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Determining the magnitude and duration of acute Δ^9-tetrahydrocannabinol (Δ^9-THC)-induced driving and cognitive impairment: A systematic and meta-analytic review

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ABSTRACT

The increasing legal availability of cannabis has important implications for road safety. This systematic review characterised the acute effects of Δ^9-THC on driving performance and driving-related cognitive skills, with a particular focus on the duration of Δ^9-THC-induced impairment. Eighty publications and 1534 outcomes were reviewed. Several measures of driving performance and driving-related cognitive skills (e.g. lateral control, tracking, divided attention) demonstrated impairment in meta-analyses of "peak" Δ^9-THC effects (p's<0.05). Multiple meta-regression analyses further found that regular cannabis users experianced less impairment than 'other' (mostly occasional) cannabis users ($p = 0.003$) and that the magnitude of oral ($n = 243$ effect estimates [EE]) and inhaled ($n = 481$ EEs) Δ^9-THC-induced impairment depended on various factors (dose, post-treatment time interval, the performance domain (skill) assessed) in other cannabis users (p's<0.05). The latter model predicted that most driving-related cognitive skills would 'recover' (Hedges' g=–0.25) within ~5-hs (and almost all within ~7-hs) of inhaling 20 mg of Δ^9-THC; oral Δ^9-THC-induced impairment may take longer to subside. These results suggest individuals should wait at least 5 -hs following inhaled cannabis use before performing safety-sensitive tasks.

1. Introduction

The introduction of legal access to both medical and non-medical cannabis products is a recent global phenomenon that is reframing social, political, and clinical perspectives toward this ancient natural product. A major public health issue concerns the detrimental effects of cannabis use on car driving performance (and other 'safety-sensitive' tasks) and how to provide clear, evidence-based advice and associated legal frameworks to manage cannabis-induced impairment (Macdonald, 2019; Ramaekers, 2018). This requires a comprehensive understanding of cannabis and Δ^9-tetrahydrocannabinol's (Δ^9-THC: the main intoxicating component of cannabis) acute effects on skilled performance.

The deleterious effects of cannabis use on driving have been explored in epidemiological and experimental studies as summarised in recent systematic reviews (Hartman and Huestis, 2013; Li et al., 2012; National Academies of Sciences Engineering and Medicine, 2017; Rogeberg, 2019; Rogeberg and Elvik, 2016, 2017). Findings from epidemiological studies suggest that cannabis use bestows a moderately increased risk of being involved in, or responsible for, a car crash (Rogeberg, 2019; Rogeberg and Elvik, 2016, 2017). Experimental studies in which a fixed dose of Δ^9-THC is administered (e.g. smoked, vaporised, oral) prior to performing a driving test (e.g. simulated, on-road) or a discrete neuropsychological test measuring some driving-related cognitive skill (e.g. information processing, divided attention, tracking performance) have likewise observed an impairing effect (Broyd et al., 2016; Hartman and Huestis, 2013; Oomen et al., 2018), although a comprehensive, meta-analytic review of this evidence is currently lacking. Notably, such effects appear to be less pronounced in regular (compared to occasional) cannabis users, likely due to the development of tolerance (Colizzi and Bhattacharyya, 2018). Some aspects of driving performance also appear

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to be more susceptible to Δ^9-THC-induced impairment than others. For example, while a number of studies have shown that Δ^9-THC increases standard deviation of lane position (SDLP) ("weaving" during simulated and on-road driving tests) (Arkell et al., 2019; Bosker et al., 2012; Brown et al., 2019; Hartman et al., 2015; Micallef et al., 2018; Ramaekers et al., 2000; Ronen et al., 2008; Veldstra et al., 2015), average driving speed is not typically affected (Anderson et al., 2010a; Arkell et al., 2019; Bosker et al., 2012; Brands et al., 2019; Ronen et al., 2010, 2008).

One of the most critical, yet unresolved, issues relating to cannabis use and road safety is the duration of Δ^9-THC-induced driving impairment. The complex pharmacokinetics of Δ^9-THC (e.g., rapid and transient peak in blood concentrations, lengthy persistence in biological matrices) mean that, unlike alcohol, there is no clear relationship between blood Δ^9-THC concentrations and impairment (Arkell et al., 2020b; Ginsburg, 2019; Madras, 2017). Put simply, it is difficult to determine the point at which Δ^9-THC-induced driving impairment typically subsides. Legal frameworks to manage cannabis-induced impairment are therefore inconsistent (e.g., in some jurisdictions it is illegal to drive with any detectable amount of Δ^9-THC or Δ^9-THC metabolites in blood, urine, or oral fluid, whereas others tolerate low to moderate *per se* Δ^9-THC concentrations in blood) (Wong et al., 2014), and public health advice regarding how long an individual should wait following cannabis use before operating a motor vehicle, limited. Currently, the Canadian 'Lower Risk Cannabis Use Guidelines' (endorsed by the Public Health Agency of Canada) recommend waiting at least 6 -hs following cannabis use before driving (Health Canada, 2019), while expert advice provided on the not-for-profit organisation 'Mothers Against Drunk Driving' (MADD Canada) website suggests waiting a minimum of 4–6 -hs (MADD Canada, 2019). Recent reports also indicate that the behaviour of cannabis users with respect to delaying driving is variable; with 13–50 % of individuals admitting to driving within 3 -hs of cannabis use in recent surveys from the United States, Canada and Australia (Arkell et al., 2020a; Bonar et al., 2019; DiGuiseppi et al., 2019; Rotermann, 2020).

Accordingly, the current systematic review summarised evidence from recent studies investigating the acute effects of Δ^9-THC on car driving performance and discrete cognitive skills related to car driving. Meta-analytic techniques were then used to estimate the magnitude and duration of Δ^9-THC-induced impairment. As the pharmacokinetic profiles of oral and inhaled (i.e. smoked, vaporised) Δ^9-THC differ substantially (Spindle et al., 2019; Vandrey et al., 2017), these different routes of administration were investigated in separate analyses as were the effects of Δ^9-THC in regular and 'other' (mostly occasional) cannabis users.

2. Methods

The methods of this systematic review are reported in accordance with the PRISMA-P 2015 Statement (Moher et al., 2015).

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). The star symbol (*) was used to capture derivatives of search terms (by suffixation) and enclosed quotation marks were used to capture exact phrases. The search was then refined by 'Document Type' (article, only) and 'Language' (English, only), if permitted by the database. Given the large number of terms that could potentially be used to retrieve relevant studies on cognitive function, and the large number of texts identified (>8000; Supplementary File 1), the authors performed a modified secondary search. This search included 15 of the 21 original terms (ensuring adequate overlap; i.e. retrieving 76 % of the records identified in the primary search), but used the terms "information processing", attention and "crystallised intelligence" instead of "processing speed", drive, perception, vigilance, psychomotor and tracking to maximise breadth.

Two investigators (D.M. & T.R.A.) independently screened the titles and abstracts against the following criteria: (1) English language; (2) full-length article; (3) original research; and (4) controlled trial in which Δ^9-THC was administered. Suitable records were then screened for eligibility by full text (see Sect. 2.2 'Eligibility Criteria'). The final decision to include (or discard) a study was made between these two investigators and discrepancies were resolved in consultation with a third investigator (I.S.M.). One investigator (D.M.) also hand-searched the reference lists of two previous systematic reviews (Broyd et al., 2016; Oomen et al., 2018) to ensure all relevant articles were captured.

2.2. Eligibility criteria

Studies that measured either simulated or on-road car driving performance, or a discrete cognitive skill related to car driving (see Sect. 2.3 'Performance Outcomes'), $\leq$12 h following a single, acute dose of Δ^9-THC in a placebo-controlled (within- or between-subject) experimental trial were eligible for inclusion. Only full-length, English-language, original research articles were accepted; all other documents were discarded.

Studies were excluded if: (1) Δ^9-THC was administered in combination with another treatment (this did not include placebo treatments, other cannabinoids or cannabis constituents, tobacco or participants' usual medication); (2) more than one dose of Δ^9-THC was administered prior to the performance test(s) during the study session; (3) either the dose of Δ^9-THC administered, or the length of time between Δ^9-THC administration and the performance test(s), was not reported and could not be estimated (e.g. in regard to dose, reporting the number of 'puffs' smoked from a cannabis cigarette was not considered adequate to estimate dose) (see Sect. 2.5' Data Extraction'); (4) results were reported in another included paper; or (5) results were not adequately reported; at a minimum studies had to report either mean performance scores or the results of relevant statistical comparisons (descriptively) (e.g. paired analyses or complex comparisons within which the effect of Δ^9-THC could be isolated; see Sect. 2.6.2 'Qualitative Synthesis'). Studies that reported sufficient data to facilitate the computation of independent-groups Hedges' *g* effect estimates were eligible for quantitative synthesis. If these data were not reported and the study was published within the previous 10 years (2010–2020), the corresponding author was contacted via email in an attempt to retrieve it. Where data were presented in graphical format only, a web-based tool (see: WebPlotDigitizer; https://apps.automeris.io/wpd/) was used to extract numeric values. 'Peak', 'minimum' and 'maximum' performance scores and scores that were averaged across Δ^9-THC and non-Δ^9-THC treatments (e.g. alcohol) were ineligible for review; performance scores that were averaged across time (i.e. > 1 h apart) or across multiple Δ^9-THC treatments were eligible for qualitative synthesis only (unless the corresponding author could provide the required data).

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 (identifiable by the additional letters (e.g. a–d) in the citation). As single trials often measured serial performance (i.e., multiple times across the trial) and/or used several tasks that generated multiple outcomes, each one could contribute multiple effect estimates to the review. (Nb. Multilevel models were used to account for dependency of effect estimates in statistical analyses (Assink and Wibbelink, 2016) (see sect. 2.6.3 'Quantitative Synthesis')).

Table 1
Driving-related cognitive performance tests.

