Lack of Consistent Sex Differences in the Acute Effects of Smoked Cannabis: A Potency- Ranging, Controlled Administration, Human Laboratory Experiment

Madison Wright
Centre for Addiction and Mental Health
Justin Matheson
Centre for Addiction and Mental Health
Adam Zaweel
Centre for Addiction and Mental Health
Christine M. Wickens
Centre for Addiction and Mental Health
Patricia Di Ciano
Centre for Addiction and Mental Health
Beth Sproule
Centre for Addiction and Mental Health
Bernard Le Foll
Bernard.LeFoll@camh.ca

Centre for Addiction and Mental Health
Bruna Brands
Centre for Addiction and Mental Health

Research Article

Keywords: Cannabis, THC, Sex differences, Pharmacokinetics, Pharmacodynamics, Blood cannabinoid concentrations, Oral fluid cannabinoid concentrations, Subjective effects, Δ9-tetrahydrocannabinol, Cognition

Posted Date: May 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9441659/v1

Additional Declarations: Competing interest reported. Dr. Bernard Le Foll has obtained funding from Indivior for a clinical trial sponsored by Indivior. He was part of Steering Board for a clinical trial for Indivior. He will be receiving funding for a clinical trial sponsored by Lilly. Dr. Le Foll has received in-kind donations of placebo edibles from Indiva. He is consultant for Shinogi, ThirdBridge, Guidepoint, and Changemark. He is part of a scientific advisory board for NFL Biosciences. He is supported by CAMH, Waypoint Centre for Mental Health Care, a clinician-scientist award from the department of Family and Community Medicine of the University of Toronto and a Chair in Addiction Psychiatry from the department of Psychiatry of University of Toronto. Dr. Christine Wickens serves on the Executive Committee of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) and on the Canadian Society of Forensic Science's Drugs and Driving Committee, which acts as an advisory body to the Department of Justice with respect to issues of drug impaired driving. She also served on the Board of Directors of the Canadian Association of Road Safety Professionals (CARSP). All other authors have nothing to disclose.

Abstract

Rationale

Sex differences in the effects of cannabis have been demonstrated in animals, though the human evidence is more equivocal. In particular, more work is needed to better understand interactions between sex and dose in determining acute pharmacological effects of cannabis, especially at higher potencies of Δ^9-tetrahydrocannabinol (THC).

Objectives

Sex differences were examined following a range of potencies of smoked cannabis (0%/0 mg, 6.25%/47 mg, 12.5%/94 mg, 22.0%/165 mg THC).

Methods

Thirty-five adults (18 females; 17 males) who used cannabis 1–5 days/week participated in a within-subject, double-blind, placebo-controlled, randomized, and counterbalanced human laboratory experiment. Analyses compared peak change from baseline scores between females and males for smoking topography, blood and oral fluid THC and metabolites concentrations, vital signs, pharmacokinetic-pharmacodynamic relationships, subjective effects, mood, and cognition.

Results

Females and males smoked similar amounts in each condition, yet females spent significantly more time smoking across all conditions. While both sexes achieved similar blood THC concentrations, females had significantly lower oral fluid THC concentrations. Aside from differences the onset of some peak subjective effects, minimal evidence of sex differences was found in other outcomes, as well as in pharmacokinetic-pharmacodynamic relationships.

Conclusions

Our findings indicate a lack of consistent sex differences in the acute effects of smoked cannabis across a range of potencies. While previous research has examined the influences of sex on the effects of THC, to our knowledge this was the first study to evaluate sex differences testing a large range of smoked cannabis potencies (up to 22%/165 mg THC) under placebo-controlled laboratory conditions.

Introduction

The legalization of non-medical cannabis use in Canada and other jurisdictions has led to a number of considerable changes in the use, availability, perceptions, and harms of cannabis (Matheson & Le Foll, 2023). In 2024, 26% of Canadian adults reported past-year cannabis use, with 15% of these individuals reporting daily cannabis use (Health Canada, 2024). Sex and gender differences have been reported in the use, harms, and effects of cannabis (Cooper & Craft, 2018; Hemsing & Greaves, 2020). Historically, men have been much more likely to use cannabis than women, though this sex/gender gap is narrowing based on reported prevalence of use (UNODC, 2022). Sex/gender differences have also been found in cannabis use disorder (CUD) and cannabis-related problems. For example, men are more likely to use cannabis in unhealthy ways (e.g., larger quantities, more frequently) and meet criteria for CUD (Cuttler et al., 2016; Greaves & Hemsing, 2020). Women may exhibit a faster progression to problematic use, demonstrate a greater severity of CUD, and have a lower mental health quality of life associated with CUD (Khan et al., 2013; Lev-Ran et al., 2012; Sherman et al., 2017). Similarly, women have higher rates of comorbid CUD and mental health conditions, particularly mood and anxiety disorders (Kozak et al., 2021; Kroon et al., 2022). Therefore, sex and gender have important impacts on the use and effects of cannabis, though mechanisms underlying these differences are not well understood.

Human laboratory studies have contributed to much of our understanding of the acute effects of cannabis, as well as how sex-related factors may contribute to subjective, physiological, pharmacokinetic, and cognitive responses to cannabis. For example, one study administered smoked cannabis (3.27–5.50% Δ^9-tetrahydrocannabinol; THC) to participants who used cannabis daily and found that females were more sensitive to addiction liability-related subjective effects than males (Cooper & Haney, 2014). Another study examined the acute effects of oral (10, 25 mg) and vaporized (5, 10, 20, 25 mg) cannabis in participants who used cannabis infrequently. Compared to males, females had greater peak blood concentrations of the major psychoactive metabolite of THC, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), and higher ratings of the negative effects of cannabis (e.g., anxious) (Sholler et al., 2020). Fogel et al. (2017) examined sex differences across oral THC doses in males and females who regularly used cannabis. Females demonstrated greater sensitivity to a low THC dose (5 mg), while males exhibited higher subjective responses at a high THC dose (15 mg) (Fogel et al., 2017). Our previous work examined sex differences in the acute effects of smoked cannabis (12.5%/94 mg THC) and found that females had lower blood THC concentrations than males, yet experienced the same subjective and cognitive effects (Matheson et al., 2020). Our follow-up study investigated the combined effects of cannabis and alcohol, and similarly discovered that females experienced the same acute effects after consuming significantly less cannabis than males (Wright et al., 2021). Most recently, we conducted a systematic review of sex differences in acute cognitive effects of cannabis in human laboratory studies, and found minimal evidence of sex differences, though some evidence that females may experience larger magnitude cognitive effects than males after exposure to cannabis or THC (Matheson et al., 2025). Taken together, females may more commonly experience greater responses to cannabis, though findings are mixed.

Given the rapidly changing cannabis landscape, there are several gaps in currently available evidence from human laboratory studies. First, cannabis potency has rapidly increased over the past decades, and most research has utilized lower potency cannabis below 6% THC (Burt et al., 2021), while current potency averages in Canada are around 16–21% THC (Mahamad et al., 2020). Second, sex differences in the effects of cannabis have been shown to differ in direction and magnitude of effects depending on dose (Fogel et al., 2017), yet little is known about how dose-varying effects may differ by sex, particularly at higher doses. Third, preclinical models have identified clear sex differences in the endocannabinoid system, behavioural responses to cannabinoids, and cannabinoid pharmacokinetics (Calakos et al., 2017; Cooper & Craft, 2018), though the human evidence is more inconsistent and limited. To help address these gaps, we aimed to investigate sex differences in the acute physiological, pharmacokinetic, subjective, and cognitive effects of a range of cannabis potencies (0%/0 mg, 6.25%/47 mg, 12.5%/94 mg, and 22.0%/165 mg THC).

Methods

This was a double-blind, placebo-controlled, randomized, counterbalanced, within-subject experiment conducted at a single site in Toronto, Ontario, Canada. This study was approved by the Centre for Addiction and Mental Health (CAMH) (Protocol #007/2018) and the Health Canada/Public Health Agency of Canada (Protocol #2017-0032) Research Ethics Boards, was in accordance with the Declaration of Helsinki and Good Clinical Practices, and was registered on clinicaltrials.gov (NCT03656029). This secondary analysis was part of a larger study examining the effects of smoked cannabis on simulated driving (Brands et al., *2026*).

Participants

Healthy adults were recruited through the community and public transit advertisements in Toronto between June 2021 and June 2022. Initial eligibility of interested participants was determined through a Research Electronic Data Capture (REDCap) (Harris et al., 2019) or telephone pre-screener. Following eligibility screening, participants provided written informed consent at an in-person session to further determine their eligibility. Inclusion criteria were: (1) use of cannabis 1-5 days/week; (2) 19-45 years of age; (3) holds a class G or G2 Ontario driver's license (or equivalent from another jurisdiction) for at least 12 months; (4) willing to abstain from using alcohol for 48 h and cannabis for 72 h prior to practice and test sessions; (5) willing to abstain from all other drugs not prescribed for medical purposes for the duration of the study (beginning 48 h before the practice session); and (6) provides written informed consent. Exclusion criteria were: (1) diagnosis of severe medical or psychiatric condition; (2) meets criteria for current or lifetime alcohol or substance use disorder (DSM-5), except tobacco and caffeine use disorders; (3) uses medications that may affect cognitive functioning; (4) has a family history of schizophrenia or another psychotic disorder; and (5) is pregnant, looking to become pregnant, or breastfeeding.

Study Procedures

Participants attended six sessions over approximately one month, including an eligibility assessment, a practice session, and four drug administration sessions, which were separated by at least 72 h. The purpose of the practice session was to familiarize participants with the study procedures. Test sessions began with measures of ongoing eligibility, including breath alcohol content measurements to confirm a level of 0 (AlertTM J5 model Breathalyzer, Alcohol Countermeasure Systems), a urine toxicology screen (QuickscreenTM CLIA-Waived 10-Panel Multi Drug Test), a cannabis saliva test (Securetec DrugWipe® 3s 25 ng/ml), and self-report measures (Timeline Follow-Back [TLFB]) (Sobell & Sobell, 1992) to confirm abstinence from alcohol, cannabis, and other substance use. Female participants were required to have a negative urine pregnancy test and asked to track their menstruation beginning from 3 months prior to their eligibility assessment and throughout their participation in the study. The TLFB was used to determine which females were menstruating on test sessions. However, there were only 16 females with a regular menstrual period and approximately half were on some method of birth control (e.g., oral contraceptive, intrauterine device). Due to the small sample size and an unbalanced number of females that were and were not menstruating during test sessions, we could not conduct meaningful or accurate comparisons between groups.

