Driving Under the Influence of Cannabis (DUIC)

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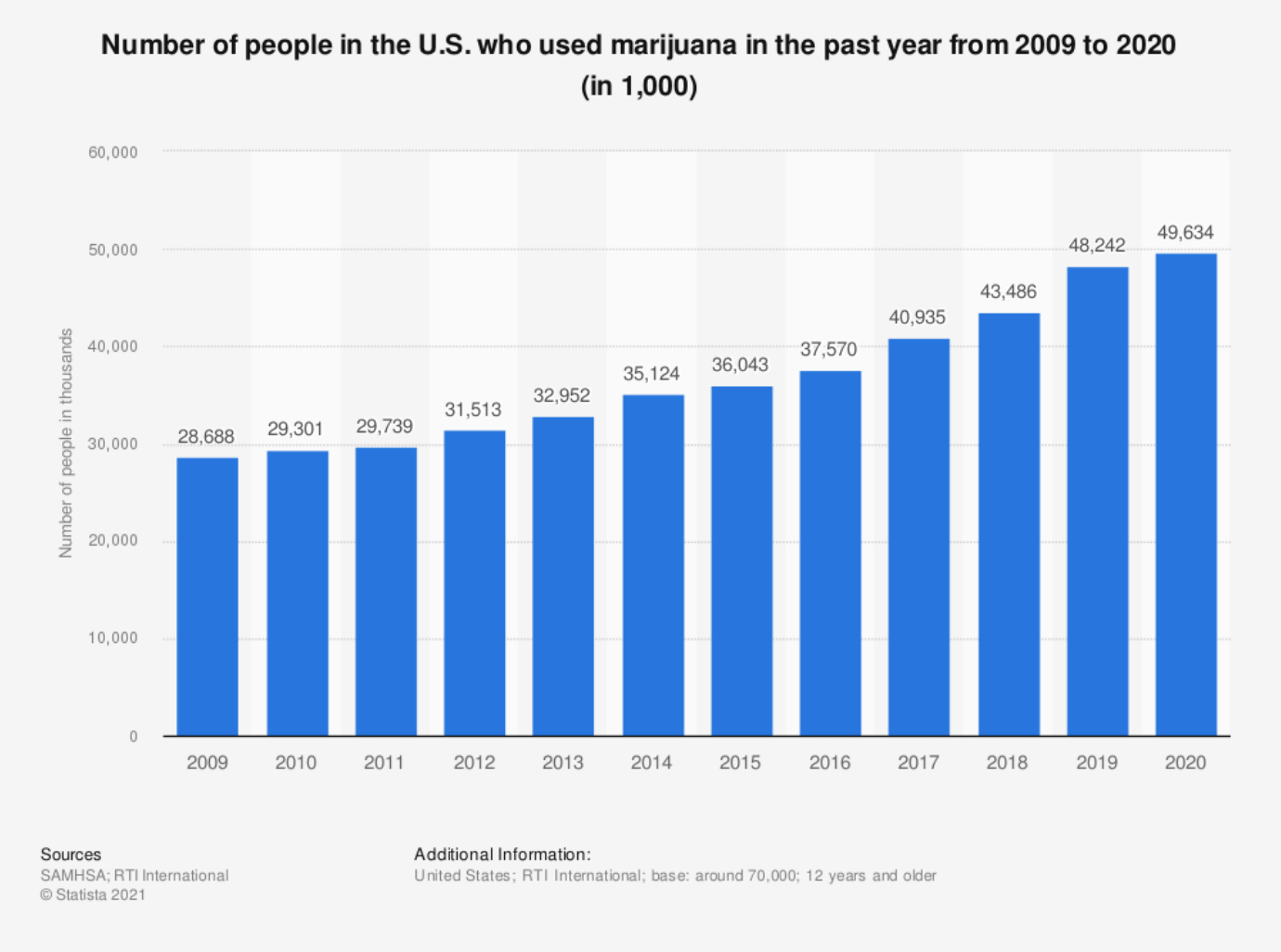
QUALITOX LABORATORIES

THREE RIVERS DIAGNOSTICS

UC San Diego HEALTH SYSTEM

Driving under the influence of cannabis (DUIC)



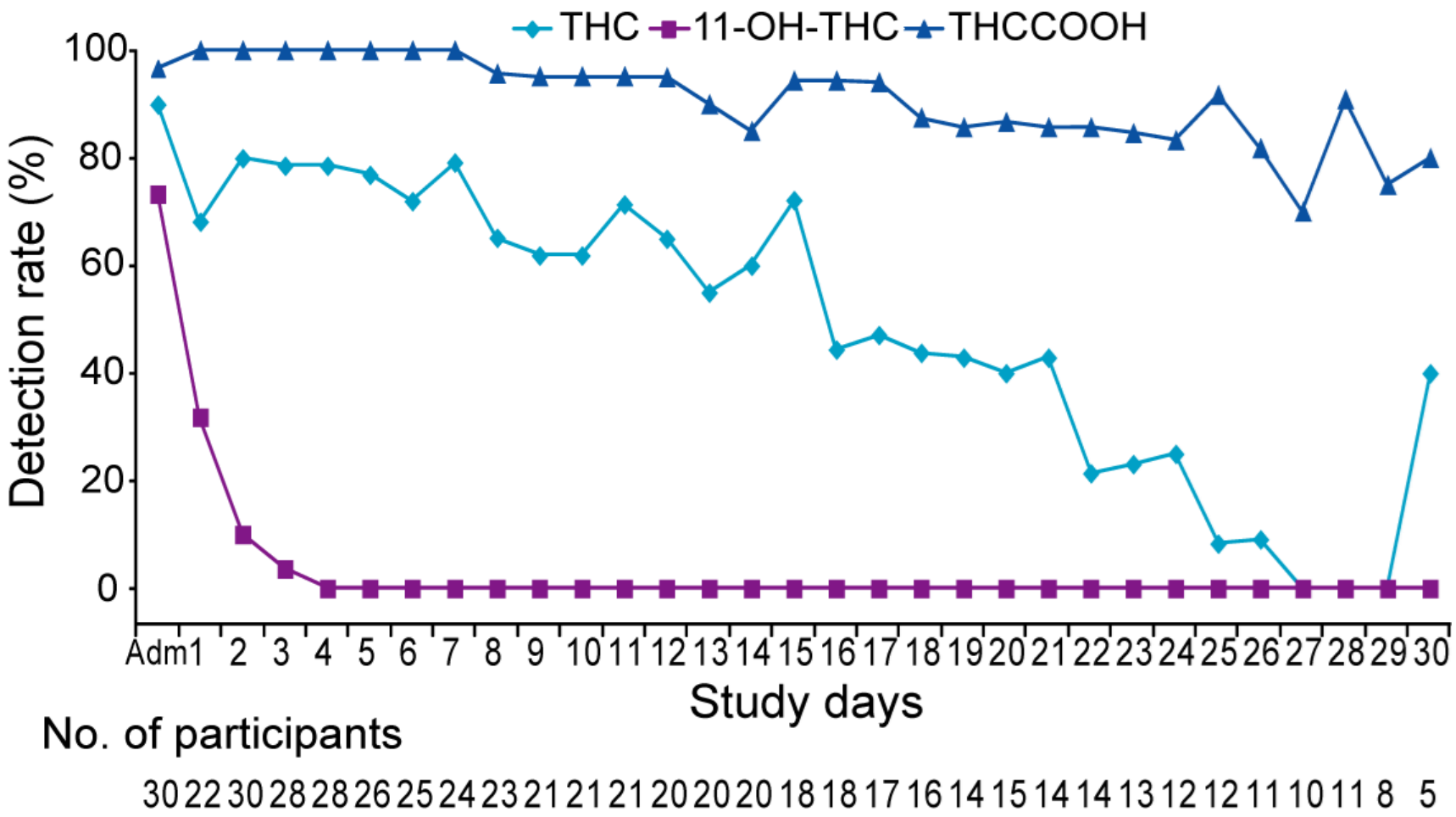
SAMSHA, 2021

- Deleterious cognitive and psychomotor effects
- Increased crash risk while DUIC compared to driving unimpaired

Interpretation challenges

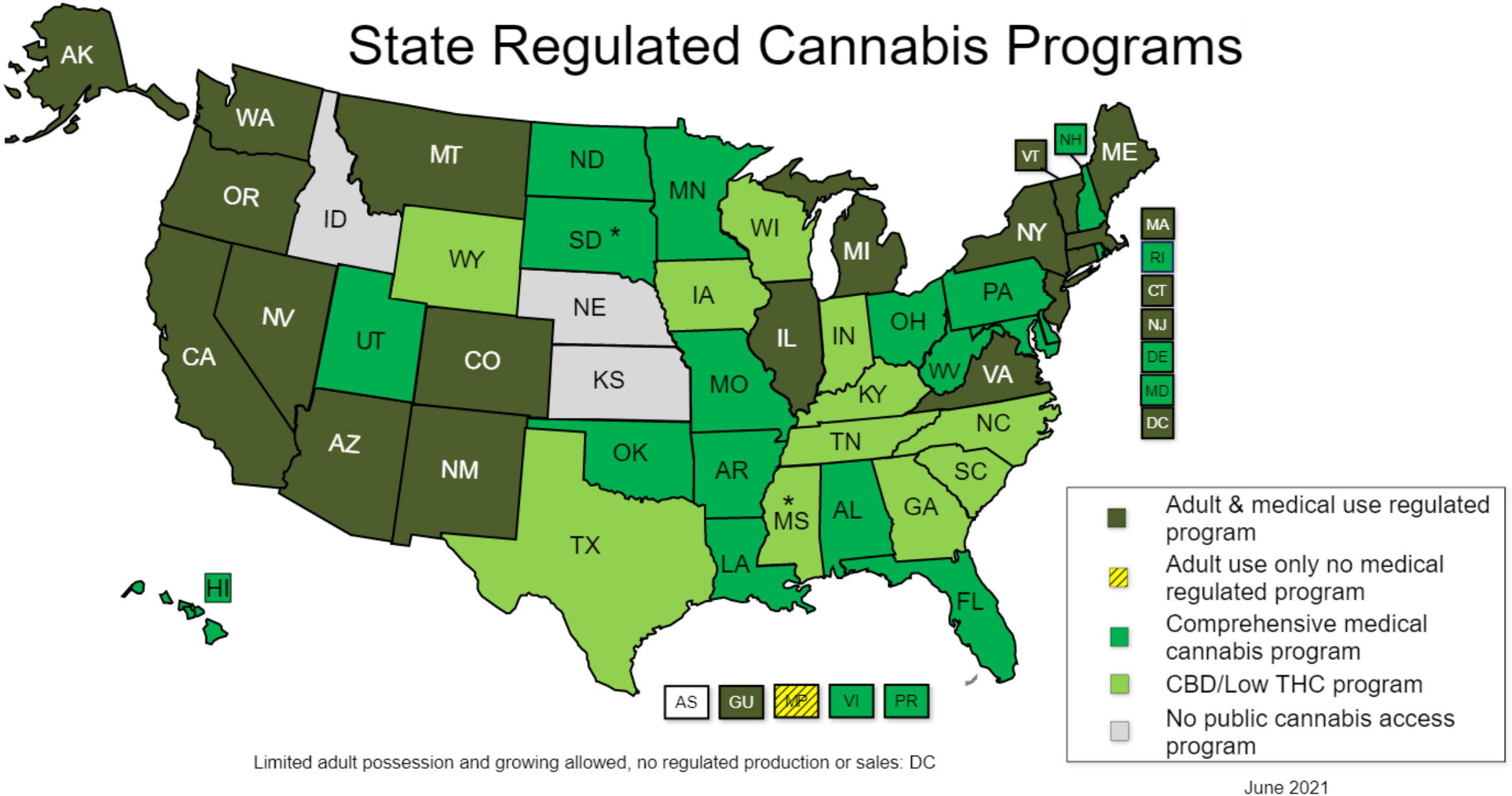
- Polysubstance abuse in motor vehicle crash reports
- Crash risk controversial and length of impairment unknown
- Difficult to study
  - Schedule I substance at federal level
  - Lower potency cannabis
  - Controlled dosing environment
- Large inter-individual variation

