Neuroscience and Biobehavioral Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Are blood and oral fluid Δ^9-tetrahydrocannabinol (THC) and metabolite concentrations related to impairment? A meta-regression analysis

Danielle McCartney [a,b,c,*], Thomas R. Arkell [d], Christopher Irwin [e], Richard C. Kevin [a,b,c], Iain S. McGregor [a,b,c]

[a] The University of Sydney, Lambert Initiative for Cannabinoid Therapeutics, Sydney, New South Wales, Australia
[b] The University of Sydney, Brain and Mind Centre, Sydney, New South Wales, Australia
[c] The University of Sydney, Faculty of Science, School of Psychology, Sydney, New South Wales, Australia
[d] Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, Victoria, Australia
[e] Menzies Health Institute Queensland and School of Health Sciences and Social Work, Griffith University, Gold Coast, Queensland, Australia

ARTICLE INFO

Keywords:
Cannabis
Driving
Drug driving
Per se limits
Biomarker relationships
Impairment
Cognition
Cannabinoid
THC

ABSTRACT

Blood and oral fluid Δ^9-tetrahydrocannabinol (THC) concentrations are often used to identify cannabis-impaired drivers. We used meta-analytic techniques to characterise the relationships between biomarkers of cannabis use, subjective intoxication, and impairment of driving and driving-related cognitive skills. Twenty-eight publications and 822 driving-related outcomes were reviewed. Each outcome was measured in concert with one or more biomarkers of cannabis/THC use and/or subjective intoxication. Higher blood THC and 11−OH-THC concentrations, oral fluid THC concentrations and subjective ratings of intoxication were associated with greater impairment in 'other' (mostly occasional) cannabis users (p's<0.05). Blood 11−COOH-THC concentrations were associated with impairment after inhaling, but not orally ingesting, cannabis/THC. However, these 'biomarker–performance' relationships (R) were only *very weak* (blood $THC_{post\text{-}ingestion}$: -0.08; blood $THC_{post\text{-}inhalation}$: -0.10; blood 11−OH-$THC_{post\text{-}ingestion}$: -0.13), *weak* (blood 11−OH-$THC_{post\text{-}inhalation}$: -0.24; oral fluid $THC_{post\text{-}inhalation}$: -0.36; subjective intoxication: -0.29) or *moderate* (blood 11−COOH-$THC_{post\text{-}inhalation}$: -0.43) in strength. No significant biomarker-performance relationships were observed in 'regular' (weekly or more often) cannabis users (p's>0.10), although the analyses were less robust. Blood and oral fluid THC concentrations are relatively poor indicators of cannabis/THC-induced impairment.

1. Introduction

The number of individuals performing safety-sensitive tasks such as driving (e.g., motor vehicles, heavy machinery) after recent cannabis use is likely to increase as legislation restricting cannabis use is relaxed (Chow et al., 2019). Accurate methods of identifying cannabis-impaired drivers in the public domain and workplace are therefore of growing importance.

The different methods used to identify cannabis-impaired drivers can be broadly categorised as: effect-based, zero-tolerance and *per se*. Effect-based methods test for functional impairment (e.g., using field sobriety tests), while zero-tolerance and *per se* methods test for Δ^9-tetrahydrocannabinol (THC: the main intoxicating component of cannabis (Banister et al., 2019)) and/or THC metabolites in biological specimens (typically blood or oral fluid). Under the zero-tolerance approach, it is an offence to drive with *any amount* of THC in a biological specimen. In some instances, prohibition also extends to THC-metabolites (e.g., 11−OH-THC, 11−COOH-THC). In contrast, *per se* methods prohibit driving *at or above* a predefined concentration, analogous to a legal blood alcohol concentration (BAC) limit.

Seven US states currently use *per se* methods to identify and prosecute cannabis-impaired drivers (Chow et al., 2019; Wong et al., 2014) with "legal limits" for whole blood THC, 11−OH-THC and 11−COOH-THC ranging between 1–5 ng·mL^{-1} (Arkell et al., 2020a). *Per se* limits are also enforced in several European countries (Chow et al., 2019), including Norway which has a three-tiered sanction system with limits of 1.3, 3 and 9 ng·mL^{-1} (Pasnin and Gjerde, 2021). Some jurisdictions (e.g., Australia) and workplaces use zero-tolerance methods but enact *per se* limits in practice through the use of point-of-collection testing devices (e.g., Securetec DrugWipe® 5S) that have elevated

* Corresponding author at: Lambert Initiative for Cannabinoid Therapeutics, Brain and Mind Centre, University of Sydney, Camperdown, NSW, 2050, Australia.
E-mail address: danielle.mccartney@sydney.edu.au (D. McCartney).

https://doi.org/10.1016/j.neubiorev.2021.11.004
Received 6 September 2021; Received in revised form 29 October 2021; Accepted 5 November 2021
Available online 9 November 2021

limits of detection (e.g., ~10 ng·mL^{-1} of THC in oral fluid (Arkell et al., 2020a; McCartney et al., 2021a).

The validity of the *per se* approach is contingent upon a strong and meaningful relationship between the relevant biomarker(s) and 'impairment'. Such a relationship is readily seen with BAC, which has been shown to correlate well with driving performance (indexed by standard deviation of lateral position [SDLP], a well-established marker of impaired driving (Verster and Roth, 2011; Irwin et al., 2017) and relative crash risk (Blomberg et al., 2005). However, the relationships between different THC-related biomarkers and measures of driving performance (or driving-related cognitive skills, e.g., tracking, reaction time, divided attention, information processing) appear more complex with higher blood THC, 11−OH-THC and 11−COOH-THC concentrations and oral fluid THC concentrations associated with increased impairment in some, but not all, studies (Arkell et al., 2020a; Ramaekers et al., 2006; Vandrey et al., 2017; Schlienz et al., 2020). Further research characterising these 'biomarker–performance' relationships is therefore required. Notably, a large-scale analysis combining data from studies employing different research methods (e.g., THC doses) should provide useful insights since *per se* limits are enforceable regardless of the circumstances surrounding a positive test.

Here, we used meta-analytic techniques to better characterise the relationships between THC-related biomarkers and impairment of driving and driving-related cognitive skills. The relationship between subjective ratings of intoxication and impairment was also examined as individuals using cannabis should self-evaluate their fitness to drive regardless of the regulatory approach being applied. The strength of this relationship might better inform public health advice on the optimal strategies individuals should use to determine fitness to drive (e.g., subjective feelings *vs* objective measures of impairment).

2. Methods

Studies investigating the acute effects of cannabis/THC (hereafter termed THC) on driving performance and driving-related cognitive skills were collated in a recent systematic review (McCartney et al., 2021b). The review used meta-analytic techniques to: (1) determine which aspects of driving and cognitive performance were susceptible to impairment; and (2) model the relationship between 'impairment' (quantified as Hedges' *g*) and contextual factors (e.g., type of "skill" assessed, participants' cannabis use behaviour, THC dose, route of administration, post-treatment time interval). The same set of driving and cognitive performance data (i.e., Hedges' *g* effect estimates) were used in the current review. However, some additional eligibility criteria were applied to investigate the relationships between THC-related biomarkers, subjective intoxication, and impairment; the literature search was also updated to capture recent publications. Hence, the methods used to derive these data are only briefly described here (see McCartney et al., (2021b) for full details). The current analyses were not conducted in the previous review as they were of limited relevance to its primary aim.

