Title

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Driving performance and cannabis users' perception of safety:

A randomized clinical trial of smoked cannabis of different THC content

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Key Points

Question: What factors affect the impact of smoked cannabis on driving and the users' perception of driving ability?

Findings: In this randomized trial of 191 regular cannabis users, simulator driving worsened in those smoking THC vs placebo, but this was not universal, and unrelated to THC content (5.9% v 13.4%), use history, or blood THC concentration. Performance recovery was complete at 4.5h, while perception of impairment lessened starting at 1h 30min.

Meaning: When users control their own intake, one cannot infer impairment based upon the product THC content, and the disconnect between performance and self-perceived impairment is important for public safety messaging.

Abstract

Importance: Expanding cannabis medicalization and legalization increases the urgency to understand the factors associated with acute driving impairment.

Objective – To determine, in a large sample of regular cannabis users, the magnitude and time course of driving impairment produced by smoked cannabis of different THC content, the effects of use history, and concordance between perceived impairment and observed performance.

Design – Double-blind, placebo-controlled parallel randomized clinical trial (February 2017-June 2019)

Setting – Center for Medicinal Cannabis Research, University of California San Diego

Participants – Cannabis users (N=191)

Intervention – Placebo, 5.9% THC or 13.4% THC cannabis smoked *ad libitum*

Main Outcome and Measures: The primary endpoint was the Composite Drive Score (CDS), comprised of key driving simulator variables, assessed prior to smoking and at multiple timepoints post-smoking. Additional measures included self-perceptions of driving impairment and cannabis use history.

Results: Participants were 61.8% male, age 29.9 (8.3) y, with a mean of 16.7 (9.8) days of use in the past month. Compared to Placebo, the THC group significantly declined on CDS at 30min (Cohen's d=.59 [95% CI .28, .90]; p<0.001) and 1h 30min (Cohen's d=.55 [95% CI .24, .86];

p<.001), but not at 3h 30min or 4h 30min. The THC group performed worse than the placebo group on average, yet a sizeable proportion exhibited performance similar to the placebo group. CDS did not differ based on THC content (*p*=.349) or use intensity (quantity x frequency) in the past 6 months (*p*=.964). However, post-smoking blood THC concentrations were higher in individuals with the highest use intensity. Participants reported increased readiness to drive at 1h 30min despite performance being similar to that observed at 30min.

Conclusions and relevance: Smoking cannabis ad libitum by regular users resulted in simulated driving decrements that fully resolved by 4h 30min, but not all drivers' performance declined. Perceived impairment was generally consistent with actual driving performance at 30min. However, increasing numbers of THC participants conveyed being ready to drive in the subsequent hour, even though there was no substantive improvement in performance, possibly indicating a false sense of driving safety. When users control their intake, driving impairment cannot be inferred based on THC content, behavioral tolerance, or THC blood concentration. Further research is needed on the impact of individual biologic differences, cannabis use history, and administration methods on driving performance.

Trial registration: Clinicaltrials.gov: NCT02849587

INTRODUCTION

As jurisdictions legalize cannabis for medicinal and recreational use, there are growing concerns regarding a potential increased prevalence of cannabis-impaired drivers[1, 2]. Acute consumption of ∆9-tetrahydrocannabinol (THC) negatively affects cognitive functioning[3] and reduces driving performance, particularly in lane position control (standard deviation of lateral position [SLDP])[4-9], and ability to adjust to lead car speed changes (car following[10]). However, epidemiological data regarding the impact of legalization on crash risk are not consisent[11-14]. The varied findings partially reflect challenges in accessing robust pre- and post-legalization data and determining acute intoxication[1], but also show a disconnect between impairing effects observed in controlled studies and expectations regarding crash rates.

Questions remain regarding the magnitude and time course of the effects of cannabis on those most likely to be on the road – regular users smoking to a desired level of intoxication - as well as the impact of different product THC amounts. While seminal studies examined these questions, most utilized small sample sizes (e.g.,<25 participants), low THC content product within a cross-over design, and structured dosing protocols, with some exceptions, for example using an ad libitum approach[5]. Such studies provide critical data regarding THC dose effects, but do not reflect real-world use. This is particularly important given concerns that the increasing THC content of products may result in greater impairment. Small sample sizes may also limit generalizability, while cross-over designs using psychoactive substances present blinding challenges[15].

The appropriate waiting period before driving after cannabis smoking is also a significant public safety concern, with some suggesting 3-5h[16-18], and others recommending longer[19]. Since this decision may be self-determined based upon “feeling impaired”, it is important to understand the accuracy of these self-evaluations. In addition, while frequency of cannabis use is associated with increased behavioral tolerance[20], the relationship to driving remains poorly understood, because individuals may counteract tolerance by consuming greater amounts to

achieve desired psychoactive effects. Recent systematic reviews concluded that major limitations in cannabis-related driving research include a lack of studies examining regular users over a 4-6 hour post-smoking timeframe[21], as well as small sample sizes[22].

Within a sample of nearly 200 regular cannabis users instructed to smoke cannabis as they do at home to achieve a usual level of intoxication, the aims of this study were to determine, with respect to driving outcomes, the 1) magnitude and time course of effects, 2) impact of cannabis with different THC amounts, 3) possible tolerance effects, and 4) accuracy of self-perception of impairment. The primary outcome was the Composite Drive Score (CDS), a measure comprised of key driving simulator variables.

