Sex Differences in the Acute Effects of Oral THC: A Randomized, Placebo-Controlled, Crossover Human Laboratory Study

Ardavan Mohammad Aghaei, M.D., M.P.H. [1]; Lia Urban Spillane B.A.[1]; Brian Pittman, M.S.[1]; L. Taylor Flynn[2], Joao P. De Aquino M.D.[1]; Anahita Bassir Nia, M.D.[1]*; Mohini Ranganathan, M.B.B.S.[1]*

[1] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[2] Drexel University School of Medicine MD/PhD program, Philadelphia, PA, USA

* MR and ABN contributed to this work in the same capacity as senior authors.

Corresponding author info:

Mohini Ranganathan, M.B.B.S.

Email: mohini.ranganathan@yale.edu

Department of Psychiatry, University School of Medicine, VA Connecticut Healthcare System/116A, 950 Campbell Ave, West Haven, CT 06516, USA

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Conflict of interest statement

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Abstract

Rationale: Cannabis is one of the most commonly used psychoactive substances, and recent reports have shown increased use among women, leading to growing concerns about cannabis use disorder. Some evidence suggests a faster progression to addiction in women, known as the "telescoping effect." While there is preclinical evidence suggesting biological sex influences cannabinoid effects, human research remains scant. We investigated sex differences in the response to oral tetrahydrocannabinol (THC) in humans.

Methods: 55 healthy men and women with prior exposure to cannabis but no history of cannabis use disorder participated in a randomized, placebo-controlled, double-blind, counter-balanced study, receiving a single 10 mg dose of oral THC (dronabinol). Subjective intoxicating effects were assessed by the Visual Analog Scale (VAS) of "high", psychotomimetic effects by the Clinician-Administered Dissociative Symptoms Scale (CADSS) and Psychotomimetic States Inventory (PSI), cognitive effects by Rey Auditory Verbal Learning Test (RAVLT), and physiologic effects by heart rate. Outcomes were regularly measured on the test day, except for the RAVLT, which was assessed once. Peak differences from baseline were analyzed using a nonparametric method for repeated measures.

Results: Oral THC demonstrated significant dose-related effects in psychotomimetic and physiologic domains, but not in cognition. A notable interaction between THC dose and sex emerged concerning the subjective "high" scores, with women reporting heightened sensations (ATS=3.81, num df=1, p=0.05). No other significant effects of sex and THC dose interaction were observed.

Conclusion: Oral THC yields similar psychotomimetic and physiologic effects across sexes, but women may experience a pronounced subjective intoxicating effect. Given the escalating accessibility of cannabinoids, further research is needed to identify individual vulnerabilities and facilitate tailored interventions addressing cannabis use disorder.

Keywords: Cannabis; Marijuana; Cannabinoids; Gender; Endocannabinoid system; substance use disorders

1. Introduction

With the shifting landscape of cannabis legalization worldwide and especially in the U.S., both cannabis usage and its associated disorders are anticipated to surge (Weinberger et al. 2022). Over the last decade, cannabis consumption has consistently risen (Center for Behavioral Health Statistics and Quality 2023; Mitchell et al. 2020). The National Survey on Drug Use and Health (NDSU) reveals that in 2021, 18.7% of Americans (52.4 million) aged 12 or older used cannabis, with 0.9% (2.6 million) being first-time users. Alarmingly, 5.8% (16.2 million) met the criteria for cannabis use disorder (Center for Behavioral Health Statistics and Quality 2023). As cannabis becomes more accessible, understanding the individual biopsychosocial vulnerabilities that lead to the development of cannabis use disorder is imperative to develop preventive and treatment measures.

Over the past decade, the incidence of first-time cannabis use has risen among women, and the gap between the rates of cannabis use in men and women has narrowed (Chapman et al. 2017; Johnson et al. 2015). Epidemiologic data suggest that women develop cannabis use disorder sooner than men, after their primary exposure to cannabis use. This compressed timeline from first use to cannabis use disorder is referred to as the “telescopic phenomenon” (Gräfe et al. 2023; Hernandez-Avila et al. 2004; Khan et al. 2013). Similarly, women are more likely to experience cannabis withdrawal symptoms (Copersino et al. 2010) and report a greater impact of cannabis use on their quality of life (Lev-Ran et al. 2012).