2.1. Literature search

Studies were identified by searching the online databases Web of Science (Thomas Reuters) and Scopus from the year 2000 until April 2020 using the Boolean expression: (cogniti* OR driving OR drive OR "processing speed" OR "reaction time" OR vigilance OR "executive function" OR memory OR psychomotor OR tracking OR perception) AND (cannabinoid* OR cannabis OR marijuana OR tetrahydrocannabinol OR THC OR nabiximols OR Sativex OR dronabinol OR marinol OR namisol) as described elsewhere (McCartney et al., 2021b). The literature search from the previous review (McCartney et al., 2021b) was updated on the 18th of October 2021.

2.2. Eligibility criteria

Studies that measured either simulated or on-road driving performance, or a discrete cognitive skill related to driving, ≤12 h following a single, acute dose of THC in a placebo-controlled experimental trial were eligible for inclusion in the previous review (McCartney et al., 2021b). For the current review, studies also had to have: (1) been eligible for inclusion in the quantitative synthesis of McCartney et al., (2021b) (see Sect. 2.6.3 of McCartney et al., (2021b)); (2) administered THC via inhalation or oral ingestion; (3) measured performance on an eligible domain (see Sect. 2.3 'Performance Outcomes'); and (4) measured and reported subjective intoxication and/or one or more THC-related biomarkers at an appropriate time relative to the performance test(s) (see Sect. 2.5 'Data Extraction').

Studies were excluded if: (1) THC was administered in combination with another treatment; (2) more than one dose of THC was administered prior to the performance test(s); (3) either the dose of THC administered or length of time between THC administration and the performance test(s) was not reported; (4) results were reported in another included paper; or (5) performance data were not adequately reported as described elsewhere (McCartney et al., 2021b).

If a study contained multiple "intervention-arms", where more than one was eligible for inclusion, the separate "arms" were treated as discrete studies, termed trials.

2.3. Performance outcomes

The following driving-related cognitive "skills" (hereafter termed *Performance Domains*) were included in the previous review (McCartney et al., 2021b): (1) Divided Attention; (2) Tracking Performance; (3) Information Processing; (4) Executive Function (subcategorised as Conflict Control and Fluid Intelligence); (5) Reaction Time; (6) Motor Function (subcategorised as Fine and Gross Motor Function); (7) Perception (subcategorised as Sensory Discrimination and Time Perception); (8) Sustained Attention; and (9) Working Memory. The following measures of driving performance were also included: Lateral Control, SDLP (Only), Speed, Speed Variability, Car Following (CF) Headway, CF Headway Variability, Reaction Time and Other (e.g., scanning frequency).

However, as McCartney et al. (2021b) were unable to determine the effect of THC on Gross Motor Function and Other (driving) and found no significant effect of THC on Sensory Discrimination, Time Perception, Speed, Speed Variability, CF Headway or CF Headway Variability, these domains were omitted from the current review. Performance Domains that were not included in the previous (separate) meta-regression analyses of oral and inhaled THC's effects in 'Other Cannabis Users' (see Sect. 2.5 'Data Extraction') (e.g., as there was limited data) were also excluded as these models were used in the current investigation (see Sect. 2.6.2 'Meta-Regression Analysis'). That is, the Fluid Intelligence, Lateral Control, SDLP (Only) and Reaction Time (driving) domains were omitted when oral THC was administered to Other Cannabis Users and the Fine Motor Function, Fluid Intelligence, Lateral Control and Reaction Time (driving) domains were omitted when inhaled THC was administered to Other Cannabis Users. As the previous review was unable to model THC's effects in 'Regular Cannabis Users' (see Sect. 2.5 'Data Extraction'), all Performance Domains (except those where the effect of THC was unknown or non-significant) were accepted for this population and analysed in an exploratory fashion without controlling for the influence of Performance Domain (see Sect. 2.6.2 'Meta-Regression Analysis').

Each driving-related cognitive performance test was reviewed and categorised into a Performance Domain as described elsewhere (McCartney et al., 2021b).

2.4. Quality assessment

The methodological quality of included studies was assessed using the Rosendal scale (see Table II in Van Rosendal et al. (2010)) as described elsewhere (McCartney et al., 2021b).

2.5. Data extraction

Data were extracted as described elsewhere (McCartney et al., 2021b). The following methods relevant to the current review should also be noted:

Eligible studies must have measured subjective intoxication, or a THC-related biomarker at an 'appropriate' time relative to the performance test(s). Measures were considered appropriate if: (1) the test (or cognitive battery) took ≤10 min to complete and the measure(s) was taken within 20 min of the start time (or, within 10 min if the test was performed <1 h post-treatment and THC was inhaled); or (2) if the test (or cognitive battery) took >10 min to complete and the measure(s) was taken within 20 min of the mid-way point (or, within 10 min if the test was performed <1 h post-treatment and THC was inhaled) or, within 20 min of the test starting and finishing (values were then averaged over time). Tests were assumed to last ≤10 min unless otherwise stated.

Acceptable measures of 'subjective intoxication' included ratings of '*intoxication*', '*strength of drug effect*' (or similar) and '*high*'; preferenced in this order (if more than one scale was used). All mean scores were converted to a 0–100 scale.

Mean plasma and serum THC, 11−OH-THC and 11−COOH-THC concentrations were divided by conversion factors of 1.5, 1.6 and 1.7, respectively to approximate equivalent whole blood concentrations for analysis (Giroud et al., 2001).

The terms used to describe participants' cannabis use behaviour are defined in Table 2 of McCartney et al., (2021b). Each participant population was categorised based on the range of use behaviours exhibited by its participants. These categories were collapsed into two main groups for all analyses: *Regular Cannabis Users* (which included populations of Daily Users, Weekly Users and Weekly–Daily Users) and *Other Cannabis Users* (all other populations).

2.6. Data synthesis

2.6.1. Hedges' g effect estimates

Hedges' *g* effect estimates were calculated by standardising the mean difference between control (placebo) and intervention (THC) performance scores against either the standard deviation (SD) of the performance change (SD_{Δ}) (corrected for correlation) (if a within-subject design was used) or the pooled SD (SD_{pooled}) (if a between-subject design was used) and correcting for bias due to small sample size as described elsewhere (McCartney et al., 2021b). Variances were derived via standard methods (Borenstein et al., 2011). Negative effect estimates were used to signify an impairing effect of THC irrespective of the performance outcome.

Unless either raw data, the SD_{Δ}, or a *p*-value (or *t*-statistic) derived from a paired *t*-test was reported (or provided on request), the SD_{Δ} was estimated using the mean correlation coefficient ($R = 0.530$) as described elsewhere (McCartney et al., 2021b). (Raw data were available for two of the studies identified in the updated literature search (Arkell et al., 2020b; Spindle et al., 2021)). Sensitivity analyses were performed using values calculated at $R = 0.2$ and $R = 0.8$ to determine the robustness of the imputed *R*.

2.6.2. Meta-regression analysis

Four-level restricted maximum likelihood meta-regression analyses were performed to investigate the relationships between different THC-related biomarkers, subjective intoxication, and impairment of driving and driving-related cognitive skills. A two-level analysis is equivalent to a traditional random effects analysis (where there is only one random effect) (Assink and Wibbelink, 2016). We added random effects to account for dependency among effect estimates derived from the same studies and trials. The four sources of variance modelled were therefore: (1) the sampling variance for the observed effect estimates; (2) the variance between effect estimates derived from the same studies; (3) the variance between effect estimates derived from different trials in the same studies; and (4) the variance between studies.