- **Divided Attention**
  - DAT (Secondary Target Identification Task)
    - DAT (Primary Mental Arithmetic Task)
    - Multi-attribute Task (Secondary Target Identification Task)
- **Tracking Performance**
  - Critical Tracking Task
    - DAT (Primary Tracking Task)
    - Multi-attribute Task (Primary Tracking Task)
    - Pursuit Tracking Task
    - Rotor Pursuit Task
    - Unstable Tracking Task
- **Information Processing**
  - Digit Cancellation Task
    - Digit Symbol Substitution Task
    - Road Sign Search Task
    - Trail Making Task (Part A)
- **Executive Function**
  - ***Conflict Control:**
    - Flanker Task
    - Go/No Go Task
    - Matching Familiar Figures Task
    - Stop Signal Task
    - Stroop Word-Colour Association Task
    - Attention Switch Task
    - Wisconsin Card Sorting Task
  - **Fluid Intelligence:**
    - Baddeley Reasoning Task
    - Stockings of Cambridge
    - Tower of London Task
- **Reaction Time**
  - Choice Reaction Time Task
    - Simple Reaction Time Task
    - Vienna Reaction Time Task
- **Motor Function**
  - **Fine Motor Function:**
    - Gibson Spiral Maze Task
    - Grooved Pegboard Task
    - Finger Tapping Task
    - Paced Finger Tapping Task
    - Secondary Finger Tapping Task
    - Smooth Pursuit Eye Movements
    - Saccadic Eye Movements
  - **Gross Motor Function:**
    - Motor Screening Task
    - Static (2-Leg) Balance
    - Dynamic Balance
- **Perception**
  - **Sensory Discrimination:**
    - 3D Structure from Motion Task
    - Auditory Oddball Detection Task
    - Dichotic Listening Task
    - Distance Estimation
    - Useful Field of View Task
    - Visual Oddball Detection Task
  - **Time Perception:**
    - Time Estimation
    - Time Reproduction
    - Self-Paced Counting Task
    - Self-Paced Finger Tapping Task
- **Sustained Attention**
  - Continuous Performance Test
    - Distracted Continuous Performance Test
    - Psychomotor Vigilance Task
    - Rapid Visual Information Processing Task
    - Sustained Attention Task
    - Signal Detection Task
    - Visual Selective Attention task
- **Working Memory**
  - Digit Span (Backward)
    - Trail Making Task (Part B)
    - *N-Back Task
    - Paced Auditory Serial Addition Task
    - Spatial N-Back Task
    - Serial Sevens Subtraction
    - Spatial Working Memory Task
    - Sternberg Memory Task
    - Verbal Fluency Task (Errors)

A description of each task and its associated outcomes can be found in Supplementary File 2. *"Non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks were analysed in the Reaction Time domain (see Sect. 2.6.3 'Quantitative Synthesis').

2.3. Performance outcomes

Studies were required to have measured either car driving performance, or a discrete cognitive "skill" related to car driving. The following "skills" (hereafter referred to as *Performance Domains*) were accepted as per Moskowitz and Fiorentino (2000): (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. Measures of car driving performance were likewise subcategorised as 'Lateral Control' (outcomes included standard deviation of lane position [SDLP], lane crossings, steering deviations, maximum lateral acceleration and time out of lane), 'SDLP (Only)' (since this is often recognised as the most sensitive measure of driving impairment (Irwin et al., 2017; Verster and Roth, 2011)), 'Speed', 'Speed Variability', 'Car Following (CF) Headway' (outcomes included CF headway and gain),' CF Headway Variability' (outcomes included CF headway variability and coherence), 'Reaction Time', and 'Other'.

Each driving-related cognitive performance test used in the included studies was categorised into one of the above Performance Domains (Table 1). Tests that were not considered indicative of a driving-related skill (or those based on subjective assessment, e.g. field sobriety tests) were excluded. While the majority of outcomes measured on eligible performance tests were included in this review, a small number were excluded for various reasons (e.g. reaction time on incorrect trials was considered unsuitable as no single direction of change (i.e. an increase or decrease) is consistently indicative of 'impairment'). In addition, if an outcome could be broken down into multiple "sub-outcomes" (e.g. both the total and individual number of within- and between-search errors on a working memory task), and all measures were reported, only the sub-outcomes were included. All excluded tasks and excluded outcomes (with reasons for exclusion) are listed in Supplementary File 2.

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)). This scale, which combines the Jadad scoring system (Jadad et al., 1996), PEDro scale (Maher et al., 2008), and Delphi List (Verhagen et al., 1998), assesses a number of factors associated with the minimization of experimental bias (e.g. blinding, participant selection, randomisation, data reporting). Excellent methodological quality is indicated by a Rosendal Score $\geq$60 % (Jadad et al., 1996). Rosendal scores were calculated by dividing the total number of 'Yes' responses by the total number of applicable items. Studies were ineligible for quantitative synthesis (but included in the qualitative synthesis) if they received a Rosendal score $<$50 %.

2.5. Data extraction

Data were extracted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* Checklist of Items to Consider in Data Collection for Data Extraction (Chandler et al., 2019). Extracted data included: (1) the study design; (2) participant characteristics (e.g. age, body weight, sex, cannabis use behaviour); (3) treatment characteristics (e.g. type, composition, route of administration, dose); (4) performance test characteristics (e.g. procedure, number of assessments, the length of time between Δ^9-THC administration and the performance test(s)), and;

Table 2
Terms used to describe participants' cannabis use behaviour.

Population	Definition
Cannabis Naïve	No lifetime exposure
Current Non-Users	No use ≥1 month and ≥1 lifetime exposure
Infrequent Users	<1 use per month and ≥1 lifetime exposure
Monthly Users	1 to <4 uses per month
Weekly Users	1 to <4 uses per week
Daily Users	≥4 uses per week
Unclear	Insufficient information provided

See Sect. 2.5 'Data Extraction' for full details. For analytical purposes, those trials in which all participants used cannabis weekly or more often were considered to involve "Regular Users"; all other trials were considered studies of "Other Uses".

(5) blood Δ^9-THC and 11-OH-Δ^9-THC concentrations as well as subjective ratings of intoxication at the time of performance testing (where available). (Nb. The latter were included for descriptive purposes only and were not formally analysed).

The following methods should be noted:

If a study administered the same performance test more than once within a one-hour period, only one of these assessments was included. In each case, the assessment that took place *first* within the hour; or, if more than two assessments were completed, the assessment that would result in the greatest loss of data (i.e. the exclusion of more assessments), was omitted to reduce data dependency.

The *Post-Treatment Time Interval* was typically estimated as the total length of time between Δ^9-THC administration and the beginning of the performance test (or cognitive battery, if multiple tasks were performed and the start time of individual tasks was not reported). However, if the test (or battery) took >10 min to complete, it was taken as the length of time to the 'mid-way' point of the assessment. If the exact timing of the assessment was not reported, but it clearly took place shortly following Δ^9-THC administration, the interval was approximated as 15 min. Tests were assumed to last ≤10 min unless otherwise stated.

The terms used to describe participants' *Cannabis Use Behaviour* are defined in Table 2. Each population was categorised based on the range of use behaviours exhibited by its participants (e.g., if participants used cannabis on between 2–16 days [or between 2–16 times] within the last 3 months, the population were termed [on average] 'Infrequent–Weekly Users'). If only the Mean ± SD number of uses was reported, the range was estimated as ±3SDs from the mean. However, if the lower limit was <0 (or if the SD was not reported), the behaviour of the population was considered 'Unclear'. The population's Cannabis Use Behaviour was also considered 'Unclear' if only > *x* or < *x* uses was reported, unless the reported value was ≥1 use (or more) per week (i.e. Weekly–Daily Users or Daily Users, as appropriate) or ≤4 uses (or less) per month (i.e. Infrequent–Monthly Users or Infrequent Users, as appropriate). These terms were developed for descriptive purposes only. When Cannabis Use Behaviour was included as a covariate in the meta-regression analyses (see Sect.2.6.3b 'Meta-Regression Analysis'), these categories were collapsed into two groups: '*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* intervention effect estimates were calculated by standardising the mean difference between control (placebo) and intervention (Δ^9-THC) performance scores against either the SD of the performance change (SD_Δ) (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 (where sufficient data were reported) (Borenstein et al., 2011). The magnitude of effect was then defined in accordance with Cohen (1988), where Hedges' *g* values of approximately ≤0.2 (range: <0.00–0.39), 0.5 (range: 0.40–0.79), and ≥0.8 were considered small, medium and large, respectively. Negative effect estimates were used to signify an impairing effect of Δ^9-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), the SD_Δ was estimated using the formula indicated below (Chandler et al., 2019):

$$SD_\Delta = \sqrt{\left(SD^2_{Placebo} + SD^2_{\Delta 9\text{-THC}}\right) - \left(2 \times R \times SD_{Placebo} \times SD_{\Delta 9\text{-THC}}\right)} \quad (1)$$

where *R* is the correlation coefficient. *R* was approximated as the mean correlation coefficient ($R = 0.530$) calculated using raw performance data from 16 trials (Arkell et al., 2019; Ballard and de Wit, 2011; Brown et al., 2019; Pabon and de Wit, 2019; Schlienz et al., 2020; Spindle et al., 2020, 2018) and 18 *p*-values derived from paired *t*-tests (Bhattacharyya et al., 2015; Morrison et al., 2009; van den Elsen et al., 2017). Where these Hedges' *g* effect estimates were meta-analysed (see Sect. 2.6.3 'Quantitative Synthesis'), the meta-analyses were repeated using values calculated at $R = 0.2$ and $R = 0.8$ to examine their robustness to the imputed *R*.

Where a *t*-statistic derived from a paired *t*-test was reported, the formula indicated below was used to calculate the the SD_Δ (Chandler et al., 2019):

$$SD_\Delta = \frac{\text{Mean Difference}}{t\text{-statistic}} \times \sqrt{n} \quad (2)$$

where *n* is the sample size. If a *p*-value (i.e. $p = x$ or $p < x$) derived from a paired *t*-test was reported, it was used to derive a *t*-statistic to substitute into this equation.

The SD_{pooled} was calculated using the formula indicated below (Chandler et al., 2019):

$$SD_{pooled} = \sqrt{\frac{\left(SD^2_{Placebo} + SD^2_{\Delta 9\text{-THC}}\right)}{2}} \quad (3)$$

The above calculations were performed using median performance scores (instead of mean) if this was all that was reported. If required, missing SDs were estimated from 95 % confidence intervals (CIs), standard error (SE) values, and interquartile ranges as described by Chandler et al. (2019).