Test Sessions The only difference in the four test sessions was the dose of cannabis administered. The order participants received the four doses was randomized and counterbalanced. To maintain double-blind conditions for the study personnel, the CAMH Research Pharmacy maintained the randomization codes. Following ongoing eligibility procedures, baseline measures were collected including vital signs, oral fluid, subjective effect scales, and cognitive tests. A registered nurse then inserted an indwelling intravenous catheter to facilitate the collection of blood draws at baseline and throughout the day. Participants were then escorted to a dedicated reverse airflow smoking room with external ventilation. Blood, oral fluid, vital signs, subjective effects, and cognitive performance were reassessed after cannabis consumption.

Cannabis Administration Participants received a single cannabis cigarette that contained approximately 750 mg of plant material in all four conditions. The high potency contained 22.0 ± 4.4% (165 mg) THC, medium potency contained 12.5 ± 2.5% (94 mg) THC, low potency contained 6.25% (47 mg) THC, and placebo contained <0.1% (0 mg) THC. The cannabis was obtained from Aurora Cannabis Enterprises Inc, which is a licensed producer approved by Health Canada. Placebo cannabis was provided by the National Institute on Drug Abuse Drug Supply Program. In some cases, the placebo cannabis and the high potency were mixed to prepare the low and medium potencies, as they had later expiration dates. The study began by using a cued smoking paradigm adapted from procedures used in previous studies (Anderson et al., 2010a; Cooper & Haney, 2010). Participants followed a PowerPoint presentation, where they were asked to light the cigarette, wait 30 seconds, inhale for 3 seconds, hold smoke in their lungs for 7 seconds, and then exhale. Participants took one puff of the cigarette every minute until the entire cigarette was pyrolyzed. Many participants were not able to tolerate smoking the entire cannabis cigarette according to this fixed smoking procedure, and experienced adverse events with the high dose

such as nausea, vomiting, and intense anxiety. After consulting with the Drug Safety Monitoring Board established at the beginning of the study, an *ad libitum* smoking procedure was adopted part way through the study. We used this paradigm in our previous studies (Matheson et al., 2020; Wright et al., 2021), which allowed participants to smoke to their desired high and they were not asked to finish the cigarette. For both procedures, participants were observed through a one-way mirror to monitor safety, count the number of puffs taken, and measure the length of time spent smoking. Cigarettes were weighed before and after smoking to calculate the approximate amount of cannabis and THC consumed. The end of cannabis administration marked time 0.

Outcome Measures

Blood Cannabinoid Concentrations Blood samples were collected at baseline, 5, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min following completion of cannabis administration by a registered nurse. Each 10 mL blood sample was collected (Becton-Dickinson Vacutainer® Venous Blood Collection Whole Blood Tube K2 EDTA Additive), transferred into a cryovial (Simport Cryovial T310-10A Polypropylene Vial), and frozen at -20°C, then -80°C, and then -30°C. The first 10 participants' samples were analyzed by the CAMH Clinical Laboratory and due to unforeseen circumstances, the remaining 26 participants' samples were analyzed by Dynacare Medical Laboratories. Whole blood THC, 11-OH-THC, and THC-COOH were analyzed by gas chromatography with mass spectrometry by the CAMH Clinical Laboratory, and by liquid chromatography with mass spectrometry by Dynacare Medical Laboratories. Limits of quantification (LOQ) for THC, 11-OH-THC, and THC-COOH were 0.5, 1.0, and 1.0 ng/ml, respectively. Values below the LOQ were entered as zero.

Oral Fluid Cannabinoid Concentrations Oral fluid samples were collected at baseline, 30, 90, 120, and 360 min after completion of cannabis smoking. Each 1-2 mL oral fluid sample was collected in a 10 mL glass vial (Distribution LabSphere Inc, 10ml Precision Thread Headspace-Vial, with 18mm Universal Screw Cap/Seal) and then frozen at -80°C. All samples were analyzed by Dynacare Medical Laboratories. Samples were analyzed by liquid chromatography with tandem mass spectrometry. The LOQ for THC, 11-OH-THC, and THC-COOH were 0.58, 0.49, and 0.19 ng/mL, respectively. Values below the LOQ were entered as zero.

Vital Signs Heart rate and systolic and diastolic blood pressure were collected with a digital vital signs monitor (Welch Allyn Spot Vital Signs, model 42N0B). Vital signs were collected at baseline, 5, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min following cannabis administration.

Subjective Effect Scales Visual Analog Scales (VAS) were collected to measure participants' subjective cannabis effects at baseline, 5, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min following dosing. VAS were "I like this drug effect", "This feels like cannabis", "I feel this effect", "I feel high", "I feel the good effects", "I feel the bad effects", and "I feel the rush", which were administered on REDCap with a sliding scale ranging from "not at all" (0) to "extremely" (100). In addition, the Addiction Research Centre Inventory (ARCI) (Martin et al., 1971) short form (49-item) assessed drug-class-specific subjective effects including seven subscales: amphetamine, morphine-benzedrine, lysergic acid diethylamine,

benzedrine, pentobarbital-chlorpromazine-alcohol, euphoria, and sedation. Finally, the Profile of Mood States (POMS) (McNair et al., 1971) 72-item version assessed changes in mood including ten subscales: tension-anxiety; anger-hostility; depression-dejection; friendliness; fatigue; confusion; vigor; elation; arousal; and positive mood. The ARCI and POMS were collected on REDCap at baseline and approximately 60 min after dosing.

Cognitive Measures The verbal-free recall (VFR) task, which is based on the Hopkins Verbal Learning Test (Wickens et al., 2022; Wright et al., 2021), tested for immediate recall (trial 1), immediate total recall (trials 1 + 2 + 3), delayed recall (trial 4, 23 minutes later), and percent retained (delayed recall divided by best recall score during the second and third recall trials). Second, the Useful Field of View (UFOV) test (Martin et al., 1971) assessed processing speed, selective attention, and divided attention. Both cognitive tests were collected on REDCap at baseline and approximately 60 min following dosing.

Safety Monitoring Participants were monitored for any adverse events (AEs) using a modified version of the SAFTEE questionnaire (Guy et al., 1986; Rabkin & Markowitz, 1986). Based on a list of selected terms, AEs were coded and the date of onset, duration, severity, relationship to study drug, and action taken were recorded.

Statistical Analyses

Effects of condition and sex are reported here, though only effects of sex are focused on, as follow up comparisons between potencies are reported elsewhere (Brands et al., *2026*). All data were analyzed using SPSS 26.0. Differences between female and male demographics and cannabis use measures were compared with independent samples *t*-tests.

Outcome measures including multiple time points (blood and oral fluid cannabinoid concentrations, VAS, vitals) were represented as peak change from baseline values (peak value – baseline value). Outcome measures including baseline and one post-cannabis administration time point (cognitive tests, ARCI, POMS) were represented as change scores (post-cannabis administration score – baseline score). All outcome measures were analyzed using linear mixed-effect models, with potency (placebo, low, medium, high), order (order of drug exposure), smoking procedure (fixed or *ad libitum*), and sex (male or female) included as fixed effects, and participant as the random effect. Four separate models were tested with the addition of different covariates. Model 1 was unadjusted (no covariates), model 2 included participant weight as a covariate, model 3 included participant weight and peak change from baseline THC concentration as covariates, and model 4 included participant weight and peak change from baseline 11-OH-THC concentration as covariates. Significant sex by condition interactions were followed up with Bonferroni-corrected pairwise comparisons to compare males and females in each condition. Pairwise comparisons were two-tailed tests and statistical significance was selected as $p \leq 0.05$ for all analyses.

The estimated THC dose was calculated as the difference in mass of the cannabis cigarette multiplied by the potency of THC in the active plant material. To further analyze blood, oral fluid, and VAS measures,

area-under-the-curve ($AUC_{0à360min}$) was calculated using the trapezoidal method. Pearson correlation coefficients were calculated to explore relationships between peak change from baseline THC and 11-OH-THC concentrations and peak change from baseline VAS effects and heart rate in males and females separately. Finally, the time to peak effects were calculated for VAS measures.

Results

The flow of participants through each stage of the study is presented in Fig. **1**. A total of 36 participants completed all study sessions and 35 participants (18 females; 17 males) were included in the final analyses. Participants who had higher than 2 ng/mL of THC in blood at baseline were removed from all analyses for that session. In total, nine individual test sessions were removed. Fifty-six blood samples from 12 participants were not collected. All post-cannabis administration measures from one session were not collected from two participants.

Participant Characteristics

Sample characteristics are presented in Table **1**. Females and males did not differ on any measures except for weight and height. Compared to males, females had significantly lower body weight (63.60±3.64 vs. 79.51±3.23 kg; p=0.003) and height (1.63±0.016 vs. 1.80±0.014 meters; p<0.0001). Outcomes from the four tested models are summarized in Table **2**.

Smoking Topography

A total of 10 participants (4 females; 6 males) completed their sessions using the fixed dose smoking procedure and 25 participants (14 females; 11 males) completed their sessions using the *ad libitum* smoking procedure. There were no significant sex × condition interactions for any smoking topography outcomes. There was a significant main effect of sex for time spent smoking (F(1,30)=7.79, p=0.009), where females spent significantly longer smoking across all conditions than males. This effect remained significant when covariates were introduced. See Fig. **2**.

Blood THC and Metabolites Concentrations

There were no significant sex × condition interactions or main effects of sex for blood THC, THC-COOH, or 11-OH-THC peak change from baseline or AUC concentrations. See Fig. **3**.

Oral Fluid THC and Metabolites Concentrations

THC-COOH and 11-OH-THC concentrations were not analyzed, as values were negligible and mostly below the LOQ. There were no significant sex × condition interactions for oral fluid THC peak change from baseline or AUC concentrations. There was a main effect of sex for peak change from baseline oral fluid THC concentrations (F(1,33)=4.34, p=0.045), where females had significantly lower concentrations across all conditions. There was also a main effect of sex for AUC oral fluid THC concentrations

(F(1,33)=4.34, p=0.045), where females had significantly lower concentrations across all conditions. See Fig. **3**.

Vital Signs

For peak change from baseline systolic blood pressure, there was a significant sex × condition interaction (F(3, 93)=2.96, p=0.036). Follow-up pairwise comparisons revealed that females had significantly lower peak change from baseline systolic blood pressure in the high potency condition (11.53±2.83 vs. 21.68±2.95 mmHg). This interaction remained significant when covariates were introduced. In addition, there was a significant main effect of sex for peak change from baseline diastolic blood pressure (F(1, 33)=7.01, p=0.0012), where females had significantly lower peak change from baseline diastolic blood pressure across all conditions. This effect remained significant when covariates were introduced. See Fig. **4**.