Only one covariate (i.e., either subjective intoxication or a THC-related biomarker) was included in each meta-regression model. However, effect estimates were manually adjusted (prior to analysis) to control for the influence of Performance Domain; that is, domain-specific differences in sensitivity to THC's effects. This was done by subtracting the relevant meta-regression coefficient from each effect estimate (e.g., the Reaction Time coefficient was subtracted from effect estimates obtained on Reaction Time performance tests) and adding the average meta-regression coefficient to each value[1] ; the adjusted effect estimates therefore represent a standardised performance domain with average sensitivity to THC's effects. All coefficients were obtained from the previous (separate) meta-regression analyses of oral and inhaled THC's effects in Other Cannabis Users (see Table 8 of McCartney et al., (2021b)). The previous models were used (in favour of new models) because these were developed using a larger data set than was available for the current review. As the previous review was unable to model THC's effects in Regular Cannabis Users, the data for this population were analysed in an exploratory fashion without controlling for Performance Domain. This precluded a 'combined analysis' incorporating data from Regular and Other Cannabis Users. Those data obtained after inhaling (i.e., smoking, vaporising) and orally ingesting THC were also separated to investigate the relationships between THC-related biomarkers and impairment. This was done because oral and inhaled THC have strikingly different pharmacokinetic profiles (Vandrey et al., 2017; Spindle et al., 2019) and the multi-level analyses employed might otherwise have masked this 'pharmacokinetic variance' (i.e., the different levels and routes of administration always 'overlap' with one another making their effects difficult to disentangle).

All statistical analyses were performed using R Studio (version 4.0.1); the accompanying R scripts are available in Supplementary File 4. Meta-regression analyses were performed using the metafor-package (Viechtbauer, 2010) with syntax adapted from Assink and Wibbelink (2016). Effect estimates were weighted as described elsewhere (Viechtbauer, 2010); weightings were proportionate to the variance in performance, only (not in THC-related biomarkers or subjective intoxication). Statistical significance was attained if the 95 % CI did not include zero. Heterogeneity was assessed using Cochran's Q, the I^2-index and the within-cluster and between-cluster variance components (i.e., σ_1^2, σ_2^2 and σ_3^2). Significant heterogeneity was indicated by a *p*-value <0.05 for Cochran's Q (Borenstein et al., 2011).

Non-meta-analytic multilevel correlation analyses were used to approximate the strength of the linear relationship (correlation coefficient, *R*) between each covariate and 'impairment' (i.e., adjusted Hedges' *g*; described above). While pseudo-R^2 is typically used to assess goodness of fit in meta-regression analysis, this approach proved inappropriate in the current instance as some initial (un-moderated) models contained less variance than the final (moderated) model, yielding erroneous pseudo-R^2 values. These multilevel correlation analyses (which account for dependency among effect estimates derived from the

[1] For example, the Reaction Time coefficient derived from the analysis of inhaled THC's effects in Other Cannabis Users (–0.1080) was subtracted from all effect estimates obtained on Reaction Time performance tests in studies where inhaled THC was administered to Other Cannabis Users (and so forth, using the relevant meta-regression coefficient for each effect estimate). The average meta-regression coefficient across all Performance Domains (i.e. –0.1328 where inhaled THC was administered to Other Cannabis Users), was then added to each value.

same studies and trials but do not 'weight' effect estimates as meta-regression does) were performed using the correlation package (Makowski et al., 2019). Correlations were interpreted as 'very weak' (R <0.2), 'weak' (R = 0.2−0.4), 'moderate' (R = 0.4−0.6), 'strong' (R = 0.6−0.8), and 'very strong' (R >0.8) (Swinscow, 1997).

3. Results

3.1. Overview of included studies and study quality

Twenty-eight publications (n = 824 participants; 71 % male) were included in this review. These publications measured a total of 822 eligible outcomes across 57 trials; that is, there were 822 instances where the effects of THC were measured in concert with subjective intoxication and/or one or more THC related-biomarkers. In all, 768 outcomes had a corresponding measure of subjective intoxication; 768 had blood THC, 211 had blood 11−OH-THC and 152 had blood 11−COOH-THC concentrations; and 45 outcomes had a corresponding measure of oral fluid THC concentration. Outcomes are summarised by Cannabis Use Behavior, Route of THC Administration and Performance Domain in Tables 1 & 2 . The study selection process is detailed in Supplementary File 1 and summarised in Fig. 1. The quality assessment generated a Mean ± SD Rosendal score of 70 ± 10 % (53–93 %) (Supplementary File 2).

3.2. Meta-regression and correlation analyses of THC effects

The characteristics of the included studies are summarised in Supplementary File 3 with the results of the meta-regression analyses summarised in Table 3 and Figs. 2 & 3 . The results of the sensitivity analyses are presented in Supplementary File 5.

3.2.1. Other Cannabis users

Higher blood THC, 11−OH-THC and 11−COOH-THC concentrations and oral fluid THC concentrations were associated with increased impairment (i.e., more negative Hedges' g effect estimates) after *inhalation* of THC in Other (i.e., mostly occasional) Cannabis Users (Table 3; Fig. 2). However, a significant amount of residual heterogeneity was present in each analysis. Correlations (R [95 % CIs]) were very weak (blood $THC_{post\text{-}inhalation}$: -0.10 [-0.19, -0.01]), weak (blood 11−OH-$THC_{post\text{-}inhalation}$: -0.24 [-0.38, -0.08]; oral fluid $THC_{post\text{-}inhalation}$: -0.36 [-0.59, -0.08]) and moderate (blood 11−COOH-$THC_{post\text{-}inhalation}$: -0.43 [-0.58, -0.25]) in strength.

Higher blood THC and 11−OH-THC concentrations, but not blood 11−COOH-THC concentrations, were associated with increased impairment after *ingestion* of THC in Other Cannabis Users (Table 3; Figs. 2 & S1). However, (1) a significant amount of residual heterogeneity was present in the analysis of THC; and (2) the initial (unmoderated) versions of the remaining analyses (11−OH-THC and 11−COOH-THC) demonstrated a high degree of homogeneity, making it difficult to determine the influence of a particular covariate. All correlations (R [95 % CIs]) were very weak (blood $THC_{post\text{-}ingestion}$: -0.08 [-0.19, 0.04]; blood 11−OH-$THC_{post\text{-}ingestion}$: -0.13 [-0.46, 0.24]; blood 11−COOH-$THC_{post\text{-}ingestion}$: <0.01 [-0.45, 0.44]) in strength. No eligible studies measured oral fluid THC concentrations after ingestion of THC.

Higher subjective ratings of intoxication were associated with increased impairment after ingestion/inhalation of THC (combined) in Other Cannabis Users (Table 3; Fig. 2). However, a significant amount of

Table 2
The number of outcomes (effect estimates) for which a corresponding measurement of subjective intoxication or oral fluid THC concentration was obtained per Cannabis Use Behavior, Route of THC Administration and Performance Domain.

