Dose response relationship between blood concentrations of THC and crash culpability risk: meta-regression of culpability studies

Type: Mini review

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Abstract

Recent meta-analyses on the risk associated with the detection of tetrahydrocannabinol (THC) in blood and crash risk indicate a ~10-80% increase in crash culpability for detection of THC. However, the meta-analyses did not analyse a dose-response relationship between blood concentrations of THC and risk necessary to better understand the crash risk associated with THC and to inform public risk tolerances surrounding THC and driving. Here, we leverage these recent meta-analyses to understand whether there is a blood concentration crash culpability risk relationship. We show that crash culpability risk increases with increasing THC concentration, with an inflection around 1.5-3.0 ng/ml where risk begins to increase. There is a doubling of risk around 5 ng/ml, and a potential quadrupling of risk around 10 ng/ml. Conversely, blood THC concentrations below ~1.5 ng/ml indicate practically no risk (<30% increase). More studies are needed to better define risk for the lower and higher bands of blood THC concentrations. Consideration of blood concentration risk relationships are necessary for public discussions surrounding THC and crash risk.

Introduction

Recent meta-analyses on the risk associated with the detection of THC in blood and crash risk have come to the conclusion that there is a 1.1-1.8 odds of an increase in culpability when THC is detected (Rogeberg 2019; Preuss et al. 2021; White and Burns 2021). Interestingly, White and Burns (2021) stated:

> *"Overall, the evidence for THC dose effects from the 17 studies is unconvincing"*

While a review published around the same time by Preuss et al. (2021) stated:

> *"High quality culpability studies (SIGN) noted that there is a dose effect of higher THC blood concentrations with increased risk for fatal crashes and those with injuries."*

Some of the disparity potentially comes from the lack of a formal meta-regression analysis on this same group of papers investigating the blood-concentration crash culpability risk relationship. Indeed, much of the discussion in White et al. (2021) on the lack of relationship is likely due to insufficient power present in any single study to properly identify the association and there was no attempt to formally pool studies that attempted to answer the dose question together into a single meta-regression analysis. Another component to the disparity is because of the high fat solubility of THC, and therefore its distribution kinetics are incredibly divergent between individuals and relates inconsistently to impairment. For example, a recent meta-analysis of neuropsychological performance studies by McCartney et al. (2022) demonstrates a fairly weak relationship between blood THC concentrations and cognitive impairment. Although, the meta-analysis regressed performance on blood THC concentrations using a linear function, when most blood-concentration or dose-response curves are sigmoidal on a logarithmic scale (or hyperbolic on a linear scale). It would also be beneficial to examine more specific domains (e.g., in their previous analysis where they broke down tests into sub-domains: McCartney et al. 2021).

Importantly, the failure to properly separate out blood concentrations and identify risk-curves has led to situations where the "detection"-based association with crash risk is presented as the crash risk for THC. For example, in a recent hearing before the New South Wales State Australian parliament, it was repeatedly stated that the crash risk from THC is a general modest increase of ~40% (Standing Committee on Law and Justice 2022). But this is a detection-only based crash risk, potentially missing important risk stratification for lower and higher blood concentrations of THC. A clearer delineation around blood-concentration crash culpability risk relationships is needed to better inform and calibrate risk tolerances.

Aims

Here, we leverage these recent meta-analyses to show that there is indeed a clear blood concentration crash-risk/culpability relationship. The risk is practically negligible for low concentrations under ~1 ng/ml, but increases to ~4x for concentrations >~10 ng/ml and may be larger for concentrations >~10 ng/ml due to uncertainty.

Methods

Included papers and search

We extracted papers from three recent meta-analyses on THC associations with crash culpability risk (Rogeberg 2019; Preuss et al. 2021; White and Burns 2021). As the previous meta-analyses were thorough in their search criteria and execution, we do not repeat the whole meta-analysis procedure here. We attempted to update the meta-analyses by including more recent papers using the search strategy in White and Burns (2021), amended to focus only on "culpability" or "responsibility" papers through inclusion of these search terms in the search. Search terms are included in the supplementary material (S1). A total of 37 records were retrieved from the initial search across 4 databases (PubMed, PsycInfo, Embase, Scopus), following removal of duplicates (n=15), 23 records remained to be assessed against inclusion criteria. Screening of the abstracts and full text was conducted by MA and HZ independently. No new papers were identified for inclusion.