Cannabinoids detected in blood of chronic users



Bergamaschi *et al.*, 2013, *Clin Chem*

State Regulated Cannabis Programs



Limited adult possession and growing allowed, no regulated production or sales: DC

June 2021

National Conference of State Legislature

Cannabis driving limits

Legal Limit	Number of states
Zero tolerance THC and metabolites	9
Zero tolerance THC only	3
Per se limits 2-5 ng/mL	6
No law established	33

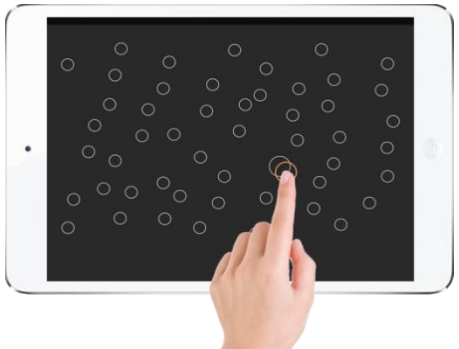
GHSA.org - updated 2/26/2021

- Are current per se laws reasonable?
- Do concentrations of THC in blood correlate with impairment?

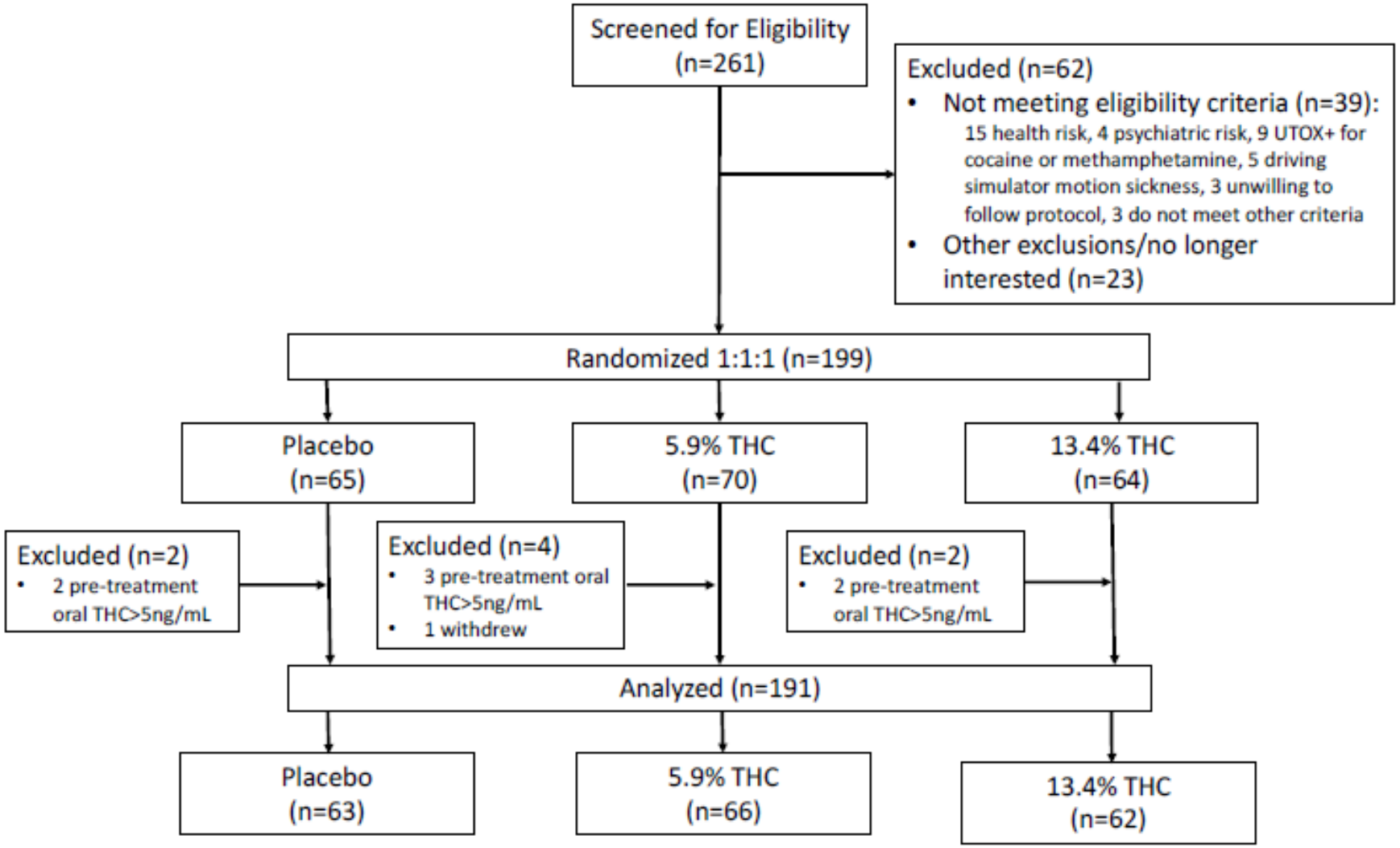
State of California Assembly Bill 266 (AB266)

- Project goal
  - Quantify the concentration of cannabinoids in blood, oral fluid, and breath
  - Associate with impairment while driving under the influence of cannabis

- Study design
  - Smoke 0.02% (placebo), 5.9% (low), or 13.4% (high) THC *ad libitum*
  - Complete driving simulations, iPad-based performance assessment, and SFST
  - Collect oral fluid (OF), blood, and breath samples

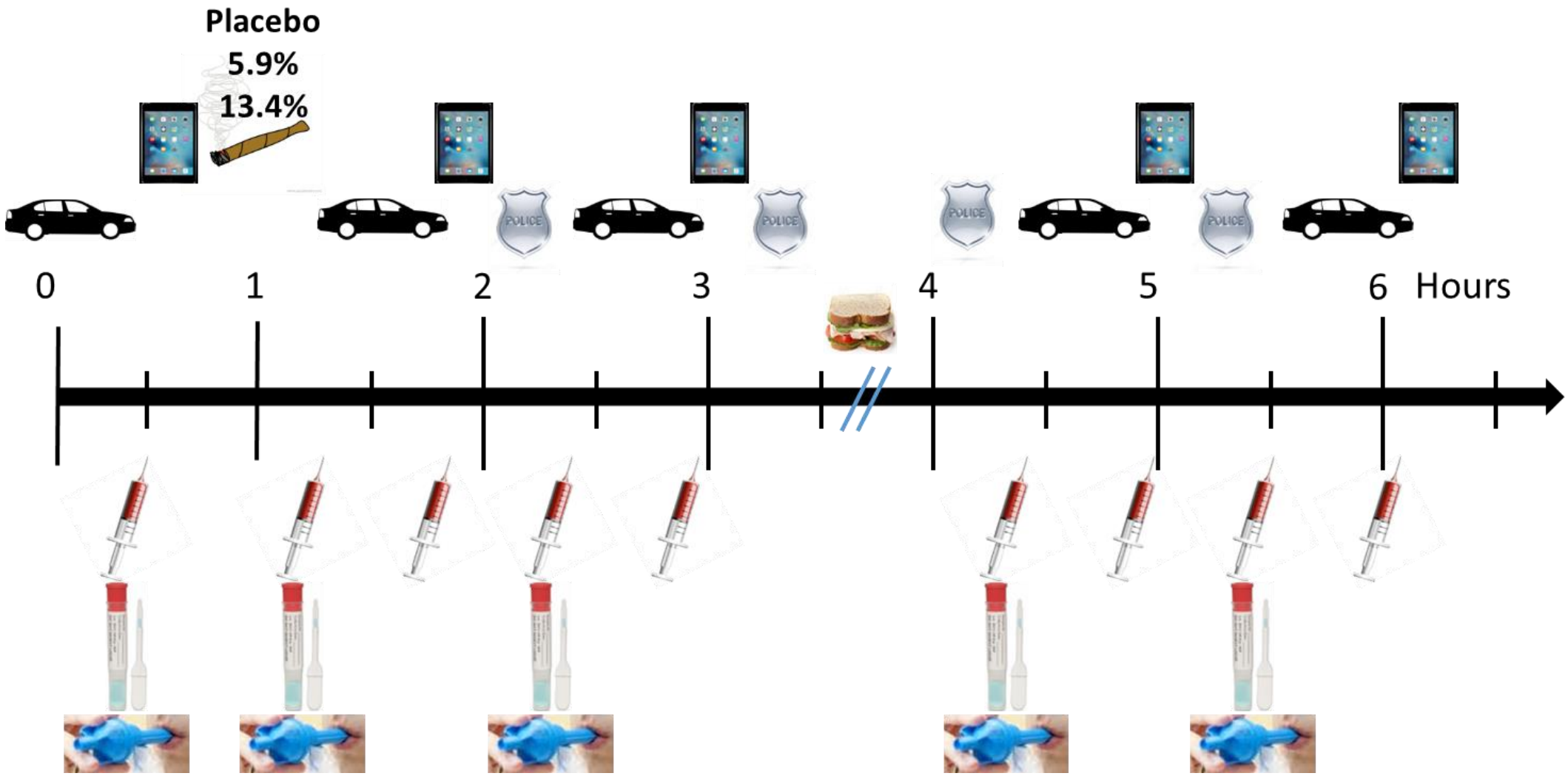


Participant summary



	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
Gender				
Male	32 (50.8%)	47 (71.2%)	39 (62.9%)	.066
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				
African American	8 (12.6%)	6 (9.0%)	4 (6.4%)	.467
Asian	5 (7.9%)	8 (12.1%)	4(6.4%)	
Hispanic	15 (23.8%)	19 (28.7%)	22 (35.4%)	
Indigenous	5 (7.9%)	2 (3.0%)	1 (1.6%)	
Multiracial	2 (3.1%)	3 (4.5%)	2 (3.2%)	
Non-Hispanic White	28 (44.4%)	28 (42.4%)	27 (43.5%)	
Unknown	0	0	2 (3.2%)	
Cannabis				
Occasional Cannabis user (<4 times/week)	54.0%	50.0%	50.0%	.875
Days used (last 30 days)	16.9 (9.7)	16.0 (9.6)	17.3 (10.2)	.769