	Subjective Intoxication (Total effect estimates = 570)			Oral Fluid THC (Total effect estimates = 45)		
	Other		Regular	Other		Regular
Performance Domain	Inhaled	Oral	Inhaled	Inhaled	Oral	Inhaled
Divided Attention	111	74	4	8	0	0
Tracking Performance	77	37	7	12	0	0
Information Processing	82	58	4	8	0	0
Conflict Control	12	0	5	9	0	0
Fluid Intelligence	- [a]	- [a]	0	- [a]	- [a]	0
Reaction Time	15	2	0	0	0	0
Fine Motor Function	- [a]	26	4	- [a]	0	0
Sustained Attention	15	12	12	0	0	0
Working Memory	114	76	8	8	0	0
SDLP (Only)	5	- [a]	8	0	- [a]	0
Reaction Time (Driving)	- [a]	- [a]	0	- [a]	- [a]	0
Total Outcomes	431	285	52	45	0	0

Inhaled: Inhaled THC; Oral: Oral THC; Other: Other Cannabis Users; Regular: Regular Cannabis Users; SDLP: Standard Deviation of Lateral Position. *a*: Performance domain is ineligible for inclusion as per Sect. 2.3 'Performance Outcomes'. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction'. Details of the included studies are presented in Supplementary File 3. Nb. No eligible studies measured oral THC's effects in Regular Cannabis Users.

Table 1
The number of outcomes (effect estimates) for which a corresponding measurement of blood THC, 11−OH-THC or 11−COOH-THC concentration was obtained per Cannabis Use Behavior, Route of THC Administration and Performance Domain.

	Blood THC (Total effect estimates = 568)			Blood 11-OH-THC (Total effect estimates = 195)			Blood 11-COOH-THC (Total effect estimates = 135)		
	Other		Regular	Other		Regular	Other		Regular
Performance Domain	Inhaled	Oral	Inhaled	Inhaled	Oral	Inhaled	Inhaled	Oral	Inhaled
Divided Attention	115	70	4	19	0	4	16	0	4
Tracking Performance	79	35	7	38	0	7	26	0	7
Information Processing	84	59	4	12	3	4	12	0	4
Conflict Control	12	0	1	20	0	1	17	0	1
Fluid Intelligence	- [a]	- [a]	0	- [a]	- [a]	0	- [a]	- [a]	0
Reaction Time	15	5	0	16	5	0	1	2	0
Fine Motor Function	- [a]	26	4	- [a]	18	4	- [a]	18	4
Sustained Attention	15	5	12	7	5	12	4	0	12
Working Memory	118	70	0	30	0	0	18	0	0
SDLP (Only)	5	- [a]	8	2	- [a]	4	2	- [a]	4
Reaction Time (Driving)	- [a]	- [a]	0	- [a]	- [a]	0	- [a]	- [a]	0
Total Outcomes	443	285	40	144	31	36	96	20	36

Inhaled: Inhaled THC; Oral: Oral THC; Other: Other Cannabis Users; Regular: Regular Cannabis Users; SDLP: Standard Deviation of Lateral Position. *a*: Performance domain is ineligible for inclusion as per Sect. 2.3 'Performance Outcomes'. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction'. Details of the included studies are presented in Supplementary File 3. Nb. No eligible studies measured oral THC's effects in Regular Cannabis Users.

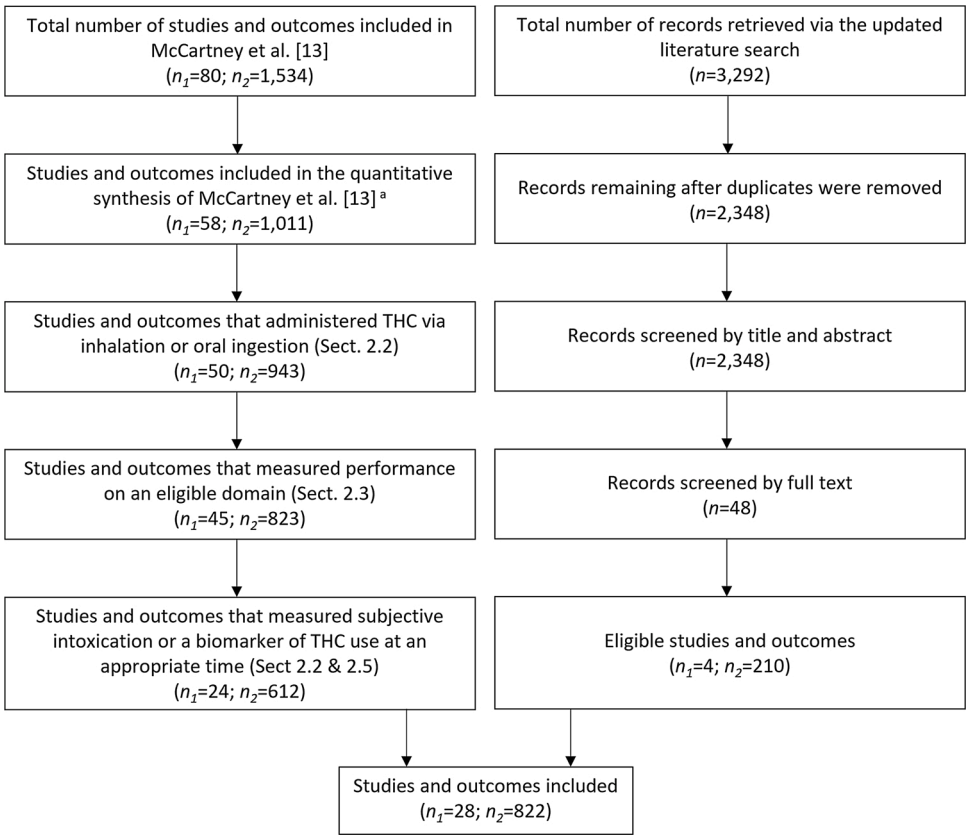

Fig. 1. Study Selection. *a*: Outcomes that were not adequately reported, derived from studies of clinical populations, or derived from studies that scored <50 % on the methodological quality assessment (see McCartney et al. (2021b) Supplementary File 2) were ineligible for quantitative synthesis; *b*: Several studies reported their oral fluid THC and blood cannabinoid concentrations in separate papers (i.e., from their performance test results) as referenced here: (Ramaekers et al. (2006); Arkell et al. (2019b)). n_1: number of studies; n_2: number of outcomes (effect estimates). Excluded studies are listed in Supplementary File 1. Note: Studies were only excluded if they did not contain any eligible outcomes (meaning that some excluded outcomes are derived from included studies).

residual heterogeneity was present in the analysis. The correlation (*R* [95 % CIs]) was weak (-0.29 [-0.36, -0.22]) in strength.

3.2.2. *Regular Cannabis users*

Blood THC, 11−OH-THC and 11−COOH-THC concentrations and subjective ratings of intoxication were not associated with impairment after *inhalation* of THC in Regular Cannabis Users (Table 3; Fig. 3). However, the initial (un-moderated) versions of these analyses demonstrated a high degree of homogeneity, making it difficult to determine the influence of a particular covariate. All correlations (*R* [95 % CIs]) were very weak in strength (blood $THC_{post\text{-}inhalation}$: +0.09 [-0.23, +0.39]; blood 11−OH-$THC_{post\text{-}inhalation}$: <0.01 [-0.33, +0.33]; blood 11−COOH-$THC_{post\text{-}inhalation}$: -0.05 [-0.37, +0.28]; subjective intoxication: -0.02 [-0.29, +0.26]). No eligible studies of regular cannabis users measured oral fluid THC concentrations at an appropriate time relative to the performance test(s) or administered THC via the oral route.

4. Discussion

Per se concentrations of THC and THC-metabolites are often used to identify cannabis-impaired drivers on public roads and in the workplace. Yet, research validating the relationships between THC-related biomarkers, subjective intoxication, and impairment of driving and driving-related cognitive skills is relatively limited (Arkell et al., 2020a; Ramaekers et al., 2006; Vandrey et al., 2017; Schlienz et al., 2020). The current investigation used meta-analytic techniques to better characterise these relationships in 'regular' (i.e., weekly, or more often) and 'other' (i.e., mostly occasional) cannabis users.