2.6.2. Qualitative synthesis

Results were synthesised qualitatively if an effect estimate: (a) could not be calculated (but mean performance scores or the results of relevant statistical comparisons were reported; see Sect. 2.2 'Eligibility Criteria'); or (b) could be calculated but was not eligible for quantitative synthesis (see Sect. 2.6.3 'Quantitative Synthesis'). If an effect estimate could not be calculated, results were described in terms of whether Δ^9-THC was reported to have had a statistically significant effect ($p < 0.05$) on the outcome of interest. However, if this information was unavailable, the direction of the mean change was reported. If an outcome was analysed within a complex model (e.g. including more than two treatments and/or other factors, e.g. time), and no main effect of treatment or relevant interactions were observed, the comparison of interest was assumed to be non-significant. If a main effect of treatment or relevant interaction was observed, significance was determined on the basis of post hoc comparisons. If these comparisons were not performed, or there was any ambiguity in the reported result, the statistical significance was not reported (i.e. the direction of the mean change was reported or, if this was unavailable, the outcome was considered ineligible for inclusion).

2.6.3. Quantitative synthesis

An outcome was eligible for quantitative synthesis if: (a) an effect estimate could be calculated; and (b) it was not derived from a study of a clinical population (as the medical conditions studied were considered too heterogenous to consolidate into a meaningful analysis) or a study

that scored <50 % on the Rosendal scale. The quantitative synthesis comprised of a series of four-level meta-analyses and four-level meta-regression analyses with multiple random effects (Assink and Wibbelink, 2016). A two-level analysis is equivalent to a traditional random effects analysis in which there is only one random effect. We added random effects at two additional levels to account for dependency among effect estimates derived from: (1) the same studies; and (2) the same trials. The four sources of variance modelled were therefore: (Level 1) the sampling variance for the observed effect estimates; (Level 2) the variance between effect estimates derived from the same studies; (Level 3) the variance between effect estimates derived from different trials in the same studies, and; (Level 4) the variance between studies. All statistical analyses were performed using R (version 4.0.1) with the metafor-package, using syntax adapted from Assink and Wibbelink (2016). The accompanying R scripts are available in Supplementary File 7. Effect estimates were weighted by the inverse variance of the performance change and 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). Data are reported as Mean ± SD, unless otherwise stated. Note that although they are presented in the Executive Function and Working Memory domains, "non-conflict" outcomes (e.g., Go Reaction Time, Non-Switch Reaction Time, Congruent Reaction Time) and outcomes measured on '0-Back' Tasks were analysed in the Reaction Time domain due to their relative simplicity.

2.6.3.1. Meta-Analysis. Meta-analyses were initially performed to gain a general understanding of Δ^9-THC's acute (or "peak") effects on car driving performance (see Sect. 2.3 'Performance Outcomes'). Only those outcomes measured "shortly" post-treatment (or, if Δ^9-THC was administered orally, when blood Δ^9-THC/11-OH-Δ^9-THC concentrations and subjective feelings of intoxication were expected to be elevated (Schlienz et al., 2020)); that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously, or between 1.5 and 3.5 h of oral Δ^9-THC administration, were included in these analyses.

2.6.3.2. Meta-regression analysis. Restricted maximum likelihood multiple meta-regression analyses were performed to generate models that facilitate estimation of the duration of Δ^9-THC-induced cognitive impairment; in other words, the time it takes for an individual to "recover" (i.e. have their cognitive abilities return to baseline or a level at which Δ^9-THC's effects are no longer meaningful) following acute Δ^9-THC administration. Given the differences in their pharmacokinetic profiles (Spindle et al., 2019; Vandrey et al., 2017)], the effects of orally administered and inhaled (i.e. smoked or vaporised) Δ^9-THC were investigated in separate models. Effect estimates derived from trials that administered Δ^9-THC intravenously were not analysed as data were limited and (although this route of administration produces a similar pharmacokinetic profile to inhaled Δ^9-THC (Ohlsson et al., 1980)) the doses administered via this route were not comparable to others. The following covariates were included in each model as applicable: Performance Domain (see Sect. 2.3 'Performance Outcomes'), Cannabis Use Behaviour (Regular vs. Other Cannabis Users; see Sect. 2.5 'Data Extraction'), Δ^9-THC Dose, Route of Administration, and Post-Treatment Time Interval (see Sect. 2.5 'Data Extraction'). Post-Treatment Time Interval was also included as a curvilinear (quadratic) factor in the analysis of oral Δ^9-THC effects (following inspection of scatterplots). Performance Domains that did not indicate significant impairment in the initial meta-analyses of "peak" Δ^9-THC effects or that contained a limited amount of data (<10 effect estimates) were not analysed. The 'SDLP (Only)' domain was included in place of the 'Lateral Control' domain to aid interpretation, since drug-induced changes in SDLP have been well-researched (Dassanayake et al., 2011; Irwin et al., 2017). The Post-Treatment Time Interval covariate was centred (i.e. rescaled to have a mean of zero) in the analysis of oral Δ^9-THC effects to ensure values were not correlated with the quadratic computations. Categorical variables were dummy transformed with m – 1, where m is the number of levels of the original variable. Goodness of fit was approximated using the pseudo-R^2 value as standard R^2 values cannot be derived for multi-level meta-regression models (Nakagawa and Schielzeth, 2013). Unlike the standard value, the pseudo-R^2 does not provide an 'absolute' quantification of model fit, rather, an indication of how much better the full model is once the moderators have been incorporated.

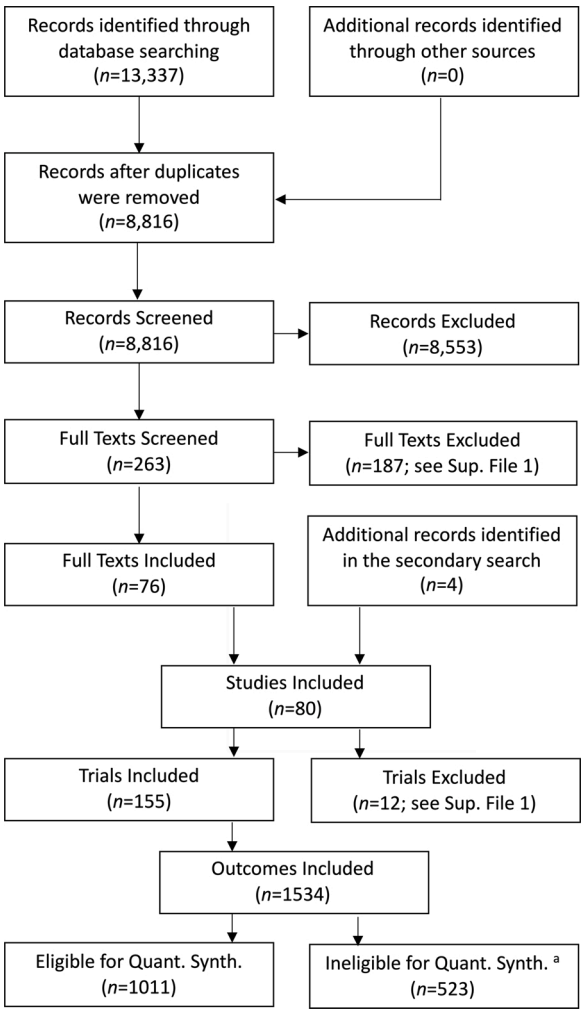

Fig. 1. Shortened PRISMA Flow Diagram. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations, or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis. The term 'trial' is defined in Sect. 2.2 'Eligibility Criteria'. A full PRISMA Flow Diagram can be found in Supplementary File 1).

3. Results

3.1. Overview of included studies and study quality

155 trials ($n = 3454$ participants; 71 % male) derived from 80 original research studies were included in this systematic review. Details of the study selection process are available in Supplementary File 1 and summarised in Fig. 1. The methodological quality assessment yielded a Mean ± SD Rosendal score of 62 ± 10 % (43–93 %) (see Supplementary File 3); six studies scored <50 % and were therefore ineligible for

Table 3
Summary of all included outcomes and trials.

	Total (*n*)			Eligible for Quantitative Synthesis (*n*)			Ineligible for Quantitative Synthesis [a] (*n*)		
	Outcomes	Trials	Participants	Outcomes	Trials	Participants	Outcomes	Trials	Participants
Total:	1534	155	3454 (71 % M)	1011	108	2583 (72 % M)	523	73	1497 (69 % M)
Cognitive Functions:									
Divided Attention	166	26	510 (70 % M)	148	23	486 (72 % M)	18	3	24 (50 % M)
Tracking Performance	137	31	646 (72 % M)	122	27	606 (66 % M)	15	7	87 (74 % M)
Information Processing	205	27	473 (65 % M)	128	16	290 (61 % M)	77	11	183 (72 % M)
Conflict Control	97	31	899 (79 % M)	59	27	805 (81 % M)	38	15	370 (71 % M)
Fluid Intelligence	70	16	448 (76 % M)	22	10	346 (80 % M)	48	8	154 (69 % M)
[b] Reaction Time	110	39	846 (67 % M)	49	28	647 (68 % M)	61	16	279 (68 % M)
Fine Motor Function	56	14	334 (59 % M)	52	12	310 (60 % M)	4	2	24 (50 % M)
Gross Motor Function	17	6	110 (46 % M)	5	3	74 (43 % M)	12	3	36 (50 % M)
Sensory Discrimination	25	10	201 (67 % M)	12	5	67 (88 % M)	13	6	149 (60 % M)
Time Perception	48	16	376 (60 % M)	16	6	150 (53 % M)	32	10	226 (65 % M)
Sustained Attention	114	35	751 (75 % M)	67	26	524 (81 % M)	47	14	321 (65 % M)
Working Memory	264	44	974 (70 %)	222	38	800 (71 % M)	42	12	363 (67 % M)
Car Driving:									
Lateral Control	65	23	438 (71 % M)	39	18	378 (71 % M)	26	5	60 (70 % M)
SDLP (Only)	32	19	389 (67 % M)	28	17	353 (69 % M)	4	2	36 (50 % M)
Speed	17	12	237 (69 % M)	17	12	237 (69 % M)	0	–	–
Speed Variability	13	10	112 (63 % M)	13	10	112 (63 % M)	0	–	–
CF Headway	16	10	160 (60 % M)	12	8	124 (63 % M)	4	2	36 (50 % M)
CF Headway Variability	16	10	160 (60 % M)	12	8	124 (63 % M)	4	2	36 (50 % M)
Reaction Time	14	10	160 (59 % M)	10	8	124 (61 % M)	4	2	36 (50 % M)
Other	6	2	65 (88 % M)	6	2	65 (88 % M)	0	–	–
Clinical Populations:	78	11	204 (70 % M)	–	–	–	78	11	204 (70 % M)

CF: Car Following; M: Males; SDLP: Standard Deviation of Lane Position. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis (qualitative synthesis only); *b*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Trials that include a combination of eligible and ineligible outcomes are presented in both relevant categories. Trials that did not report the sex of their participants were omitted when calculating the proportion of males.