We sub-selected papers in these meta-analyses that had attempted to better identify blood-concentration relationships with THC by presenting the outcomes from different bands of THC (e.g., <1 ng/ml, 1-5 ng/ml, and >5 ng/ml). Further inclusion criteria were that the papers needed to describe odds ratios adjusted for alcohol (and possibly other covariates) or present THC-alone odds ratios. Data were extracted for each category, and included the concentration band, odds ratio, and 95% confidence interval. Given that the presented data were in categories, we took the midpoint of bounded THC concentration categories and treated unbounded concentration categories by adding 0.5 ng/ml to the lower limit of the unbounded category. We also attempted to find reference in the paper to a median or average THC concentration for the unbounded category, but this was only available in 1 paper.

Table 1 presents the included papers excluding duplicate analyses (Longo et al. 2000; Drummer et al. 2004, 2020; Laumon et al. 2005; Poulsen et al. 2014; Martin et al. 2017; Brubacher et al. 2019).

Table 1. Included papers and data extraction

			THC Concentrations		Odds Ratios			Study Characteristics		
Study	Author	Year	Bands Reported	Value Modelled	Estimate	Lower 95%CI	Upper 95%CI	Sample Size	Severity	Adjusted/ THC-only
1	Drummer et al.	2020	0	0	1			1728	Injured	Adjusted
			1-4.9	2.5	1.6	0.9	2.7	59		
			5-9.9	7.5	1.9	0.7	5	19		
			>5	5.5	3.2	1.3	7.2	31		
			>10	10.5	10	1.3	82	12		
2	Brubacher et al.	2019	0	0	1			1660	Injured	Adjusted
			0-1.9	1	1.09	0.63	1.92	77		
			2-4.9	3.5	1.16	0.66	2.13	68		
			>5	5.5	1.74	0.59	6.36	20		
3	Martin et al.	2017	<1	0	1			3734	Fatal	Adjusted
			1-2.9	2	1.4	0.86	2.23	159		
			3-4.9	4	1.92	0.84	4.42	64		
			>5	5.5	2.47	1.2	5.09	102		
4	Drummer et al.	2004	0	0	1			1704	Fatal	THC-only
			<5	2.5	0.827	0.238	3.78	11		
			>5	5.5	6.6	1.5	28	49		
5	Laumon et al.	2005	0	0	1			9013	Fatal	Adjusted
			<1	0.5	1.57	0.84	2.95	78		
			1-2.9	1.5	1.54	1.09	2.18	298		
			3-4.9	3.5	2.13	1.22	3.73	143		
			>5	5.5	2.21	1.32	3.38	240		
6	Poulsen et al.	2014	0	0	1			533	Fatal	Adjusted
			<2	1.5	1.42	0.63	3.24	88		
			2-4.9	3.5	0.98	0.44	2.21	80		
			>5	5.5	1.61	0.62	4.22	72		
7	Longo et al.	2000	0	0	1			1887	Injured	THC-only
			<1	0.5	0.36	0.07	1.85	7		
			1-2	1.5	0.52	0.2	1.33	19		
			>2.1	2.5	1.79	0.67	4.79	18		

Analysis - Meta-Regression

Data were imported into R version 4.1.1 for analysis. The weights for each odds ratio were derived by calculating the standard error of the $\log_e$ odds ratio ([upper 95% CI – lower 95% CI]/[2 * 1.96]) and taking the inverse square of the $\log_e$ odds ratio standard error ($1/se^2$). The $\log_e$ odds ratios were then entered into a mixed-effects regression model as the dependent variable, with random intercepts and slopes for each study. The fitting of the overall intercept was suppressed and defined as 0 at a $\log_{10}$ THC concentration of –0.8 (~0.16 ng/ml), and a sensitivity analysis was conducted by reducing the value to -2. The intercept suppression was done because – by definition – the control group has an odds ratio of 1 or $\log_e$ odds ratio of 0. The relationship between the $\log_e$ odds ratio and blood concentration of THC was modelled on the $\log_{10}$ scale using a restricted cubic spline with 4 knots, to account for any non-linearity in effect. Knots were located at the 5%, 40%, 60% and 95% quantiles, which corresponded to THC concentrations of 0.5, 2.5, 3.5, and 7.5 ng/ml (on the $\log_{10}$ scale, these were located at -0.30, 0.40, 0.54, and 0.88).