METHODS

The study was approved by the Human Research Protections Program at the University of California, San Diego, the U.S. Food and Drug Administration, and the Research Advisory Panel of California, and conducted in accordance with the Declaration of Helsinki.

Participants

Participants were recruited in San Diego via fliers, community outreach, and clinicaltrials.gov. Inclusion criteria were age 21-55 years, cannabis use $\geq$4 times in the past month, holding a valid driver's license, driving at least 1,000 miles in the past year, and willing to abstain from cannabis for 2 days prior to the training and experimental study days.

Exclusion criteria were history of traumatic brain injury, significant cardiovascular, hepatic or renal disease, uncontrolled hypertension, chronic pulmonary disease, positive pregnancy test, positive urine screen for cocaine, amphetamines, opiates, and phencyclidine, current (past year) substance use disorder (no participant met criteria for cannabis use disorder) history of schizophrenia, bipolar depression with mania and/or current suicidal ideation,

unwilling to refrain from driving after consuming study medication, and oral fluid THC > 5ng/mL on the testing day. Participants provided written informed consent.

Study Design

This was a double-blind, placebo-controlled, parallel clinical trial in which participants were randomized using permuted blocks stratified by prior cannabis exposure (using ≥4x per week or <4x per week in the past month, based upon stratifications that previously differentiated among users[9, 23]) to smoke a cannabis cigarette with either 13.4%, 5.9%, or 0.02% THC (placebo) content. Participants were instructed to abstain from cannabis for 48h prior to the training and experimental days and underwent a 1h simulator training session prior to the testing day. The training session exposed participants to all of the individual components of the drive, culminating in a 25-minute drive similar to what they would encounter on the testing day. On the experimental day, they completed a urine drug screen and breathalyzer for alcohol and drugs, and oral fluid (OF) sample for THC presence (Draeger 5000, Houston, TX). If the OF was positive (>5ng/mL THC), suggesting relatively recent use, the assessment was canceled. OF samples were also quantified by liquid chromatography/tandem mass spectrometry (LC-MS/MS) as the final indicator of possible recent use, with participants OF >5ng/mL THC excluded from analyses.

Participants completed driving simulations and blood collections prior to and following cannabis smoking (detailed toxicology findings reported elsewhere[24, 25]).

Driving Simulations

Driving simulations, approximately 25 minutes in length, were presented on a STISIM M300WS-Console Driving Simulator System (Systems Technology, Inc; Hawthorne, CA) consisting of 3-screen, wide field-of-view monitors, steering wheel, and accelerator and brake pedals, and programmed using STISIM Drive v3.14[26]. The simulations emulated city and

country driving, including common traffic challenges (e.g., freeway merging), as well as scenarios providing outcomes similar to those widely used in drug-impaired driving studies[5, 7, 8, 27]. At a specified distance, the mSuRT, modified from the Surrogate Reference Task[28], required participants to maintain their lane position and speed in a straight roadway, while responding to a divided attention task on an iPad to the side of the dashboard. Key variables included standard deviation of lateral position (SDLP) or "swerving", standard deviation (variability) of speed, and number of correct divided attention stimuli identified while driving. At another distance, Car Following required participants to adjust their speed to a lead car that speeds up and slows down according to a sinusoidal wave. The key variable is coherence between the participant and lead car (a correlation ranging from 0–1). A Composite Drive Score (CDS), comprised of the key variables described above, normalized to a common metric (z scores derived from the pre-smoking drive of all 191 participants), was calculated to globally represent driving performance and, by not being dependent upon a single outcome variable, provide a more stable indicator of driving performance (see **Supplemental Materials**). A higher score indicated worse performance. Similar approaches have been used elsewhere[29, 30], and address concerns regarding the use of multiple dependent outcomes in cannabis and driving research[22]. Post-smoking driving simulations occurred approximately 30min, 1h 30min, 3h 30min, and 4h 30min after smoking.

Study Drug and Administration

Bulk cannabis plant material containing 5.9% THC, 13.4% THC, or placebo was acquired from the NIDA Drug Supply Program and hand-rolled into 700 mg cigarettes. An *ad libitum* regimen was utilized within a negative pressure room, with participants instructed to "*Smoke the cigarette the way you do at home to get high. You may take up to 10 minutes*." A minimum of 4 puffs was required. Venous blood was collected from an indwelling intravenous arm catheter (See **Supplemental Materials**).

Perceptions of impairment

After smoking, but prior to each driving session, participants were asked “How high are you?”, “How impaired are you to drive?” (both ratings from 0 [not at all] to 100 [Extremely]), and “Would you drive in your current state?” (yes/no). After each post-smoking driving session participants were asked “How much did the study drug affect your driving?” (0 [not at all] to 100 [Extremely]), as well as “How well did you drive?” (0 [Not at all well] to 100 [Extremely well]).