Table 4
Key characteristics of all included trials.

	Trials (*n*)	Studies (*n*)	Outcomes (*n*)		Route of Administration (*n* Outcomes)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Outcomes)	
								Regular	Other
All Trials	155	80	1534	Oral:	578	16 ± 13	234 ± 164	32	546
				Vaporised:	344	14 ± 8	153 ± 132	63	281
				Smoked:	478	30 ± 20	137 ± 133	87	391
				Intravenous:	134	2.6 ± 1.3	48 ± 61	21	113
Trials Eligible for Quantitative Synthesis	108	58	1011	Oral:	307	20 ± 15	222 ± 148	12	295
				Vaporised:	305	14 ± 8	158 ± 137	57	248
				Smoked:	331	32 ± 22	139 ± 129	46	285
				Intravenous:	68	2.5 ± 1.3	28 ± 10	1	67
Trials Ineligible for Quantitative Synthesis [a]	73	38	523	Oral:	271	13 ± 9	248 ± 183	20	251
				Vaporised:	39	14 ± 9	111 ± 78	6	33
				Smoked:	147	23 ± 7	129 ± 140	41	106
				Intravenous:	66	2.7 ± 1.2	67 ± 82	20	46

Tx: Treatment. *a*: Outcomes that were not adequately reported, derived from trials of clinical populations or derived from studies that scored <50 % on the methodological quality assessment (see Supplementary File 3) were ineligible for quantitative synthesis. Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. Trials that include a combination of eligible and ineligible outcomes are presented in both relevant categories.

quantitative synthesis. Overall, the included trials measured a total of 1534 relevant outcomes; 1011 of which were eligible for quantitative synthesis. The number of outcomes included in each individual Performance Domain is presented in Table 3; characteristics of all included trials and those eligible for quantitative synthesis are summarised in Tables 4 and 5, respectively. A detailed qualitative synthesis is available in Supplementary File 4.

3.2. Meta-Analyses of "peak" Δ^9-THC effects

The characteristics of trials eligible for meta-analyses (see Sect. 2.6.3a 'Meta-Analysis') are summarised in Table 6; with results of the meta-analyses summarised in Table 7. The results of the analyses completed using different correlation coefficients ($R = 0.2$ and 0.8) are available in Supplementary File 5.

3.2.1. Cognitive performance

Meta-analyses revealed significant detrimental effects of Δ^9-THC on Divided Attention, Tracking Performance, Information Processing, Conflict Control, Fluid Intelligence, Reaction Time, Fine Motor Function, Sustained Attention and Working Memory (Table 7). Neither Sensory Discrimination nor Time Perception demonstrated significant impairment. Gross Motor Function was not subject to meta-analysis due to the limited amount of available data.

Table 5
Key characteristics of trials that were eligible for quantitative synthesis.

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Cognitive Functions:								
Divided Attention	23	148	*Oral:	42	28 ± 17	249 ± 136	0	42
			*Vaporised:	59	14 ± 8	200 ± 142	5	54
			*Smoked:	47	20 ± 11	203 ± 149	4	43
			Intravenous:	0	–	–	–	–
Tracking Performance	27	122	*Oral:	33	25 ± 15	275 ± 181	0	33
			*Vaporised:	39	15 ± 8	163 ± 142	8	31
			*Smoked:	50	30 ± 16	188 ± 42	7	43
			Intravenous:	0	–	–	–	–
Information Processing	16	128	*Oral:	46	27 ± 17	268 ± 158	0	46
			*Vaporised:	50	13 ± 8	226 ± 139	0	50
			*Smoked:	32	25 ± 22	225 ± 142	4	28
			Intravenous:	0	–	–	–	–
Conflict Control	27	59	*Oral:	11	10 ± 2	94 ± 5	0	0
			*Vaporised:	24	17 ± 6	34 ± 9	16	0
			*Smoked:	24	28 ± 13	93 ± 97	3	21
			Intravenous:	0	–	–	–	–
Fluid Intelligence	10	22	Oral:	0	–	–	–	–
			*Vaporised:	14	21 ± 0	51 ± 10	13	1
			*Smoked:	6	27 ± 10	165 ± 142	0	6
			Intravenous:	2	2.3 ± 0.3	40 ± 14	0	2
Reaction Time	28[a]	49[a]	*Oral:	18	11 ± 3	108 ± 24	0	18
			*Vaporised:	6	17 ± 7	30 ± 9	5	1
			*Smoked:	23	36 ± 23	88 ± 98	2	21
			Intravenous:	2	1.3 ± 0.0	30 ± 0	0	2
Fine Motor Function	12	52	*Oral:	32	6 ± 5	154 ± 80	0	32
			Vaporised:	0	–	–	–	–
			Smoked:	4	80 ± 7	60 ± 0	4	0
			Intravenous:	16	1.6 ± 0.5	20 ± 0	0	16
Gross Motor Function	3	5	Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	0	–	–	–	–
			Intravenous:	5	1.7 ± 0.5	20 ± 0	0	5
Sensory Discrimination	5	12	Oral:	10	10 ± 0	90 ± 0	0	10
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Time Perception	6	16	Oral:	14	11 ± 4	106 ± 9	0	14
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Sustained Attention	26	67	*Oral:	11	11 ± 4	382 ± 213	0	11
			*Vaporised:	6	21 ± 0	20 ± 12	2	4
			*Smoked:	31	59 ± 20	106 ± 37	10	21
			Intravenous:	19	3.4 ± 1.2	32 ± 11	0	19
Working Memory	38	222	*Oral:	50	25 ± 17	242 ± 127	0	50
			*Vaporised:	72	11 ± 7	176 ± 139	8	64
			*Smoked:	76	32 ± 21	123 ± 127	0	76
			Intravenous:	24	2.8 ± 1.3	30 ± 10	1	23
Car Driving:								
Lateral Control	18	39	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	19	19 ± 8	107 ± 70	0	19
			Smoked:	12	41 ± 33	37 ± 9	4	8
			Intravenous:	0	–	–	–	–
SDLP (Only)	17	28	Oral:	8	15 ± 5	203 ± 42	2	6
			*Vaporised:	13	18 ± 7	117 ± 79	0	13
			*Smoked:	7	55 ± 36	36 ± 8	4	3
			Intravenous:	0	–	–	–	–
Speed	12	17	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	9	47 ± 36	34 ± 9	4	5
			Intravenous:	0	–	–	–	–
Speed Variability	10	13	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	5	18 ± 5	37 ± 11	0	5
			Intravenous:	0	–	–	–	–
CF Headway	8	12	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	4	14 ± 0	135 ± 104	0	4
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
CF Headway Variability	8	12	Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	4	14 ± 0	135 ± 104	0	4

(*continued on next page*)

Table 5 (*continued*)

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Reaction Time	8	10	Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
			Oral:	8	15 ± 5	203 ± 42	2	6
			Vaporised:	0	–	–	–	–
Other	2	6	Smoked:	2	15 ± 3	45 ± 0	0	2
			Intravenous:	0	–	–	–	–
			Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	6	9 ± 7	38 ± 6	0	6
			Intravenous:	0	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position; Tx: Treatment. *Included in a meta-regression analysis. *a*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. A description of each cognitive task can be found in Supplementary File 2.

3.2.2. Car driving performance

Meta-analyses revealed significant detrimental effects of Δ^9-THC on Lateral Control, SDLP (Only) and Reaction Time (Table 7). Neither CF Headway, CF Headway Variability, Speed, nor Speed Variability were significantly influenced by Δ^9-THC. 'Other Outcomes' were not analysed due to the limited amount of available data.

3.3. Estimated duration of Δ^9-THC effects

The characteristics of trials eligible for meta-regression analysis (see Sect. 2.6.3a 'Meta-Regression') are summarised in Table 5; with results of the meta-regression analyses summarised in Table 8. The results of the analyses completed using different correlation coefficients ($R = 0.2$ and 0.8) are available in Supplementary File 5.

3.3.1. Smoked and vaporised Δ^9-THC

Effect estimates derived from trials that administered Δ^9-THC via smoking or vaporisation were included in the multiple meta-regression analyses of inhaled Δ^9-THC effects. The covariates included in each analysis are listed in Table 8.

An initial (combined) analysis of Regular and Other Cannabis Users included 579 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 3.7–94 mg (Interquartile Range [IQR]: 10–26 mg) and 1–480 min (IQR: 45–240 min) respectively. The following covariates were significantly related to effect size: Performance Domain, Cannabis Use Behaviour, Route of Administration, Δ^9-THC Dose and Post-Treatment Time Interval (p's<0.050; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased and less negative as the Post-Treatment Time Interval increased. It also differed across the Performance Domains. Regular Cannabis Use and Smoking were associated with less impairment (i.e., less negative Hedges' g effect estimates) than Other Cannabis Use and Vaporisation, respectively. However, the model retained a significant amount of unexplained heterogeneity ($p < 0.001$; pseudo-$R^2 = 0.0$) and the omission of outcomes derived from trials of Regular Cannabis Users strengthened it substantially (pseudo-$R^2 = 0.64$). Thus, the initial (combined) analysis of Regular and Other Cannabis Users may be limited in its ability to simultaneously describe inhaled Δ^9-THC's effects in these populations. Separate analyses were therefore also performed for Regular and Other Cannabis Users.

The subsequent analysis of Regular Cannabis Users included 59 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 5.5–86 mg (IQR: 21–26 mg) and 20–440 min (IQR: 40–60 min), respectively. None of the covariates included were significantly related to effect estimate (p's>0.050; pseudo-$R^2 = 0.0$; Table 8). It was therefore unsuitable to predict the magnitude and duration of inhaled Δ^9-THC's cognitive effects in this population.