Some preclinical and clinical evidence suggests that sex can be a moderating factor of acute cannabis effects. For instance, female rats appear to be more sensitive to the rewarding effects of cannabis, as they demonstrate a quicker acquisition of cannabinoid receptor 1 (CB1-R) agonist self-administration behaviors than male rats (Cooper and Craft 2018; Fattore et al. 2007). Female rats also show more pronounced drug- and cue-induced reinstatement of cannabinoid agonist-

seeking behaviors (Fattore et al. 2010). Crucially, sex hormones appear to play a key role in the sensitization to cannabinoid agonists, as gonadectomized female animals show significantly lower intensity of self-administration and drug reinstatement than females with intact gonads (Fattore et al. 2007; Fattore et al. 2010). Unlike preclinical studies, however, human studies investigating sex differences in the acute effects of cannabis and delta-9-tetrahydrocannabinol (THC), the active constituent of cannabis, have presented mixed results. While earlier research found no difference in the acute subjective effects of cannabis or THC among sexes, or reported more effects in men (Cocchetto et al. 1981; Haney 2007; Penetar et al. 2005), recent studies align with the preclinical findings, showing a heightened sensitivity to subjective effects in women (Cooper and Haney 2009; 2014; Fogel et al. 2017; Makela et al. 2006; Mathew et al. 2003), especially to lower doses (Fogel et al. 2017). Likewise, some research suggests comparable subjective effects across sexes, but with women exhibiting lower THC plasma concentrations (Matheson et al. 2020).

Likewise, in a previous double-blind, placebo-controlled, randomized trial, we showed that while intravenously administered THC elicited similar psychotomimetic and cognitive effects across both sexes, women experienced a significantly greater subjective “high”, especially at lower doses (Bassir Nia et al. 2022). While using IV THC enabled us to control the exact dose delivery and account for other confounding factors, such as differences in absorption rates and metabolism (i.e., first pass effect), the IV administration paradigm limits the ecological validity of the findings. Cannabis is usually smoked or ingested, rather than injected, and sex differences in the absorption rate, metabolism, and peak concentration of cannabinoids (Lunn et al. 2019; Nadulski et al. 2005; Narimatsu et al. 1991; Wall et al. 1983) could contribute to the overall sex differences in the cannabis effect we observe in the community. Therefore, in this study, we sought to investigate the sex differences of acute subjective intoxicating, psychotomimetic, cognitive, and physiologic effects of oral THC in healthy individuals who have had exposure to cannabis without meeting the criteria for cannabis use disorder.

2. Methods

This randomized, placebo-controlled, double-blind, counter-balanced human laboratory study evaluated the acute subjective intoxicating, psychotomimetic, cognitive, and physiological effects of oral THC in 55 healthy individuals (32 women and 23 men). The study protocol was approved by the Institutional Review Boards of the VA Connecticut Healthcare System and Yale University School of Medicine.

2.1 Participants

Healthy men and women between the ages of 18 and 55 years were recruited from the community using flyers, digital advertisements, and word-of-mouth. Inclusion criteria included having used cannabis at least once over the three months prior to study participation, without ever meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for cannabis use disorder. Exclusion criteria included lifetime or current DSM-5 major psychiatric disorders such as schizophrenia, schizoaffective disorder, or bipolar disorder; major or clinically unstable medical conditions; major current or recent stressors over the previous 6 weeks (based on clinical interview); IQ less than 80 per Wechsler Test of Adult Reading; or blood donation within the previous 8 weeks. Participants were also excluded if they met DSM-5 criteria for lifetime cannabis use disorder and other substance use disorders (except for tobacco) within the last three months. Participants were required to have negative urine toxicology and pregnancy tests.

2.2 Screening

After an initial phone screening, participants were provided with a full, written explanation of the study procedures. All the procedures were explained verbally by trained staff, and participants completed a brief questionnaire to confirm their understanding of the risks of the study. Participants were provided enough time to ask questions, addressed by study physicians and

research staff. Once signed informed consent was obtained, participants underwent medical and psychiatric examinations, and blood and urine samples were collected. The Structured Clinical Interview (SCID) for DSM-5 was conducted by trained staff. Participants' sex refers to their self-designation of sex assigned at birth. For clarity and consistency in this manuscript, we refer to female participants as "women" and male participants as "men". The participants were required to have a negative urine toxicology. The absence of pregnancy in women was confirmed by urine pregnancy testing on screening and on the morning of each test day (**Table 1**).

2.3 Assessments

2.3.1 Subjective intoxicating effects: The subjective "high" induced by THC was gauged using a visual analog scale (VAS). Participants were instructed to rate the intensity of their perceived "high" on a 100mm line, with reference points at 0 (indicating "not at all") and 100 (indicating "extremely"). These assessments were conducted both before and at multiple intervals post-THC/placebo administration. The efficacy of this measure in capturing THC effects has been validated in prior research (D'Souza et al. 2008).

2.3.2 Psychomimetic and dissociative effects: To evaluate thought and perceptual changes, we employed the Clinician-Administered Dissociative Symptoms Scale (CADSS) and the Psychotomimetic States Inventory (PSI). Both the CADSS and the PSI are recognized for their validity and have demonstrated sensitivity to THC-induced effects (Bassir Nia et al. 2022). The CADSS is a 28-item questionnaire containing 23 participant-rated and five observer-rated items aimed to capture perceptual alterations and dissociative effects on a scale of 0 (not at all) to 4 (extreme) (Bremner et al. 1998). The PSI has 48 items, each scored on a Likert scale of 0 to 3, covering the six domains of psychotic-like experiences (Mason et al. 2008). A trained rater administered these behavioral ratings.