Subjective Effects

VAS Results from all VAS measures are shown in Fig. **5** (peak change from baseline scores), Fig. **6** (AUC), and Fig. **7** (time to peak effects). There were no significant sex × condition interactions or main effects of sex for any VAS peak change from baseline scores or AUC in the unadjusted model. In the adjusted models, there were no significant sex × condition interactions for any VAS peak change from baseline, though there were main effects of sex for three AUC measures. First, there was a significant main effect of sex for “I like this drug effect” in model 4 (F(1,32)=4.74, p=0.037), where females had significantly smaller AUC. Peak change from baseline concentrations of 11-OH-THC was a significant predictor of this subjective effect (F(1,113)=10.48, p=0.002). Second, there were main effects of sex for “This feels like cannabis” in models 2 (F(1,32)=4.48, p=0.042), 3 (F(1,30)=6.62, p=0.015), and 4 (F(1,32)=6.74, p=0.014), where females had significantly smaller AUC. Peak change from baseline concentrations of THC (F(1,108)=10.44, p=0.002) and 11-OH-THC (F(1,110)=6.32, p=0.013) were significant predictors of this effect in models 3 and 4, respectively. Third, there were significant main effects of sex for “I feel the rush” in models 3 (F(1,31)=14.23, p=0.048) and 4 (F(1,31)=4.86, p=0.035), where females had significantly smaller AUC. Weight was a significant predictor in both models 3 (F(1,30)=6.15, p=0.019) and 4 (F(1,30)=6.22, p=0.018). Finally, there was a significant sex × condition interaction in model 1 for the time to peak effect for “I feel this effect” (F(3,93)=2.89, p=0.040). Pairwise comparisons revealed that females had a faster onset of peak effects in the placebo (6.11±9.72 vs. 49.05±10.10 min) and high potency (10.91±9.85 vs. 39.88±10.19 min) conditions. This interaction remained significant when covariates were introduced. Finally, there was also a main effect of sex in model 1 for this measure (F(1,33)=4.16, p=0.049), where females had a faster onset of peak effects across all conditions for “I feel this effect”.

ARCI Among the ARCI subscales there were no significant sex × condition interactions or main effects of sex.

POMS Among the POMS subscales there were no significant sex × condition interactions. There was a main effect of sex for the depression-dejection subscale ($F(1,33)=4.95$, $p=0.033$), where females had significantly lower change scores across all conditions.

Cognitive Measures

VFR There were no significant sex × condition interactions or main effects of sex for any VFR outcome. See Fig. **8**.

UFOV There were no significant sex × condition interactions for any UFOV outcome. There was a significant main effect of sex for selective attention ($F(1,32=6.80$, $p=0.014$), where females had significantly lower change scores across all conditions. This effect remained significant when covariates were introduced. Peak change from baseline concentrations of 11-OH-THC was a significant predictor of selective attention in model 4 ($F(1,79)=4.20$, $p=0.044$). See Fig. **8**.

Pharmacokinetic-Pharmacodynamic Correlations

Correlations between peak change from baseline concentrations of THC and 11-OH-THC and peak change from baseline VAS outcomes and heart rate are presented in Table **3**. There were very few significant correlations, and most did not differ between females and males.

Adverse Events

In total, 24 AEs were reported in 18 participants (6 females; 12 males). A full list and description of these AEs are reported elsewhere (Brands et al., *2026*).

Discussion

This study examined sex differences in the acute pharmacological effects of a range of smoked cannabis potencies in adults who regularly used cannabis. While active cannabis elicited significant changes in most outcome measures, we uncovered limited evidence of consistent sex differences in blood cannabinoid concentrations, subjective responses, pharmacokinetic-pharmacodynamic correlations, mood, and cognitive effects. Some sex differences were found in smoking behaviour, vitals, onset of peak subjective effects, and oral fluid THC concentrations. Both sexes exhibited similar blood THC concentrations, though females had significantly lower oral fluid THC concentrations than males. While previous research has examined sex differences in the acute effects of THC, to our knowledge this was the first study to evaluate sex differences at such a high potency of smoked cannabis (22%/15 mg THC) under placebo-controlled laboratory conditions.

Our findings revealed that females and males smoked similar amounts of cannabis across all conditions and had correspondingly similar concentrations of THC and metabolites in blood. These results correspond with our previous study, where females and males smoked similar amounts of cannabis (12.5%/94 mg THC), and no evidence of sex differences in cannabinoid blood concentrations were found

(Wright et al., 2021). However, these results differ from our earlier study, where we found that females had significantly lower THC and THC-COOH blood concentrations after smoking cannabis (12.5%/94 mg THC) under the same conditions (Matheson et al., 2020). In the previous two studies, females smoked numerically less cannabis than males, though females smoked numerically more cannabis than males in the current study. Several factors may contribute to these differences, including that females were older and used cannabis slightly more frequently than in the previous two studies. Similarly, in the current study, females initiated first cannabis use and weekly cannabis use two years younger than males, potentially indicating they had more experience using cannabis. Indeed, a previous human laboratory experiment found that the number of years participants reported having frequently used cannabis was a strong predictor of increased cannabis consumption in the study (McClure et al., 2012). Finally, in our previous two studies, both sexes smoked more cannabis across all conditions compared to the current study. While the study designs and participant characteristics were similar across studies, the potencies of cannabis received may have played a role. In the previous two studies, participants knew they were either smoking placebo or 12.5%/94 mg THC. However, in the current study, participants were aware they would be receiving 22%/165 mg THC during one of the test sessions, and perhaps smoked less cannabis across all sessions in anticipation of receiving a higher potency.

In the current study, our smoking topography results may point to small observational sex differences in smoking behaviour. Both females and males titrated the amount of cannabis they smoked, yet how they achieved this titration may have differed. On average, males took 14 puffs of the cannabis cigarette in each condition. However, on average females took 17 puffs of the placebo, 18 puffs of the low potency, 16 puffs of the medium potency, and 14 puffs of the high potency. This indicates that males potentially titrated the length and inhalation of their puffs, while females titrated their number of puffs. Similarly, while females and males did not differ in the amount of cannabis they consumed, females spent significantly more time smoking across all conditions. This may suggest that females allowed more of the cannabis cigarette to burn and took shorter puffs over a longer duration of time, rather than inhaling all the cannabis. This possibly could have resulted in lower doses of cannabis consumed, suggesting females may have experienced the same effects after being exposed to potentially lower concentrations of THC. This would be consistent with some reports of females experiencing greater subjective effects (Cooper & Haney, 2014; Sholler et al., 2020) and higher blood cannabinoid concentrations (Klumpers et al., 2012; Nadulski et al., 2005; Spindle et al., 2019) after receiving the same dose as males. This may also help explain why females appeared to smoke numerically more cannabis than males in this study, compared to the opposite observation in our previous two studies. However, it is difficult to draw comparisons and conclusions across studies without extensive measures of smoking behaviour (e.g., depth of inhalation). Future studies should capture additional measures of smoking topography to definitively examine sex differences in smoking topography.

Despite having similar concentrations of THC in blood as males, females had significantly lower peak change from baseline and AUC measures of THC concentrations in oral fluid across all conditions. To our knowledge, only two other studies have analyzed sex differences in oral fluid THC concentrations (Spindle et al., 2020; Spindle et al., 2019). Spindle et al. (2020) reported females had higher maximum

concentrations of THC after a 50 mg dose of oral cannabis, but not at a 10 or 25 mg oral doses. Conversely, Spindle et al. (2019) found that males had qualitatively higher maximum concentrations of oral fluid THC, despite females having higher observed blood THC concentrations following administration of 10 and 25 mg of smoked and vaporized THC. However, the authors noted that the higher THC oral fluid concentrations in males were driven by three male participants with extremely high concentrations of THC in oral fluid despite low concentrations in blood (Spindle et al., 2019). This issue may also have contributed to our sex differences. Particularly in the placebo condition, three male participants had high concentrations of oral fluid THC, and if removed, there would be no sex difference. However, although there were a few male participants with higher THC concentrations in the active cannabis conditions, if excluded, the sex differences would remain. An alternative explanation for sex differences in oral fluid THC relates to smoking topography. During smoking, THC is deposited in the oral cavity, which is the main source of THC collected and measured in oral fluid testing (Huestis & Cone, 2004). Consequently, concentrations can depend on serval factors including oral cavity volume, smoking patterns and history, smoking topography, eating, drinking, and oral hygiene (Huestis & Cone, 2004; Kauert et al., 2007; Robertson et al., 2022). Therefore, females may have held the smoke in their mouths/lungs for a shorter duration of time (as suggested above), resulting in lower concentrations of THC depositing in the oral cavity and consequently oral fluid. In addition, on average, females have smaller oral cavity volume (Nascimento et al., 2012) and lower salivary flow rates (Inoue et al., 2006), which may also contribute to this sex difference. These findings are particularly important to further investigate and consider for cannabis-impaired driving roadside testing.

Across all other outcomes there were very few sex differences, indicating that females and males experienced similar subjective, mood, and cognitive responses to cannabis. However, females experienced a significantly earlier onset of feeling the effects of cannabis across all conditions, particularly in the placebo and high dose. Lipophilic drugs (like THC) can have a faster onset of effects in females because they tend to have higher body fat content than males (Soldin & Mattison, 2009). Similarly, Pabon & de Wit (2023) demonstrated estrogen levels across menstrual cycle phase were related to the time course of cannabis effect on multiple subjective measures in a cannabis administration study. Together, this finding indicates that the time course of THC-induced subjective effects may be more closely related to sex, rather than acute peak effects.