The current meta-regression analyses identified significant, linear relationships between most THC-related biomarkers (i.e., blood THC, 11−OH-THC and 11−COOH-THC concentrations and oral fluid THC concentrations) and impairment of driving and driving-related cognitive skills in occasional cannabis users. However, each analysis (except one without initial heterogeneity) contained a significant amount of residual heterogeneity, suggesting that these biomarkers have only a limited capacity to predict impairment. In fact, most of these 'biomarker–performance' relationships were found to be weak in strength (R<0.4). Blood THC concentration was the poorest correlate of impairment demonstrating a 'very weak' relationship after both ingestion (R=-0.08) and inhalation (R=-0.10) of THC. Indeed, it is possible that blood THC concentrations do not accurately reflect brain THC concentrations (Hložek et al., 2017), which may be more closely related to impairment. In any case, these findings suggest that some cannabis-impaired drivers may be mistakenly identified as not-meaningfully-impaired (and vice-versa) when *per se* limits are used to identify impairment.

The 'strongest' (although still only 'moderate', R = 0.43) biomarker–performance relationship observed was for the inactive metabolite, 11−COOH-THC (after inhalation of THC). This finding was unexpected given that 11−COOH-THC is non-intoxicating, but could reflect differences in the pharmacokinetics of THC, 11−OH-THC, and 11−COOH-THC. Indeed, while blood THC and 11−OH-THC concentrations peak and then decline rapidly following inhalation of THC, blood 11−COOH-THC concentrations decline *gradually* (Vandrey et al., 2017; Spindle et al., 2019). This trajectory may better match the time course of impairment – even if 11−COOH-THC is not contributing to the impairment. It is worth noting, however, that 11−COOH-THC persists in blood for prolonged periods following THC use (e.g. > 7-days (Karschner et al., 2009)) – well beyond the usual period of impairment (i.e., ~3–10 -hs) (McCartney et al., 2021b). Studies employing longer assessment periods (e.g., >12-hs) would therefore be expected to observe weaker relationships. In addition, no significant relationship was observed between blood 11−COOH-THC concentration and impairment after ingestion of THC (although this analysis was less robust).

A previous meta-regression analysis investigating the relationship

Table 3
Results of the meta-regression analyses in Other and Regular Cannabis Users.

Covariate	Effect Estimates (*n*)	Hedges' *g* (95% CIs)	*p*-value	Initial Heterogeneity[a] (*p*-value)	Residual Heterogeneity				
					p-value	I^2-value	σ_1^2	σ_2^2	σ_3^2
Analyses of Other Cannabis Users (Oral THC):									
Intercept	–	−0.212 (-0.334, -0.091)	<0.001	$p<0.001$	$p=0.006$	36.3	0.000	0.011	0.011
Blood THC	270	−0.047 (-0.081, -0.014)	0.006						
Intercept	–	0.194 (-0.215, 0.604)	0.340	$p = 0.841$	$p=0.994$	18.2	<0.001	0.002	0.009
Blood 11-OH-THC	31	−0.224 (-0.437, -0.010)	0.040						
Intercept	–	0.515 (-1.059, 2.089)	0.501	$p = 0.979$	$p=0.985$	0.2	<0.001	<0.001	<0.001
Blood 11-COOH-THC	20	−0.044 (-0.130, -0.042)	0.294						
Analyses of Other Cannabis Users (Inhaled THC):									
Intercept	–	−0.352 (-0.489, -0.216)	<0.001	$p<0.001$	$p<0.001$	63.1	0.004	0.006	0.055
Blood THC	442	−0.004 (-0.007, -0.001)	0.017						
Intercept	–	−0.283 (-0.420, -0.150)	<0.001	$p<0.001$	$p = 0.002$	40.7	0.010	<0.001	0.027
Blood 11-OH-THC	144	−0.095 (-0.133, -0.057)	<0.001						
Intercept	–	−0.159 (-0.389, 0.070)	0.172	$p<0.001$	$p<0.001$	64.0	0.013	0.002	0.063
Blood 11-COOH-THC	96	−0.033 (-0.050, -0.017)	<0.001						
Intercept	–	−0.220 (-0.391, -0.048)	0.013	$p = 0.002$	$p=0.038$	38.4	0.020	0.020	0.007
Oral Fluid THC	45	−0.001 (-0.001, -0.001)	0.007						
Analyses of Other Cannabis Users (Oral and Inhaled THC):									
Intercept	–	−0.171 (-0.262, -0.080)	<0.001	$p<0.001$	$p<0.001$	47.5	0.003	0.005	0.027
Subjective Intoxication	728	−0.004 (-0.005, -0.003)	<0.001						
Analyses of Regular Cannabis Users (Inhaled THC):									
Intercept	–	−0.274 (-0.443, -0.105)	0.002	$p = 0.896$	$p = 0.893$	14.4	<0.001	<0.001	0.012
Blood THC	40	0.005 (-0.008, 0.018)	0.468						
Intercept	–	−0.323 (-0.496, -0.150)	<0.001	$p = 0.941$	$p=0.938$	5.1	<0.001	0.004	<0.001
Blood 11-OH-THC	36	0.020 (-0.049, 0.089)	0.583						
Intercept	–	−0.340 (-0.520, -0.161)	<0.001	$p = 0.941$	$p=0.948$	6.4	<0.001	0.005	<0.001
Blood 11-COOH-THC	36	0.002 (-0.004, 0.008)	0.429						
Intercept	–	−0.203 (-0.502, 0.095)	0.178	$p = 0.075$	$p=0.108$	30.9	0.015	0.003	0.011
Subjective Intoxication	52	−0.002 (-0.007, 0.004)	0.531						

'-': Not applicable. *a*: All covariates were omitted from these analyses. Details of included studies are summarised in Table 1 & 2 and presented in Supplementary File 3. No eligible studies measured oral fluid THC concentrations in Regular Cannabis Users.

between BAC and SDLP puts the current findings in a wider context. This analysis identified a significant relationship between BAC and SDLP with BAC explaining a high proportion ($R^2 = 0.8–1.0$) of the variance observed (Irwin et al., 2017). Such observations support the use of *per se* limits in identifying alcohol-intoxicated drivers and demonstrate the validity of a key biomarker–performance relationship that is enshrined in current legislation. It is important to acknowledge that unlike this earlier analysis of BAC and SDLP, the current investigation incorporated a range of different driving-related outcome measures. These measures could have differed in their sensitivity to THC's effects and introduced additional variance into the analyses, thus, reducing the strength of the relationships observed. However, effect estimates were adjusted to control for the influence of Performance Domain. Very few studies have measured the effects of THC on SDLP in combination with a relevant (and appropriately timed) biomarker (Arkell et al., 2019a; Brands et al., 2019; Micallef et al., 2018; Hartman et al., 2015; Ronen et al., 2010; Fares et al., 2021). Further research using simulated and on-road driving methods (or other measures that have a known relationship with driving performance) would permit better characterisation of the relationships between THC-related biomarkers and driving impairment.