2.3.3 Cognitive Assessments: To assess the deficits in verbal learning induced by THC, we used the Rey Auditory Verbal Learning Test (RAVLT), which has been shown to be sensitive to THC effects in previous studies (Ranganathan et al. 2017). The RAVLT is a 15-word list learning task of verbal memory and hippocampal function. It includes five alternate versions and encompasses five learning trials, an interference list, and both free short- and long-delayed recall and recognition recall trials (Schmidt 1996). To minimize practice effects, we used alternative RAVLT forms and a counterbalanced design to address any differences in form difficulty. The RAVLT was administered once during the test day.

2.4 Study Drug

This study used oral THC in the form of dronabinol (10 mg capsule). Approved by the FDA to treat anorexia in AIDS and other wasting diseases, and emesis in cancer patients undergoing chemotherapy, dronabinol is a synthetic form of THC. When consumed orally, THC exhibits a distinct pharmacokinetic profile compared to when inhaled. Specifically, oral THC shows slower absorption, lower and more delayed peak concentrations, and its effects manifest slower (between 30 to 120 minutes post-consumption) but persist longer (Huestis 2007; Lemberger et al. 1971; Ohlsson et al. 1980; Reyes et al. 1973; Wall et al. 1983).

2.5 Test Session

Participants were required to arrive at the test facility at 8 AM after fasting overnight. Participants were not permitted to drive to and from the test facility, and transportation was provided if needed. Urine drug and pregnancy tests (in women) were conducted each test morning to rule out pregnancy and any recent substance use. Weight, height, and body mass index were calculated for all subjects. IV lines were inserted, and baseline behavioral, subjective, and physiological measures were collected. After the administration of dronabinol, outcome measures were

repeated periodically throughout the test day as described below, except for the cognitive outcomes (RAVLT), which were assessed once. Vital signs (heart rate) were assessed as part of the medical monitoring of the subjects. **Table 1** represents an approximate schedule of testing. Test days were at least three days apart.

2.6 Statistical analyses

Initially, data were examined descriptively using means, standard deviations, and graphs. Each outcome was tested for normality using Kolmogorov–Smirnov test statistics and normal probability plots. Subjective (VAS) and psychomimetic and dissociative (CADSS, PSI) effects were analyzed as peak changes from baseline. These and cognitive (RAVLT) outcomes were highly skewed, even after log transformation. Thus, these outcomes were analyzed using the nonparametric approach for repeated measures data by Brunner et al. (2002), in which data first are ranked and then fitted using a mixed-effects model with an unstructured variance–covariance matrix and p values adjusted for analysis of variance-type statistics (ATS). In the models, sex was included as a between-subjects factor and THC (active, placebo) was included as a within-subjects factor. The THC by sex interaction was modeled with subject as the clustering factor. Physiologic outcomes (e.g., heart rate) were sufficiently normal and analyzed with linear mixed models using the same factors as above with time (see study time points) included as an additional within-subjects factor. Data were analyzed using SAS, version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1 Participants

Of the 55 participants who completed the study, 23 were men and 32 were women. Men and women showed no significant differences in baseline characteristics such as age, education, race, ethnicity, and BMI (**Table 2**). Both groups had comparable exposure to cannabis, and the majority

of participants had used cannabis less than five times in the month leading up to the screening (**Table 3**).

3.2 Subjective Intoxicating Effects

Peak subjective effects were most commonly observed at 80 minutes post THC administration. A significant THC by sex interaction effect was observed for subjective effects of “high” (ATS=3.81, num df=1, p=0.05, d=0.43) where a significant THC effect was observed among women (ATS=4.76, num df=1, p=0.03, Cohen's d’=0.48) but not men (ATS=0.49, num df=1, p=0.48, d=0.11). The effects are depicted in Figure 1.

3.3 Psychotomimetic and Dissociative Effects

CADSS: Oral THC induced a significant increase in both observer-rated (ATS= 31.3, num df=1, p=0.0001) and subjective-items CADSS scores (dose effect: ATS= 42.0, num df=1, p=.0001). However, no main effects of sex in observer-rated (ATS= 0.47, num df=1, p= 0.49) or subjective-items scores (ATS: 2.77, num df=1, p=0.9) were observed. Additionally, no dose by sex interaction effects in observer-rated (ATS= 0.19, num df=1, p=0.66) or subjective rated items score (ATS=2.21, num df=1, p=0.14) were observed.

PSI: Oral THC produced significantly higher PSI scores across both sexes (ATS= 52.7, num df=1, p<0.0001). However, the main effect of sex (ATS=0.46, num df=1, p=0.50) and the THC by sex interaction effect (ATS=0.1, num df=1, p=0.76) were not significant (**Figure 2**).