AB266 experimental schedule

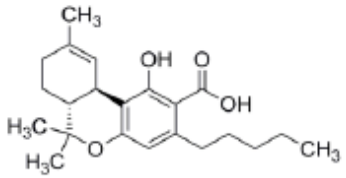


Detection of cannabinoids using LC-MS/MS

Hubbard, J.A., Smith, B.E., Sobolesky, P.M., Kim, S., Hoffman, M.A., Stone, J., Huestis, M.A., Grelotti, D.J., Grant, I., Marcotte, T.S., Fitzgerald, R.L. (2020) Validation of a liquid chromatography tandem mass spectrometry (LC-MS/MS) method to detect cannabinoids in whole blood and breath. *Clin Chem Lab Med,* 58(5): 673-681.

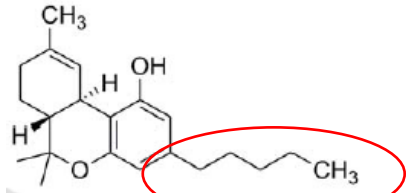
Sobolesky, P.M., Smith, B.E., Hubbard, J.A., Stone, J., Fitzgerald R.L. (2019) Validation of a liquid chromatography-tandem mass spectrometry method for analyzing cannabinoids in oral fluid. *Clin Chim Acta,* 491: 30-38.

Cannabinoid Metabolism

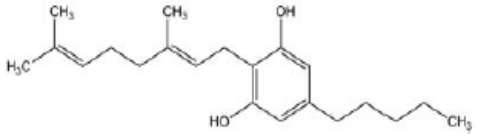


Δ^9-Tetrahydrocannabinolic Acid A (THCA-A)
$C_{22}H_{30}O_4$
M.W. = 358.47

Converts upon smoking

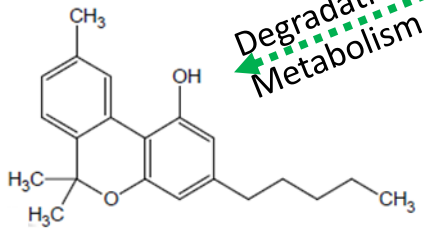


(-)-Δ^9-Tetrahydrocannabinol (THC)
$C_{21}H_{30}O_2$
M.W. = 314.46

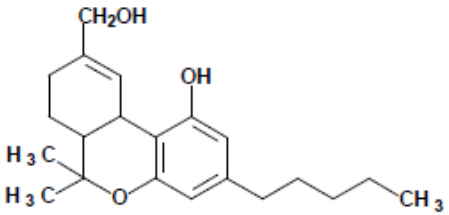


Cannabigerol (CBG)
$C_{21}H_{32}O_2$
M.W. = 316.48

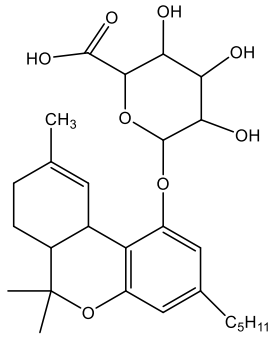
Degradation
Metabolism



Cannabinol (CBN)
$C_{21}H_{26}O_2$
M.W. = 310.43

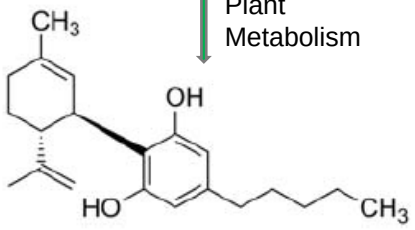


(±)-11-Hydroxy-Δ^9-THC (11-OH-THC)
$C_{21}H_{30}O_3$
M.W. = 330.46

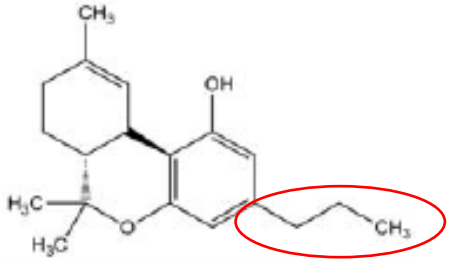


THC-glucuronide (THC-gluc)
$C_{27}H_{38}O_8$
M.W. = 490.58

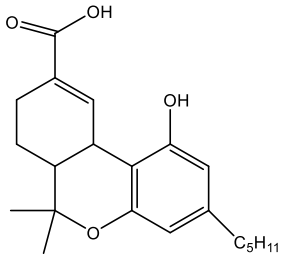
Plant
Metabolism



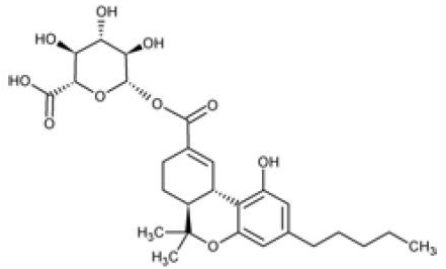
Cannabidiol (CBD)
$C_{21}H_{30}O_2$
M.W. = 314.46



Δ^9-Tetrahydrocannabivarol (THC-V)
$C_{19}H_{26}O_2$
M.W. = 286.41



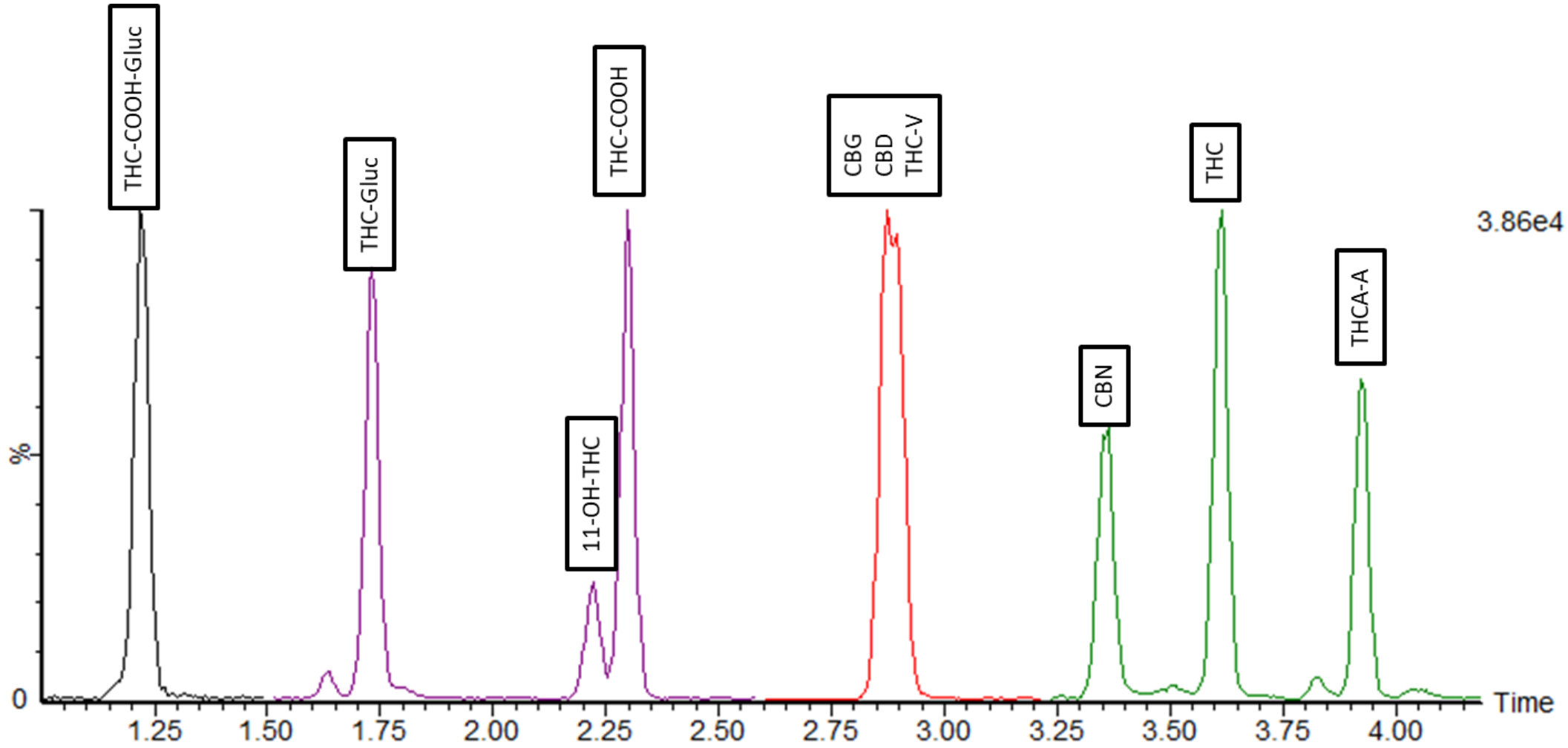
(±)-11-nor-9-Carboxy-Δ^9-THC (THC-COOH)
$C_{21}H_{28}O_4$
M.W. = 344.44



(+)-11-nor-9-Carboxy-Δ^9-THC-glucuronide
(THC-COOH-gluc)
$C_{27}H_{36}O_{10}$
M.W. = 520.57

Total ion chromatogram

10 ng/mL Cannabinoids



Limits of quantification

Analyte	Oral fluid		Blood		Breath	
	LLOQ (ng/mL)	ULOQ (ng/mL)	LLOQ (ng/mL)	ULOQ (ng/mL)	LLOQ (pg/pad)	ULOQ (pg/pad)
CBN	0.4	200	0.5	1,000	-	-
CBD	0.4	200	0.5	100	-	-
THC	0.4	2,000	0.5	1,000	80	500,000
11-OH-THC	0.4	200	1	100	-	-
THCCOOH	1.0	200	1	1,000	-	-
THC-gluc	0.4	200	-	-	-	-
THCCOOH-gluc	1.0	200	2	1,000	-	-
CBG	1.0	200	1	100	-	-
THCV	0.4	200	0.5	100	-	-
THCA-A	1.0	200	-	-	-	-

