if all the following potentially confounding factors are controlled for: Age, gender, km driven, drug use history, dose of drug, use of other drugs, use of alcohol, health status (co-morbidity), place of residence

2 = additional points if multiple other potentially confounding factors are controlled for

1 = additional point if one other potentially confounding factor is controlled for | 11 (55 % of total score) |
Test of dose-response	2 = tested and found; 1 = tested but not found; 0 = not tested or not relevant	2 (10 % of total score)
	Scoring of studies	
	Points counted and divided by maximum possible score (20 = 5 + 2 + 11 + 2). Expressed as relative score, e.g. 12/20 = 0.60	

Laboratory analyses of blood samples for all subjects included in a study was rated as providing the best information on acute intoxication while driving. The second best indicator is saliva. Urine is a less informative indicator, since inactive metabolites of cannabis can be detected in samples of urine

a long time after the substance became inactive. Prescription data, which would be more relevant for medicinal drugs than for cannabis, and self-reported use, were regarded as the least reliable data on the use of cannabis.

Several illicit drugs are known to increase the risk of serious crashes more than the risk of less serious crashes. To test whether there is such a severity gradient, a study should estimate crash risk for at least two levels of severity. Evidence regarding a severity gradient based on different studies is less conclusive, since different studies may differ in many ways that influence estimates of crash risk.

Nine potential confounding factors have been listed; in addition to these a study may earn a bonus if it controls for more confounding factors.

Finally, testing for a dose-response pattern, and confirming its existence, is essential if one wants to support causal inferences, i.e. claims that cannabis intoxication is causally, not merely statistically, related to crash occurrence.

Points have been assigned to the various characteristics in Table 1. The use of formal quality scoring is controversial in meta-analysis [26,27]. One may, however, use the study characteristics listed in Table 1 as a screening device, without applying a formal quality scoring.

Synthesis of results

Driving under the influence of cannabis is a behaviour that tends to be concentrated in sub-populations with raised risks of crashes irrespective of cannabis use. It is statistically associated with being a young adult, male, and holding "high-risk" attitudes towards driving and traffic as reflected in, e.g., higher rates of driving under the influence of alcohol [28–31]. For this reason, the adjusted estimates of risk and their associated standard errors were always employed when available.

Subgroup analyses were performed to assess differences associated with study design (culpability vs. case control), study quality, crash severity, the measure of cannabis intoxication used, and whether or not individual studies adjusted for simultaneous alcohol intoxication.

Meta-analyses were performed using two approaches: Random effects modelling using the DerSimonian-Laird estimator in the Metafor R-package [24]. Given the presence of small sample (and possibly publication) bias, we also employ a weighted least squares meta-regression technique (PEESE) that has been shown to handle such biases better than random effects models [32,33]. In addition, trim-and-fill methods were employed to test and correct for publication bias [34–36].

Results

Study selection

The primary criterion for study inclusion was the quality of the information given about cannabis use, in particular if, based on the information given, there was reason to believe that cannabis had been used while driving or recently enough before driving for effects to persist.

The earlier reviews considered 9 [5], 9 [6] and 42 [25] estimates relating to cannabis and traffic crashes. New and additional studies found increased this to a total of 74 risk estimates from 46 studies, of which 28 estimates from 22 studies (Table 2) fit our specified study selection criteria.

Characteristics of included studies

The studies included (table 2) were published between 1982 and 2015. A case-control or culpability design was used in all studies. Nearly all studies estimated the risk of injury accidents or fatal accidents. All studies used the odds ratio as estimator of risk. Use of cannabis was determined by laboratory analysis of body fluids in all studies except one. Studies differed greatly in terms of which potentially confounding variables they controlled for. A minority of studies tried to find a dose-response relationship between the amount of cannabis taken and the size of the change in crash risk.

Risk of bias assessment

The quality of information regarding cannabis use is known to be an issue, in that poor quality (e.g., measuring inactive metabolites in urine) will produce a bias towards zero effect (OR=1). This risk can be assessed using our quality scores: Included studies scored an average of 4.11 on the five point scale for quality of information about cannabis use. Studies not included scored an average of 2.16.