Although we found some significant sex differences, overall females and males had similar physiological, pharmacokinetic, subjective, and cognitive responses to varying cannabis potencies. Females and males did not differ in age, race/ethnicity, BMI, substance use, cannabis use frequency, average dose of cannabis used per occasion, age of cannabis use initiation, age of regular cannabis use initiation, or cannabis effect expectancies, which perhaps partly contributes to sex similarities. Our findings are consistent with other literature demonstrating a lack of sex differences following cannabis administration in physiological (Cooper & Haney, 2014), subjective (Anderson et al., 2010b; Cooper & Haney, 2016), and cognitive (Anderson et al., 2010b; Crane et al., 2013; Matheson et al., 2025; Schlienz et al., 2020) responses, indicating a lack of consistent sex differences. Other studies have demonstrated sex differences in these outcomes, though findings are mixed. Inconsistencies across studies may be

driven by differences in study designs, procedures, and participants. Varying cannabis products and potencies, routes of administration, smoking procedures, and participant populations have been tested, which can all impact the presence of sex differences. For example, Cooper and Haney (2014) found that in participants who used cannabis daily, females reported greater addiction liability-related subjective effects compared to males. Whereas Sholler et al. (2020) found that in participants who used cannabis infrequently, females experienced greater negative subjective effects than males. Finally, perhaps sex does not strongly impact the acute effects of cannabis in humans. Nevertheless, there are several factors to consider when drawing conclusions regarding the influences of sex-related factors on the acute effects of cannabis, highlighting the need for additional research. Further methodological limitations and considerations for future research were recently discussed in a commentary paper, which highlighted the need for hypothesis-driven measurement of sex and gender variables to meaningfully advance our understanding of sex, gender, and cannabis effects (Matheson et al., 2026).

This study has a few limitations to consider. First, our total sample size was relatively small, which may have impacted our ability to detect sex differences. Second, it is not possible to make conclusive comparisons of smoking topography without extensive measures of smoking behaviour such as duration, depth, and hold of puff inhalation. Third, the study was originally designed to use a paced-puff smoking procedure to allow for administration of a more standardized dose, however, many participants experienced AEs involving intense cannabis intoxication. Due to safety concerns, the smoking paradigm was changed part way through data collection, though we controlled for potential differences in smoking procedure in our statistical models. Fourth, the storage of blood samples was suboptimal. Scheidweiler et al. (2013) recommends that blood should not be stored at -20°C for longer than three months before analysis, as THC begins to degrade beyond this time. Some of our samples were stored at -20°C for longer than three months, resulting in potentially lower-than-expected THC concentrations. Fifth, due to unforeseen circumstances, two different laboratories had to analyze our blood samples. The CAMH Clinical Laboratory used gas chromatography with mass spectrometry and Dynacare Medical Laboratories used liquid chromatography with mass spectrometry. However, these methods are very comparable, and both laboratories are fully accredited; thus, the same results should have been produced from the two laboratories. Sixth, we cannot comment on the potential role of gonadal hormones on the effects of cannabis, as we did not control for menstrual cycle phase in females, which is an important area for future research. Lastly, more research is needed to generalize our findings to other populations, as our sample mostly consisted of young adults who regularly used cannabis and identified their race as white.

Conclusions

There is limited research investigating sex differences in the acute pharmacological effects of cannabis across a range of potencies. We found minimal evidence of consistent sex differences across pharmacokinetic, physiological, subjective, and cognitive outcomes. Some sex differences were revealed in smoking behaviour, oral fluid THC concentrations, and the onset of peak subjective effects, suggesting the need for further research to explore and clarify these potential differences. Our results provide new

insight into how females and males respond to incrementally higher potencies of smoked cannabis, which are more representative of products used by the public, compared to most previous studies. Taken together, findings on sex differences in the acute effects of cannabis are inconsistent, with even less understanding of dose-varying differences, particularly using higher potency and novel cannabis products. Additional research is required to further explore the influences of sex on the acute effects of cannabis and to better understand the mechanisms underlying these sex differences to inform education, risk prevention, policy, and treatment.

Declarations

This study was approved by the Centre for Addiction and Mental Health (CAMH) (Protocol #007/2018) and the Health Canada/Public Health Agency of Canada (Protocol #2017-0032) Research Ethics Boards, was in accordance with the Declaration of Helsinki and Good Clinical Practices, and was registered on clinicaltrials.gov (NCT03656029).

Conflicts of Interest:

Dr. Bernard Le Foll has obtained funding from Indivior for a clinical trial sponsored by Indivior. He was part of Steering Board for a clinical trial for Indivior. He will be receiving funding for a clinical trial sponsored by Lilly. Dr. Le Foll has received in-kind donations of placebo edibles from Indiva. He is consultant for Shinogi, ThirdBridge, Guidepoint, and Changemark. He is part of a scientific advisory board for NFL Biosciences. He is supported by CAMH, Waypoint Centre for Mental Health Care, a clinician-scientist award from the department of Family and Community Medicine of the University of Toronto and a Chair in Addiction Psychiatry from the department of Psychiatry of University of Toronto. Dr. Christine Wickens serves on the Executive Committee of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) and on the Canadian Society of Forensic Science's Drugs and Driving Committee, which acts as an advisory body to the Department of Justice with respect to issues of drug impaired driving. She also served on the Board of Directors of the Canadian Association of Road Safety Professionals (CARSP). All other authors have nothing to disclose.

Funding:

Public Safety Canada

Author Contribution

Study Design: BB, BLFFunding Acquisition: BBManuscript Conceptualization: MW, JMData Analyses: MWFigure Development: MWSupervision: BB, BLF, BSWriting– original draft: MWWriting– review & editing: MW, JM, AZ, CMW, PDC, BS, BLF, BB

Acknowledgement

We would like to extend our deepest gratitude to the dedicated nurses who were instrumental in the success of this study: Paige Blanchard, Emily Simpkin, Jiah Jethava, and Sharon Atendido. Additionally, we wish to acknowledge the invaluable support of the staff at the CAMH (Centre for Addiction and Mental Health) research pharmacy and clinical laboratory. Furthermore, we are thankful for the guidance and oversight provided by the members of the Drug Safety Monitoring Board (DSMB) and Research Quality Assurance team. Finally, we wish to acknowledge all our study participants who volunteered their time to support the advancement of science.

Data Availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

References

1. Anderson, B. M., Rizzo, M., Block, R. I., Pearlson, G. D., & O'Leary, D. S. (2010a). Sex differences in the effects of marijuana on simulated driving performance. *Journal of psychoactive drugs*, *42*(1), 19-30. https://doi.org/10.1080/02791072.2010.10399782
2. Anderson, B. M., Rizzo, M., Block, R. I., Pearlson, G. D., & O'Leary, D. S. (2010b). Sex, Drugs, and Cognition: Effects of Marijuana. *Journal of Psychoactive Drugs*, *42*(4), 413-424. https://doi.org/10.1080/02791072.2010.10400704
3. Brands, B., Zaweel, A., Wright, M., Di Ciano, P., Wickens, C. M., Matheson, J., Fares, A., Hasan, O. S. M., Sanches, M., Sproule, B., Huestis, M. A., Brown, T., & Le Foll, B. (*2026*). Potency-related effects of smoked cannabis on simulated driving performance: a randomized, controlled crossover trial. *Scientific Reports*. https://doi.org/https://doi.org/10.1038/s41598-026-43045-2
4. Burt, T. S., Brown, T. L., Milavetz, G., & McGehee, D. V. (2021). Mechanisms of cannabis impairment: Implications for modeling driving performance. *Forensic Sci Int*, *328*, 110902. https://doi.org/10.1016/j.forsciint.2021.110902
5. Calakos, K. C., Bhatt, S., Foster, D. W., & Cosgrove, K. P. (2017). Mechanisms Underlying Sex Differences in Cannabis Use. *Curr Addict Rep*, *4*(4), 439-453. https://doi.org/10.1007/s40429-017-0174-7
6. Cooper, Z. D., & Craft, R. M. (2018). Sex-Dependent Effects of Cannabis and Cannabinoids: A Translational Perspective. *Neuropsychopharmacology*, *43*(1), 34-51. https://doi.org/10.1038/npp.2017.140
7. Cooper, Z. D., & Haney, M. (2010). Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology (Berl)*, *211*(2), 141-148. https://doi.org/10.1007/s00213-010-1875-y

8. Cooper, Z. D., & Haney, M. (2014). Investigation of sex-dependent effects of cannabis in daily cannabis smokers. *Drug Alcohol Depend*, *136*, 85-91. https://doi.org/10.1016/j.drugalcdep.2013.12.013
9. Cooper, Z. D., & Haney, M. (2016). Sex-dependent effects of cannabis-induced analgesia. *Drug Alcohol Depend*, *167*, 112-120. https://doi.org/10.1016/j.drugalcdep.2016.08.001
10. Crane, N. A., Schuster, R. M., Fusar-Poli, P., & Gonzalez, R. (2013). Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. *Neuropsychol Rev*, *23*(2), 117-137. https://doi.org/10.1007/s11065-012-9222-1
11. Cuttler, C., Mischley, L. K., & Sexton, M. (2016). Sex Differences in Cannabis Use and Effects: A Cross-Sectional Survey of Cannabis Users. *Cannabis Cannabinoid Res*, *1*(1), 166-175. https://doi.org/10.1089/can.2016.0010
12. Fogel, J. S., Kelly, T. H., Westgate, P. M., & Lile, J. A. (2017). Sex differences in the subjective effects of oral Delta(9)-THC in cannabis users. *Pharmacol Biochem Behav*, *152*, 44-51. https://doi.org/10.1016/j.pbb.2016.01.007
13. Greaves, L., & Hemsing, N. (2020). Sex and Gender Interactions on the Use and Impact of Recreational Cannabis. *Int J Environ Res Public Health*, *17*(2). https://doi.org/10.3390/ijerph17020509
14. Guy, W., Wilson, W. H., Brooking, B., Manov, G., & Fjetland, O. (1986). Reliability and validity of SAFTEE: preliminary analyses. *Psychopharmacol Bull*, *22*(2), 397-401.
15. Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., & Duda, S. N. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*, *95*, 103208. https://doi.org/https://doi.org/10.1016/j.jbi.2019.103208
16. Health Canada. (2024). *Canadian Cannabis Survey 2024: Summary*.
17. Hemsing, N., & Greaves, L. (2020). Gender Norms, Roles and Relations and Cannabis-Use Patterns: A Scoping Review. *Int J Environ Res Public Health*, *17*(3). https://doi.org/10.3390/ijerph17030947
18. Huestis, M. A., & Cone, E. J. (2004). Relationship of Delta 9-tetrahydrocannabinol concentrations in oral fluid and plasma after controlled administration of smoked cannabis. *J Anal Toxicol*, *28*(6), 394-399. https://doi.org/10.1093/jat/28.6.394
19. Inoue, H., Ono, K., Masuda, W., Morimoto, Y., Tanaka, T., Yokota, M., & Inenaga, K. (2006). Gender difference in unstimulated whole saliva flow rate and salivary gland sizes. *Archives of Oral Biology*, *51*(12), 1055-1060. https://doi.org/https://doi.org/10.1016/j.archoralbio.2006.06.010
20. Kauert, G. F., Ramaekers, J. G., Schneider, E., Moeller, M. R., & Toennes, S. W. (2007). Pharmacokinetic Properties of Δ9-Tetrahydrocannabinol in Serum and Oral Fluid. *Journal of Analytical Toxicology*, *31*(5), 288-293. https://doi.org/10.1093/jat/31.5.288
21. Khan, S. S., Secades-Villa, R., Okuda, M., Wang, S., Perez-Fuentes, G., Kerridge, B. T., & Blanco, C. (2013). Gender differences in cannabis use disorders: results from the National Epidemiologic