Restricted cubic splines were obtained from the "rms" package (Harrell 2024), fit using the "glmmTMB" package (Brooks et al. 2017), and effects plot using "ggplot2" (Wickham 2016) and the "ggeffects" (Lüdecke 2018) packages.

Table 2 – coefficients for THC from the meta-regression model

Parameter	Estimate	SE	z	p
log(THC)	0.16	0.099	1.57	0.12
log(THC)'	0.64	0.24	2.72	0.0065
log(THC)''	4.84	4.51	1.08	0.28

** log(THC)' and log(THC)'' represents the restricted cubic spline variables*

Results

THC blood concentration and culpability risk relationship

There was a significant relationship between crash culpability risk and blood concentration (X^2_3 = 95.1, p < 0.0001). Restricted cubic spline coefficients for log(THC) predicting $\log_e$(OR) are presented in table 2. Figure 1 shows the blood concentration vs crash risk relationship. Risk increased with increasing THC concentration, with an inflection around 1.5-3 ng/ml and a doubling of risk around 5 ng/ml. Risk was predicted to increase to the available limits of the data at ~10 ng/ml, estimated to confer an increased risk of culpability by 4.0x (95% CI = 3.0 – 5.5).

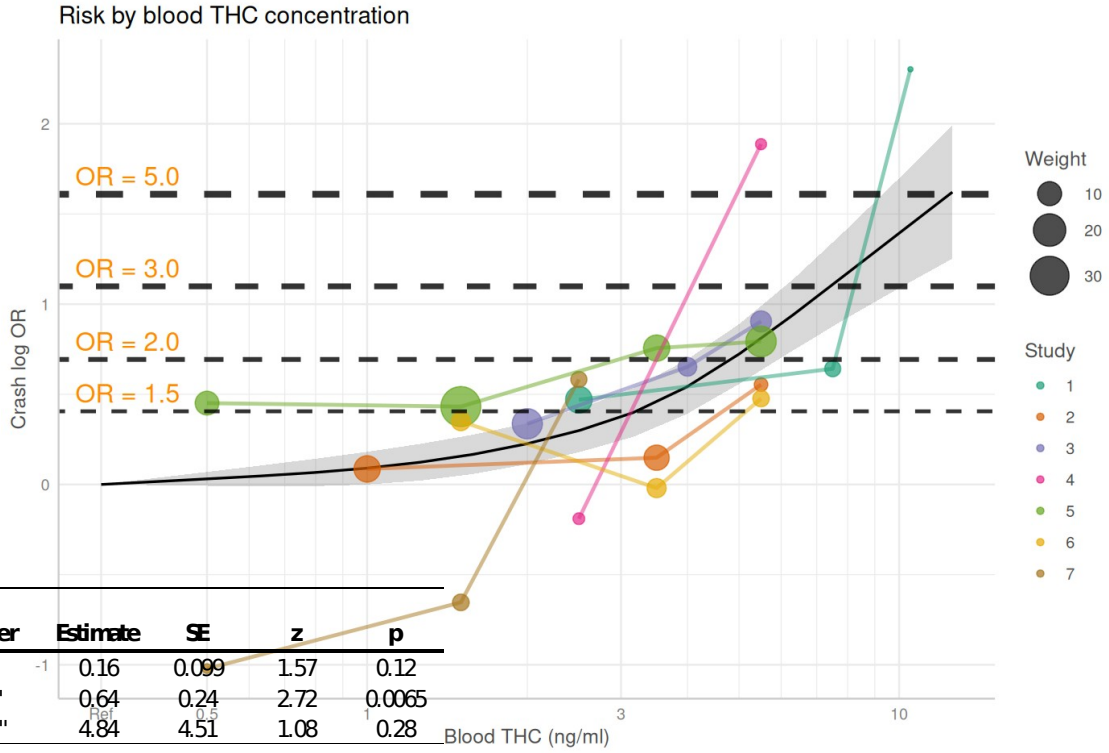

Figure 1 - Culpability risk vs blood concentration of THC. Solid black line is the predicted relationship from the restricted cubic spline with grey shading indicating the 95% CI.

Discussion

We show a robust blood-concentration crash culpability risk relationship for THC. Moreover, nearly every paper shows an increase in risk with increasing concentration. This suggests that previous

failures to demonstrate a concentration-risk relationship are due to low sample sizes for the necessary blood THC concentration bands. Studies that assess risk relationships by categorising studies into THC concentration bands are inadvertently hindering power to detect a relationship; categorising continuous variables reduces power and leads to non-physiological arbitrary cut offs between categories (Bennette and Vickers 2012).