A recent analysis of cannabis-and-traffic studies from a cross-national project highlighted the issues of selection bias, small sample sizes and cell counts [38]. Small sample bias is likely to be an issue for several studies given the typically low count of positive cases and controls, inflating estimates upwards. Selection bias (non-random sampling) in case-control studies are due to non-response rates, particularly from controls stopped in traffic-side stops. Non-response is likely to be more common for potential controls influenced by drugs or alcohol, inflating the odds ratio [39]. In culpability studies using administrative data registers, toxicological testing may be conducted more often when the driver is seen as culpable and/or suspected of intoxication. This can result in both upwards or downwards bias of estimates depending on the details. A related issue present in some studies (e.g. Mura [14] as pointed out in Baldock [40]) is the use of control groups not drawn from non-crash involved drivers, raising issues of comparability.

Table 2: Studies included in the meta-analysis

Reference	Authors	Year	Country	Design	Accident severity	Estimator of risk	Measure of drug use	Confounders controlled (see Table 1)	Dose-response assessed	Dose-response found
[17,37]	Terhune	1983	United States	Culpability	Mostly PDO	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[41]	Williams et al.	1985	United States	Culpability	Fatal	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[19]	Terhune et al.	1992	United States	Culpability	Fatal	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[42]	Longo et al.	2000	Australia	Culpability	Injury	Odds ratio	Lab analysis	Alcohol, other drug use	Yes	Yes
[43]	Lowenstein	2001	United States	Culpability	Injury	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[14]	Mura et al.	2003	France	Case-control	Injury	Odds ratio	Lab analysis	Age, gender	No	No
[11]	Brault et al.	2004	Canada	Case-control	Fatal	Odds ratio	Lab analysis	Age, gender, time of day	No	No
[18]	Drummer et al.	2004	Australia	Culpability	Fatal	Odds ratio	Lab analysis	Age, gender, other drug use, alcohol, type of accident, place of residence	Yes	Yes
[44]	Assum	2005	Norway	Case-control	Mostly fatal	Odds ratio	Lab analysis	Region	No	No
[12]	Blows et al.	2005	New Zealand	Case-control	Injury	Odds ratio	Self report	Age, gender, ethnicity, education, alcohol, km driven, speed, time of day	No	No
[20]	Laumon et al.	2005	France	Culpability	Fatal	Odds ratio	Lab analysis	Age, alcohol, time of day	Yes	Yes
[45]	Mathijssen	2005	Netherlands	Case-control	Injury	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[15]	Woratanarat et al.	2009	Thailand	Case-control	Injury	Odds ratio	Lab analysis	None	No	No
[46]	Kuypers et al	2012	Belgium	Case-control	Serious injury	Odds ratio	Lab analysis	Age gender, time of day	Yes	No
[47]	Hels et al	2011	Denmark, Italy, Netherlands	Case-control	Serious injury	Odds ratio	Lab analysis	Age, gender	No	No
[47]	Hels et al	2011	Lithuania	Case-control	Serious injury	Odds ratio	Lab analysis	None	No	No
[47]	Hels et al	2011	Norway	Case-control	Fatality	Odds ratio	Lab analysis	Age, gender	No	No
[47]	Hels et al	2011	Portugal	Case control	Fatality	Odds ratio	Lab analysis	None	No	No
[48]	Gjerde et al	2013	Norway	Case-control	Fatal	Odds ratio	Lab analysis	Age, gender, region, season, time period, road type	No	No
[49]	Li et al	2013	United States	Case-control	Fatal	Odds ratio	Lab analysis	None	No	No
[50]	Poulsen et al	2014	New Zealand	Culpability	Fatal	Odds ratio	Lab analysis	Age, gender, alcohol, other drug use, license status, vehicle type, road class, crash type	Yes	No
[51]	Romano et al	2014	United States	Case-control	Fatal	Odds ratio	Lab analysis	Alcohol, other drug use	No	No
[52]	Compton et al	2015	United States	Case-control	Mostly PDO	Odds ratio	Lab analysis	Age, gender, ethnicity, alcohol	No	No
[53]	Dubois et al	2015	United States	Culpability	Fatal	Odds ratio	Lab analysis	Age, gender, alcohol, other drug use,	No	No

Primary and secondary analyses

The primary analysis is shown in Figure 5. For culpability studies, point estimates were adjusted using their baseline culpability rates, for studies based on crude counts, Laplace correction was applied.