Results

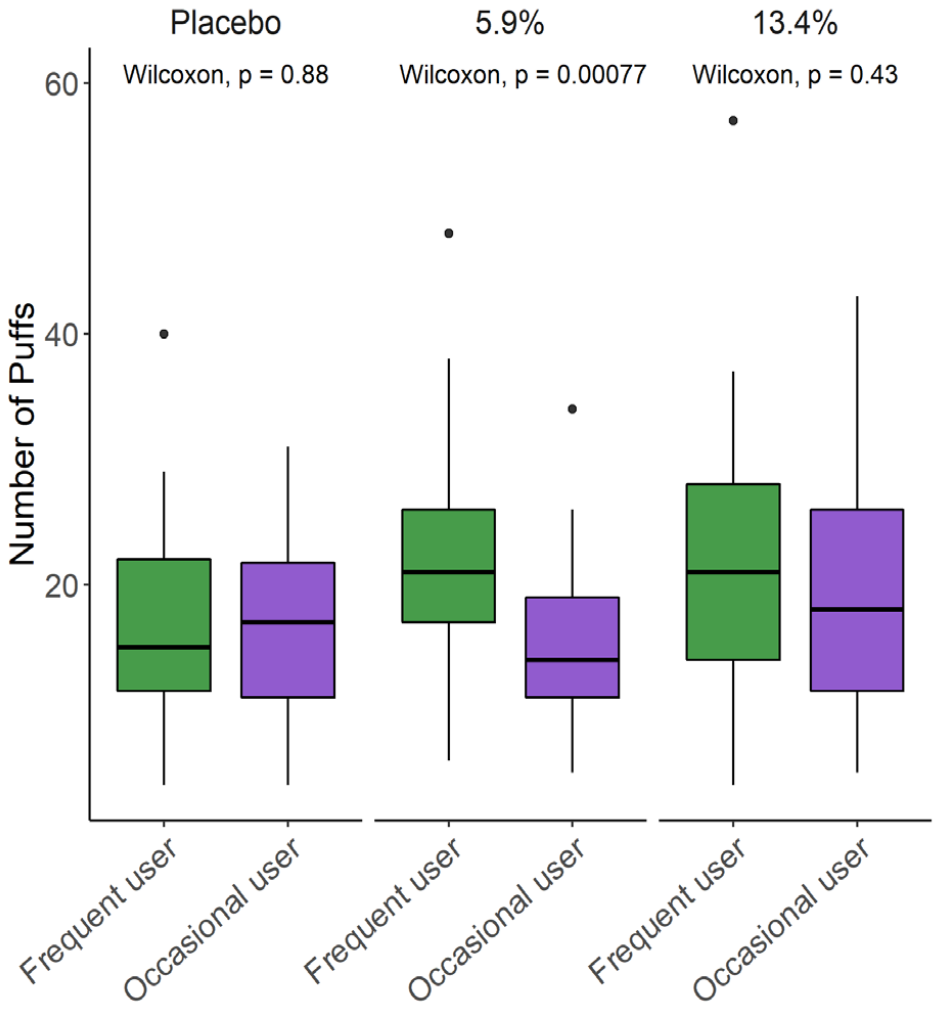
1. Smoking topography
2. Concentrations of cannabinoids after smoking
3. Driving performance and perceived impairment
4. Biomarkers for impairment?

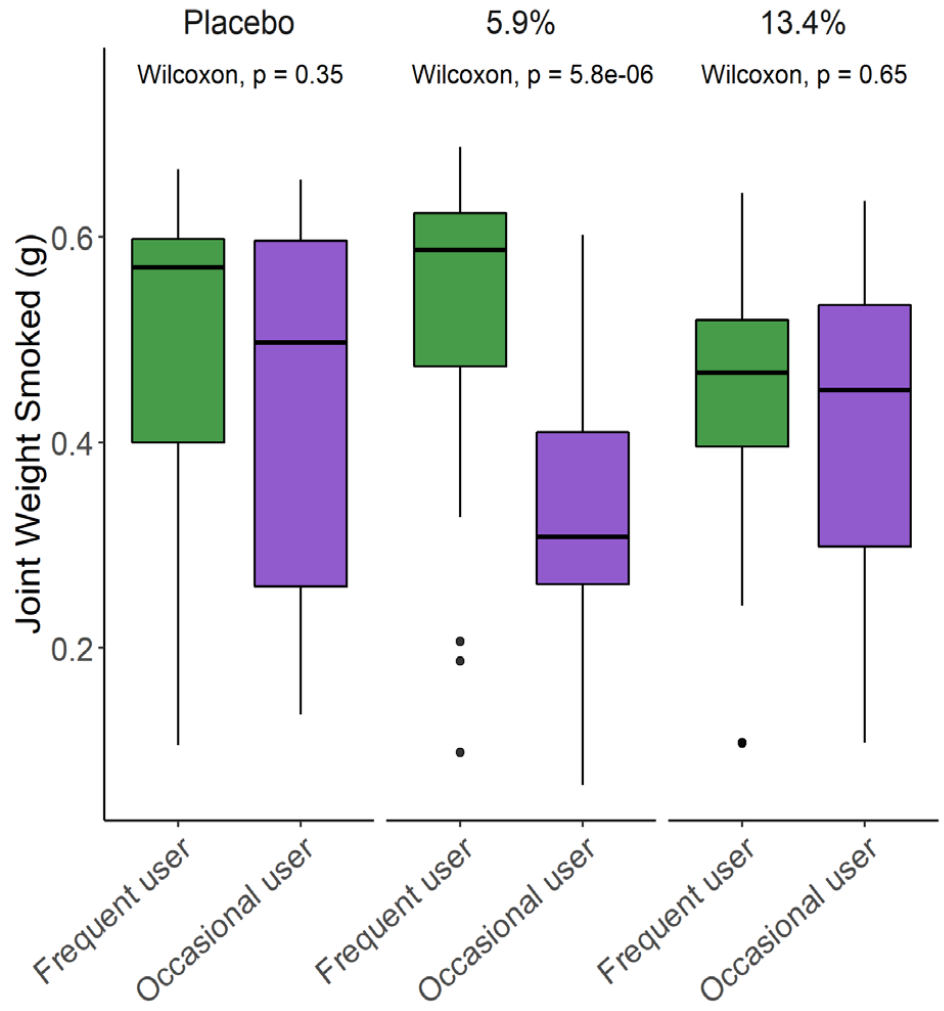
Hubbard, J.A., Hoffman, M.A., Ellis, S.E., Sobolesky, P.M., Smith, B.E., Suhandynata, R.T., Sones, E.G., Sanford, S.K., Umlauf, A., Huestis, M.A., Grelotti, D.J., Marcotte, T.D., Fitzgerald, R.L. (2021) Biomarkers of recent cannabis use in blood, oral fluid, and breath. *J Anal Tox,* 17;45(8): 820-828.

Hoffman, H.A., Hubbard, J.A., Sobolesky, P.M., Smith, B.E., Suhandynata, R.T., Sanford, S., Sones, E.G., Ellis, S., Umlauf, A., Huestis, M.A., Grelotti, D.J., Grant, I., Marcotte, T.D., Fitzgerald, R.L. (2021) Blood and oral fluid cannabinoid profiles of frequent and occasional cannabis smokers. *J Anal Tox,* 17;45(8): 851-862.

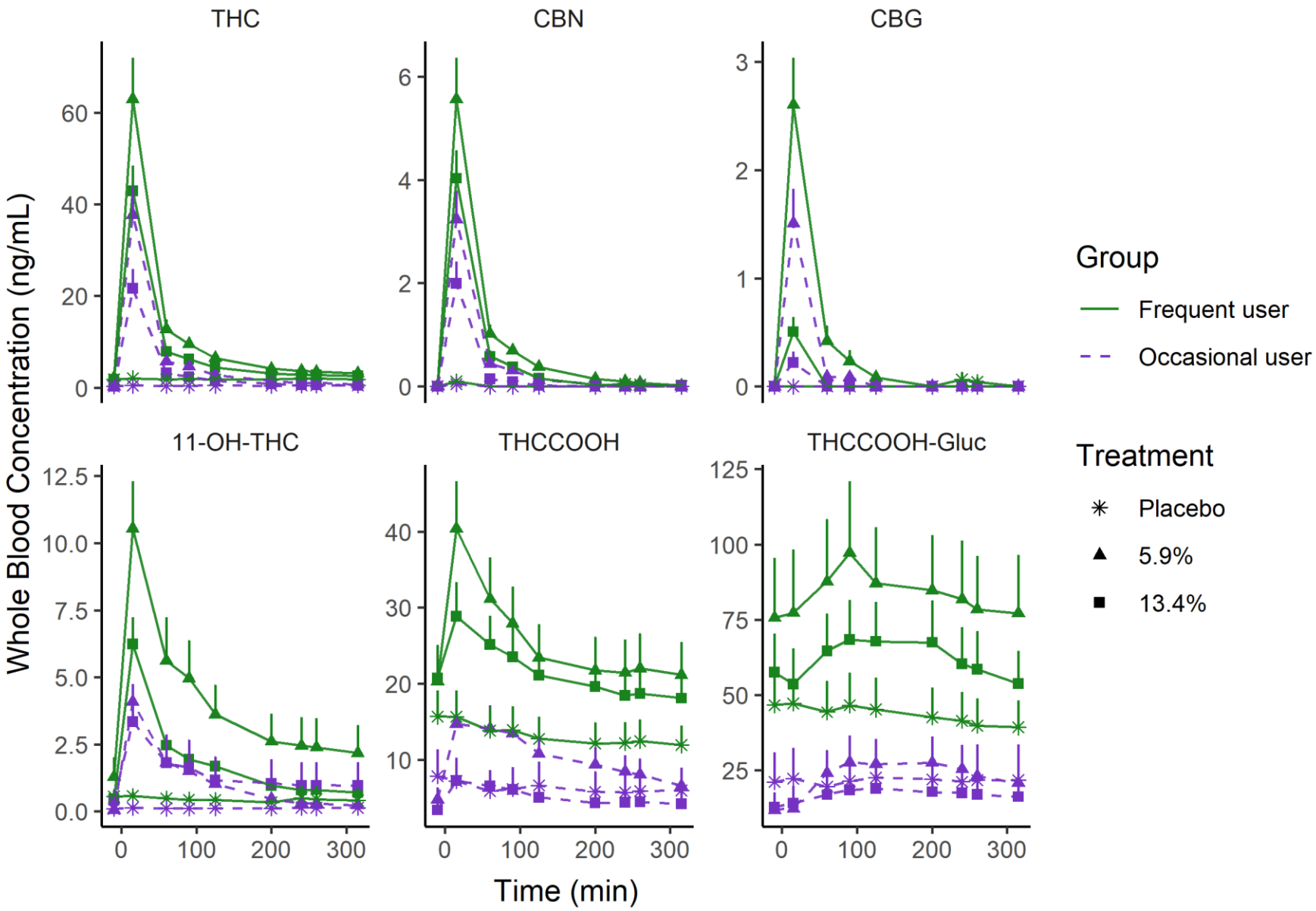
Marcotte, T.D., Umlauf, A., Grelotti, D.J., Sones, E.G., Sobolesky, P.M., Smith, B.E., Hoffman, M.A., Hubbard, J.A., Severson, J., Huestis, M.A., Grant, I., Fitzgerald, R.L. (2022) Driving Performance and cannabis users' perception of safety: a randomized clinical trial of smoked cannabis of different THC content. *JAMA Psych*, in press.