Survey of Alcohol and Related Conditions. *Drug Alcohol Depend*, *130*(1-3), 101-108. https://doi.org/10.1016/j.drugalcdep.2012.10.015

22. Klumpers, L. E., Cole, D. M., Khalili-Mahani, N., Soeter, R. P., te Beek, E. T., Rombouts, S. A. R. B., & van Gerven, J. M. A. (2012). Manipulating brain connectivity with δ9-tetrahydrocannabinol: A pharmacological resting state FMRI study. *NeuroImage*, *63*(3), 1701-1711. https://doi.org/https://doi.org/10.1016/j.neuroimage.2012.07.051
23. Kozak, K., H. Smith, P., Lowe, D. J. E., Weinberger, A. H., Cooper, Z. D., Rabin, R. A., & George, T. P. (2021). A systematic review and meta-analysis of sex differences in cannabis use disorder amongst people with comorbid mental illness. *The American Journal of Drug and Alcohol Abuse*, 1-13. https://doi.org/10.1080/00952990.2021.1946071
24. Kroon, E., Mansueto, A., Kuhns, L., Filbey, F., Wiers, R., & Cousijn, J. (2022). Gender Differences in Cannabis Use Disorder Symptoms: A Network Analysis. *Drug and Alcohol Dependence*, 109733. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2022.109733
25. Lev-Ran, S., Imtiaz, S., Taylor, B. J., Shield, K. D., Rehm, J., & Le Foll, B. (2012). Gender differences in health-related quality of life among cannabis users: Results from the national epidemiologic survey on alcohol and related conditions. *Drug and Alcohol Dependence*, *123*(1), 190-200. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2011.11.010
26. Mahamad, S., Wadsworth, E., Rynard, V., Goodman, S., & Hammond, D. (2020). Availability, retail price and potency of legal and illegal cannabis in Canada after recreational cannabis legalisation [https://doi.org/10.1111/dar.13069]. *Drug and Alcohol Review*, *39*(4), 337-346. https://doi.org/https://doi.org/10.1111/dar.13069
27. Martin, W. R., Sloan, J. W., Sapira, J. D., & Jasinski, D. R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther*, *12*(2), 245-258. https://doi.org/10.1002/cpt1971122part1245
28. Matheson, J., Behzad, D., Galea, L., & Di Ciano, P. (2026). Sex differences in the acute effects of cannabis: the need for hypothesis-driven research. *J Psychiatry Neurosci*, *51*, 1-8. https://doi.org/10.1139/jpn-2025-0164
29. Matheson, J., Behzad, D., Zakala, C., Hawken, T., Brands, B., Le Foll, B., Wickens, C. M., Ruocco, A. C., Rodak, T., & Di Ciano, P. (2025). Sex differences in the acute effects of cannabis on human cognition: A systematic review. *Frontiers in Neuroendocrinology*, *79*, 101215. https://doi.org/https://doi.org/10.1016/j.yfrne.2025.101215
30. Matheson, J., & Le Foll, B. (2023). Impacts of recreational cannabis legalization on use and harms: A narrative review of sex/gender differences [Review]. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1127660
31. Matheson, J., Sproule, B., Di Ciano, P., Fares, A., Le Foll, B., Mann, R. E., & Brands, B. (2020). Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. *Psychopharmacology*, *237*(2), 305-316. https://doi.org/10.1007/s00213-019-05369-y

32. McClure, E. A., Stitzer, M. L., & Vandrey, R. (2012). Characterizing smoking topography of cannabis in heavy users. *Psychopharmacology*, *220*(2), 309-318. https://doi.org/10.1007/s00213-011-2480-4
33. McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). *Manual for the Profile of Mood States*.
34. Nadulski, T., Pragst, F., Weinberg, G., Roser, P., Schnelle, M., Fronk, E. M., & Stadelmann, A. M. (2005). Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit*, *27*(6), 799-810. https://doi.org/10.1097/01.ftd.0000177223.19294.5c
35. Nascimento, W. V., Cassiani, R. A., & Dantas, R. O. (2012). Gender effect on oral volume capacity. *Dysphagia*, *27*(3), 384-389. https://doi.org/10.1007/s00455-011-9379-4
36. Pabon, E., & de Wit, H. (2023). Effects of Oral Delta-9-Tetrahydrocannabinol in Women During the Follicular Phase of the Menstrual Cycle. *Cannabis & Cannabinoid Research*, *8*(6), 1117-1125. https://doi.org/10.1089/can.2022.0045
37. Rabkin, J. G., & Markowitz, J. S. (1986). Side effect assessment with SAFTEE: pilot study of the instrument. *Psychopharmacology bulletin*, *22*(2), 389-396. http://europepmc.org/abstract/MED/3774932
38. Robertson, M. B., Li, A., Yuan, Y., Jiang, A., Gjerde, H., Staples, J. A., & Brubacher, J. R. (2022). Correlation between oral fluid and blood THC concentration: A systematic review and discussion of policy implications. *Accident Analysis & Prevention*, *173*, 106694. https://doi.org/https://doi.org/10.1016/j.aap.2022.106694
39. Scheidweiler, K. B., Schwope, D. M., Karschner, E. L., Desrosiers, N. A., Gorelick, D. A., & Huestis, M. A. (2013). In vitro stability of free and glucuronidated cannabinoids in blood and plasma following controlled smoked cannabis. *Clin Chem*, *59*(7), 1108-1117. https://doi.org/10.1373/clinchem.2012.201467
40. Schlienz, N. J., Spindle, T. R., Cone, E. J., Herrmann, E. S., Bigelow, G. E., Mitchell, J. M., Flegel, R., LoDico, C., & Vandrey, R. (2020). Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. *Drug Alcohol Depend*, *211*, 107969. https://doi.org/10.1016/j.drugalcdep.2020.107969
41. Sherman, B. J., McRae-Clark, A. L., Baker, N. L., Sonne, S. C., Killeen, T. K., Cloud, K., & Gray, K. M. (2017). Gender differences among treatment-seeking adults with cannabis use disorder: Clinical profiles of women and men enrolled in the achieving cannabis cessation—evaluating N-acetylcysteine treatment (ACCENT) study. *The American Journal on Addictions*, *26*(2), 136-144. https://doi.org/10.1111/ajad.12503
42. Sholler, D. J., Strickland, J. C., Spindle, T. R., Weerts, E. M., & Vandrey, R. (2020). Sex differences in the acute effects of oral and vaporized cannabis among healthy adults [https://doi.org/10.1111/adb.12968]. *Addiction Biology*, *n/a*(n/a), e12968. https://doi.org/https://doi.org/10.1111/adb.12968

43. Soldin, O. P., & Mattison, D. R. (2009). Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*, *48*(3), 143-157. https://doi.org/10.2165/00003088-200948030-00001
44. Spindle, T. R., Cone, E. J., Herrmann, E. S., Mitchell, J. M., Flegel, R., LoDico, C., Bigelow, G. E., & Vandrey, R. (2020). Pharmacokinetics of Cannabis Brownies: A Controlled Examination of Δ9-Tetrahydrocannabinol and Metabolites in Blood and Oral Fluid of Healthy Adult Males and Females. *Journal of Analytical Toxicology*. https://doi.org/10.1093/jat/bkaa067
45. Spindle, T. R., Cone, E. J., Schlienz, N. J., Mitchell, J. M., Bigelow, G. E., Flegel, R., Hayes, E., & Vandrey, R. (2019). Acute Pharmacokinetic Profile of Smoked and Vaporized Cannabis in Human Blood and Oral Fluid. *J Anal Toxicol*, *43*(4), 233-258. https://doi.org/10.1093/jat/bky104
46. UNODC. (2022). *Word Drug Report 2022*.
47. Wickens, C. M., Wright, M., Mann, R. E., Brands, B., Di Ciano, P., Stoduto, G., Fares, A., Matheson, J., George, T. P., Rehm, J., Shuper, P. A., Sproule, B., Samohkvalov, A., Huestis, M. A., & Le Foll, B. (2022). Separate and combined effects of alcohol and cannabis on mood, subjective experience, cognition and psychomotor performance: A randomized trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *118*, 110570. https://doi.org/https://doi.org/10.1016/j.pnpbp.2022.110570
48. Wright, M., Wickens, C. M., Di Ciano, P., Sproule, B., Fares, A., Matheson, J., Mann, R. E., Rehm, J., Shuper, P. A., George, T. P., Huestis, M. A., Stoduto, G., Le Foll, B., & Brands, B. (2021). Sex differences in the acute pharmacological and subjective effects of smoked cannabis combined with alcohol in young adults. *Psychol Addict Behav*, *35*(5), 536-552. https://doi.org/10.1037/adb0000749

Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

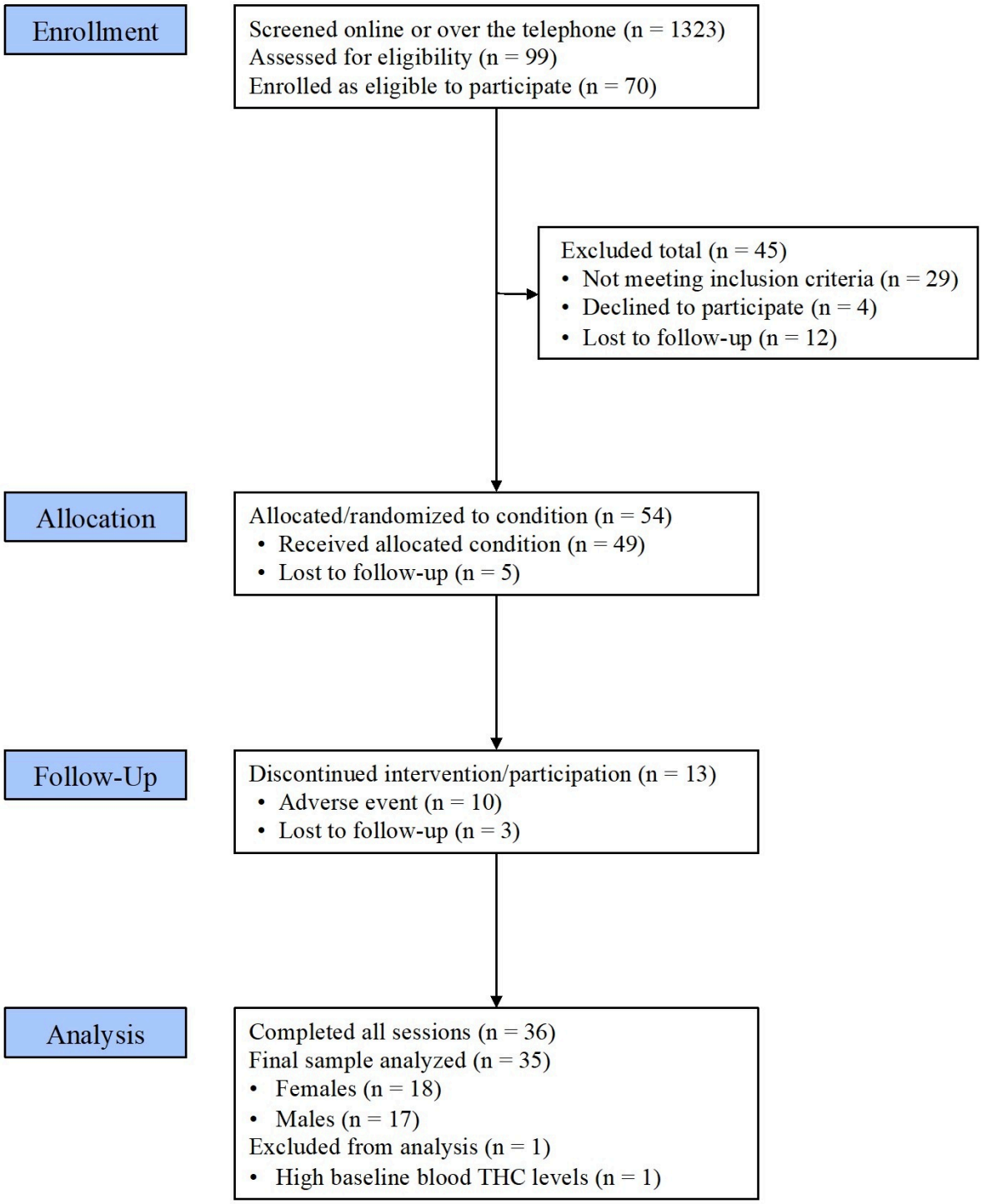

Figure 1

Flow of participants through each stage of the study

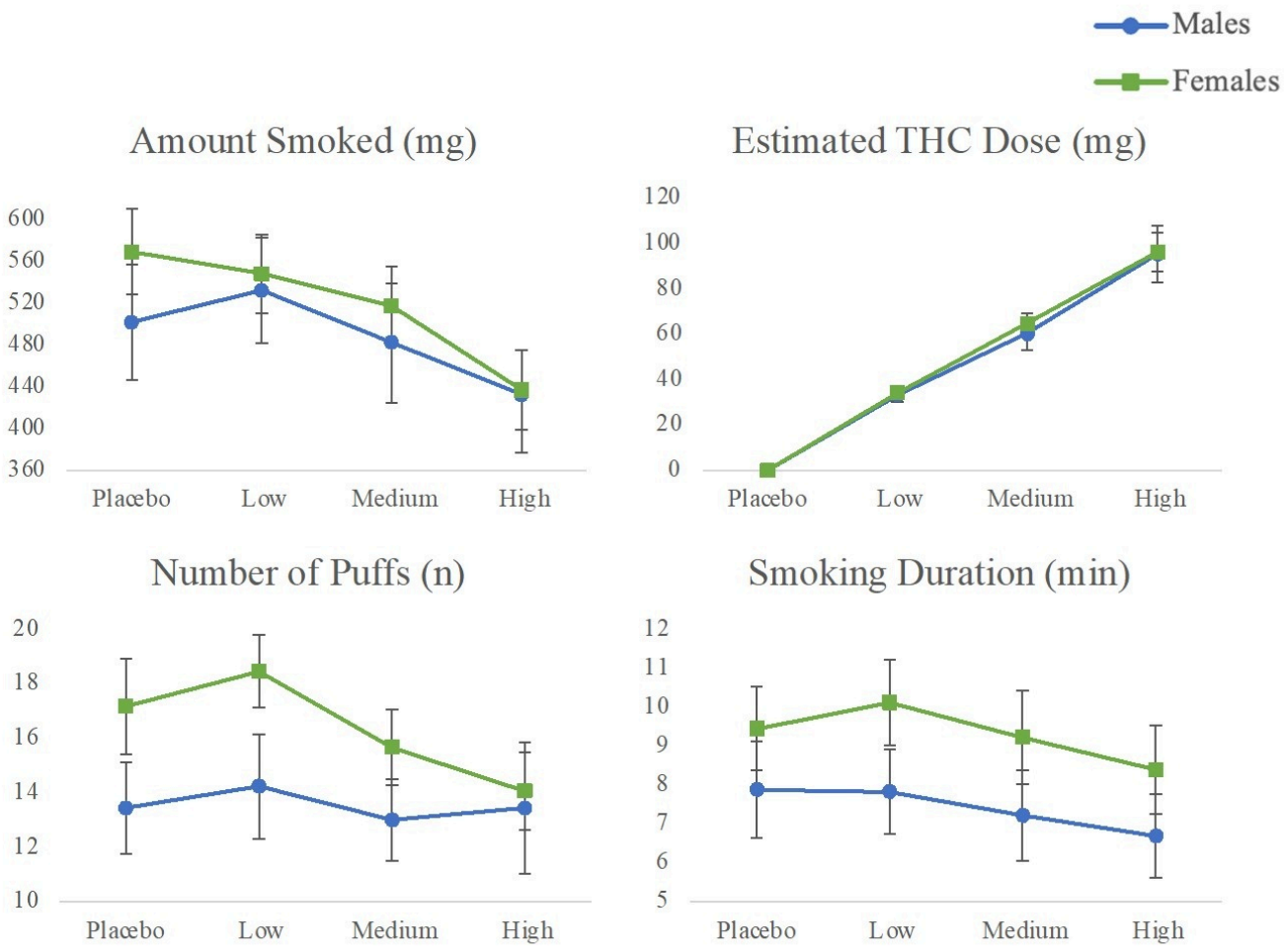

Figure 2

Smoking topography measures are presented for amount smoked (mg), estimated THC dose (mg), number of puffs (n), and smoking duration (min) across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). There was a significant main effect of sex for smoking duration; $p < 0.05$

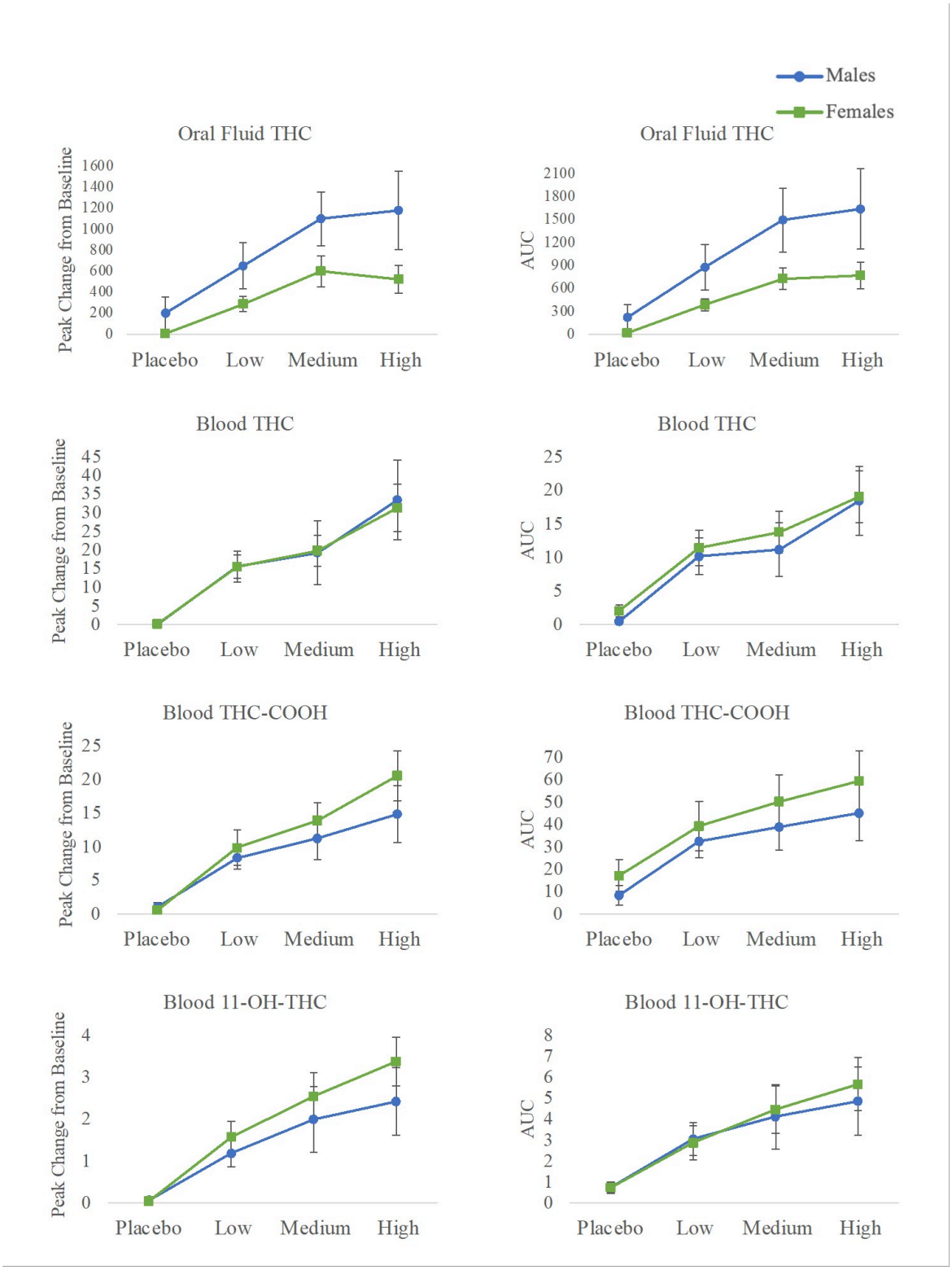

Figure 3

Peak change from baseline and $AUC_{0 \rightarrow 360min}$ are presented for oral fluid and blood THC and metabolite concentrations (ng/ml) across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). There were main effects of sex for both oral fluid measures; $p < 0.05$