Statistical analysis

Generalized least squares models were employed for numeric outcomes with covariance structure selected by minimum Akaike Information Criterion (AIC). Poisson and logistic regression models with generalized estimating equation (GEE) method were used for discrete and binary outcomes, respectively. Time was treated as a factor to accommodate non-linear changes in the outcomes. Treatment was first considered as a three-level variable - Placebo, 5.9% THC, and 13.4% THC, and then as a two-level treatment variable (Placebo and THC) where the 5.9% and 13.4% groups were combined. For all models, three terms were included: treatment, time (5 time points), and treatment-time interaction. For effect sizes estimating differences at multiple time points, correction for multiple comparisons was applied using false discovery rate (FDR) method (subscore and secondary analyses only).

Cannabis use intensity, estimated as total THC exposure, was based upon self-reported frequency and quantity of use in the past 6 months using a timeline follow-back approach, and split into 3 groups (lowest quartile, two middle-quartiles combined, and highest quartile). See **Supplemental Materials**.

RESULTS

A total of 261 individuals were screened for eligibility, with 199 randomized to one of three arms - placebo, 5.9% THC, or 13.4% THC (**Figure 1**). Seven were subsequently excluded due to pre-smoking elevated oral fluid THC levels and 1 withdrew immediately post-smoking. The final sample was 191 participants (61.8% male, mean age of 29.9 (8.3) y) who used cannabis a mean of 16.7 (9.8) days in the past 30, approximately 1 cigarette (.5 gms) when using, with 51.3% using <4 times per week. There were no significant group differences on key background variables (**Table 1**).

Smoking topography and blinding. There were no significant group differences in grams of cannabis/placebo material used during the session (estimated from the weight returned) – Placebo: 0.47 (.17), 5.9% THC: 0.44 (.17), and 13.4% THC: 0.43 (.15); p=.422. At ~15min after smoking initiation there was a significant difference (p<.001) in blood THC concentrations between all three groups (Placebo: 1.3 (1.9) ng/mL; 5.9 THC%: 50.6 (40.8) ng/mL; 13.4% THC: 32.7 (29.3) ng/mL), with the 5.9% THC group reaching the highest concentration[31]. Ninety-two percent of the THC group correctly guessed their treatment assignment (no difference (p=.613) between the 5.9% THC and 13.4% THC groups); 48.3% of the Placebo group believed they received active THC.

Primary Outcomes

Crashes. There were no significant differences between the 3 groups on the number of crashes at any timepoint (all p>.750).

Composite Drive Score (CDS). Compared to Placebo, the THC groups had a significant decline in CDS performance; there were no differences between the two THC groups in change over time (p>.77; **Figure 2a**). The two groups were thus combined for subsequent analyses (**eFigure 1**).

Table 2 summarizes the CDS results, with change from pre-smoking score as the primary outcome. Compared to changes in the Placebo group, the THC group (column 2c) had

significantly greater declines at 30min and 1h 30min. The differences were no longer statistically significant at 3h 30min (*p*=.067) or 4h 30min (*p*=.869). The CDS did not differ by sex (p=.114) and controlling for sex (since THC/Placebo groups differed: 67.2% vs 50.8% male, respectively; *p* = .039) did not change results. There were no significant practice effects in the Placebo group (column 2a).

While the THC group performed significantly worse than the Placebo group at 30min, many participants performed similarly to those in the Placebo group (**Figure 2b**; **eFigure 2**). Based upon a 15%ile cutpoint in the distribution of CDS change scores from the Placebo group, 45.6% of the THC group would be classified as "impaired" at 30min (see **Supplemental Materials**).

The effect sizes, an indicator of the potential clinical significance of the differences, are shown in **Table 2**, column 2c. When comparing changes in performance, Cohen's *d* was .59 at 30m, .55 at 1h 30m, dropping to .29 at 3h 30m and -.03 at 4h 30m.

Drive Subscores. The changes in performance for the individual driving variables comprising the CDS (collected at the specified distances) were generally consistent with the CDS, showing significant changes at 30min and 1h 30min (**eTable 1**). Differences in changes on the divided attention task were only seen at 30min. In addition, time driving out of lane during the mSuRT was significantly different at 1h 30min.

Perception of effects and performance

After smoking, but prior to driving, the THC group reported being significantly more impaired to drive at all timepoints, with the rating dropping at each timepoint (**eTable 2a**)**.** At 30min, 47.5% of the THC group would drive in their current state; this number increased to 68.6% at 1h 30min, and above 90% at the last two timepoints (**eTable 2b; Figure 2c**).

After driving, the THC group rated cannabis as affecting their performance more than the Placebo group at all timepoints. Their rating of how well they drove, however, was worse than the Placebo group only at 30min (**eTables 3a and 3b**)**.**

Driving performance and THC blood concentrations

Within the THC group, there was no relationship between blood THC concentrations at 30min and the CDS (*r*=.025, p=.780; **Figure 3a**) or any of the subsequent timepoints (**eTable 4**).

Cannabis use history (intensity) and driving performance

Within the THC group, after smoking there were no differences between the groups with the highest, middle, or lowest intensity of use (in the past 6 months) in how high they felt (*p*=.178), nor the CDS changes at 30min (*p*=.243; **Figure 3b**) or across all time periods (*p*=.380). However, post-smoking blood THC concentrations significantly differed across all 3 groups (*p*<.001), with the lowest intensity group having the lowest concentrations (p=.003 vs Middle, p<0.001 vs High) and the highest intensity group having the highest concentrations (p=.079 vs Middle) (**Figure 3c**).

