The role of sex in daily levels of high-risk alcohol and cannabis co-use

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HIGHLIGHTS

- Any alcohol use on any given day and total drinks per day predict same-day cannabis use.
- Among males but not females, any alcohol use in a day increases likelihood of same-day cannabis use.
- Total drinks predict same-day cannabis use in males, but not females, who co-use at risky levels.

ARTICLE INFO

ABSTRACT

Background: Co-use of alcohol and cannabis is highly prevalent and may be associated with negative outcomes. The intersection between alcohol and cannabis use remains poorly understood. The present study assessed this intersection and the moderating effects of sex on the daily levels of high-risk alcohol and cannabis co-use.
Methods: A secondary analysis of an experimental pharmacology study specifically designed to recruit individuals using both alcohol and cannabis was conducted. Thirty-three non-treatment seeking subjects (19 M/14F) reporting high-risk levels of alcohol and cannabis use completed a 30-day Timeline Follow-back (TLFB) assessment for alcohol and cannabis use, resulting in a total of $N = 990$ observations. Logistic models tested the probability of same day cannabis use as predicted by alcohol use (any use, total drinking, and binge drinking), sex, and alcohol use by sex interactions.
Results: Drinking any alcohol on a given day was associated with a significant increase in the likelihood of same-day cannabis use ($b = 0.61$, $p = 0.001$) as was amount of alcohol consumed on a given day ($b = 0.083$, $p = 0.012$). These relations were significantly moderated by sex ($b = 1.58$, $p<0.001$; $b = 0.14$, $p = 0.044$). Male-identifying individuals demonstrated an increased probability of concurrent cannabis use with any alcohol use on a given day, and this relationship increased linearly as the number of drinks consumed increased.
Conclusions: The present study investigated the patterns associated with co-using alcohol and cannabis in individuals reporting *high-risk* levels of both alcohol and cannabis use. The sex-dependent findings suggest that males are at higher risk for co-using alcohol and cannabis compared with females.

1. Introduction

Co-use of alcohol and cannabis is rising in prevalence, with about one-quarter of young adult Americans reporting using both substances in the past year (Lee et al., 2022; McCabe et al., 2021). Alcohol use may increase the probability of same-day cannabis use (Roche et al., 2019), such that drinking alcohol on a given day is associated with a 2.5-fold increase in the likelihood of same-day cannabis use (Roche et al.,

2019). Further, a higher frequency of drinking days and heavier alcohol use in a given day have been associated with moderate to heavy cannabis use (Venegas et al., 2022).

The correlates of cannabis and alcohol co-use include increased alcohol consumption and alcohol-related negative consequences compared to alcohol use alone (Midanik et al., 2007; Subbaraman and Kerr, 2015). These consequences include increased odds of driving while intoxicated and harms to relationships, finances, and health (2015).

Moreover, greater consequences are observed as the number of drinks in a co-use day increases (Gunn et al., 2021; Sokolovsky et al., 2020). Co-use may be predictive of the development and maintenance of alcohol use disorder (Blanco et al., 2016; Hayley et al., 2017; Weinberger et al., 2016) and poorer prognosis for alcohol use treatment (Subbaraman et al., 2017; Wardell et al., 2020). Despite these alcohol-related negative consequences of co-use, little is known about cannabis-related negative consequences of co-use.

Given the negative consequences and the rise in prevalence of co-use, there is a need to understand variables that contribute to the high-risk patterns of co-use. Patterns of co-use and their outcomes may vary between males and females, as any co-use at all is associated with being male (Venegas et al., 2020), and moderate-heavy cannabis users are more likely to be male (Venegas et al., 2022). Moreover, the increased probability of same-day cannabis use when alcohol is consumed is greater for males than for females (Roche et al., 2019). However, findings of co-use patterns are limited by low prevalence of female participants (Metrik et al., 2018), characterization of alcohol use dichotomously (Venegas et al., 2022), and lack of moderate to heavy cannabis users in samples (Grodin et al., 2021; Roche et al., 2019; Venegas et al., 2022, 2020; Waddell, 2022) given that secondary investigations of co-use typically leverage data from samples recruited specifically for high alcohol use and not for cannabis use. The present study examined same day co-use in a sample of individuals reporting *high-risk* levels of both alcohol and cannabis use, as defined by scores of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) and the Cannabis Use Disorders Identification Test – Revised (CUDIT-R; (Adamson et al., 2010)). The study also tested the moderating effects of sex on the daily level of alcohol use (i.e., any *use, total drinks, binge drinking*) and cannabis co-use on the same day. We hypothesized that measures of alcohol use would be associated with same-day cannabis use, and that this association would be stronger in males compared to females.