The subsequent analysis of Other Cannabis Users included 481 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 3.7–69 mg (IQR: 10–25 mg) and 1–480 min (IQR: 60–240 min) respectively. The following covariates were significantly related to effect size: Performance Domain, Δ^9-THC Dose and Post-Treatment Time Interval (p's<0.05; pseudo-$R^2 = 0.64$; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased and less negative as the Post-Treatment Time Interval increased. It also decreased across the following Performance Domains (ordered from least to most sensitive to inhaled Δ^9-THC effects): Sustained Attention, Conflict Control, Reaction Time, Working Memory, Divided Attention, Tracking Performance, SDLP (Only) and Information Processing. The duration of inhaled Δ^9-THC's cognitive effects (based on the model presented in Table 8) are predicted in Table 9 and graphed in Fig. 2 (Nb. Tracking Performance is used as an example in this Figure; the average duration across all aggregated Performance Domains is graphed in Supplementary File 8). Values can also be imputed using the spreadsheet presented in Supplementary File 6.

3.3.2. Oral Δ^9-THC

The following covariates were included in the multiple meta-regression analysis of oral Δ^9-THC effects: Performance Domain, Post-Treatment Time Interval (linear and curvilinear) and Δ^9-THC Dose. Cannabis Use Behaviour was not included as a covariate as all outcomes were derived from trials of Other Cannabis Users. The resulting model included 243 effect estimates across which the Δ^9-THC Dose and Post-Treatment Time Interval ranged between 2.5–50 mg (IQR: 10–25 mg) and 60–720 min (IQR: 120–360 min), respectively. Three of the four covariates were significantly related to effect size (p's<0.050, pseudo-$R^2 = 0.28$; Table 8). Hedges' g became more negative (i.e. indicated greater impairment) as the Δ^9-THC Dose increased. It also decreased across the following Performance Domains (i.e. ordered from least to most sensitive to oral Δ^9-THC effects): Working Memory, Sustained Attention, Divided Attention, Fine Motor Function, Reaction Time, Information Processing, Tracking Performance, and Conflict Control. The curvilinear component of the relationship between Hedges' g and the Post-Treatment Time Interval was U shaped (i.e. indicating a delay to peak impairment and subsequent recovery). The duration of oral Δ^9-THC's cognitive effects (based on the model presented in Table 8) are predicted in Table 9 and graphed in Fig. 3 (Nb. Tracking Performance is used as an example in this Figure; the average duration across all aggregated Performance Domains is graphed in Supplementary File 8). Values can also be imputed using the spreadsheet presented in Supplementary File 6.

Table 6
Key characteristics of trials that were eligible for inclusion in meta-analyses of peak Δ^9-THC effects.

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Cognitive Functions:								
Divided Attention	22	46	Oral:	11	30 ± 17	153 ± 31	0	11
			Vaporised:	17	16 ± 7	42 ± 16	5	12
			Smoked:	17	22 ± 16	52 ± 28	1	16
			Intravenous:	0	–	–	–	–
Tracking Performance	27	49	Oral:	10	25 ± 16	150 ± 32	0	10
			Vaporised:	17	18 ± 6	41 ± 11	8	9
			Smoked:	22	40 ± 18	59 ± 22	1	21
			Intravenous:	0	–	–	–	–
Information Processing	13	31	Oral:	13	26 ± 18	146 ± 33	0	13
			Vaporised:	10	13 ± 7	44 ± 21	0	10
			Smoked:	8	49 ± 34	60 ± 0	4	4
			Intravenous:	0	–	–	–	–
Conflict Control	27	53	Oral:	11	10 ± 2	94 ± 5	0	11
			Vaporised:	24	17 ± 7	35 ± 7	16	8
			Smoked:	18	30 ± 14	49 ± 24	3	15
			Intravenous:	0	–	–	–	–
Fluid Intelligence	10	18	Oral:	0	–	–	–	–
			Vaporised:	14	21 ± 0	51 ± 10	13	1
			Smoked:	2	27 ± 13	45 ± 0	0	2
			Intravenous:	2	2.3 ± 0.3	40 ± 14	0	2
Reaction Time	24 [a]	38 [a]	Oral:	13	11 ± 3	119 ± 35	0	13
			Vaporised:	6	17 ± 7	30 ± 9	5	1
			Smoked:	17	32 ± 23	35 ± 12	2	15
			Intravenous:	2	1.3 ± 0.0	30 ± 0	0	2
Fine Motor Function	12	48	Oral:	28	6 ± 5	124 ± 11	0	28
			Vaporised:	0	–	–	–	–
			Smoked:	4	80 ± 7	60 ± 0	4	0
			Intravenous:	16	1.5 ± 0.5	20 ± 0	0	16
Gross Motor Function	3	5	Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	0	–	–	–	–
			Intravenous:	5	1.7 ± 0.5	20 ± 0	0	5
Sensory Discrimination	5	12	Oral:	10	10 ± 0	90 ± 0	0	10
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Time Perception	6	16	Oral:	14	11 ± 4	106 ± 9	0	14
			Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	80 ± 0	2	0
			Intravenous:	0	–	–	–	–
Sustained Attention	16	40	Oral:	2	15 ± 0	120 ± 0	0	2
			Vaporised:	6	21 ± 0	20 ± 12	2	4
			Smoked:	13	73 ± 17	67 ± 13	10	3
			Intravenous:	19	3.4 ± 1.2	32 ± 11	0	19
Working Memory	36	116	Oral:	14	25 ± 18	144 ± 33	0	14
			Vaporised:	26	10 ± 5	45 ± 15	8	18
			Smoked:	52	38 ± 22	51 ± 17	0	52
			Intravenous:	24	2.8 ± 1.3	30 ± 10	1	23
Car Driving:								
Lateral Control	16	28	Oral:	6	15 ± 5	180 ± 0	2	4
			Vaporised:	10	20 ± 9	51 ± 5	0	10
			Smoked:	12	41 ± 33	37 ± 9	4	8
			Intravenous:	0	–	–	–	–
SDLP (Only)	15	19	Oral:	6	15 ± 5	180 ± 0	2	4
			Vaporised:	6	17 ± 8	48 ± 5	0	6
			Smoked:	7	55 ± 36	36 ± 8	4	3
			Intravenous:	0	–	–	–	–
Speed	12	15	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	9	47 ± 36	34 ± 9	4	5
			Intravenous:	0	–	–	–	–
Speed Variability	10	11	Oral:	4	15 ± 6	180 ± 0	2	2
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	5	18 ± 5	37 ± 11	0	5
			Intravenous:	0	–	–	–	–
CF Headway	8	8	Oral:	6	15 ± 6	180 ± 0	2	4
			Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
CF Headway Variability	8	8	Oral:	6	15 ± 6	180 ± 0	2	4

(*continued on next page*)

Table 6 (*continued*)

	Trials (*n*)	Effect Estimates (*n*)		Route of Administration (*n* Effect Estimates)	Δ^9-THC Dose (mg) (Mean ± SD)	Post-Tx Interval (min) (Mean ± SD)	Cannabis Use Behaviour (*n* Effect Estimates)	
							Regular	Other
Reaction Time	8	8	Vaporised:	2	14 ± 0	45 ± 0	0	2
			Smoked:	0	–	–	–	–
			Intravenous:	0	–	–	–	–
			Oral:	6	15 ± 6	180 ± 0	2	4
Other	2	6	Vaporised:	0	–	–	–	–
			Smoked:	2	15 ± 3	45 ± 0	0	2
			Intravenous:	0	–	–	–	–
			Oral:	0	–	–	–	–
			Vaporised:	0	–	–	–	–
			Smoked:	6	9 ± 7	38 ± 6	0	6
			Intravenous:	0	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position; Tx: Treatment. *a*: total includes "non-conflict" outcomes (e.g. Go Reaction Time, Congruent Reaction Time, Non-Switch Reaction Time) and outcomes measured on '0-Back' Tasks (see Sect. 2.6.3 'Quantitative Synthesis'). Details of included studies are presented in Supplementary File 4. 'Cannabis Use Behaviour' is defined as per Sect. 2.5 'Data Extraction' and Table 2. The 'Post-Treatment Time Interval' was estimated as per Sect. 2.5 'Data Extraction'. A description of each cognitive task can be found in Supplementary File 2. Only those assessments conducted "shortly" post-treatment; that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously or between 1.5–3.5 h of oral Δ^9-THC administration were eligible for meta-analysis.

Table 7
Results of meta-analyses investigating the 'peak' effect of Δ^9-THC on car driving and related cognitive functions.

Performance Domain	Trials (n)	Effect Estimates (n)	Effect of Δ^9-THC		Heterogeneity				
			Hedges' *g* (95% CIs)	*p*-value	I^2-value	*p*-value	σ_1^2	σ_2^2	σ_3^2
Cognitive Functions:									
Divided Attention	22	46	–0.28 (–0.36, –0.20)	<0.001	14.2	0.291	<0.001	0.009	<0.001
Tracking Performance	27	49	–0.42 (–0.58, –0.25)	<0.001	64.8	0.002	<0.001	0.019	0.059
Information Processing	13	31	–0.38 (–0.55, –0.21)	<0.001	23.8	0.306	<0.001	0.002	0.021
Conflict Control	27	53	–0.34 (–0.42, –0.25)	<0.001	58.4	<0.001	0.047	<0.001	<0.001
Fluid Intelligence	10	18	–0.37 (–0.46, –0.27)	<0.001	16.6	0.283	0.005	<0.001	<0.001
Reaction Time	24	38	–0.28 (–0.43, –0.13)	<0.001	53.3	0.002	<0.001	0.009	0.047
Fine Motor Function	12	48	–0.36 (–0.60, –0.12)	0.004	61.9	<0.001	<0.001	0.026	0.048
[a]Gross Motor Function	3	5	–	–	–	–	–	–	–
Sensory Discrimination	5	12	+0.09 (–0.08, +0.25)	0.275	0.0	0.458	<0.001	<0.001	<0.001
Time Perception	6	16	–0.05 (–0.30, +0.20)	0.670	54.4	0.070	0.008	<0.001	0.028
Sustained Attention	16	40	–0.23 (–0.37, –0.10)	<0.001	20.3	0.675	<0.001	<0.001	0.019
Working Memory	36	116	–0.36 (–0.52, –0.20)	<0.001	69.6	<0.001	0.003	0.019	0.084
Car Driving:									
Lateral Control	16	28	–0.24 (–0.41, –0.08)	0.005	35.7	0.394	<0.001	<0.001	0.031
SDLP (Only)	15	19	–0.29 (–0.47, –0.11)	0.003	32.3	0.322	<0.001	<0.001	0.027
Speed	12	15	+0.14 (–0.01, +0.29)	0.061	0.0	0.636	<0.001	<0.001	<0.001
Speed Variability	10	11	–0.16 (–0.35, +0.02)	0.074	0.7	0.786	<0.001	<0.001	0.001
CF Headway	8	8	–0.03 (–0.32, +0.27)	0.843	44.4	0.085	0.021	0.023	0.005
CF Headway Variability	8	8	–0.24 (–0.58, +0.11)	0.151	37.1	0.488	<0.001	<0.001	0.038
Reaction Time	8	8	–0.47 (–0.70, –0.23)	0.002	15.7	0.230	0.007	0.005	<0.001
[a]Other	2	6	–	–	–	–	–	–	–