Previous studies investigating the relationships between THC-related biomarkers and impairment of driving and driving-related cognitive skills have generated somewhat inconsistent results (Arkell et al., 2020a; Ramaekers et al., 2006; Vandrey et al., 2017; Schlienz et al., 2020). For example, (Arkell et al., 2020a) found no significant relationship between the change (from placebo) in SDLP and plasma or oral fluid THC concentrations (τ_b= -0.011 & -0.033) following vaporisation of THC (13.75 mg; $n = 14$). Whereas (Schlienz et al. (2020)) observed a number of significant correlations (ranging from weak to strong in strength) between the change (from placebo) in performance on two discrete cognitive tests and blood THC, 11−OH-THC and 11−COOH-THC concentrations following oral ingestion of THC (10, 25 & 50 mg; $n = 17$). Other studies have reported a mixture of weak, significant and non-significant correlations between similar biomarkers and outcome measures (Ramaekers et al., 2006; Vandrey et al., 2017). This inconsistency could partly reflect the fact these studies have administered

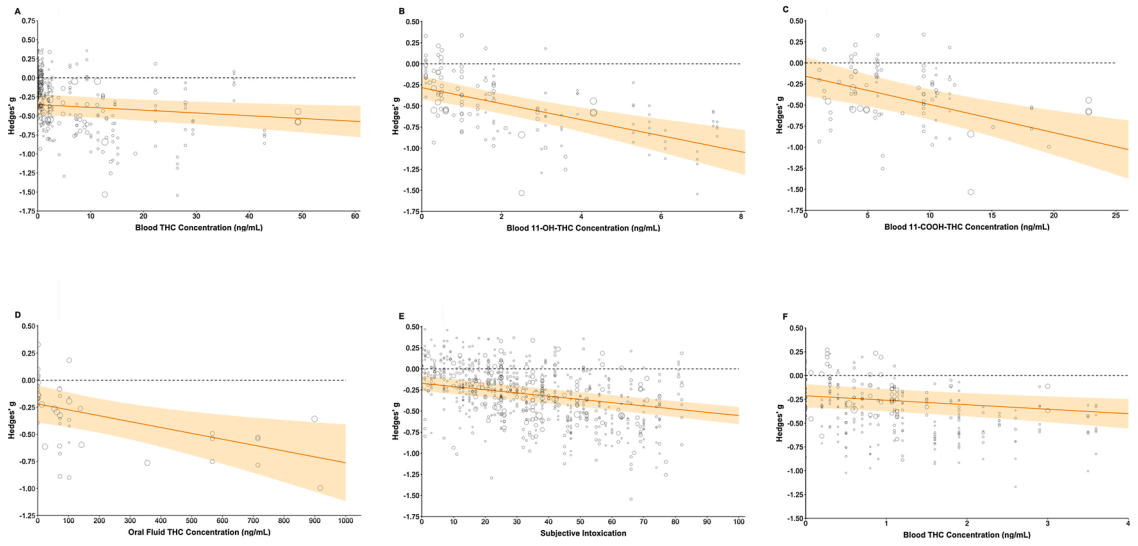

Fig. 2. The predicted relationships between blood (A) THC, (B) 11−OH-THC and (C) 11−COOH-THC concentration post-inhaled THC, (D) oral fluid THC concentration post-inhaled THC, (E) subjective intoxication and (F) blood THC concentration post-ingested THC and the Hedges' *g* (95 % CI) effect of THC on driving and driving-related cognitive skills in Other Cannabis Users (per the analyses presented in Table 3). Dashed line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Negative effect estimates indicate an impairing effect of THC. The predicted relationships between blood 11−OH-THC and 11−COOH-THC concentration post-ingested THC and the Hedges' *g* (95 % CI) effect of THC on driving and driving-related cognitive skills in Other Cannabis Users can be found in Supplementary File 5.

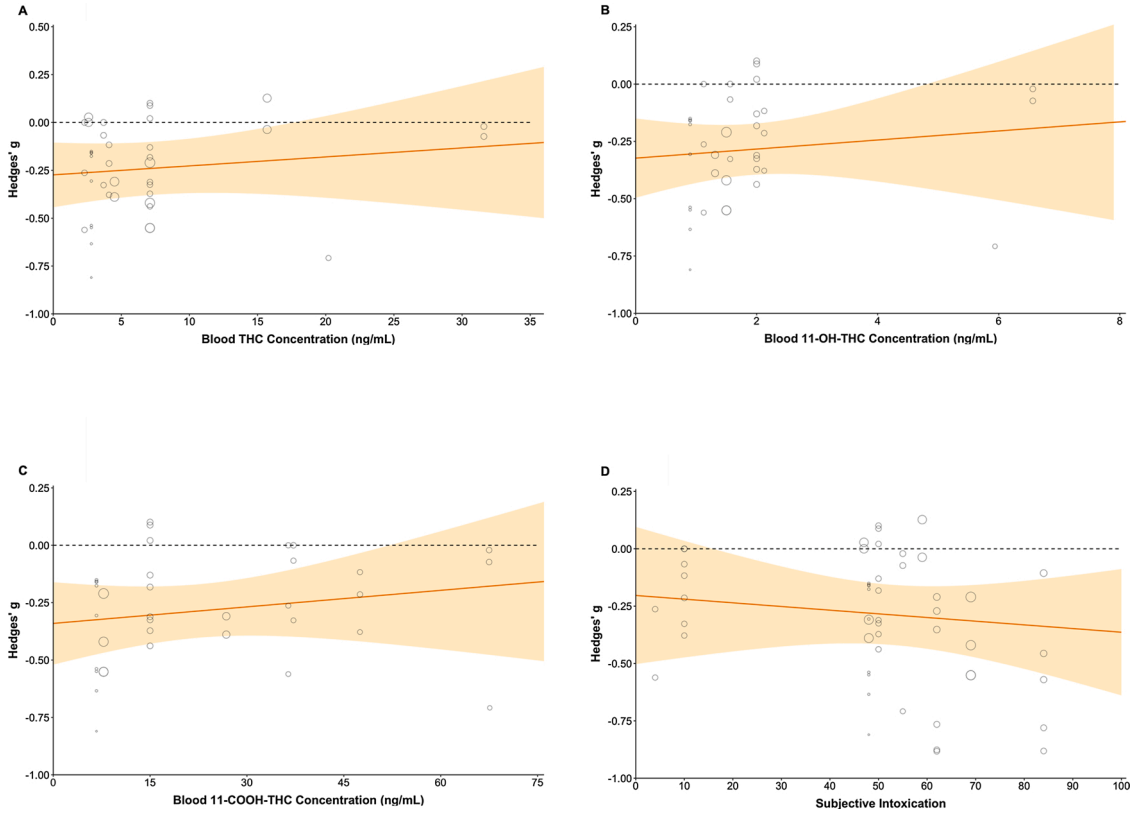

Fig. 3. The predicted relationships between blood (A) THC, (B) 11−OH-THC and (C) 11−COOH-THC concentration post-inhaled THC and (D) subjective intoxication post-inhaled THC and the Hedges' *g* (95 % CI) effect of THC on driving and driving-related cognitive skills in Regular Cannabis Users (per the analyses presented in Table 3). Dashed line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Negative effect estimates indicate an impairing effect of THC.

fixed doses of THC, via fixed routes, at fixed times relative to their performance test(s). The 'fixing' of these factors may impact the amount of variance in the dataset, potentially masking correlations or making them appear more pronounced. The current analyses, which incorporate data from studies using different research methods, should provide a more ecologically-valid representation of the variable conditions under

which people might use cannabis and therefore yield more generalisable results. That said, the observed biomarker–performance relationships would have been more representative if data derived from regular and occasional cannabis users and data obtained after inhalation and oral ingestion of THC could have been combined in a single analysis, and if the sample had had a more balanced distribution of male and female participants. Indeed, it is important to acknowledge that almost three-quarters of the current sample were male (71 %) and that some recent studies have observed sex differences in both the pharmacokinetics and subjective effects of THC (Sholler et al., 2021; Cooper and Haney, 2014).