3.4 Cognitive Effects

During the immediate recall test, women recalled 51.4 ± 10.5 (sd) and 52.7 ± 11.1 words after THC and placebo administration, respectively, whereas men recalled 52.1 ± 12.8 and 51.7 ± 13.5 words, respectively. No effects of dose (ATS= 1.22, num df=1, p= 0.27), sex (ATS= 0.02, num

df=1, p= 0.89), or dose by sex interaction (ATS= 0.56, num df=1, p= 0.45) effects were observed. During short-delayed recall, women remembered 11.1 ± 3.1 and 11.0 ± 3.3 words after THC and placebo, respectively, while men remembered 11.8 ± 3.2 and 11.7 ± 3.8 words after each condition. Similar to immediate recall, no effects of dose (ATS= 0.06, num df=1, p= 0.80), sex (ATS= 1.64, num df=1, p= 0.20), or dose by sex interaction (ATS= 0.04, num df=1, p= 0.84) effects were observed during short-delayed recall. Similar, non-significant patterns of long-delay recall were observed. Specifically, 10.7 ± 3.1 and 10.3 ± 3.4 words for women, and 10.8 ± 3.5 and 11.2 ± 3.4 words for men were recalled after long delay following THC and placebo conditions, respectively. No significant dose (ATS= 0.1, num df=1, p= 0.75), sex (ATS= 0.27, num df=1, p= 0.60), or sex by dose (ATS= 0.63, num df=1, p=0.43) effects were observed.

3.5 Physiologic Effect

Significant increases in heart rate over time were observed during THC administration (dose by time; F(5, 560)=3.45, p=0.004). However, THC-induced heart rates did not differ by sex (sex by dose by time F(5, 560)=1.33, p= 0.25) (**Figure 3**).

4. Discussion

In this double-blind, placebo-controlled, counter-balanced, randomized human laboratory study, we examined the subjective intoxicating, psychotomimetic, cognitive, and physiologic effects of 10 mg oral THC on men and women without cannabis use disorder. Our results underscore that while both men and women experienced equivalent psychotomimetic and physiologic changes due to the 10 mg dose of oral THC, a subjective “high” was notably observed only in women. Conversely, there were no significant cognitive effects in either of the sexes. This finding might indicate that compared to men, women start experiencing subjective intoxicating effects of cannabis at doses that are lower than the threshold that induces undesirable cognitive effects. It is generally assumed that the addictive potential of a given drug is a balance between its rewarding and aversive effects. For instance, aversive effects from the initial use of tobacco or alcohol have been shown to reduce the likelihood of developing addiction (Riley et al. 2022). Thus, experiencing subjective “high” without the cognitive effects could result in greater reinforcement, potentially accelerating the progression to cannabis use disorder in women.

The magnitude of change in the subjective intoxicating effect between the sexes was also significantly different, with a small effect size (d=0.43). The observed higher sensitivity to subjective intoxicating effects of THC in this study is consistent with past findings using 0.015 mg/kg and 0.03 mg/kg of IV THC in participants without cannabis use disorder (Bassir Nia et al. 2022). Comparable findings were reported by studies of smoked cannabis. Matheson et al. (2020) reported that while plasma THC blood levels were significantly lower in women after administering smoked cannabis to young adults (12.5% THC), the subjective effects intensity was the same. Another study in frequent cannabis users showed higher plasma THC levels and subjective effects in women after smoking cannabis with different THC concentrations (1.8, and 3.6%), however, the study was not powered enough to calculate statistical significance (Cooper and Haney 2009). Also, Smoked cannabis with a dose of nearly 25 mg of THC, elicited significantly

higher subjective effects in women compared to men in a sample of frequent cannabis users(Lake et al. 2023). Parallel findings were observed in studies using other routes of administration. Makela et al. (2006) used sublingual THC with a dose of 5 mg in healthy adults and found that women show enhanced subjective effects of “mental sedation” and “tranquility” compared to men. Interestingly, one study found that sex differences in subjective effects of THC could be dose dependent. Healthy adults received 5 mg and 15 mg of oral THC and results showed that while in the lower dose, women showed greater subjective effect, in the higher dose the subjective effects were more pronounced in men (Fogel et al. 2017). A similar effect has been observed with other cannabinoids; Spindle et al. (2020a) found that women report higher “pleasant drug effects” following using vaporized cannabidiol (CBD, 100 mg) and CBD dominant vaporized cannabinoids (100 mg CBD, 3.7 mg THC). Still, Penetar et al. (2005) who administered smoked cannabis with 1.99 and 3.51% THC, and Haney (2007) who administered 2.5 mg and 5 and 10 mg of oral THC to adult subjects with no history of lifetime daily cannabis use, observed the opposite findings suggesting that men are more sensitive to subjective effects of THC. A recent naturalistic study of people who use medical cannabis concluded that the same pattern might be seen for the anxiolytic effects of cannabis, with women requiring a lower dose to achieve equivalent anxiety relief (Minhas and Lunn 2023). However, Sholler et al. (2021), administered both oral and inhaled THC at a low dose (5 or 10 mg) and higher doses (20 or 25 mg), concluding that while there was no difference in the “pleasant” effects of THC between sexes, women experienced significantly greater levels of “anxious/nervous” and “restless” effects. Notably, the MacNair et al. (2023) study suggests that the sex differences in oral THC effects could be transient. The investigators provided healthy participants with low dose (≈2.5 or ≈5 mg) and high dose (≈7.5 or ≈10 mg) oral THC twice daily for seven days. The women showed an initial grater subjective “relaxed” ratings and adverse events following THC ingestion in the high-dose arms, but the differences shrink after the first day.