CF: Car Following; SDLP: Standard Deviation of Lane Position. Details of included studies are summarised in Table 6 and presented in Supplementary File 4. A description of each cognitive task can be found in Supplementary File 2. All negative effect estimates (Hedges' *g* values) indicate a detrimental effect of Δ^9-THC, irrespective of the performance outcome. Only those assessments conducted "shortly" post-treatment; that is, within 1.5 h of Δ^9-THC being smoked, vaporised, or administered intravenously or between 1.5–3.5 h of oral Δ^9-THC administration were included in these analyses. *a*: Unsuitable for meta-analysis.

3.4. Δ^9-THC effects in clinical populations

Eleven trials ($n = 204$; 70 % male) derived from 6 studies investigated the cognitive effects of Δ^9-THC in clinical populations (Supplementary File 4). Four outcomes indicated significant, detrimental effects of Δ^9-THC; an additional 59 outcomes were not significantly affected, and the statistical significance of the 15 remaining comparisons were unclear. All significant detrimental effects were observed in one study that measured Gross Motor Function (Static 2-Leg Balance and Dynamic Balance) 120 min post-Δ^9-THC administration (1.5 mg, oral) in individuals with dementia. Moderate negative Hedges' *g* effect estimates were also reported in several trials that measured Sustained Attention (2.7 mg, oral; 21 mg, smoked; 2.5–5.0 mg, i.v.). However, 68 of the 78 outcomes that were measured indicated either small negative or positive Hedges' *g* effect estimates.

4. Discussion

This study addresses current safety-related concerns around the duration of impairment arising from acute consumption of oral or inhaled Δ^9-THC-containing cannabis. We systematically reviewed recent studies investigating the acute effects of Δ^9-THC on driving performance and discrete cognitive skills related to driving; meta-analytic techniques were then used to estimate the magnitude and duration of Δ^9-THC-induced impairment. Overall, our results confirm that Δ^9-THC impairs aspects of driving performance and demonstrate that the magnitude and duration of this impairment depends on the dose provided, route of administration and frequency with which cannabis is used. There appears to be no universal answer to the question of "*how long to wait before driving?*" following cannabis use: consideration of multiple factors is therefore required to determine appropriate delays between Δ^9-THC use and the performance of safety-sensitive tasks.

Several measures of driving performance (i.e. Lateral Control, SDLP

Table 8
Results of the inhaled and oral Δ^9-THC meta-regression analyses.

				Unexplained Heterogeneity		
Covariate	Effect Estimates (*n*)/ Mean; Median (IQR)	Hedges' *g* (95% CIs)	*p*-value	I^2-value	*p*-value	Sigma
Inhaled Δ^9-THC Model (Includes "Regular" and "Other" Users) (*n* = 579 effect estimates):						
Intercept	–	–0.2356 (–0.3753, –0.0959)	**0.001**			
Performance Domain	–	–	–			
[a]Conflict Control	48	–	–			
Divided Attention	106	–0.0767 (–0.1687, +0.0154)	0.102			
Fluid Intelligence	20	–0.0859 (–0.1945, +0.0228)	0.121			
Information Processing	82	–0.1318 (–0.2310, –0.0327)	**0.009**			
SDLP (Only)	20	–0.0686 (–0.2279, +0.0906)	0.398			
Reaction Time	29	$+4.7 \times 10^{-5}$ (–0.1209, +0.1210)	0.999			
Sustained Attention	37	+0.0696 (–0.0892, +0.2283)	0.390			$\sigma_1^2 = 0.001$
Tracking Performance	89	–0.0790 (–0.1659, +0.0079)	0.075	55.5	<0.001	$\sigma_2^2 = 0.001$
Working Memory	148	–0.0356 (–0.1261, +0.0548)	0.439			$\sigma_3^2 = 0.045$
Cannabis Use Behaviour	–	–	–			
[a]Other Users	483	–	–			
Regular Users	91	+0.1707 (+0.0572, +0.2843)	**0.003**			
Route of Administration	–	–	–			
[a]Smoking	296	–	–			
Vaporisation	278	–0.0898 (–0.1658, –0.0138)	**0.021**			
Dose of Δ^9-THC	23; 21 (10, 26)	–0.0048 (–0.0073, –0.0024)	**<0.001**			
Time Interval	155; 110 (45, 240)	+0.0005 (+0.0004, +0.0007)	**<0.001**			
Inhaled Δ^9-THC Model ("Regular" Users, Only) (*n* = 59 effect estimates):						
Intercept	–	–0.5614 (–0.9849, –0.1379)	0.101			
Performance Domain	–	–	–			
[a]Conflict Control	19	–	–			
Fluid Intelligence	13	–0.1017 (–0.2635, +0.0601)	0.213			
Sustained Attention	12	+0.0494 (–0.4163, +0.5150)	0.832			$\sigma_1^2 = 0.009$
Tracking Performance	15	+0.1443 (–0.0279, +0.3165)	0.099	36.5	0.061	$\sigma_2^2 = 0.011$
Route of Administration	–	–	–			$\sigma_3^2 < 0.001$
[a]Smoking	20	–	–			
Vaporisation	39	+0.2081 (–0.1142, +0.5305)	0.201			
Dose of Δ^9-THC	30; 21 (21, 26)	+0.0034 (–0.0057, +0.0124)	0.462			
Time Interval	72; 40 (40, 60)	+0.0004 (–0.0008, +0.0017)	0.508			
Inhaled Δ^9-THC Model ("Other" Users) (*n* = 481 effect estimates):						
Intercept	–	–0.0999 (–0.2553, +0.0555)	0.207			
Performance Domain	–	–	–			
[a]Conflict Control	29	–	–			
Divided Attention	97	–0.1877 (–0.3134, –0.0621)	**0.004**			
Information Processing	78	–0.2419 (–0.3704, –0.1135)	**<0.001**			
SDLP (Only)	16	–0.2112 (–0.3826, –0.0399)	**0.016**			
Reaction Time	22	–0.1080 (–0.2786, +0.0627)	0.214			$\sigma_1^2 < 0.001$
Sustained Attention	25	+0.0073 (–0.1679, +0.1824)	0.935	30.8	0.096	$\sigma_2^2 = 0.004$
Tracking Performance	74	–0.1894 (–0.3088, –0.0700)	**0.002**			$\sigma_3^2 = 0.013$
Working Memory	140	–0.1318 (–0.2541, –0.0094)	**0.035**			
Route of Administration	–	–	–			
[a]Smoking	256	–	–			
Vaporisation	225	–0.0233 (–0.1219, +0.0753)	0.642			
Dose of Δ^9-THC	22; 18 (10, 25)	–0.0082 (–0.0112, –0.0053)	**<0.001**			
Time Interval	171; 120 (60, 240)	+0.0005 (+0.0004, +0.0007)	**<0.001**			
Oral Δ^9-THC Model (*n* = 243 effect estimates):						
Intercept	–	–0.3345 (–0.5284, –0.1405)	**<0.001**			
Performance Domain	–	–	–			
[a]Conflict Control	11	–	–			
Divided Attention	42	+0.2833 (+0.0422, +0.5243)	**0.022**			
Fine Motor Function	32	+0.2314 (–0.0056, +0.4684)	0.056			
Information Processing	46	+0.1278 (–0.1114, +0.3670)	0.294			$\sigma_1^2 = 0.011$
Reaction Time	18	+0.1832 (–0.0187, +0.3852)	0.075	40.7	0.003	$\sigma_2^2 = 0.003$
Sustained Attention	11	+0.2960 (+0.0219, +0.5701)	**0.034**			$\sigma_3^2 = 0.015$
Tracking Performance	33	+0.1118 (–0.1299, +0.3535)	0.363			
Working Memory	50	+0.3092 (+0.0778, +0.5407)	**0.009**			
Dose of Δ^9-THC	21; 15 (10–25)	–0.0087 (–0.0129, –0.0046)	**<0.001**			
Time Interval	238; 180 (120–360)	–0.0002 (–0.0005, +0.0001)	0.267			
Time Interval (Curvilinear)	–	$+2.0 \times 10^{-6}$ ($+1.0 \times 10^{-6}$, $+3.0 \times 10^{-6}$)	**0.007**			

SDLP: Standard Deviation of Lane Position. *a*: Reference group in analyses of categorical variables. Analyses were performed as per Sect. 2.6.3b 'Meta-Regression Analysis'. Details of included studies are summarised in Table 5 and presented in Supplementary File 4. A description of each cognitive task can be found in Supplementary File 2. All effect estimates included in the analysis of oral Δ^9-THC model were derived from trials of "Other Users" (none of those derived from "Regular Users" were eligible for inclusion). The Post-Treatment Time Interval covariate was centred in the orally administered Δ^9-THC analysis; all values substituted into this equation should therefore be centred (i.e. by subtracting the mean value (see 'Effect estimates (*n*)/Mean; Median (IQR)').

Table 9
Summary of the Δ^9-THC's predicted effects of on car driving and related cognitive functions.