Smoking topography

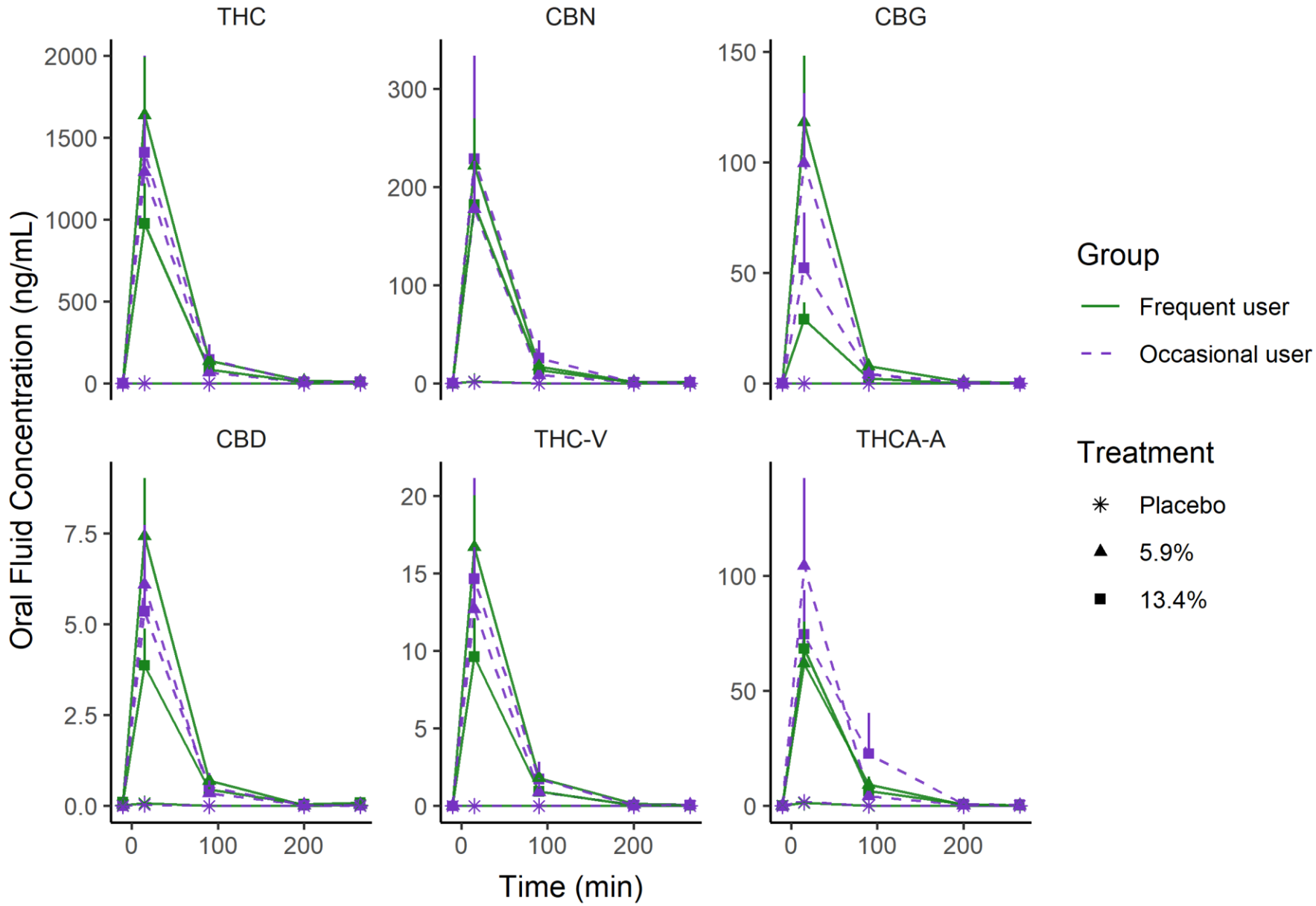




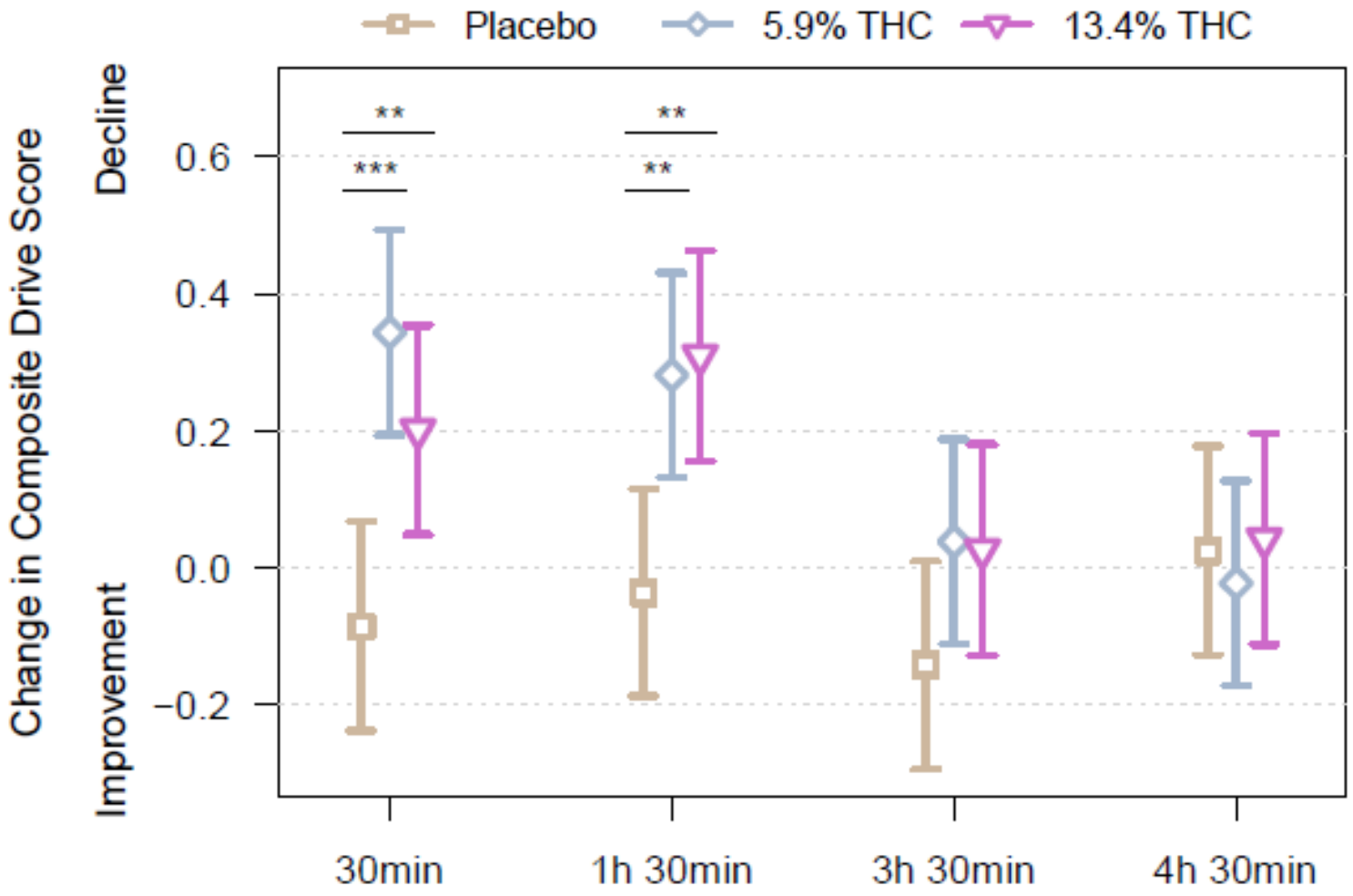
Kinetic profiles of cannabinoids in blood