The current meta-regression analyses also identified a significant, linear relationship between subjective intoxication and impairment of driving and driving-related cognitive skills in occasional cannabis users. As with the biomarkers, however, impairment varied to a greater extent than this covariate could explain with the relationship found to be 'weak' in strength ($R = 0.29$). This suggests occasional cannabis users may have difficulty self-evaluating their fitness to drive following THC use. A recent study by some of the current authors found that occasional users rated themselves impaired even when their on-road driving performance (SDLP) had normalised ~4–5 h after vaporising cannabis (Arkell et al., 2020c). Previous research also suggests that subjective intoxication is a poor predictor of BAC and alcohol-induced impairment (Starkey and Charlton, 2014). Individuals should therefore be encouraged to utilise objective measures of impairment (e.g., computerised applications such as the DRUID task (Spindle et al., 2021; Richman and May, 2019)) and to wait a minimum length of time (e.g., ~3–10 -hs, depending on the dose and route of administration (McCartney et al., 2021b)) following THC use before performing safety-sensitive tasks such as driving.

While some significant biomarker–performance relationships were observed in occasional cannabis users, none were detected in regular cannabis users. These findings suggest *per se* limits are unlikely to be effective in distinguishing between impaired and unimpaired (or not-meaningfully-impaired) regular cannabis users. This compromises the validity of *per se* limits in general; that is, it is inappropriate to have a regulatory framework that lacks validity in a key target demographic (i.e., regular cannabis users). Several factors might account the observed differences between regular and other cannabis users, including that: (1) regular cannabis users appear to be less sensitive to the impairing effects of THC than occasional cannabis users (McCartney et al., 2021b; Colizzi and Bhattacharyya, 2018); and (2) THC-related biomarkers (i.e., from prior cannabis use) can persist in biological matrices for prolonged periods of time (Karschner et al., 2009).

Caution is advised, however, as these data on regular cannabis users were analysed in an exploratory fashion without controlling for the influence of performance domain. The initial (un-moderated) (and subsequent moderated) versions of these meta-regression models also demonstrated a high degree of homogeneity, making it difficult to determine the influence of a particular covariate. This homogeneity could be due, in part, to the limited amount of data available on regular cannabis users. Further research involving regular cannabis users, including *medicinal cannabis users*, is therefore warranted. Indeed, patients using legal (i.e., prescribed) medicinal cannabis products in countries such as Australia, where they are not exempt from roadside drug testing (Arkell et al., 2021), are greatly impacted by *per se* limits and zero tolerance legislation. These individuals may also exhibit different biomarker–performance relationships, particularly if THC ameliorates clinical symptoms that impair driving performance (e.g., pain, insomnia).

One additional limitation of this investigation is that the variance in THC-related biomarkers or subjective intoxication was not incorporated in the multi-level meta-regression models; that is, weightings are proportionate to the variance in driving-related outcome measures, only. Of course, if these were, indeed, good indicators of impairment, and concentrations varied within a population, the population would be expected to perform less consistently. This additional variance would then be captured in the current weightings.

5. Conclusion

The current investigation used meta-analytic techniques to characterise the relationships between THC-related biomarkers, subjective intoxication, and impairment of driving and driving-related cognitive skills in regular and occasional cannabis users. Results indicate that blood THC, 11−OH-THC and 11−COOH-THC concentrations, oral fluid THC concentrations, and subjective ratings of intoxication are relatively poor indicators of cannabis-induced impairment. The use of *per se* limits as a means of identifying cannabis-impaired drivers should therefore be re-considered. Indeed, it seems there is a significant risk of unimpaired individuals being mistakenly identified as 'cannabis-impaired' (and vice-versa) under this approach.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Danielle McCartney and Iain S. McGregor receive salary support from the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for medicinal cannabis research at the University of Sydney.

Declaration of Competing Interest

Iain S.McGregor has acted as an expert witness in legal cases relating to the duration of impairment with cannabis and the use of biomarkers to detect cannabis-induced impairment.

Acknowledgements

This research was not funded by a specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, D. M., R.C.K. and I.S.M. receive salary support from the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for medicinal cannabis research at the University of Sydney.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.11.004.

References

Arkell, T.R., et al., 2019a. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology 236 (9), 2713–2724.
Arkell, T.R., et al., 2019b. Detection of Δ9 THC in oral fluid following vaporized cannabis with varied cannabidiol (CBD) content: an evaluation of two point-of-collection testing devices. Drug Test. Anal. 11 (10), 1486–1497.
Arkell, T.R., et al., 2020a. The failings of per se limits to detect cannabis-induced driving impairment: results from a simulated driving study. Traffic Inj. Prev. 1–6.
Arkell, T.R., et al., 2020b. Effect of cannabidiol and? 9-Tetrahydrocannabinol on driving performance: a randomized clinical trial. JAMA - Journal of the American Medical Association 324 (21), 2177–2186.
Arkell, T.R., et al., 2020c. Effect of cannabidiol and Δ9-Tetrahydrocannabinol on driving performance: a randomized clinical trial. JAMA 324 (21), 2177–2186.
Arkell, T., McCartney, D., McGregor, I., 2021. Medical cannabis and driving. Australian Journal for General Practitioners 50, 357–362.
Assink, M., Wibbelink, C.J., 2016. Fitting three-level meta-analytic models in R: a step-by-step tutorial. Quant. Methods Psychol. 12 (3), 154–174.
Banister, S.D., et al., 2019. Dark classics in chemical neuroscience: Δ9-tetrahydrocannabinol. ACS Chem. Neurosci. 10 (5), 2160–2175.
Blomberg, R.D., et al., 2005. Crash Risk of Alcohol Involved Driving: a Case-control Study.
Borenstein, M., et al., 2011. Introduction to Meta-analysis. John Wiley & Sons.