DISCUSSION

In this study of 191 regular cannabis users randomized to smoke THC or Placebo cigarettes *ad libitum*, we found worse performance in the THC group on a measure of overall driving simulator performance, as well as specific driving challenges, including a divided attention task, adding to a growing literature that THC negatively impacts driving ability[5, 32, 33]. The magnitude of the effect was in the medium range (Cohen's d ~0.5[34]), suggesting a non-trivial difference.

The THC participants performed worse than the placebo group on average, yet a sizeable proportion exhibited performance similar to the Placebo group, indicating that a subset in the active drug arm did not experience a significant drop in performance. Based upon the distribution of the Placebo group, approximately one-half of the THC group would be called "impaired", suggesting that accurately identifying those at greatest risk for impairment is not as straightforward as detecting recent use, and remains an important public safety challenge. It is worth noting that alcohol exhibits a more consistent linear effect between blood (alcohol) levels and driving impairment, although even in that case there is significant variability between studies (and individuals) in the relationship between levels of ingestion and reductions in driving [35].

The THC group generally showed good agreement between subjective driving impairment and actual performance at 30min. However, at 1h 30min participants increasingly rated themselves as safe to drive, whereas simulator data indicated on-going reduced driving performance (**Figure 2c**), including being more likely to leave their lane. These first few hours may constitute a period of greatest risk, since users who are self-evaluating whether it is safe to drive may be less likely to refrain from driving or to attempt to compensate for reduced functioning. This is an important topic for public safety messaging, since a goal is to keep impaired drivers off of the road prior to becoming a danger.

In this study of 128 user receiving active drug, THC-associated driving reductions were not fully resolved until 4.5h. At 3.5 hours THC group's driving improved to a point of being statistically indistinguishable from controls, although there remained a small effect (Cohen's d= -0.29) suggesting lingering impairment in some participants. This is generally consistent with the timeframe noted in studies using lower THC content materials[5-7, 36-38]. It is possible that impairments in other, unmeasured abilities may persist[39], or become apparent over longer drives, although a recent 60min on-road study concluded that no negative THC effects were seen 4-5h after use[6].

There was no correlation between blood THC concentrations collected 15min after smoking and simulator performance at 30min, or any other timepoint, even under our highly controlled conditions. In the real world, the time from consumption to a law enforcement stop and subsequent blood collections is highly variable, and the current results reinforce that *per se* laws based upon blood THC concentrations are not supported[33, 40].

When instructed to "*smoke as you would at home to get high*" we found no significant differences in driving performance, nor THC blood concentrations[31], based upon the THC content of the cannabis, supporting the importance of smoking topography (deepness of inhalation, period of holding, etc.)[5, 41-43]. There is concern that the increasing THC content in products will result in significantly greater road safety risks. However, the current study suggests that some users may smoke such products in a manner that results in no greater impairment than lower THC products. These findings do not necessarily translate to other methods of administration, such as dabbing, vaping, and oral consumption where self-titration is more difficult, although a recent study suggests concentrate users may self-titrate[44].

Greater intensity of cannabis use in the past 6 months was associated with reaching higher blood THC concentrations following smoking, but not self-reported greater levels of highness nor worse driving performance, than lower intensity groups, consistent with development of behavioral tolerance[20]. However, the current findings also suggest that when instructed to achieve a self-determined level of highness, users with a history of greater use intensity adapted to tolerance by increasing THC exposure, resulting in performance decrements similar to users with lower intensity use, and that they may not be less of a driving risk. Behavioral tolerance benefits may be more apparent in medicinal users who target specific symptoms (e.g., pain), and maintain a consistent dosing level.

Limitations

This study has a number of limitations. With the aim of maximizing ecological validity, we had individuals smoke to the level of highness they desire, and thus did not address participants reaching particularly elevated highness levels, nor the effects of controlled dosing. It should be noted, though, that studies using “controlled” smoking methods also find substantial variability in blood THC concentrations, suggesting an influence of smoking topography[45]. The study is not generalizable to infrequent or naïve users, vulnerable populations (e.g., older persons, individuals with medical conditions), or other methods of administration for which self-titration is difficult (e.g., edibles). Since the study did not include a non-user control group, the study only addresses how regular users exposed to THC perform on the CDS relative to regular users receiving placebo. There is evidence that acute cannabis use can impair visual function (and driving); we cannot determine the specific correlates of reduced driving (cognitive, visual) since these were not comprehensively assessed[29]. Classification of individuals as “impaired” on experimental driving simulator scenarios is dependent upon the size/composition of the reference group and may differ with other samples. Since no measurements were made between 1h 30min and 3h 30min, we cannot comment on the recovery trajectory during his period. The potential cumulative effects of serial smoking were not addressed. Lastly, while the simulations captured a reasonable sampling of driving behavior, we were unable to address whether performance over longer driving periods might show impairment.

Conclusions

In a placebo-controlled parallel study of regular cannabis users smoking cannabis with different THC content *ad libitum*, there was significant worsening on driving simulator performance at a group level, although in about half of the cases performance was similar to those receiving placebo. Of note, a lack of insight regarding driving impairments, particularly at 90 minutes, is of concern, given that users will likely self-evaluate when they feel safe to drive.