One possible explanation for these sex differences could be pharmacokinetic variations. For instance, differences in THC's distribution in adipose tissue between sexes might play a role Lunn et al. (2019) have shown that women, when fasting, exhibit notably higher plasma THC concentrations post-ingestion of a 5 mg oral THC dose. Similarly, Spindle et al. (2020b) found that women have higher THC and THC metabolites after ingestion of brownies containing 10, 25, and 50 mg of THC, a difference that authors suggested might not be only due to differences in BMI. Furthermore, oral THC undergoes first-pass metabolism in the liver, producing active metabolites like 11-OH-THC, which might be influenced by sex-specific hepatic metabolism (Lunn et al. 2019; Nadulski et al. 2005; Narimatsu et al. 1991; Wall et al. 1983). Nevertheless, as the IV THC, which does not undergo the hepatic first-pass effect and produces similar plasma THC levels in different individuals, replicated similar results of sex differences in THC subjective effects (Bassir Nia et al. 2022), it is unlikely that liver-based pharmacokinetic variations are responsible for all the sex differences observed.

The sex differences in acute effects of THC are well documented in preclinical studies (Bassir Nia et al. 2018). Compared to male rats, female rats show increased sensitivity to THC-reinforcing effects, as evidenced by their faster acquisition of THC self-administration behaviors (Fattore et al. 2007; Freels et al. 2023) and enhanced cue- and drug-induced reinstatement of THC-seeking behaviors (Fattore et al. 2010). Sex hormones, especially estrogen and progesterone, seem to be pivotal in modulating these effects. Interestingly, the sensitivity to the reinforcing effects of THC showed a reduction in gonadectomized female rats (Fattore et al. 2007; Fattore et al. 2010) Similarly, the acute antinociceptive (Craft et al. 2013; Wakley et al. 2014) and locomotor (Wiley 2003) effects of THC have been shown to be greater in female rats than in male rats. Female rats develop greater tolerance to antinociceptive and locomotor effects after chronic THC exposure (Nguyen et al. 2020; Wakley et al. 2014; Wiley 2003), although the serum THC concentrations are the same (Nguyen et al. 2020). Following THC exposure, female rats show higher

downregulation or desensitization of CB1-R across all brain regions (Burston et al. 2010; Farquhar et al. 2019). Likewise, the CB1-R selective antagonist rimonabant was up to 10 times more potent in female rats than male rats in blocking the antinociceptive effects of THC (Craft et al. 2012). Taken together, these data suggest that various cannabinoid drugs (i.e., both cannabinoid agonists and antagonists) bind with greater affinity to CB1-Rs in female than male rats, probably contributing to greater effects observed in female compared with male rats, as well as faster development of tolerance. Marusich et al. (2015) further support a role for sex hormones as gonadectomized female rats showed higher withdrawal signs of THC when supplied with estradiol and progesterone but on the other hand, female gonadectomized rats showed less withdrawal signs of THC when supplied with testosterone.

Evidence also suggests sex differences in the endocannabinoid system (eCB) both in humans and animals, which can explain the observed sex differences in subjective intoxicating effects. Animal studies have demonstrated region-specific variations in CB1-R availability in males and females (Farquhar et al. 2019; Liu et al. 2020; Llorente-Berzal et al. 2013; Paola Castelli et al. 2014), which seems to be significantly influenced by sex hormones (De Fonseca et al. 1994). Brain imaging studies have found similar region-specific sex variations on the availability of CB1-Rs in humans; yet, the results are not consistent and depend on the CB1-R-specific ligand (Laurikainen et al. 2019; Neumeister et al. 2013; Normandin et al. 2015; Van Laere et al. 2008). Additional human studies with detailed measures of plasma sex hormones, as well as THC and its phase I and II plasma metabolites, are needed to fully understand the mechanisms of sex differences in THC effects. Recruiting people who underwent gonadectomy for medical purposes, women after menopause, or transgender people before and after gender-affirming hormonal treatment can shed more light on the interaction of sex hormones and THC and the endocannabinoid system.