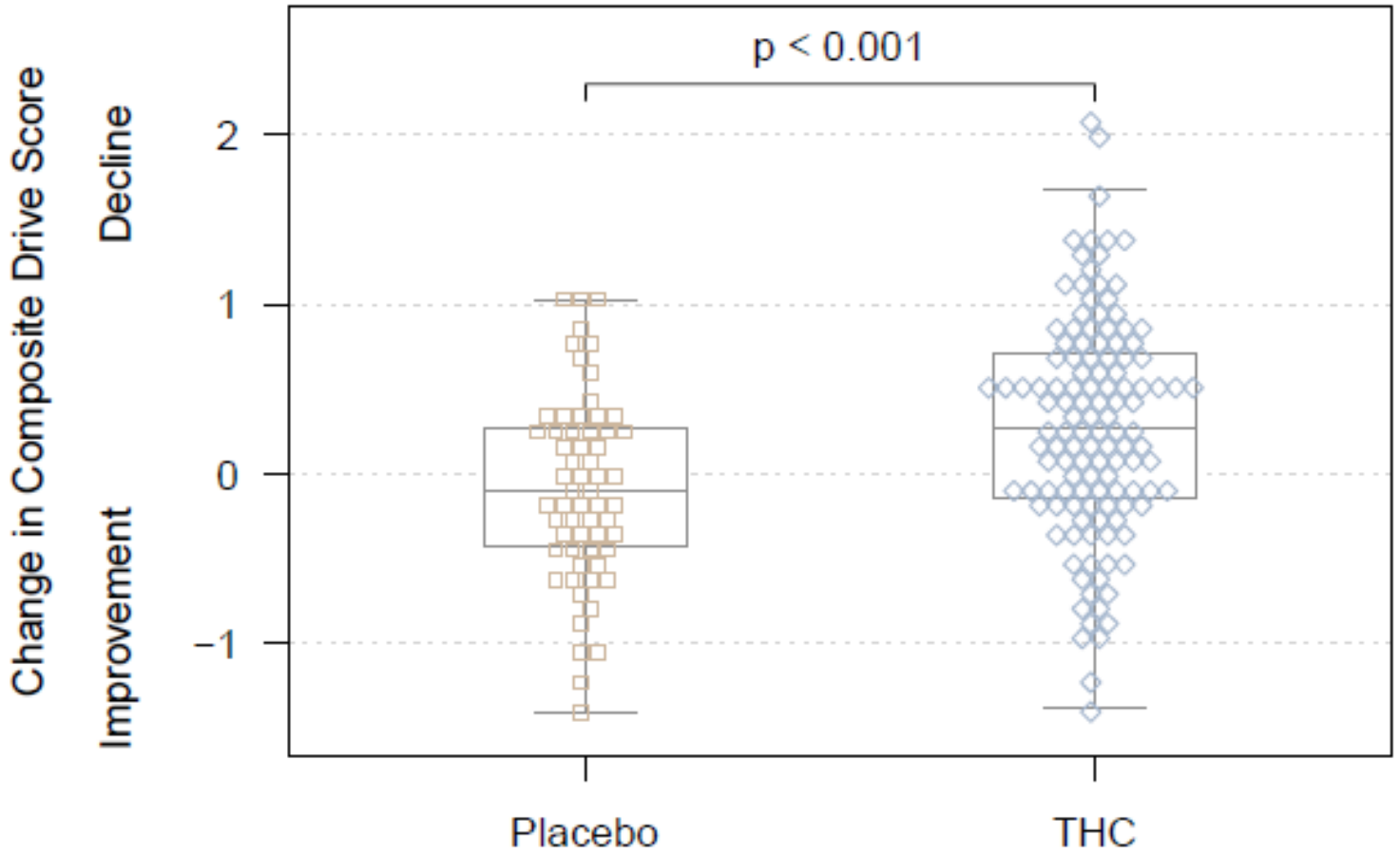
Kinetic profiles of cannabinoids in oral fluid



Driving performance after smoking



Distribution of changes in driving performance from pre-smoking to 30 minutes post-smoking



Can you tell if you are too high to drive?

Perception of high

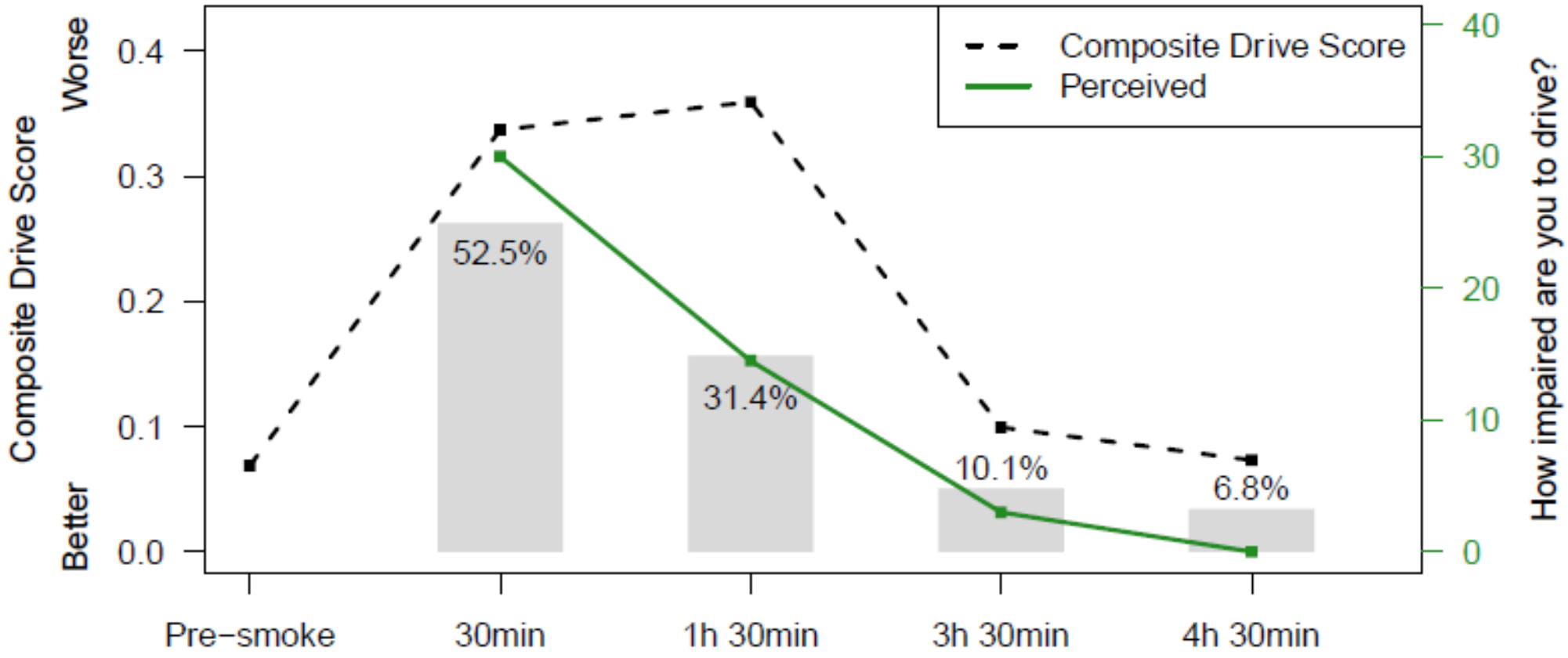
Prior to each driving session:

1. How high are you? (0-100)
2. How impaired are you to drive? (0-100)
3. Would you drive in your current state? (yes/no)

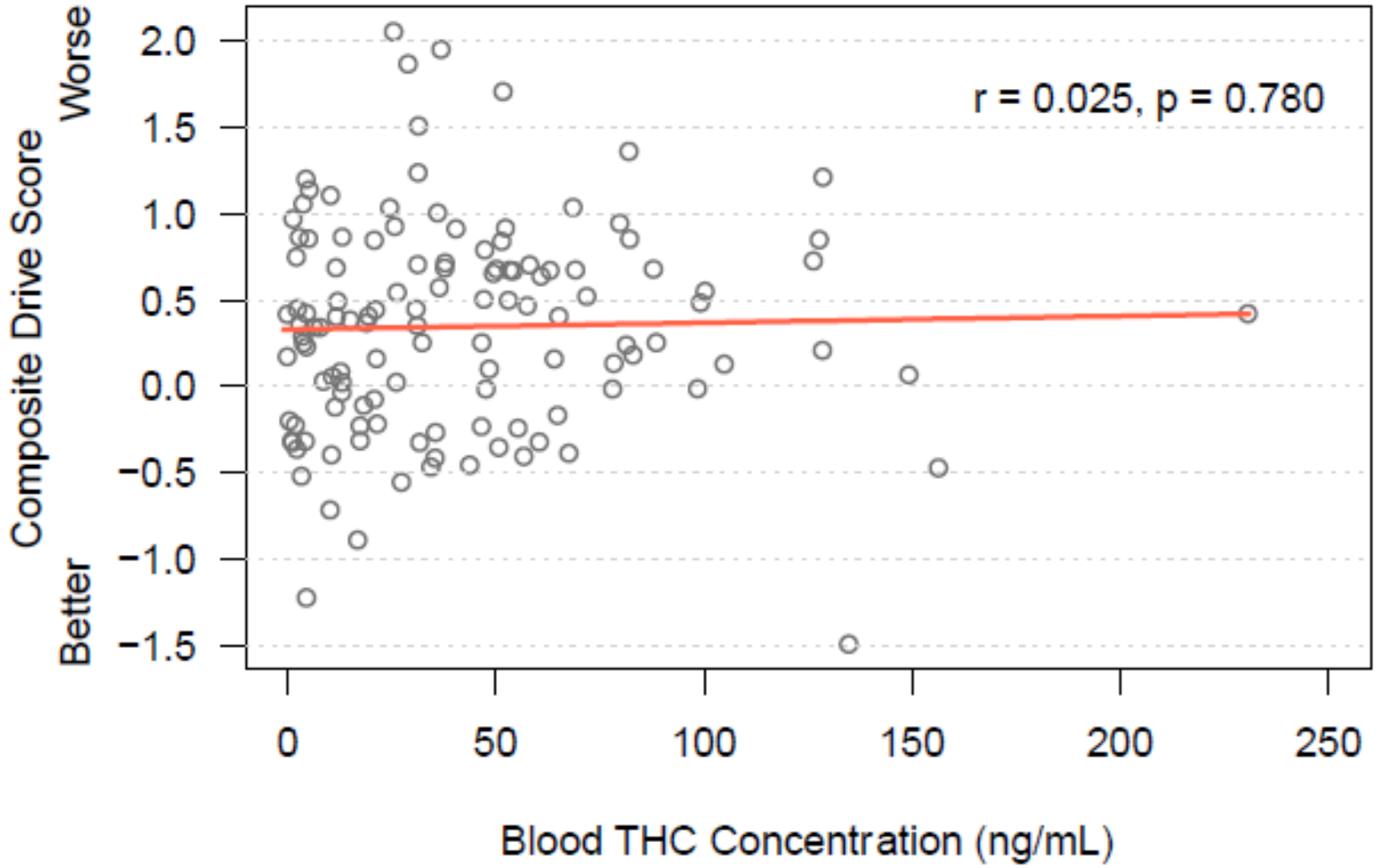
After each driving session

1. How much did the study drug affect your driving? (0-100)
2. How well did you drive? (0-100)

Relationship between perceived impairment, willingness to refrain from driving, and driving performance