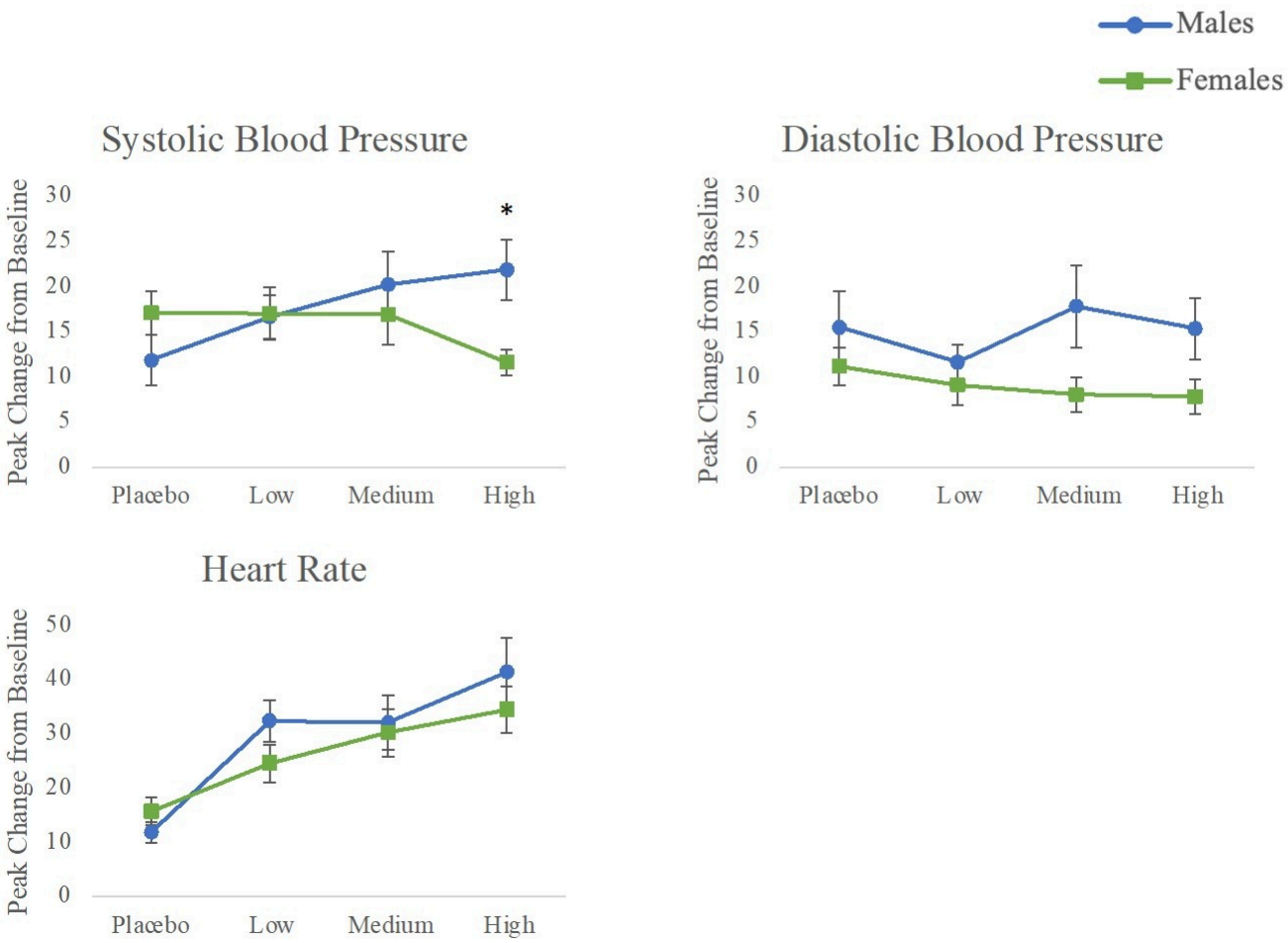

Figure 4

Peak change from baseline measures are presented for heart rate (bpm), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg) across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). * Indicates statistically significant difference detected between males and females; $p < 0.05$. There was a main effect of sex for diastolic blood pressure; $p < 0.05$

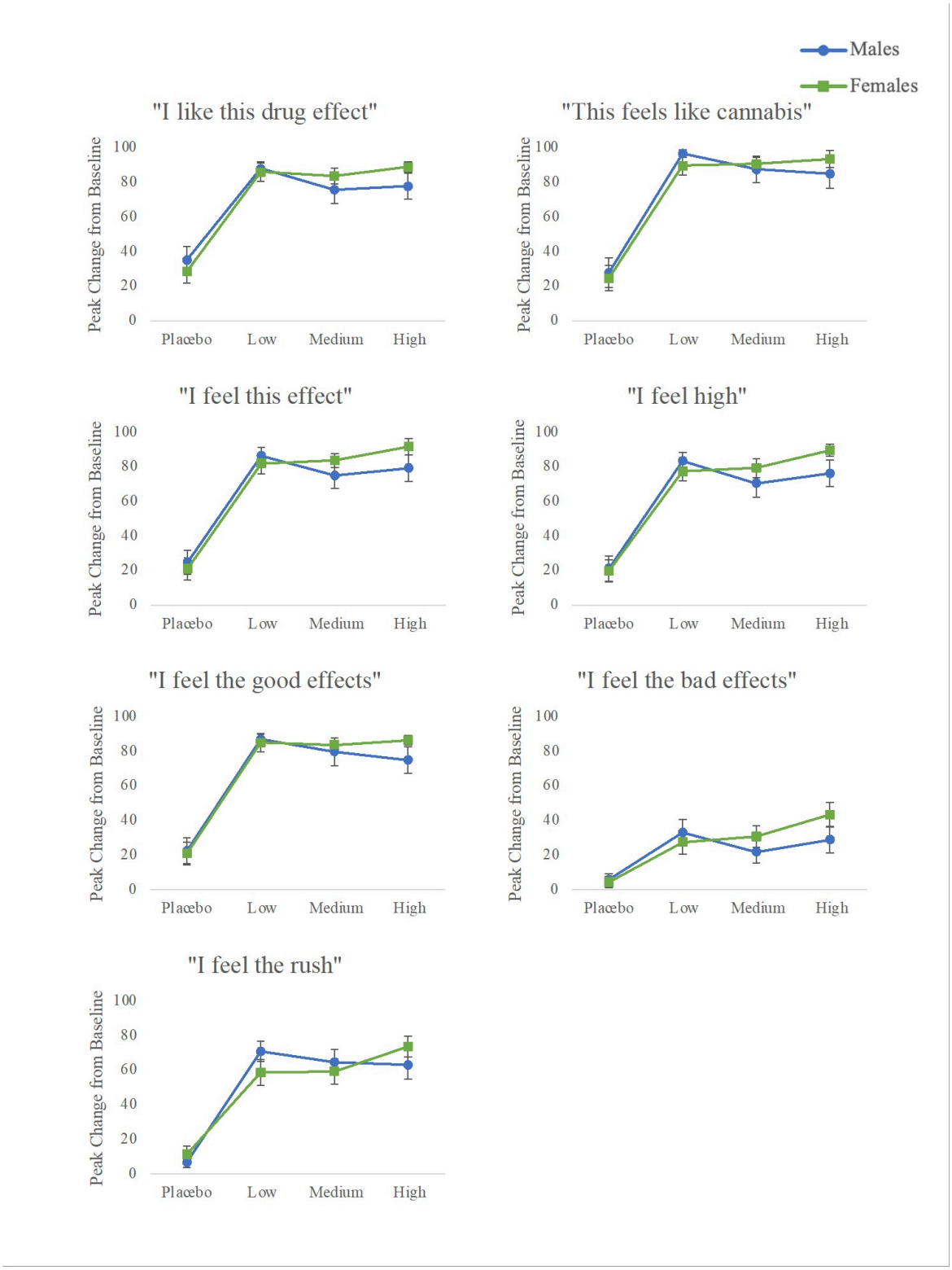

Figure 5

Peak change from baseline measures are presented for all VAS measures across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). There were no significant differences between males and females for any measure; $p < 0.05$