While our study provides valuable insights, certain limitations warrant consideration. The oral administration route, although reflecting common consumption methods, introduces variables we could account for, such as variations in body fat percentage and liver-based phase I THC metabolism. We did not measure the serum concentration of THC during test days. Hence, we cannot determine the extent to which the observed differences are attributable to variations in absorption and metabolism, versus variations in the pharmacodynamic effects of THC on the brain. We only used one dose of oral THC, which failed to produce cognitive effects in both sexes and a subjective intoxication experience in men. Given the evidence that sex differences in cannabis intoxicating effects are dose-dependent, with women significantly more sensitive to the effects at lower doses (Bassir Nia et al. 2022; Fogel et al. 2017), the results could be different in higher doses., The characteristics of our participants, individuals without cannabis use disorder, could have influenced the results. Animal studies have shown a faster development of tolerance to the THC effects in female rats (Parks et al. 2020); therefore it is plausible to assume that results could be different if we recruited people with cannabis use disorder. Finally, while body mass index affects the peak concentration of oral THC and its metabolites (Nadulski et al. 2005; Wall et al. 1983), we used a constant dose of THC for all individuals regardless of their weight and body mass index, which can act as a confounder.

5. Conclusion

A 10 mg dose of oral THC elicited a more pronounced subjective intoxication effect in women than in men. However, sex differences were not observed in psychotomimetic, physiological, or cognitive effects. To better understand THC's sex-specific pharmacokinetics and pharmacodynamics, further studies with a broader range of doses and a comprehensive analysis of serum sex hormones, plasma THC, and plasma THC metabolite levels are essential. From a clinical standpoint, these findings stress the importance of sex-specific approaches to prevention and treatment strategies, as women represent a growing segment of people using THC-based

products. Recognizing the differential sensitivity is crucial for women who might be at a heightened risk of developing cannabis use disorder.

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Tables and Figures

Table 1: Schedule of procedures in test days

Time (mins)	Procedures	Vitals Signs
-90	Urine toxicology/pregnancy test Weight/ Height/ BMI	X
-60	Subjective Rating CADSS, PSI	X
0	Dronabinol 10mg capsule or placebo	X
+80	Subjective Rating CADSS, PSI Cognitive Battery	X
+150	Subjective Rating CADSS, PSI	X
+180	Subjective Rating CADSS, PSI	X
+300	Subjective Rating CADSS, PSI MMSE and physician discharge evaluation	X

Abbreviations: BMI, Body Mass Index; CADSS, Clinician-Administered Dissociative States Scale; MMSE, Mini-Mental State Examination; PSI, Psychotomimetic States Inventory.

Table 2: Basic characteristics of participants

Participant characteristics and time of peak subjective effect				
	Men		**Women**	
	Mean/n	**SD**	**Mean/n**	**SD**
Total # (n)	23		32	
# on HCM[1]			19	
Age (years)	29.0	5.8	26.2	5.4
Education (years)	15.6	1.3	15.4	2.2
Race (n)				
Asian	0		3	
Black	4		7	
Caucasian	17		19	
Mixed	1		2	
Other	0		0	
Ethnicity				
Hispanic	6		9	
Non-Hispanic	17		23	
BMI	25.3	3.7	25.3	4.5
Height (ins)	70.0	3.1	63.6	3.2
Weight (lbs)	176.9	31.4	148.3	33.6
Time of peak subjective effect[2]				
80 minutes	13		13	
150 minutes	6		7	
180 minutes	2		8	
300 minutes	2		4	

Abbreviation: BMI, Body Mass Index; HCM, Hormonal Contraceptive medication.

[1] For women who were not using HCM, all the test days were conducted in the early follicular phase.

[2] Time of Peak subjective effect was defined as the first time point in which the participant reports the highest number of "high" effects on the visual analog scale after receiving THC.

There were no statistically significant differences between the two groups regarding age, years of education, race, ethnicity, and BMI.

Table 3: Cannabis use history in participants at baseline

Cannabis use history		
	Men	**Women**
# of participants	**23**	**32**
Age on first cannabis exposure	**Mean (SD)**	**Mean (SD)**
	17.7 (3.5)	17.7 (3.7)
Last month's cannabis exposure # of days	**N (%)**	**N (%)**
0 days	9 (53%)	10 (45%)
1-5 days	6 (35%)	9 (41%)
6-10 days	1 (6%)	1 (4%)
>10 days	1 (6%)	2 (9%)
Time since Last exposure to cannabis	**N (%)**	**N (%)**
<1 day	0 (0%)	1 (5%)
1 day to <1 week	2 (11%)	5 (24%)
1 week to <1 month	6 (33%)	4 (19%)
1 month to <6 month	4 (22%)	8 (38%)
6 month to 1 year	1 (6%)	1 (5%)
> 1 year	5 (28%)	2 (9%)
Lifetime times of cannabis use	**Mean (SD)**	**Mean (SD)**
	1571 (3676)	318.5 (615.4)
Lifetime grams of cannabis used	**Mean (SD)**	**Mean (SD)**
	401.2 (994.5)	105.3 (213.4)
Last month grams of cannabis used	**Mean (SD)**	**Mean (SD)**
	0.5 (0.9)	0.4 (0.9)

There was no significant difference between the two groups in any of the variables.