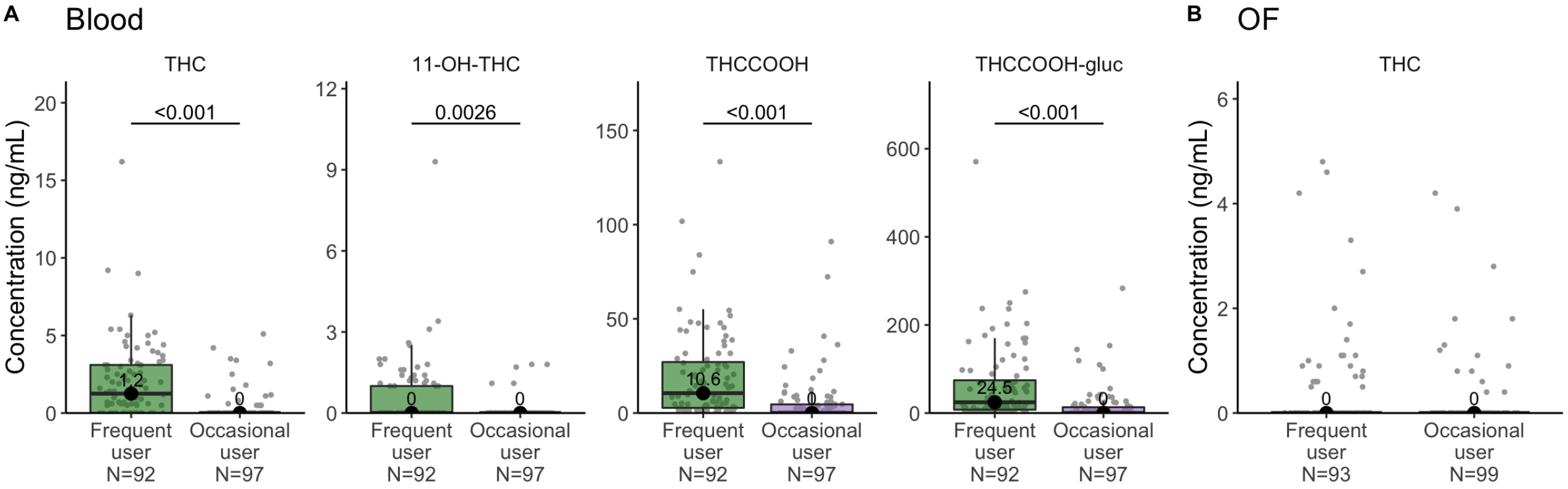
Can blood THC concentration determine impairment?



Then how can we determine DUIC?

- Is blood the best matrix?
- Alternative approach: biomarkers of recent use

Concentrations of cannabinoids prior to smoking



Biomarkers of recent use

- Sensitivity, specificity, positive (PPV) and negative (NPV) predictive value
- Recent use was defined as 0-3 hours since smoking
- All samples between pre-smoking to 3h were used for analysis
  - Blood (n=908)
  - OF (n=601)
  - Breath (n=588)

Categorization	THC group	Relative to cutoff
True positive	5.9% or 13.4%	At or above
True negative	Placebo Pre-smoking	Below
False positive	Placebo Pre-smoking	At or above
False negative	5.9% or 13.4%	Below

Youden's index to find optimal cutoff for smoking within 0-3 hours

- Youden's J statistic:

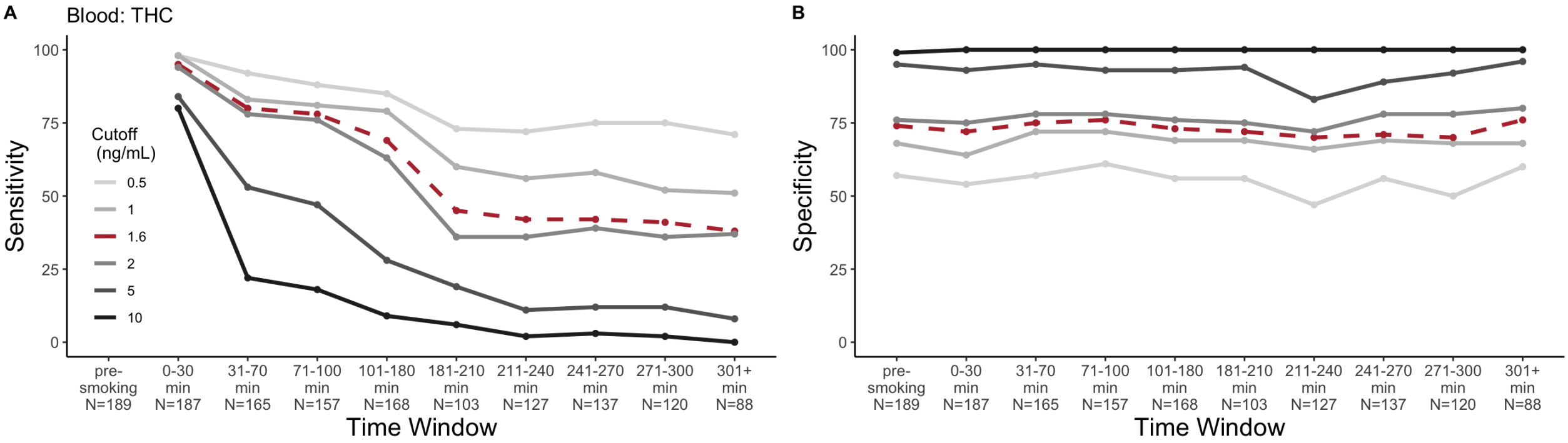
  J = (sensitivity + specificity) – 1

- Example:
  80% sensitivity
  80% specificity

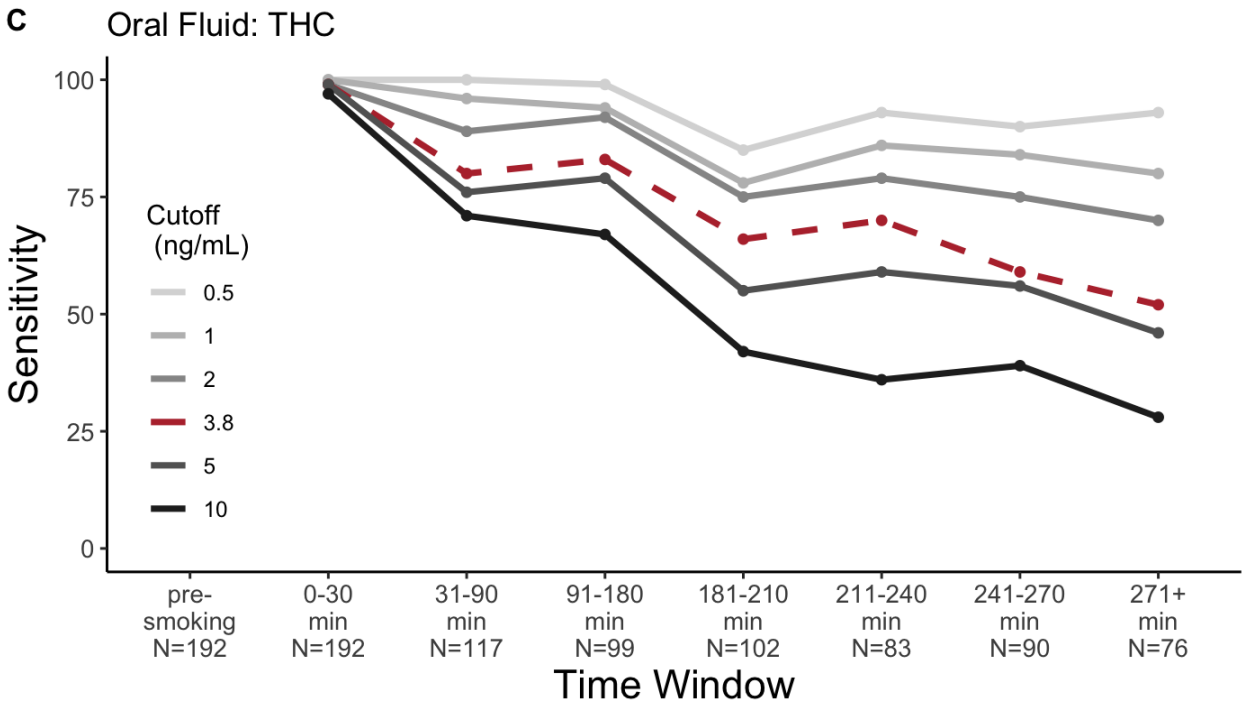
  J = (0.8 + 0.8) – 1 = 0.6

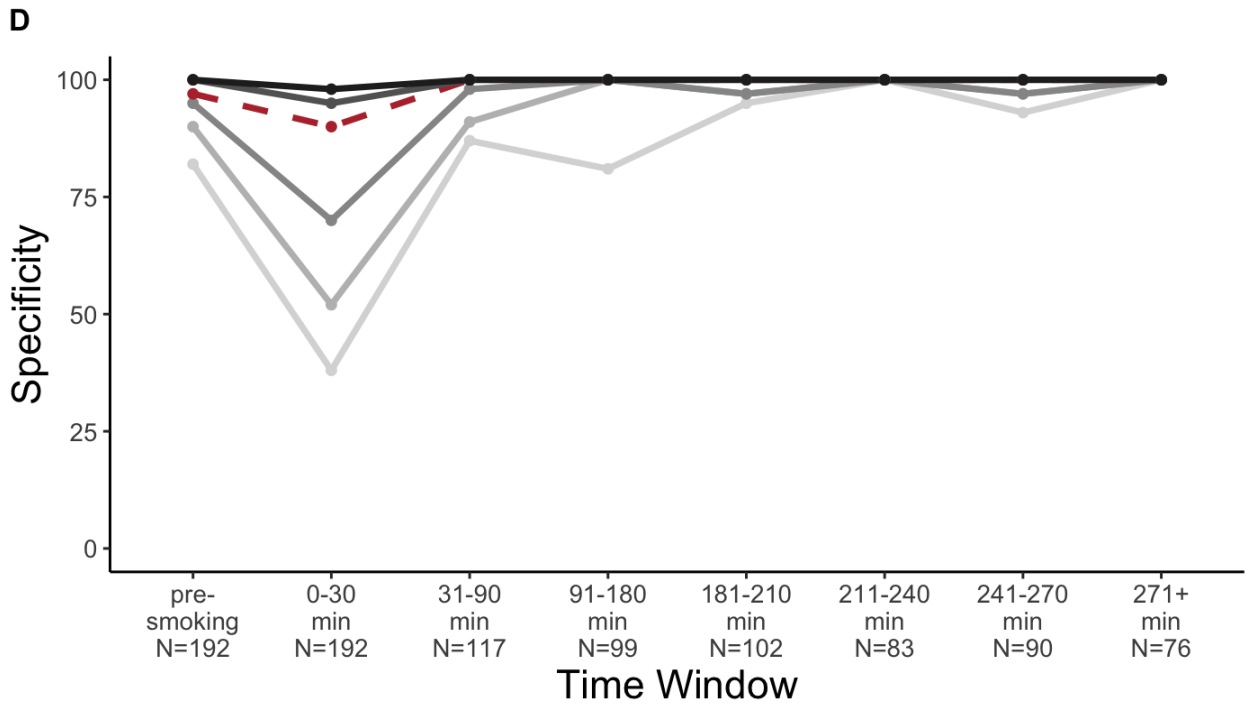
Matrix	Compound	Youden	Cutoffs
Blood	CBN	0.48	0.5
Blood	CBD	0.00	7.5
Blood	THC	0.54	1.6
Blood	11-OH-THC	0.51	1.2
Blood	THCCOOH	0.36	5.1
Blood	THCCOOH-gluc	0.22	9.6
Blood	CBG	0.17	1.0
Blood	THCV	0.00	0.5
OF	CBN	0.76	0.6
OF	CBD	0.53	0.4
OF	THC	0.87	3.8
OF	11-OH-THC	0.01	0.5
OF	CBG	0.75	1.0
OF	THCV	0.68	0.4
OF	THCA-A	0.69	1.0
Breath	THC	0.56	85.6