The THC content of the cannabis and prior history of cannabis use were not associated with driving outcomes. Performance was improving at 3.5h, though recovery was not fully seen until 4.5h post-smoking. The lack of relationship between blood THC concentration and driving performance raises questions about the validity of per se laws.

When users control their own intake, one cannot infer level of impairment based upon the THC content of the product, the level of behavioral tolerance in the individual, nor the blood THC concentration. Future research should address factors such as individual biologic differences, personal experience with cannabis, and cannabis administration methods in relation to driving impairment.

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Figure 1. CONSORT diagram showing participant inclusion/exclusion from initial screening to final sample

Figure 2A. Change in Composite Drive Score from baseline: all 3 treatment groups. Values are means±95% CI. ***p<.001, **p<0.01

Figure 2B. Distribution of Changes in the Composite Drive Score from pre-smoking to 30 minutes post-smoking; shapes represent individual values, the box shows 25^{th}, 50^{th} (median), and 75^{th} percentiles.

Figure 2C. Relationship between participant median self-report of driving impairment (green line), willingness to refrain from driving (columns showing percent of participants who would not drive), and Composite Drive Score (dashed line). THC participants only.

Figure 3A. Relationship between whole blood THC concentrations and driving performance at 30m post-smoking (THC group only)

Figure 3B. Change in Composite Drive Score by based on use history in the past 6 mos.–30m timepoint. THC Group only.

562 **Figure 3C**. Whole Blood THC concentrations immediately post-smoking, based on use
563 history in the past 6 mos. THC Group only.
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Table 1. Demographics characteristics of study participants by treatment group

	Placebo (N=63) Mean (SD) or N (%)	5.9% THC (N=66) Mean (SD) or N (%)	13.4% THC (n=62) Mean (SD) or N (%)	P-value
Age (years)	28.1 (7.3)	30.7 (8.8)	30.9 (8.6)	.112
Male	32 (50.8%)	47 (71.2%)	39 (62.9%)	.057
Female	31 (49.2%)	19 (28.8%)	23 (37.1%)	
Education (years)	15.0 (1.9)	14.9 (2.0)	15.3 (2.0)	.437
Race/Ethnicity				.624
African American	8 (12.7%)	6 (9.1%)	4 (6.5%)	
Asian	5 (7.9%)	8 (12.1%)	4 (6.5%)	
Hispanic	15 (23.8%)	19 (28.8%)	22 (35.5%)	
Indigenous	5 (7.9%)	2 (3.0%)	1 (1.6%)	
Multiracial	2 (3.2%)	3 (4.5%)	2 (3.2%)	
Non-Hispanic White	28 (44.4%)	28 (42.4%)	27 (43.5%)	
Unknown	0	0	2 (3.2%)	
Miles driven past year*	8,730 [5,420, 12,825]	9,300 [5,298, 12,665]	8,280 [5,040, 13,320]	.973
Cannabis				
Current Cannabis Use<4 times/week	34 (54.0%)	33 (50.0%)	31 (50.0%)	.875
Days used (last 30 days)	16.9 (9.7)	16.0 (9.6)	17.3 (10.2)	.769
Grams/day when using (last 30 days)*	.55 [.25, 1]	.55 [.3, 1]	.50 [.25, 1]	.620

*Median [interquartile range]

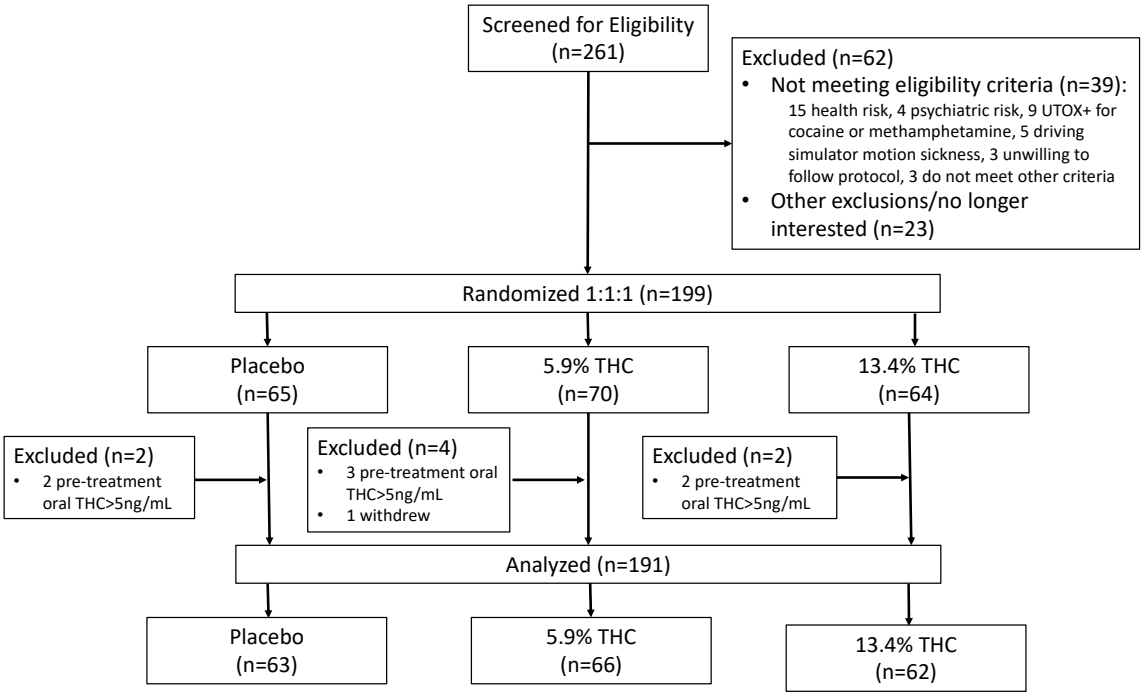
Table 2. Composite Drive Score for the Placebo and THC groups at each timepoint.