The increased delineation of risk also allows better identification of low-risk concentrations of THC. For concentrations under 1.5 ng/ml, the risk is very modest, probably under 30%. While the exact level of risk that should be publicly accepted is outside the scope of this paper, the clear blood-concentration risk relationship observed when all available studies that have attempted to stratify THC concentrations are analysed, can contribute to risk tolerance discourse. Concentration ranges around ~1.5–2.5 ng/ml shows the threshold upswing in the curve, with a cross-over to a crash risk of ~2x around a concentration of 5.0 ng/ml and ~4x around 10 ng/ml. This is roughly similar to the culpability risk associated with a blood alcohol concentration of 0.08-0.10 (Høye and Storesund Hesjevoll 2023).

Limitations

There is a restricted number of studies that have delineated the upper end of blood THC concentrations on crash risk. Additionally, studies very rarely report the delay between the collection time of the sample and the time of the incident. Reporting sample/incident delays is crucial for determining whether the concentration of THC at the time of the incident may be substantially higher. Failure to report sampling delays also misses important key considerations about quantity and recency of use that likely elevate risk. Future studies should aim to report more detailed groupings of blood THC concentrations and the delays between obtaining a sample and the incident.

Conclusion

These results indicate that the blood-concentration risk relationship is relatively well-defined for THC. Questions remain surrounding how much of an increased risk is associated with a high blood concentration of THC, i.e., does the risk continue to increase beyond ~10 ng/ml or does risk plateau around an OR of 4. Similarly, low blood THC concentrations are consistent with other papers associating detection of any THC with risk, and estimates a < 30% increase in risk for THC < 1.5 ng/ml. Dose-response relationships should be considered for future discussions surrounding THC and crash risk.

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Supplementary Material

S1 – Search

PubMed

“Accidents, Traffic”[mh]
OR
(“Motor Vehicles”[mh] or (“Automobiles”[mh] OR car[tw] OR cars[tw] OR automobile*[tw] OR vehicle*[tw] OR vehicular[tw] OR traffic*[tw] OR road[tw] OR off-road[tw]) AND (accident*[tw] OR crash*[tw] OR collision*[tw] OR collide*[tw] OR injury[tw] OR injuries[tw] OR fatal*[tw]))
AND
“Cannabis”[mh] OR “Cannabinoids”[mh] OR “Marijuana Smoking”[mh] OR “Marijuana Use”[mh] OR hemp[tw] OR cannabis[tw] OR marihuana[tw] OR marijuana[tw] OR pot[tw] OR hash[tw] OR hashish[tw] OR ganja[tw] OR thc[tw] OR tetrahydrocannabinol[tw]
AND
(culpab* OR responsib*)
Limit: English, 2020>

PsycInfo

motor traffic accidents/
OR
(motor vehicle/ or car/ or (car or cars or automobile* or vehicle* or vehicular or traffic* or road or "off-road").tw.) and (accident* or crash* or collision* or collide* or injury or injuries or fatal*).tw.
AND
exp cannabis/ or exp cannabinoids/ or "cannabis use"/ OR (hemp OR cannabis OR marihuana OR marijuana OR pot OR hash OR hashish OR ganja OR thc OR tetrahydrocannabinol).tw.
AND
(culpab* OR responsib*)
Limit: English, 2020>

Embase

traffic accident/
OR
(motor vehicle/ or car/ or (car or cars or automobile* or vehicle* or vehicular or traffic* or road or "off-road").tw.) and (accident* or crash* or collision* or collide* or injury or injuries or fatal*).tw.
AND
cannabis/ or exp cannabinoids/ or "cannabis use"/ or cannabis smoking/ OR (hemp OR cannabis OR marihuana OR marijuana OR pot OR hash OR hashish OR ganja OR thc OR tetrahydrocannabinol).tw.
AND
(culpab* OR responsib*)
Limit: English, 2020>

Scopus

Title/Abstract/Keyword
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AND
hemp OR cannabis OR marihuana OR marijuana OR pot OR hash OR hashish OR ganja OR thc OR tetrahydrocannabinol
AND

(culpab* OR responsib*)
Limit: English, 2020>