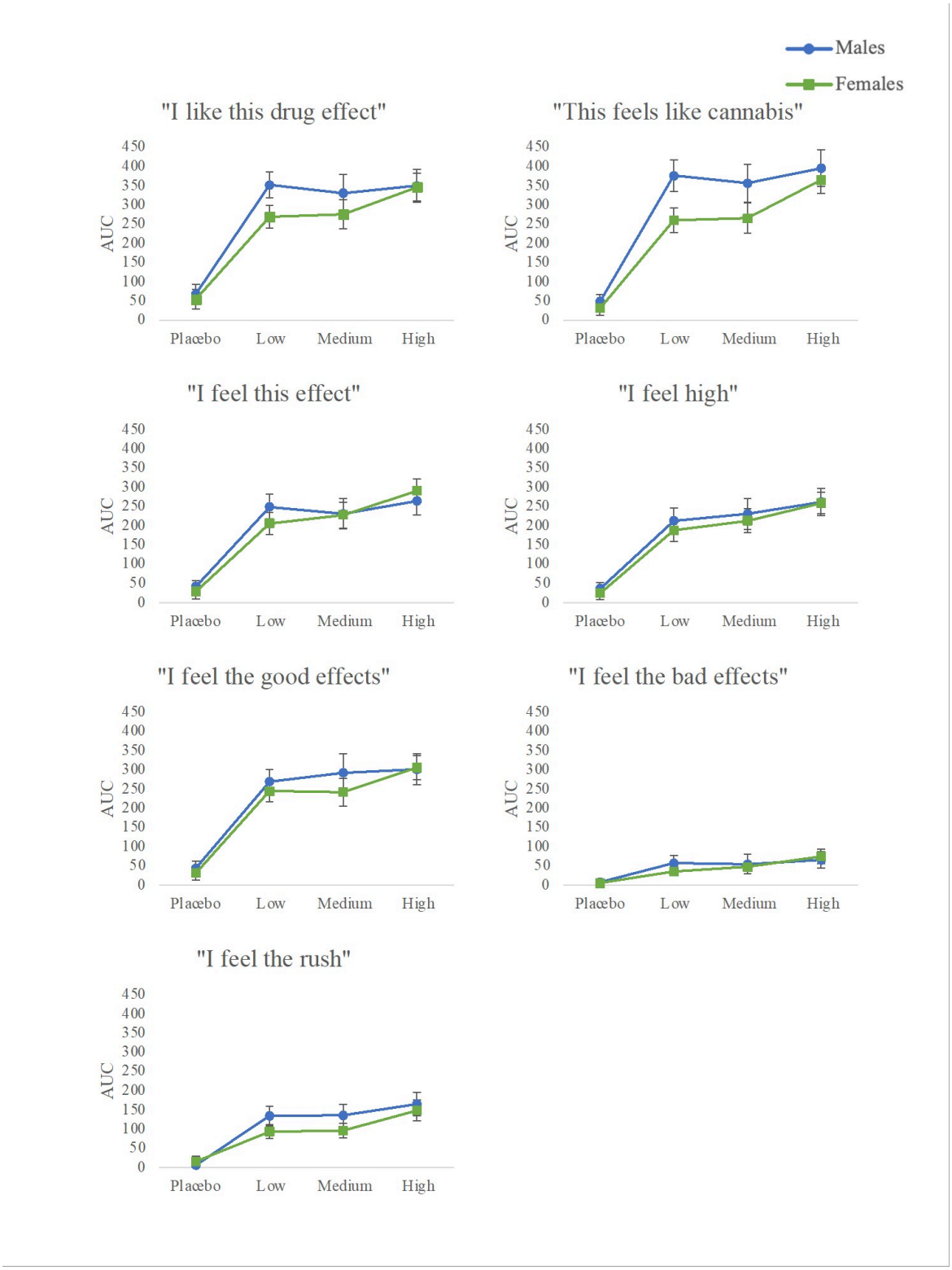

Figure 6

$AUC_{0 \rightarrow 360min}$ are presented for all VAS measures across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). There were main effects of sex for “I like this drug effect”, “This feels like cannabis”, “and “I feel the rush”; $p < 0.05$

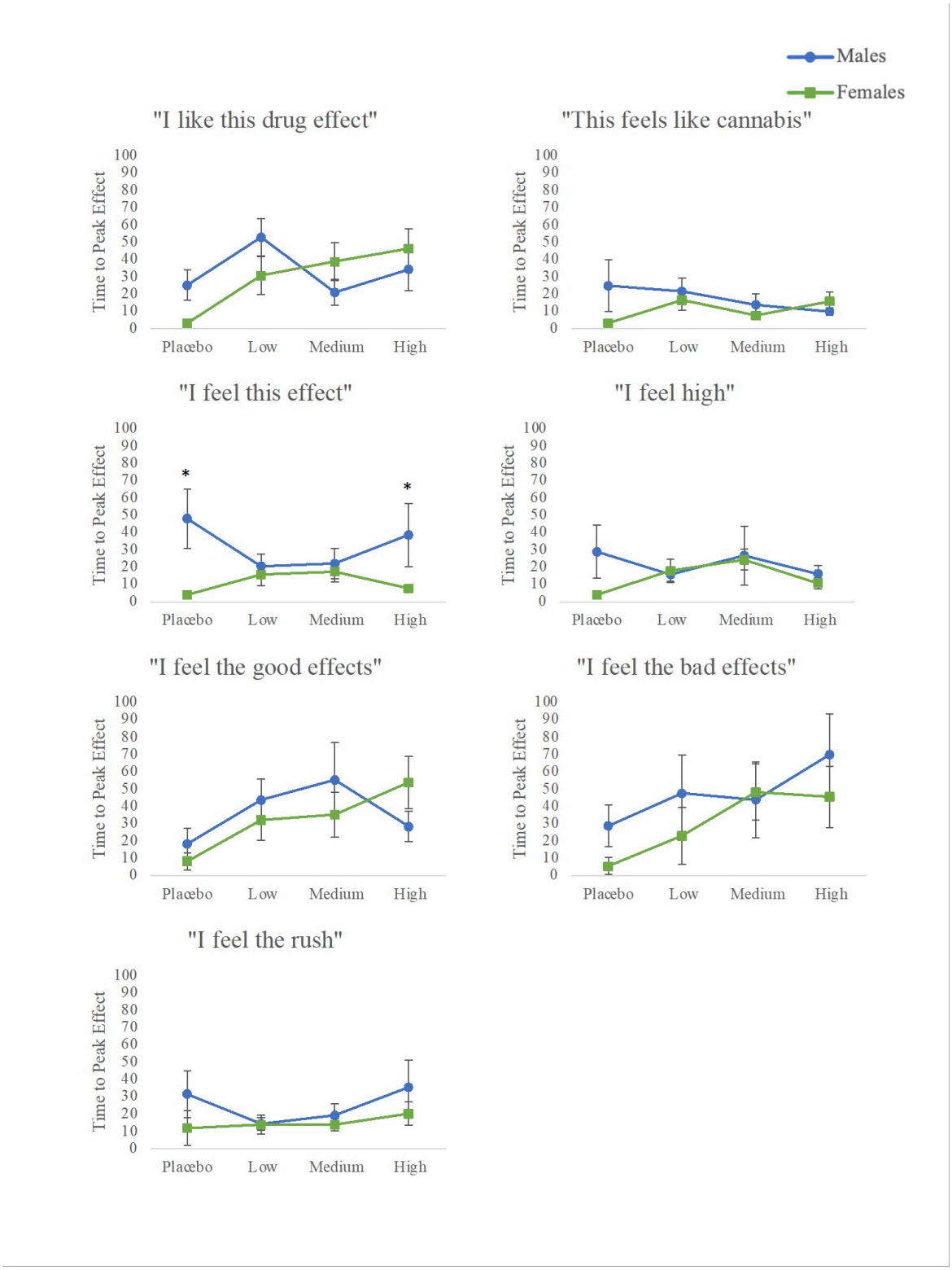

Figure 7

Time to peak effects are presented for all VAS measures across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). * Indicates statistically significant difference detected between males and females. There was a main effect of sex for “I feel this effect”; $p < 0.05$

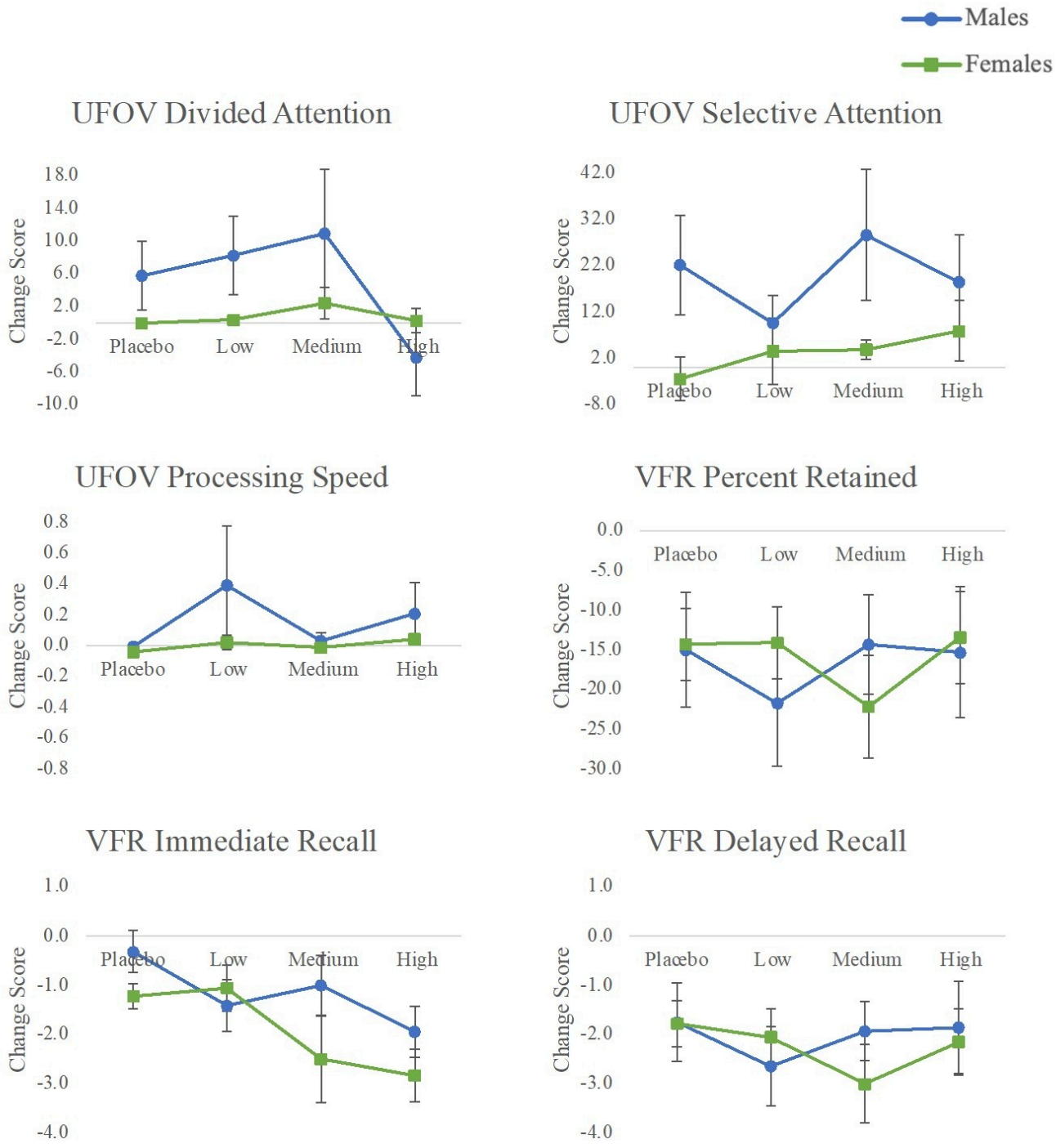

Figure 8

Post- minus pre-cannabis administration change scores are presented for the cognitive tests. For the UFOV, divided attention, selective attention, and processing speed are shown, and for the VFR, percent retained, immediate recall, and delayed recall are shown across conditions (placebo, low, medium, high) in males (blue circles) and females (green squares). There were no significant differences between

males and females for any measure, though there was a main effect of sex for selective attention; $p < 0.05$

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table123.docx