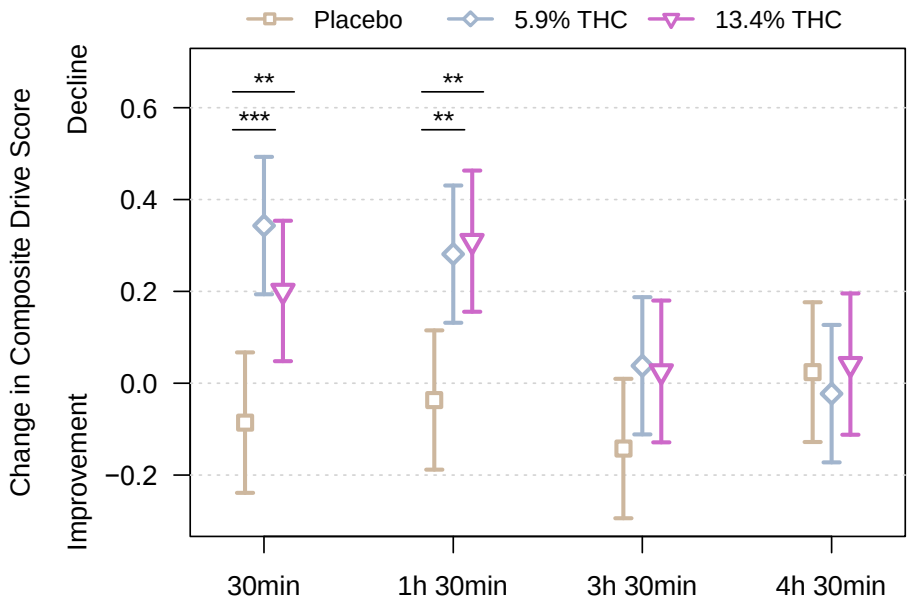
	1. Composite Drive Score		*2. Change in Mean Composite Drive Score from Time 1*					
	a. Mean (SD)		*a. Placebo*		*b. THC*		*c. Difference (THC vs Placebo)*	
	Placebo	*THC*	*Cohen's d (95% CI)*	*P-value*	*Cohen's d (95% CI)*	*P-value*	*Cohen's d (95% CI)*	*P-value*
Time 1 (pre-smoke)	-0.09 (0.64)	0.06 (0.55)	---	---	---	---	---	---
Time 2 (30min)	-0.17 (0.61)	0.34 (0.61)	-0.14 (-0.39, 0.11)	.273	**0.45 (0.28, 0.63)**	**<.001**	**0.59 (0.28, 0.90)**	**<.001**
Time 3 (1h 30min)	-0.13 (0.61)	0.36 (0.62)	-0.06 (-0.31, 0.19)	.638	**0.49 (0.31, 0.67)**	**<.001**	**0.55 (0.24, 0.86)**	**<.001**
Time 4 (3h 30min)	-0.23 (0.59)	0.10 (0.61)	-0.24 (-0.49, 0.02)	.067	0.05 (-0.13, 0.23)	.562	0.29 (-0.02, 0.60)	.067
Time 5 (4h 30min)	-0.07 (0.66)	0.07 (0.57)	0.04 (-0.21, 0.29)	.756	0.01 (-0.16, 0.19)	.877	-0.03 (-0.33, 0.28)	.869

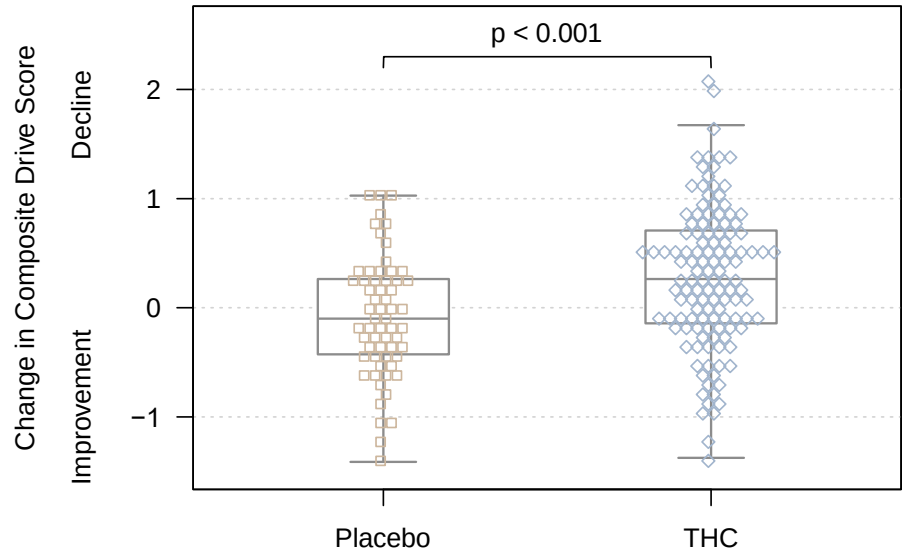
SD = standard deviation, CI = confidence interval, h = hour, m = minutes. Bold font indicates results with p<0.05.