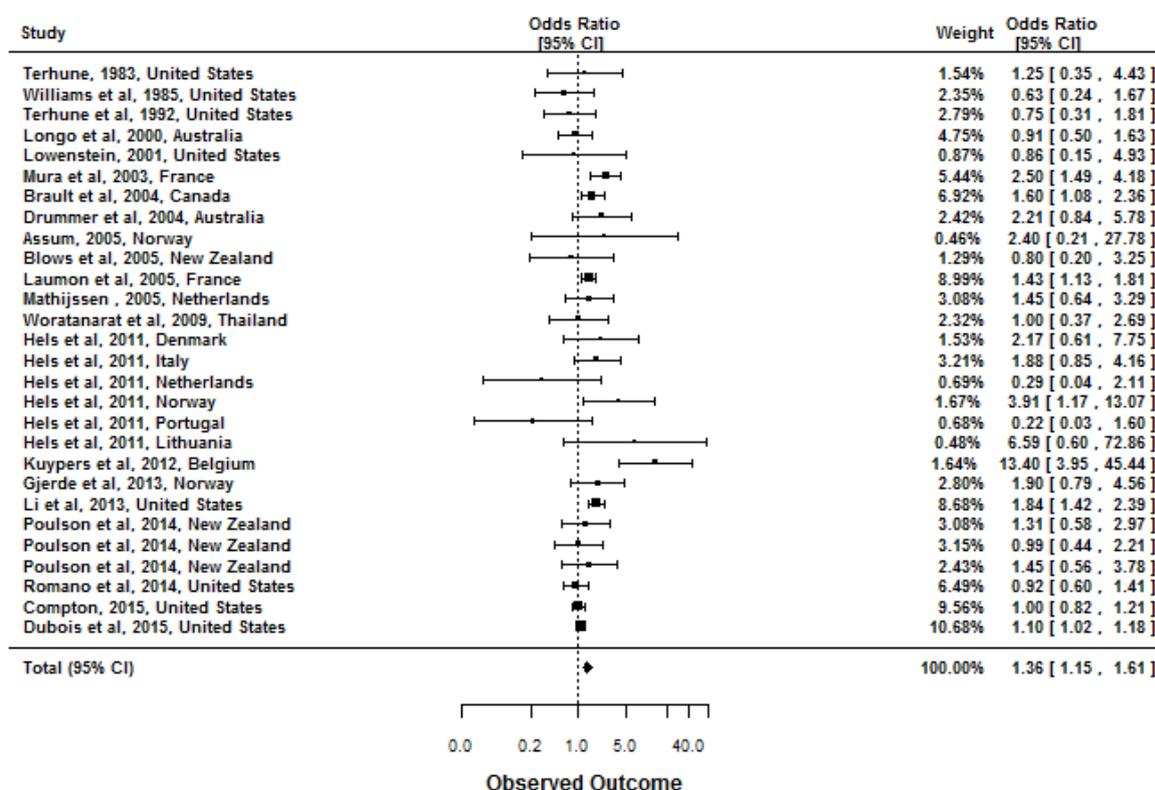| Study	Odds Ratio [95% CI]	Weight	Odds Ratio [95% CI]
Terhune, 1983, United States		1.54%	1.25 [0.35 , 4.43]
Williams et al, 1985, United States		2.35%	0.63 [0.24 , 1.67]
Terhune et al, 1992, United States		2.79%	0.75 [0.31 , 1.81]
Longo et al, 2000, Australia		4.75%	0.91 [0.50 , 1.63]
Lowenstein, 2001, United States		0.87%	0.86 [0.15 , 4.93]
Mura et al, 2003, France		5.44%	2.50 [1.49 , 4.18]
Brault et al, 2004, Canada		6.92%	1.60 [1.08 , 2.36]
Drummer et al, 2004, Australia		2.42%	2.21 [0.84 , 5.78]
Assum, 2005, Norway		0.46%	2.40 [0.21 , 27.78]
Blows et al, 2005, New Zealand		1.29%	0.80 [0.20 , 3.25]
Laumon et al, 2005, France		8.99%	1.43 [1.13 , 1.81]
Mathijssen , 2005, Netherlands		3.08%	1.45 [0.64 , 3.29]
Woratanarat et al, 2009, Thailand		2.32%	1.00 [0.37 , 2.69]
Hels et al, 2011, Denmark		1.53%	2.17 [0.61 , 7.75]
Hels et al, 2011, Italy		3.21%	1.88 [0.85 , 4.16]
Hels et al, 2011, Netherlands		0.69%	0.29 [0.04 , 2.11]
Hels et al, 2011, Norway		1.67%	3.91 [1.17 , 13.07]
Hels et al, 2011, Portugal		0.68%	0.22 [0.03 , 1.60]
Hels et al, 2011, Lithuania		0.48%	6.59 [0.60 , 72.86]
Kuypers et al, 2012, Belgium		1.64%	13.40 [3.95 , 45.44]
Gjerde et al, 2013, Norway		2.80%	1.90 [0.79 , 4.56]
Li et al, 2013, United States		8.68%	1.84 [1.42 , 2.39]
Poulson et al, 2014, New Zealand		3.08%	1.31 [0.58 , 2.97]
Poulson et al, 2014, New Zealand		3.15%	0.99 [0.44 , 2.21]
Poulson et al, 2014, New Zealand		2.43%	1.45 [0.56 , 3.78]
Romano et al, 2014, United States		6.49%	0.92 [0.60 , 1.41]
Compton, 2015, United States		9.56%	1.00 [0.82 , 1.21]
Dubois et al, 2015, United States		10.68%	1.10 [1.02 , 1.18]
Total (95% CI)		100.00%	1.36 [1.15 , 1.61]