		Predicted 'Peak' Effect at 20 mg Δ^9-THC [a] (Other Cannabis Users, Only) (Hedges' *g*)			Predicted 'Recovery' Time at 20 mg Δ^9-THC [b] (Other Cannabis Users, Only) (min)		
Cognitive Domain	Δ^9-THC Effect [c]	Smoked	Vaporised	Oral [d]	Smoked	Vaporised	Oral
Cognitive Functions:							
Divided Attention	Negative	–0.45	–0.48	–0.23	383	428	- [e]
Tracking Performance	Negative	–0.45	–0.48	–0.40	386	430	573
Information Processing	Negative	–0.51	–0.53	–0.39	486	530	557
Conflict Control	Negative	–0.26	–0.29	–0.51	<60	71	665
Fluid Intelligence	Negative	–	–	–	–	–	–
Reaction Time	Negative	–0.37	–0.40	–0.33	232	276	492
Fine Motor Function	Negative	–	–	–0.28	–	–	415
Gross Motor Function	-	–	–	–	–	–	–
Sensory Discrimination	Unclear	–	–	–	–	–	–
Time Perception	Unclear	–	–	–	–	–	–
Sustained Attention	Negative	–0.26	–0.28	–0.22	<60	<60	- [e]
Working Memory	Negative	–0.40	–0.42	–0.20	277	321	- [e]
Car Driving:							
Lateral Control	Negative						
SDLP (Only)	Negative	–0.48	–0.50	–	427	472	–
Speed	Unclear	–	–	–	–	–	–
Speed Variability	Unclear	–	–	–	–	–	–
CF Headway	Unclear	–	–	–	–	–	–
CF Headway Variability	Unclear	–	–	–	–	–	–
Reaction Time	Negative	–	–	–	–	–	–
[a]Other	–	–	–	–	–	–	–
Aggregate Effect [f]	–	–0.40	–0.42	–0.32	300	350	480

'-': Could not be calculated; CF: Car Following; SDLP: Standard Deviation of Lane Position. All negative effect estimates indicate a detrimental effect of Δ^9-THC, irrespective of the performance outcome. *a*: Values predicted on the basis of the 'Inhaled Δ^9-THC Model ("Other" Users)' in Table 8; *b*: 'Recovery Time' taken as the length of time required for Δ^9-THC's effects to dissipate to a level at which they are unlikely to have a "meaningful" impact on performance – that is, Hedges' $g = -0.25$ (with values predicted on the basis of the 'Oral Δ^9-THC Model' in Table 8); *c*: Based on the results of the meta-analyses of 'peak' Δ^9-THC effects; *d*: 'Peak' effect predicted to occur 283 min post-Δ^9-THC treatment; *e*: The 'peak' effect at a Δ^9-THC dose of 20 mg is predicted to be less impairing than Hedges' $g = -0.25$.

[Only], Reaction Time) and driving-related cognitive skills (i.e. Fluid Intelligence, Divided Attention, Tracking Performance, Information Processing, Conflict Control, Reaction Time, Fine Motor Function, Sustained Attention, Woking Memory) exhibited significant impairment in the initial meta-analyses of "peak" Δ^9-THC effects. While significant changes were not identified for some other skills (i.e. CF Headway, CF Headway Variability, Speed, Speed Variability, Sensory Discrimination, Time Perception), these results should be interpreted with caution as relatively few studies were available in these domains. Additionally, although this review found no effect of Δ^9-THC on *accuracy* of Time Perception; that is, how far the estimated times were from the target times, other studies report significant effects on *absolute* Time Perception – indicating *change* in perception, but not *impairment* per se (Anderson et al., 2010b; McDonald et al., 2003; Sewell et al., 2013). Δ^9-THC could also affect time perception in both directions; that is, it could increase the likelihood of both over- and under-estimation on time estimation and time reproduction tests, thus, increasing the spread of the data set without altering the mean performance score. The initial meta-analyses also revealed a non-significant trend for a positive effect of Δ^9-THC on driving speed (i.e. *reduced* average speed), suggesting drivers may attempt to expand their "safety margins" when operating a vehicle under the influence of Δ^9-THC (likely due to reduced driving confidence (Arkell et al., 2019, 2020)).

The current study used multiple meta-regression analyses to generate mathematical models that could predict the magnitude and duration of Δ^9-THC-induced impairment. While the first model was found to be limited in its ability to simultaneously describe inhaled Δ^9-THC's effects in 'Regular' and 'Other' (mostly occasional) cannabis users, it did reveal significant differences between these populations. Specifically, Regular Cannabis Use (i.e. weekly or more often) was associated with less cognitive impairment following acute Δ^9-THC administration. A recent systematic review likewise concluded that cannabis has less pronounced behavioural and physiological effects in regular (than occasional) users (Colizzi and Bhattacharyya, 2018). Indeed, pharmacodynamic events such as downregulation of the cannabinoid type 1 receptor, receptor conformational change, and receptor internalisation have been proposed to explain the observed tolerance to Δ^9-THC's effects (Ramaekers et al., 2020).

It is, however, important to acknowledge the limitations of this analysis. First, the Other Cannabis Users are a heterogeneous population, as studies often included participants who used cannabis at different frequencies. Second, it should be acknowledged that studies of Regular Cannabis Users used a variety of methods to 'standardise' participants' pre-trial cannabis intakes. Specifically, some instructed participants to: (1) abstain for ≥24 h (Brands et al., 2019; Mason et al., 2019; Spronk et al., 2016); (2) abstain overnight or on the morning prior to testing (Ramaekers et al., 2016; Weinstein et al., 2008); (3) continue using cannabis as 'usual' (Ramaekers et al., 2009; Van Wel et al., 2013); or (4) did not specifically state their method (Matheson et al., 2020). Each of these approaches has the potential to elicit subtly different effects (e.g. due to residual Δ^9-THC in blood or the development of withdrawal symptoms (Budney et al., 2008)). Finally, it is important to recognise that although Regular Cannabis Users appear to be less impaired than Other Cannabis Users when administered a fixed dose of Δ^9-THC, some of these individuals (e.g. recreational cannabis users) might use larger doses of Δ^9-THC (i.e. because of their increased tolerance to its effects), resulting in an equivalent amount of impairment.

None of the covariates included in the subsequent meta-regression analysis of inhaled Δ^9-THC's effects in Regular Cannabis Users (*only*) were significantly related to effect size. This may reflect the fact that most outcomes were measured under similar experimental conditions; that is, between 20–60 min post-treatment (90 % of outcomes) and at a dose of 21–26 mg Δ^9-THC (71 % of outcomes).

In contrast, several covariates were significantly related to effect size in the analysis of inhaled Δ^9-THC's effects in Other Cannabis Users (*only*). Specifically, cognitive impairment increased with Δ^9-THC Dose and decreased over the Post-Treatment Time Interval; it also varied across the Performance Domains. The model therefore explained a relatively large proportion of the variance observed (pseudo-$R^2 = 0.64$) and was used to predict the magnitude and duration of Δ^9-THC-induced

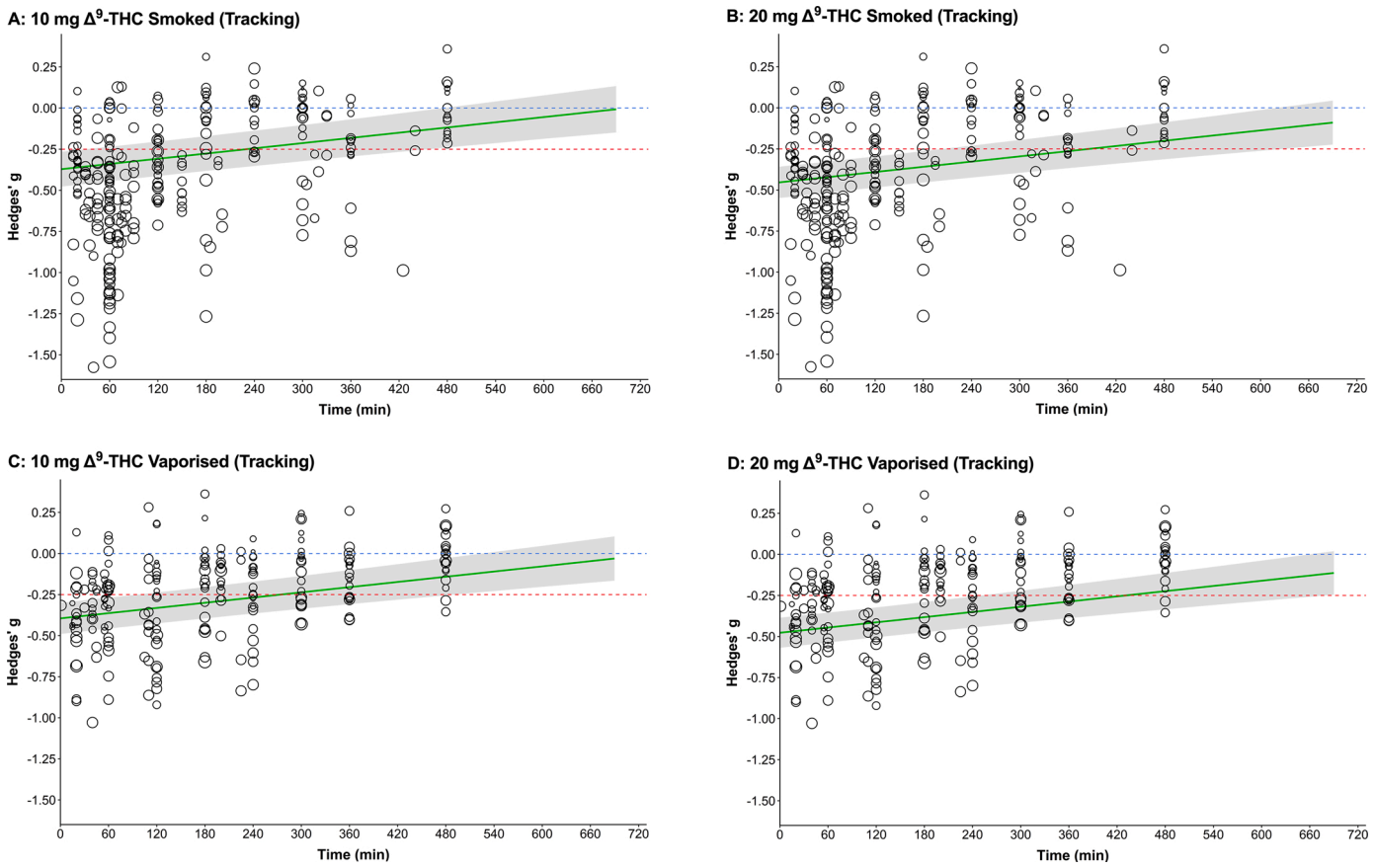

Fig. 2. The predicted relationship between the Post-Treatment Time Interval and the Hedges' *g* (95 % CI) effect of Δ^9-THC on tracking performance (as an example) when administered via (A) Smoking (10 mg); (B) Smoking (20 mg); (C) Vaporisation (10 mg); and (D) Vaporisation (20 mg) (based on models presented in Table 8). These predictions are based on 'Other Cannabis Users' (only). 'Smoked' outcomes only shown in Figures A and B and 'Vaporised' outcomes only shown in Figures C and D (although all outcomes contributed to both regression models). Red line represents a Hedges' g effect of –0.25 (likely recovered or minimal impairment detected) and the blue line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Actual (uncontrolled) effect estimates shown.