Sensitivity and specificity of THC in blood at select cutoff concentrations

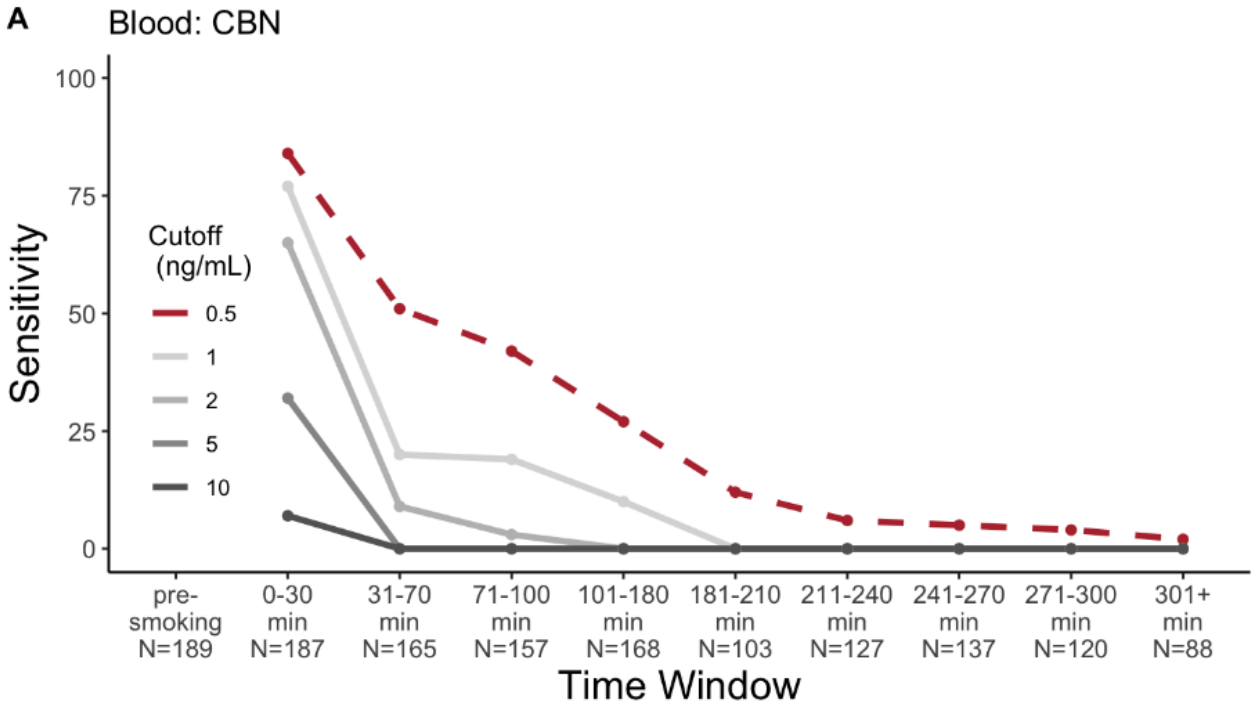


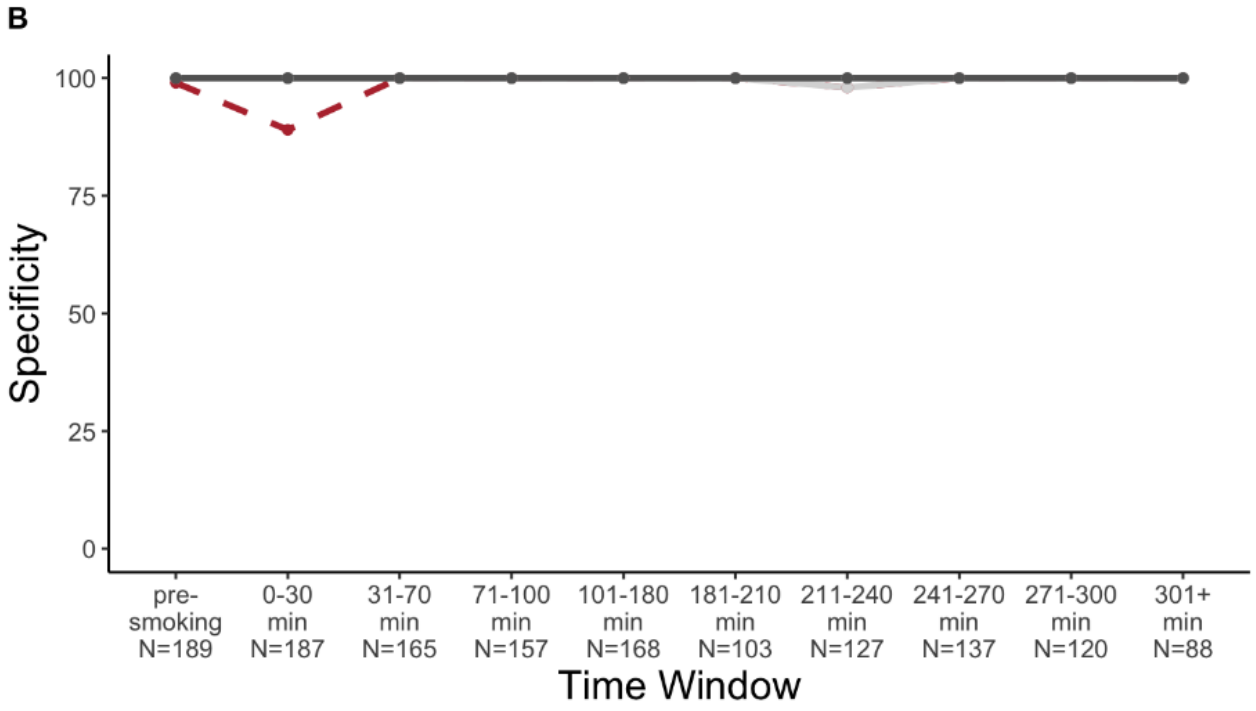
Sensitivity and specificity of THC in oral fluid at select cutoff concentrations





Sensitivity and specificity of CBN in blood at select cutoff concentrations





How do these biomarkers perform in the real world?

- Positive (PPV) and negative (NPV) predictive values
- Calculated using the percentage of weekend nighttime drivers who tested positive for THC in various jurisdictions in California
  - Low: 4.3% Fresno
  - High: 18.3% Eureka
  - Average: 8.5%

Johnson, M.B., Kelley-Baker, T., Voas, R.B., Lacey, J.H. (2012) The prevalence of cannabis-involved driving in California. *Drug and Alcohol Dependence*, **123**, 105–109.

PPV and NPV of CBN and THC as biomarkers of recent use (within 3 h post-smoking) in blood and oral fluid

Prevalence: 4.3%

Per se limits (0-5 ng/mL)

Biomarker	Matrix	Cutoffs (ng/mL)	% Sensitivity	% Specificity	PPV	NPV
THC	Blood	0.5	90.3	56.9	8.6	99.2
THC	Blood	1	84.6	68.4	10.7	99.0
THC	Blood	1.6	80	73.5	11.9	98.8
THC	Blood	2	76.2	76.5	12.7	98.6
THC	Blood	5	51.7	94.2	28.6	97.7
THC	Blood	10	32.3	99.8	87.9	97.0
THC	OF	0.5	99.6	74.2	14.8	100
THC	OF	1	97.4	83.6	21.1	99.9
THC	OF	2	94.5	91.2	32.5	99.7
THC	OF	3.8	90.1	96.7	55.1	99.5
THC	OF	5	87.9	99.1	81.4	99.5
THC	OF	10	82.4	99.7	92.5	99.2
CBN	Blood	0.5	49.6	98.2	55.3	97.7
CBN	Blood	1	31.4	100	100	97.0
CBN	Blood	2	19.8	100	100	96.5
CBN	Blood	5	8.4	100	100	96.0
CBN	Blood	10	1.9	100	100	95.8
CBN	OF	0.5	90.8	84.2	20.5	99.5
CBN	OF	0.6	89	86.6	23.0	99.4
CBN	OF	1	85.3	89.4	26.6	99.3
CBN	OF	5	66.2	97.6	55.3	98.5
CBN	OF	10	56.6	99.1	73.9	98.1

How the biomarkers of recent use perform after 3 hours?

Matrix	Compound	Cutoff	% Above cutoff
Blood	THC	0.5	54.0
Blood	THC	1.0	41.6
Blood	THC	1.6	34.2
Blood	THC	2.0	30.4
Blood	THC	5.0	6.2
Blood	THC	10.0	0.6
OF	THC	0.5	59.5
OF	THC	1.0	54.7
OF	THC	2.0	50.0
OF	THC	3.8	39.5
OF	THC	5.0	35.8
OF	THC	10.0	23.2
Blood	CBN	0.5	0.6
Blood	CBN	1.0	0.0
Blood	CBN	2.0	0.0
Blood	CBN	5.0	0.0
Blood	CBN	10.0	0.0
OF	CBN	0.5	35.8
OF	CBN	0.6	31.6
OF	CBN	1.0	23.7
OF	CBN	5.0	2.6
OF	CBN	10.0	0.5

Table II. Percentage of All Participants (Placebo, 5.9% THC and 13.4% THC Groups) above Specific Cutoffs in Blood and OF at Study Completion

Conclusions

- THC and metabolites have longer detection windows in blood than in oral fluid
- THC negatively impacts driving ability, but a subset of active THC recipients drove without signs of impairment
- The decline in driving performance lasts longer than the subjective impairment
- No correlation exists between blood THC concentration and driving performance
- THC in oral fluid or CBN in blood may be promising biomarkers of recent use, but have limitations

Future directions

- Determine the utility of standardized field sobriety testing and iPad-based cognitive testing on identifying DUIC
- Study driving impairment after alternative routes of ingestion
- Explore the impact of cannabis on driving on the “real road”

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Questions?