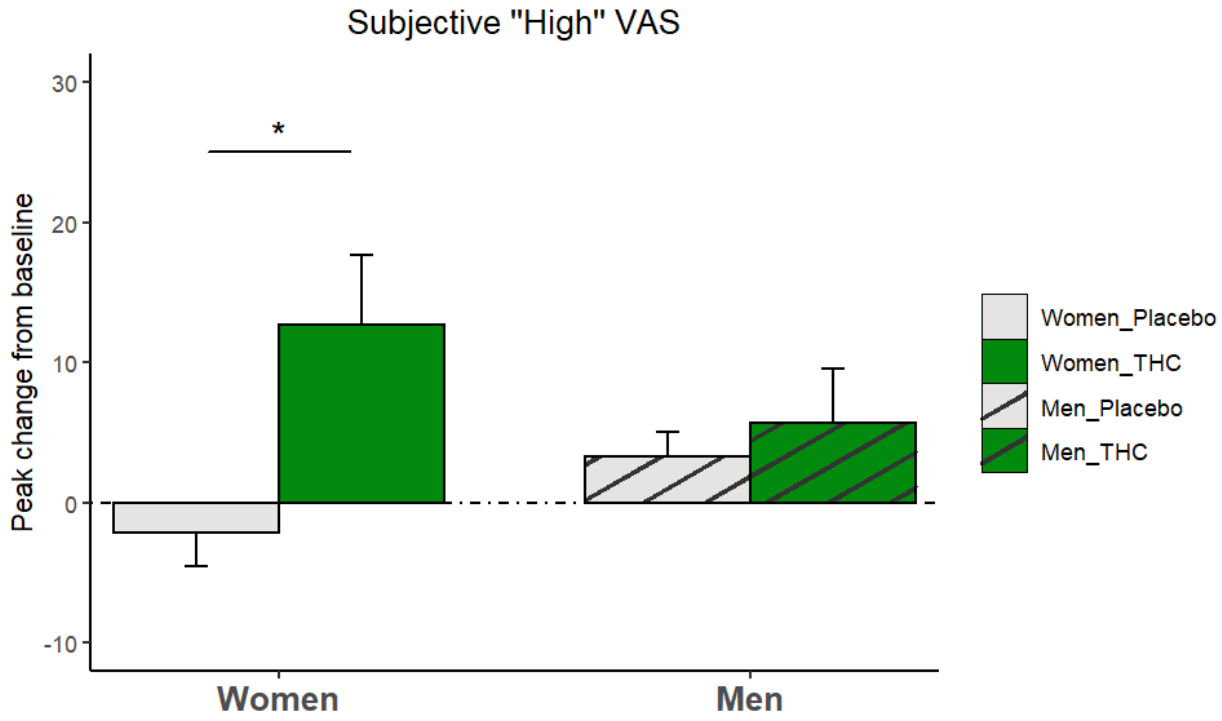

Figure 1: The mean and standard error of peak changes in visual analog scale (VAS) of subjective "high" perception among women and men on both test sessions. The Asterisk indicates statistically significant changes.