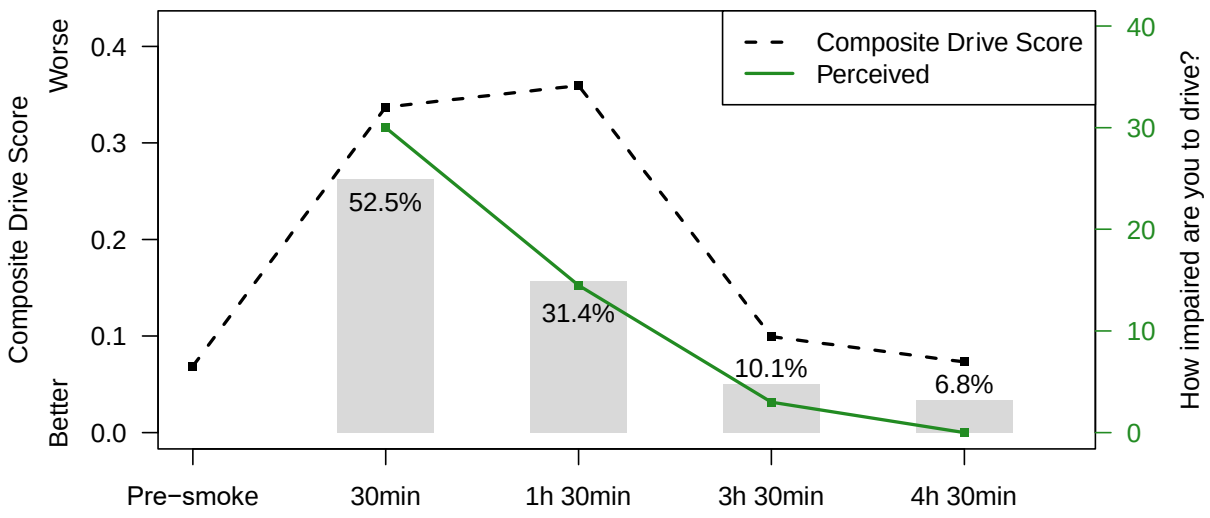
Note: The test for the overall significance in differences of changes between the THC and the Placebo was statistically significant (P<0.001).

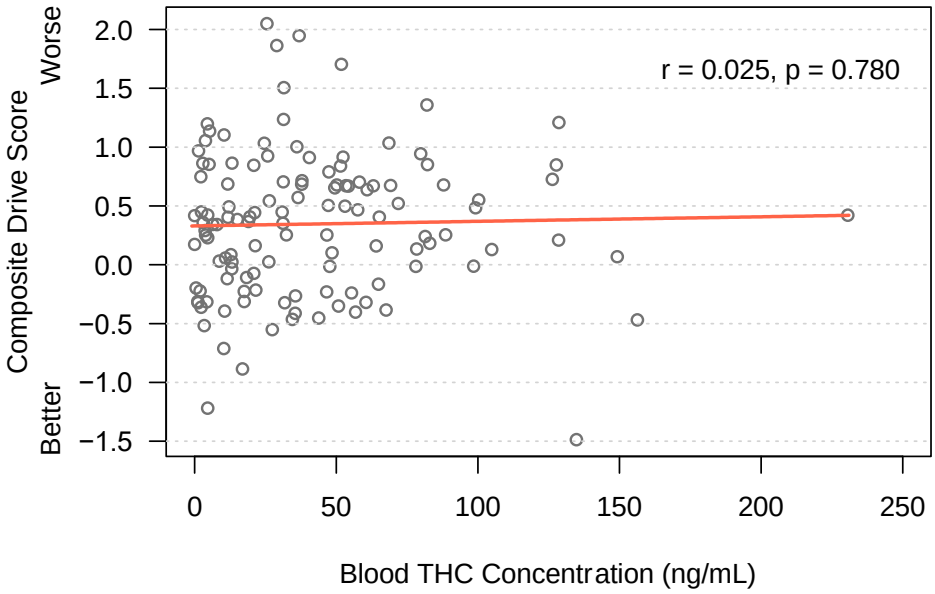
Column Descriptions: 1a. Mean (sd) for each treatment group at each timepoint; 2a. Effect size and *p*-value for each Placebo timepoint score compared to the Placebo pre-smoking score; 2b. Effect size and *p*-value for each THC timepoint score compared to the THC pre-smoking score; 2c. Effect size and p-value comparing the change from baseline between the Placebo and THC groups.