Brands, B., et al., 2019. Acute and residual effects of smoked cannabis: impact on driving speed and lateral control, heart rate, and self-reported drug effects. Drug Alcohol Depend. 205, 107641.
Chow, R.M., et al., 2019. Driving under the influence of cannabis: a framework for future policy. Anesth. Analg. 128 (6), 1300–1308.
Colizzi, M., Bhattacharyya, S., 2018. Cannabis use and the development of tolerance: a systematic review of human evidence. Neurosci. Biobehav. Rev. 93, 1–25.
Cooper, Z.D., Haney, M., 2014. *Investigation of sex-dependent effects of cannabis in daily cannabis smokers*. Drug Alcohol Depend. 136, 85–91.
Fares, A., et al., 2021. Combined effect of alcohol and cannabis on simulated driving. Psychopharmacology.
Giroud, C., et al., 2001. Δ9-THC, 11-OH-Δ9-THC and Δ9-THCCOOH plasma or serum to whole blood concentrations distribution ratios in blood samples taken from living and dead people. Forensic Sci. Int. 123 (2–3), 159–164.
Hartman, R.L., et al., 2015. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend. 154, 25–37.
Hložek, T., et al., 2017. Pharmacokinetic and behavioural profile of THC, CBD, and THC +CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion in vivo of CBD to THC. Eur. Neuropsychopharmacol. 27 (12), 1223–1237.
Irwin, C., et al., 2017. Effects of acute alcohol consumption on measures of simulated driving: a systematic review and meta-analysis. Accid. Anal. Prev. 102, 248–266.
Karschner, E.L., et al., 2009. Implications of plasma Δ9-tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers. J. Anal. Toxicol. 33 (8), 469–477.
Makowski, D., et al., 2019. Methods and algorithms for correlation analysis in r. J. Open Source Softw. 5 (51), 2306.
McCartney, D., et al., 2021a. Orally administered cannabidiol (CBD) does not produce false-positive tests for THC on the Securetec DrugWipe® 5S or Dräger Drug Test® 5000. Drug Test. Anal.
McCartney, D., et al., 2021b. Determining the magnitude and duration of acute Δ9-tetrahydrocannabinol (Δ9-THC)-induced driving and cognitive impairment: a systematic and meta-analytic review. Neurosci. Biobehav. Rev.
Micallef, J., et al., 2018. Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. Fundam. Clin. Pharmacol. 32 (5), 558–570.
Pasnin, L.T., Gjerde, H., 2021. Alcohol and drug use among road users involved in fatal crashes in Norway. Traffic Inj. Prev. 22 (4), 267–271.
Ramaekers, J.G., et al., 2006. Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: limits of impairment. Drug Alcohol Depend. 85 (2), 114–122.
Richman, J., May, S., 2019. An investigation of the Druid® smartphone/tablet app as a rapid screening assessment for cognitive and psychomotor impairment associated with alcohol intoxication. Vis. Dev. Rehabil. 5 (1), 31–42.
Ronen, A., et al., 2010. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accid. Anal. Prev. 42 (6), 1855–1865.
Schlienz, N.J., et al., 2020. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug Alcohol Depend. 211, 107969.
Sholler, D.J., et al., 2021. Sex differences in the acute effects of oral and vaporized cannabis among healthy adults. Addict. Biol. 26 (4), e12968.
Spindle, T.R., et al., 2019. Acute pharmacokinetic profile of smoked and vaporized cannabis in human blood and oral fluid. J. Anal. Toxicol. 43 (4), 233–258.
Spindle, T.R., et al., 2021. Assessment of cognitive and psychomotor impairment, subjective effects, and blood THC concentrations following acute administration of oral and vaporized cannabis. J. Psychopharmacol. 35 (7), 786–803.
Starkey, N.J., Charlton, S.G., 2014. The effects of moderate alcohol concentrations on driving and cognitive performance during ascending and descending blood alcohol concentrations. Hum. Psychopharmacol. Clin. Exp. 29 (4), 370–383.
Swinscow, T., 1997. Correlation and regression, in Statistics at Square One Ninth Edition. BMJ Publishing Group.
Van Rosendal, S.P., et al., 2010. Guidelines for glycerol use in hyperhydration and rehydration associated with exercise. Sport. Med. 40 (2), 113–139.
Vandrey, R., et al., 2017. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. J. Anal. Toxicol. 41 (2), 83–99.
Verster, J.C., Roth, T., 2011. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). Int. J. Gen. Med. 4, 359.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 1–48.
Wong, K., Brady, J.E., Li, G., 2014. Establishing legal limits for driving under the influence of marijuana. Inj. Epidemiol. 1 (1), 1–8.

Reviewed Papers

1.Spindle, T.R., et al., Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug and Alcohol Dependence, 2020: p. 107937.

2.Matheson, J., et al., Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. Psychopharmacology, 2020. 237(2): p. 305-316.

3.Schlienz, N.J., et al., Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug and Alcohol Dependence, 2020: p. 107969.

4.Brands, B., et al., Acute and residual effects of smoked cannabis: Impact on driving speed and lateral control, heart rate, and self-reported drug effects. Drug and Alcohol Dependence, 2019. 205.

5.Mason, N.L., et al., Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity. European Neuropsychopharmacology, 2019. 29(2): p. 247-256.

6.Mason, N.L., et al., Reduced responsiveness of the reward system is associated with tolerance to cannabis impairment in chronic users. Addiction Biology, 2019.

7.Arkell, T.R., et al., Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology, 2019. 236 (9): p. 2713-2724.

8.Spindle, T.R., et al., Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis A Crossover Trial. Jama Network Open, 2018. 1(7).

9.Schoedel, K.A., et al., Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. Epilepsy & Behavior, 2018. 88: p. 162-171.

10.Micallef, J., et al., Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. Fundamental & Clinical Pharmacology, 2018. 32(5): p. 558-570.

11.Ramaekers, J.G., et al., Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes. Brain Imaging and Behavior, 2016. 10 (4): p. 1254-1263.

12.Mokrysz, C., et al., Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. Translational Psychiatry, 2016. 6.

13.Theunissen, E.L., et al., Rivastigmine but not vardenafil reverses cannabis-induced impairment of verbal memory in healthy humans. Psychopharmacology, 2015. 232(2): p. 343-353.

14.Hartman, R.L., et al., Cannabis effects on driving lateral control with and without alcohol. Drug and Alcohol Dependence, 2015. 154: p. 25-37.

15.Battistella, G., et al., Weed or Wheel! fMRI, Behavioural, and Toxicological Investigations of How Cannabis Smoking Affects Skills Necessary for Driving. Plos One, 2013. 8(1).

16.Ronen, A., et al., The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accident Analysis and Prevention, 2010. 42(6): p. 1855-1865.

17.Böcker, K.B.E., et al., Cannabis with high Δ9-THC contents affects perception and visual selective attention acutely: An event-related potential study. Pharmacology Biochemistry and Behavior, 2010. 96(1): p. 67-74.

18.Ramaekers, J.G., et al., Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Journal of Psychopharmacology, 2009. 23(3): p. 266-277.

19.Hunault, C.C., et al., Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). Psychopharmacology, 2009. 204(1): p. 85-94.

20.Roser, P., et al., Psychomotor performance in relation to acute oral administration of Δ 9-tetrahydrocannabinol and standardized cannabis extract in healthy human subjects. European archives of psychiatry and clinical neuroscience, 2009. 259(5): p. 284.

21.Roser, P., et al., Effects of acute oral Δ9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. European Neuropsychopharmacology, 2008. 18(8): p. 569-577.

22.Ramaekers, J.G., et al., High-potency marijuana impairs

executive function and inhibitory motor control. Neuropsychopharmacology, 2006. 31(10): p. 2296-2303.

23.Nicholson, A.N., et al., Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. Journal of Clinical Psychopharmacology, 2004. 24(3): p. 305-313.

24.Curran, V.H., et al., Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology, 2002. 164(1): p. 61-70.

25. Adam, K.C.S., et al., Δ9-Tetrahydrocannabinol (THC) impairs visual working memory performance: a randomized crossover trial. Neuropsychopharmacology, 2020. 45(11): p. 1807-1816.

26. Arkell, T.R., et al., Effect of Cannabidiol and? 9-Tetrahydrocannabinol on Driving Performance: A Randomized Clinical Trial. JAMA - Journal of the American Medical Association, 2020. 324(21): p. 2177-2186.

27. Fares, A., et al., Combined effect of alcohol and cannabis on simulated driving. Psychopharmacology, 2021.

28. Spindle, T.R., et al., Assessment of cognitive and psychomotor impairment, subjective effects, and blood THC concentrations following acute administration of oral and vaporized cannabis. Journal of Psychopharmacology, 2021. 35(7): p. 786-803.