Observed Outcome: 0.0 0.2 1.0 5.0 40.0

Figure 5 - Meta-analysis of observational studies investigating the association between acute cannabis consumption and motor vehicle crashes (ordered by year)

A subsample analysis (table 3) was conducted by splitting the studies according to type (case control vs culpability), study quality (low vs medium vs high), control for confounders (limited vs high), use data quality (low vs. medium vs .high), control for alcohol (no vs yes) and crash severity (fatalities involved vs. not). Pooled risks and confidence intervals were calculated within each subsample using both random effects and a PEESE metaregression.

Group	#	Mixed effects model		Meta-regression model (PEES)		
		OR	CI	OR	CI	Publication bias (p-value)
All	28	1.36	[1.15, 1.61]	1.22	[1.1, 1.36]	0.52
Case control	17	1.60	[1.19, 2.15]	1.32	[1.04, 1.68]	0.55
Culpability	11	1.12	[1.05, 1.2]	1.20	[1.08, 1.35]	0.78
High quality	9	1.39	[1.06, 1.83]	1.18	[1.05, 1.34]	0.10
Medium quality	12	1.30	[0.95, 1.78]	1.15	[0.87, 1.51]	0.90
Low quality	7	1.45	[0.97, 2.17]	1.79	[1.34, 2.39]	0.36
Limited or no confounder adjustment	17	1.52	[1.07, 2.15]	1.70	[1.19, 2.41]	0.62
High confounder adjustment	11	1.17	[1.04, 1.33]	1.18	[1.06, 1.31]	0.49
Low quality use data	7	1.07	[0.92, 1.25]	1.08	[0.9, 1.3]	0.83
Medium quality use data	9	1.81	[1.23, 2.66]	1.90	[1.41, 2.55]	0.61
High quality use data	12	1.37	[1.05, 1.79]	1.20	[1.04, 1.39]	0.37
Alcohol controlled	14	1.11	[1.04, 1.18]	1.18	[1.07, 1.3]	0.75
Alcohol not controlled	14	1.79	[1.28, 2.51]	1.69	[1.25, 2.28]	0.90
Fatalities involved	15	1.32	[1.08, 1.61]	1.24	[1.1, 1.4]	0.92
Fatalities not involved	13	1.51	[1.02, 2.24]	1.11	[0.82, 1.49]	0.37

Table 3 – Subgroup analyses

Publication bias

Overall, the PEESE meta-regression technique finds no indication of publication bias in the 28 estimates (p=0.52, see Table 3), indicating a best estimate for the underlying effect of 1.23. The trim and fill method indicated a weak publication bias, with a trimmed mean summary estimate of risk of 1.23, in effect similar to that from the meta-regression model.

Discussion

The replication of Asbridge et al [5] and Li et al [6] in study 1 indicates that their published pooled estimates substantially overestimated the effect of acute cannabis intoxication on crash risk, and that the pooled estimate presented by Li et al is hard to interpret given the qualitatively different estimates pooled. The revised estimate from the studies used in Asbridge et al was in line with the results from the expanded meta-analysis in study 2, lying in between the the pooled odds from the mixed-effects model of 1.36 (CI: 1.15-1.61) and the pooled odds from the PEESE meta-regression of 1.22 (meta-regression model, CI: 1.1-1.36).