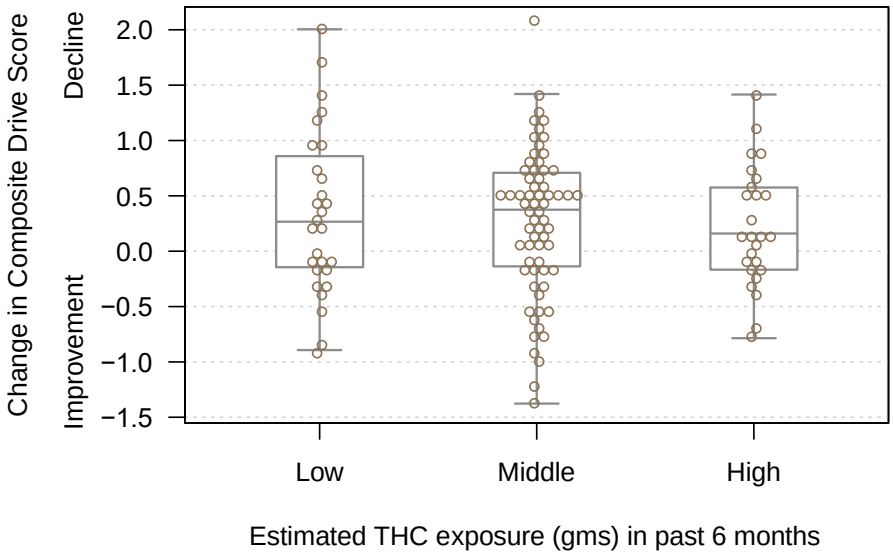

Screened for Eligibility (n=261)
Excluded (n=62)
• Not meeting eligibility criteria (n=39):
15 health risk, 4 psychiatric risk, 9 UTOX+ for cocaine or methamphetamine, 5 driving simulator motion sickness, 3 unwilling to follow protocol, 3 do not meet other criteria
• Other exclusions/no longer interested (n=23)
Randomized 1:1:1 (n=199)
Placebo (n=65)
5.9% THC (n=70)
13.4% THC (n=64)
Excluded (n=2)
• 2 pre-treatment oral THC>5ng/mL
Excluded (n=4)
• 3 pre-treatment oral THC>5ng/mL
• 1 withdrew
Excluded (n=2)
• 2 pre-treatment oral THC>5ng/mL
Analyzed (n=191)
Placebo (n=63)
5.9% THC (n=66)
13.4% THC (n=62)

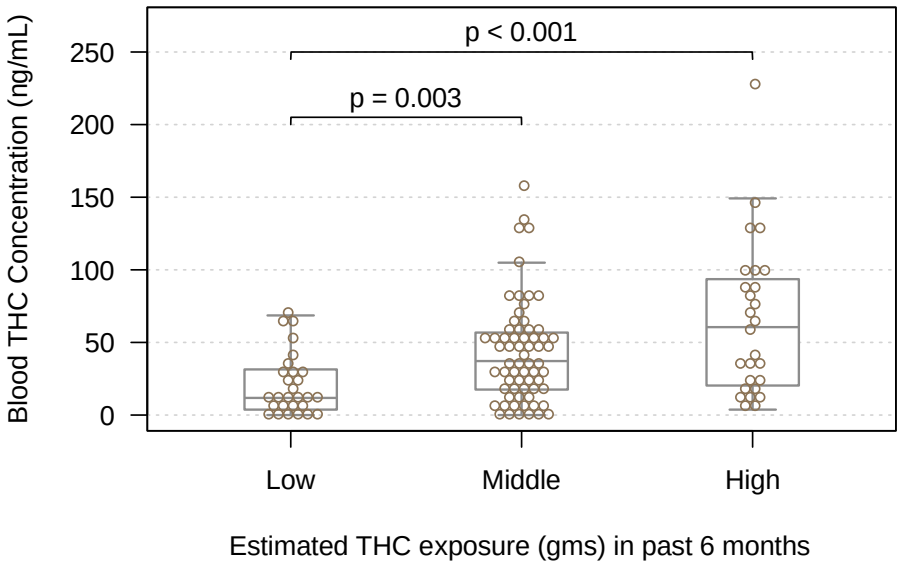

Placebo
5.9% THC
13.4% THC
Change in Composite Drive Score
Improvement
Decline
0.6
0.4
0.2
0.0
−0.2
**
***
**
**
30min
1h 30min
3h 30min
4h 30min


p < 0.001
Change in Composite Drive Score
Improvement
Decline
2
1
0
−1
Placebo
THC


Composite Drive Score
Perceived
Composite Drive Score
Worse
Better
0.4
0.3
0.2
0.1
0.0
40
30
20
10
0
How impaired are you to drive?
52.5%
31.4%
10.1%
6.8%
Pre−smoke
30min
1h 30min
3h 30min
4h 30min


Composite Drive Score
Worse
Better
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
r = 0.025, p = 0.780
0
50
100
150
200
250
Blood THC Concentration (ng/mL)


Change in Composite Drive Score
Decline
Improvement
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
Low
Middle
High
Estimated THC exposure (gms) in past 6 months


p < 0.001
p = 0.003
250
200
150
100
50
0
Blood THC Concentration (ng/mL)
Low
Middle
High
Estimated THC exposure (gms) in past 6 months