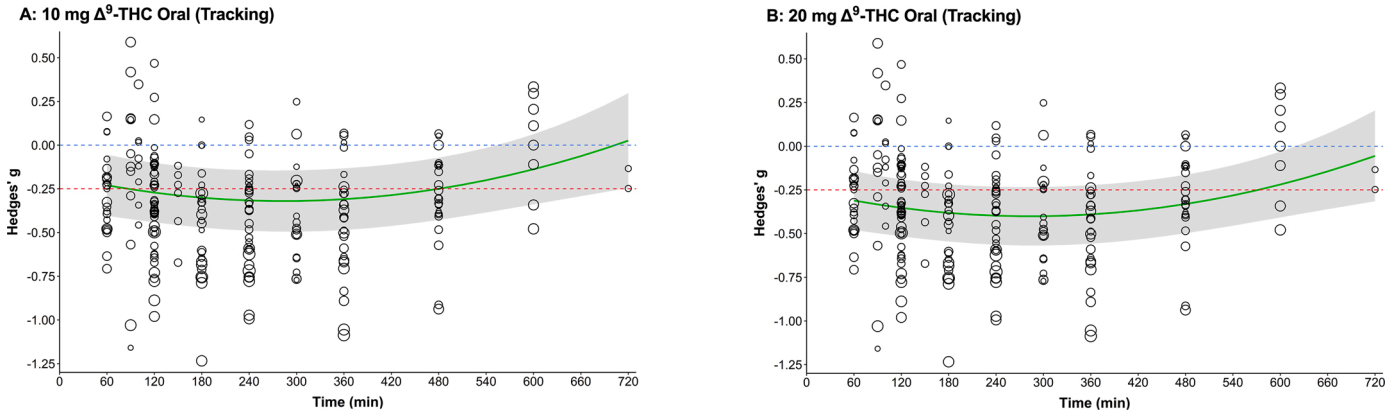

Fig. 3. The predicted relationship between the Post-Treatment Time Interval and the Hedges' *g* (95 % CI) effect of Δ^9-THC on tracking performance (as an example) when administered via (A) Oral (10 mg); and (B) Oral (20 mg) (based on models presented in Table 8). These predictions are based on 'Other Cannabis Users' (only). Red line represents a Hedges' g effect of –0.25 (likely recovered or minimal impairment detected) and the blue line represents a Hedges' g effect of zero. Circle diameter corresponds to the weight of each effect estimate. Actual (uncontrolled) effect estimates shown.

impairment (as illustrated in Table 9). Indeed, our analyses suggest that most driving-related cognitive skills recover (Hedges' *g*=–0.25) within ~3- and ~5-hs of inhaling 10 and 20 mg of Δ^9-THC, respectively (with almost all recovering within ~5- and ~7-hs, respectively).

The residual variance in both models could be due to a number of factors including: (1) the dose of Δ^9-THC being quantified as an *absolute*, rather than *relative*, amount (as too few studies reported participants' body weight to calculate relative doses); (2) the heterogenous cannabis use behaviour of the Other Cannabis Users and the different methods used to 'standardise' the pre-trial cannabis intakes of Regular Cannabis Users (as discussed above); (3) the fact that some studies administered Δ^9-THC in combination with placebo treatments (e.g. placebo alcohol),

tobacco and other cannabinoids and/or cannabis constituents; and (4) the variety of driving and neuropsychological tests employed with differing demands and sensitivities. Results should therefore be interpreted with some consideration that these potential moderators are not captured in the model. The extent to which different populations and contexts are represented in each model should also be considered. For example, these findings may be limited in their generalisability to females as they were underrepresented in the sample – particularly given that the dose was not relative and that Δ^9-THC has been reported to elicit different effects between sexes (Anderson et al., 2010a, b; Matheson et al., 2020).

Several covariates were also significantly related to effect size in the multiple meta-regression analysis of oral Δ^9-THC's effects. Specifically, cognitive impairment increased with Δ^9-THC Dose and differed across the Performance Domains and Post-Treatment Time Interval. That is, oral Δ^9-THC-induced impairment indicated a curvilinear (U-shaped) relationship with time (broadly comparable to that of its pharmacokinetic profile (Vandrey et al., 2017)). While this model was considered adequate to estimate the magnitude and duration of oral Δ^9-THC's cognitive effects (see Table 9), the larger amount of unexplained variance (pseudo-$R^2 = 0.28$) (i.e. compared to the model of inhaled Δ^9-THC) suggests that results should be interpreted with greater caution. This additional variability may be a consequence of oral Δ^9-THC's complex pharmacokinetic profile. In particular, the fact that time to reach peak blood Δ^9-THC and 11-OH-Δ^9-THC concentrations (T_{max}) tends to differ as a function of dose (i.e. higher oral doses may have longer T_{max} values than lower oral doses) (Vandrey et al., 2017); which is not typically the case for inhaled Δ^9-THC (Spindle et al., 2019) and could not be captured in this meta-regression model. Oral Δ^9-THC absorption can also be erratic, leading to an inconsistent pharmacokinetic response (Ohlsson et al., 1980). Nonetheless, this model offers some insight to the time course of oral Δ^9-THC-induced cognitive impairment (as illustrated in Table 9) suggesting that impairment of most driving-related cognitive skills takes ~8-hs to subside (Hedges' g=–0.25) after oral consumption of 20 mg of Δ^9-THC.

The results of the current review suggest that some measures of driving performance and driving-related cognitive skills may be more sensitive to the impairing effects of Δ^9-THC than others. It is also interesting to note that SDLP (Only) was one of the outcomes that demonstrated the greatest sensitivity to Δ^9-THC's effects (although it could only be investigated in the model of inhaled Δ^9-THC's effects in Other Cannabis Users). This finding highlights the importance of simulated and on-road driving studies in this area of research.

This review identified a small number of studies investigating the acute effects of Δ^9-THC on driving-related cognitive skills in clinical populations (e.g. psychotic disorders, diabetic neuropathy, Tourette syndrome, attention deficit hyperactivity disorder [ADHD], dementia). The medical conditions studied were too heterogenous to consolidate into a meaningful meta-analysis. Nonetheless, results were relatively consistent with Δ^9-THC indicating either a small negative or positive Hedges' g effect on the majority (87 %) of outcomes examined. These subtle (in most instances, non-significant) effects could partly reflect the low doses of Δ^9-THC (e.g. $\leq$ 5.0 mg orally) administered in some studies. However, these doses were still sufficient to elicit some therapeutic effects (e.g. decreased hyperactivity and impulsivity in ADHD, decreased neuropathic pain) (Cooper et al., 2017; Wallace et al., 2015). Alternatively, it is possible that Δ^9-THC ameliorated clinical symptoms that were previously impairing cognitive and psychomotor performance, thereby offsetting its detrimental effects. Further research investigating the impact of therapeutically-relevant Δ^9-THC doses on measures of driving performance and associated cognitive skills in clinical populations is therefore warranted. Importantly, the results of the above meta-regression analyses suggest that a chronic dosing phase (allowing for adaptation to Δ^9-THC's effects) should also be utilised in such studies with patients. The fact that medical cannabis users are almost invariably regular users seeking to reverse troubling clinical symptoms limits the applicability of the findings of the current review to this specific population.

This review has several other limitations. First, only English language articles were included. Second, of the 1456 outcomes (derived from studies of healthy participants) in this review, 31 % (445) were ineligible for quantitative synthesis because an effect estimate could not be calculated, or the outcome was derived from a study that scored <50 % on the Rosendal scale; additional outcomes and studies were also excluded because results were not adequately reported (Supplementary Files 1 & 2). Third, the meta-regression models developed assume a fixed rate of recovery at a given dose of Δ^9-THC, route of administration and performance domain. Fourth, as trials often measured cognitive performance multiple times and/or on multiple tasks generating multiple outcomes, these contributed different amounts of data to the review; the current analyses are therefore biased toward studies that contributed more effect estimates. However, given the aim of this review, it would not have been appropriate to average effect estimates across multiple measures (Scammacca et al., 2014)). Fifth, the few studies that measured driving performance or a driving-related cognitive skill >12 h following acute Δ^9-THC administration were excluded to minimise the influence of their unique confounding factors (e.g. sleep, access to cannabis between assessments). Finally, a limitation of the research area as a whole is the small number of studies involving regular cannabis users and longer post-treatment time intervals (e.g. 4–6 h).

This systematic review used evidence from recent studies investigating the acute effects of Δ^9-THC on car driving performance and discrete cognitive skills related to car driving to generate meta-regression models that predict the magnitude and duration of Δ^9-THC-induced impairment. Findings suggest individuals should wait at least 5-hs following inhaled cannabis use before performing safety-sensitive tasks, although the recovery time required will depend on several factors (in particular, Δ^9-THC dose); oral Δ^9-THC-induced impairment may also take longer to subside. Further research involving regular cannabis users and longer post-treatment time intervals would permit better characterisation of Δ^9-THC's effects and help inform the development of guidelines and drug-driving legislation to promote safe driving practices following Δ^9-THC and cannabis use.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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