The effect sizes found represent an average risk increase for those driving after the use of cannabis. Under a causal interpretation, this suggests that roughly 20-30% of traffic crashes involving cannabis use occur *because* of the cannabis use. By comparison, the comparable "average" relative risk for accidents with fatalities after drinking alcohol has been estimated at 7.5 [54], which would imply that around 85% of crashes involving alcohol occur *because* of alcohol. Assuming causality, the differences can be due to differences in the impairment produced at various consumption levels, and/or differences in the average consumption levels of those choosing to drive after cannabis and alcohol use respectively.

The average effect of 1.2-1.4 found for cannabis is comparable to the increased risk for any traffic crash found for a blood alcohol content (BAC) of 0.04-0.05 [55]. Since alcohol seems to be more reliably linked to an increase in risky driving, however, the risk of crashes resulting in fatalities from a 0.02-0.05 BAC is estimated to rise by 100-360% depending on age and crash type [56]. No comparable increase in the risk of crashes involving fatalities is found in the subsample analysis for cannabis studies (Table 3). This is consistent with results from the experimental literature, which reports that alcohol increases driving speed and risk taking while some cannabis users attempt to compensate for their impairment by driving more cautiously.

While there is heterogeneity across studies, the subsample analyses all show pooled effects in the range of 1.07-1.81 (random effects) and 1.08-1.9 (meta-regression), suggesting that the average risk increase after cannabis use is unlikely to be of the magnitude associated with alcohol. The importance of confounding is particularly evident the subsample analysis for alcohol-confounding, where both methods find an OR below 1.2 when alcohol is controlled for and higher estimates (1.79 and 1.69) when not. Higher estimates are associated with case control studies, low study quality, limited control of confounders, medium quality use data, not controlling for alcohol intoxication.

Alternative interpretations of the results

The causal interpretation of the above results would be that cannabis intoxication has a moderate effect on traffic risks. However, it is important to note that remaining selection effects may bias the estimates in either direction.

Since cannabis users tend to be aware of their impairment [4], this may cause selection on effect: if users are more likely to drive when they judge their impairment to be low, then the estimates above will underestimate the (unobserved) crash risk of the currently non-driving users. This matters: If the low estimates are taken as evidence that "driving after cannabis use" is unproblematic, the new users would tend to be more impaired and have a higher cannabis-induced increase in crash risk.

An opposite bias can result from residual confounding due to selection into cannabis use and selection of users into '"driving after use." In particular, deciding to drive while intoxicated is a decision correlated with traits that predict higher crash risk independently of cannabis use: high speeds, close following, dangerous lane shifts and drunk driving [7,29–31]. This would give estimates an upward bias, in that "driving after cannabis use" functions as an indicator of an underlying high-risk type of driver.

While both types of bias are possible, we note that they predict different patterns across empirical studies. When the share of users who decide to drive after use increases, selection on effect implies that OR estimates increase since the new drivers will have higher risks. Selection into "driving after use" would imply that OR estimates decline, since the new drivers would have lower underlying risk-traits.

Policy implications

The growing interest in the crash risk associated with cannabis use is related to the ongoing debate about cannabis policy. Concerns have been raised that liberalized laws would increase cannabis use, increasing the number of cannabis intoxicated drivers and raising the traffic crash rate. While our estimates suggest that the impact on crash rates would be low to moderate even if this argument were correct, we would stress that such simple extrapolations are unlikely to be robust to larger

policy changes: Driving under the influence of legal cannabis would likely be made a direct target for policy, leading to efforts with documented effects from the alcohol field [57–59]. Cannabis use may also influence traffic risks through other causal channels: an ecological study using the staggered introduction of medical marijuana laws across US states found a net reduction in traffic crashes associated with the introduction of these laws [61]. The authors suggest that this could be due to consumers shifting from alcohol (with high crash risk) to cannabis (with lower crash risk), or due to cannabis users driving less than they would have after drinking (e.g., smoking at home rather than driving to a bar). This underscores the larger policy point that a low-to-moderate causal effect of acute cannabis intoxication on crash rates is likely to play a limited role in the overall policy picture surrounding cannabis legislation.

Conclusions

A comprehensive review of the literature on acute cannabis intoxication and road traffic crashes finds that acute intoxication is related to a statistically significant risk increase of low to moderate magnitude. Higher estimates from earlier meta-reviews were found to be largely driven by methodological issues– in particular the use of counts data without adjustment for known confounders. Correcting for these issues, the pooled estimates from these reviews were in line with the results from the updated and more extensive review. Remaining selection effects discussed in the "alternative interpretations" section may complicate causal interpretations of the pooled estimates.

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