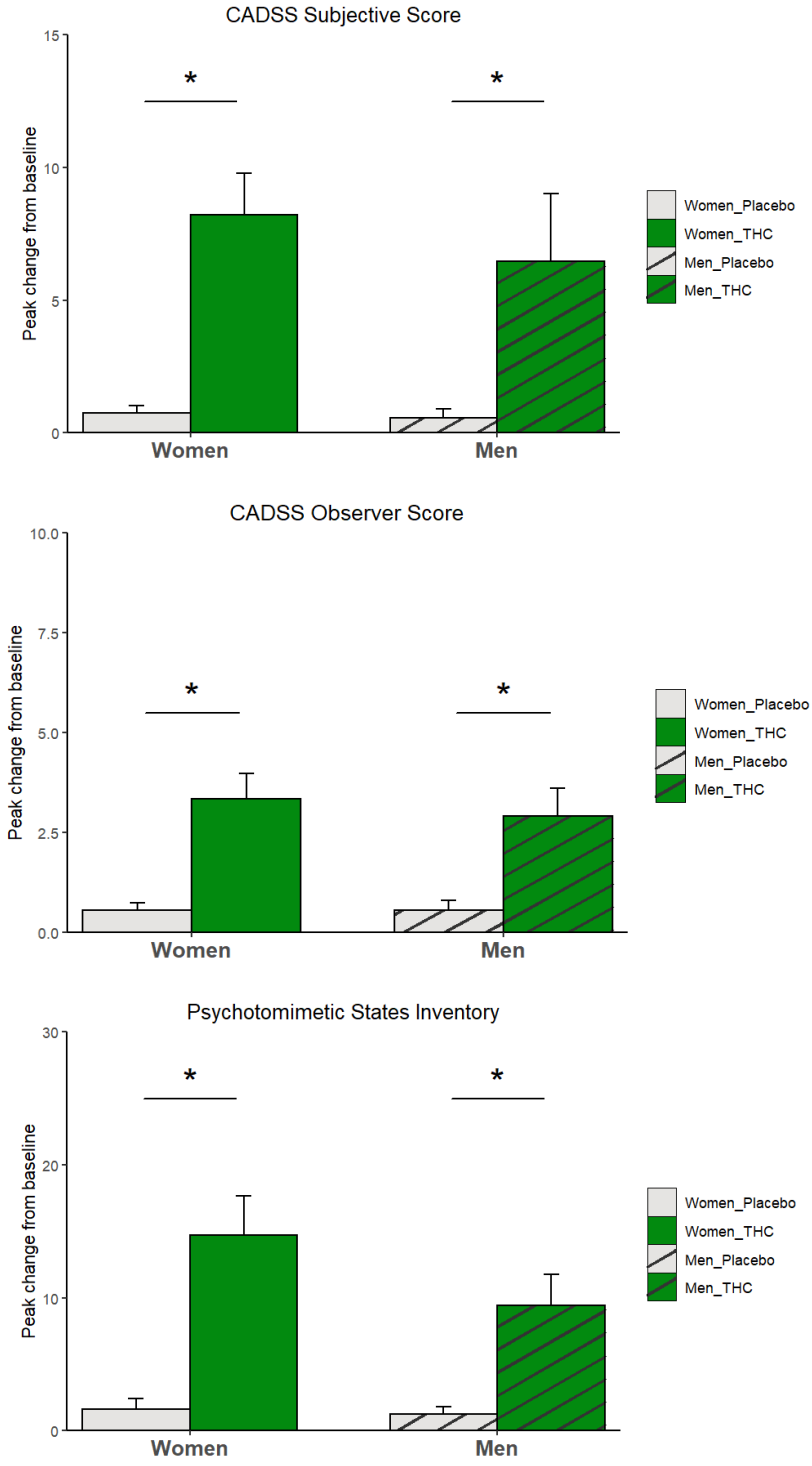

Figure 2: The mean and standard error of peak changes in psychotomimetic scales scores from baseline among women and men on both test sessions. Clinician-administered dissociative scale subjective score (top), objective score (middle), and psychotomimetic state inventory score (down). Asterisks indicate statistically significant changes.

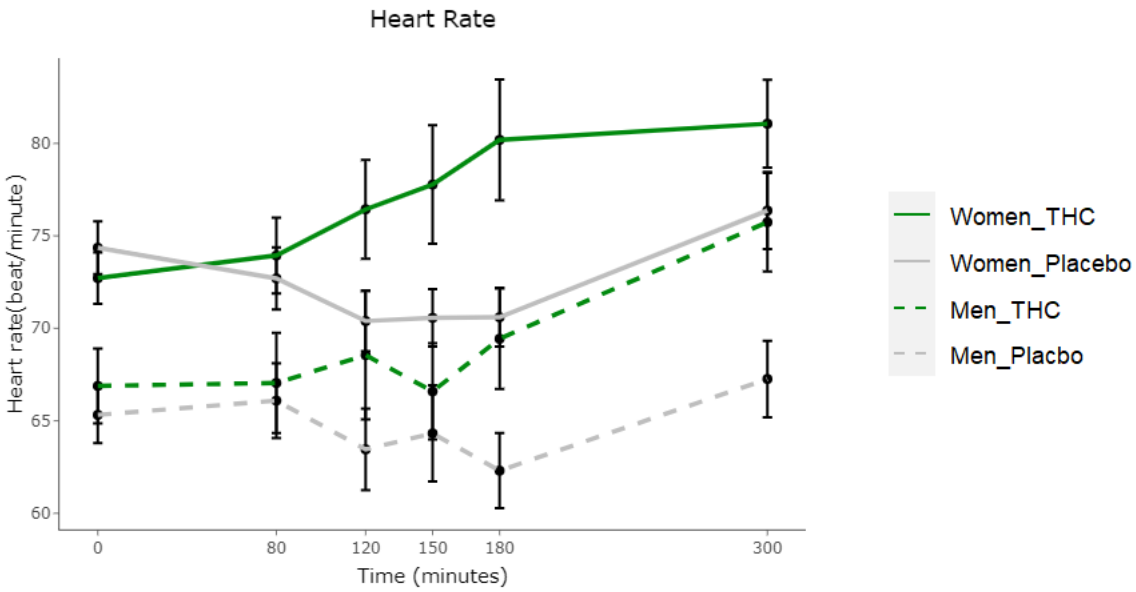

Figure 3: The mean and standard error of participants' heart rates at different time points categorized by stratified by THC/placebo administration and sex.