2. Methods

2.1. Participants

The sample consisted of individuals recruited with high-risk alcohol use and high-risk cannabis use and was drawn from assessment data collected during an experimental psychopharmacology study (Venegas and Ray, 2022). The inclusion criteria for the study were: ≥ 21 years of age, English fluency, meeting criteria for hazardous drinking and cannabis use (i.e., score of 8 or higher on the AUDIT/CUDIT-R), smoking combustibles as preferred route of cannabis administration, and negative for alcohol and all drugs (except cannabis) at the time of the study visit. Exclusion criteria for the study were: current or past (30 days) treatment for alcohol or cannabis use, meeting DSM-5 diagnostic criteria for a current (i.e., past 12-month) diagnosis of a substance use disorder other than alcohol, cannabis, and/or nicotine or for a lifetime DSM-5 diagnosis of bipolar disorder or a psychotic disorder, regular (i.e., $\geq$ once per week) use of psychoactive drugs except for alcohol, cannabis, and/or nicotine, use of psychoactive medications, and a score of 10 or higher on the Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (Sullivan et al., 1989). A sample of 33 individuals ($N = 33$, 42 % female) were included in the present analyses.

2.2. Measures

Participants completed a demographics questionnaire that assessed age, sex, and race/ethnicity as well as a 30-day Timeline Follow-back (TLFB; Sobell and Sobell, 1992) for alcohol and cannabis use. The TLFB has high reliability (>0.85) for recording alcohol use quantity and frequency (1992) and cannabis use frequency (Robinson et al., 2014). Alcohol use was assessed dichotomously and continuously (i.e., number of standard drinks per drinking day), while cannabis use was assessed

dichotomously (i.e., absence or presence of cannabis use on a given day). Route of cannabis administration was not recorded. Given that the primary outcome consists of daily use of alcohol and cannabis over the past month, observations of alcohol and cannabis use (i.e., one per day) were collected for each subject, resulting in a total of $N = 990$ observations.

2.3. Data analysis

Logistic models were run via PROC GLIMMIX in SAS version 9.4 and tested the probability of same day cannabis use as predicted by alcohol use. Alcohol use was defined in separate models as (1) any use (dichotomous Yes/No), (2) total drinks per day, and (3) binge drinking (dichotomous Yes/No for >3.9 drinks for females and >4.9 drinks for males per NIAAA guidelines; (National Institute on Alcohol Abuse and Alcoholism (NIAAA), n.d.). Models tested sex differences on probability of same day cannabis use as predicted by alcohol use and probed significant alcohol use by sex interactions. Significant amount of alcohol by sex interactions were explored by probing amount of alcohol at the mean value and at standard deviations above and below the mean (Aiken and West, 1991; Mitchell and Chen, 2005). Results are presented with accompanying odds ratio effect sizes and 95 % confidence intervals. All models were re-run with age, race, and ethnicity as covariates and no changes occurred in the below results.

3. Results

3.1. Sample characteristics

Participants were an average age of 32.97 years ($SD = 9.93$) and 42.4 % ($n = 14$) of the sample identified as female. Average AUDIT scores did not significantly differ between males ($M = 12.47$, $SD=4.89$) and females ($M = 14.93$, $SD=7.97$; $t(31)=-1.10$, $p = 0.282$). Average CUDIT scores did not significantly differ between males $M = 14.21$, $SD=5.45$) and females $M = 12.29$, $SD=4.68$; $t(31)=1.06$, $p = 0.296$) (Table 1). With the 990 observations collected over 30 days, participants co-used on 226 (105 female) days.

3.2. Effect of any alcohol use on probability of same day cannabis use

Drinking any alcohol on a given day was associated with a significant increase in the likelihood of same-day cannabis use ($b = 0.61$, SE=0.19, t (955)=3.25, $p = 0.001$, OR=1.85, 95 % CI [1.27, 2.68]). The effect of any alcohol use on the probability of same-day cannabis use was moderated by sex. A significant interaction between sex and drinking alcohol on any given day was observed ($b = 1.58$, SE=0.40, $t(955)=$ 3.98, $p<0.001$, OR=4.85, 95 % CI [2.23, 10.59]). Upon probing this interaction, it was observed that males using any alcohol on a given day were more likely to use cannabis than females, though not significantly so ($b = 1.72$, SE=1.12, $t(955)=1.53$, $p = 0.125$ OR=5.558, 95 % CI [0.619, 50.428]). Further probing revealed that the likelihood of using cannabis on alcohol use days was greater for males ($b = 2.33$, SE=0.78, t (955)=2.99, $p = 0.003$, OR=10.27, 95 % CI [2.23, 47.31]) than for females ($b = 0.61$, SE=0.82, $t(955)=0.75$, $p = 0.456$, OR=1.84, 95 % CI [0.37, 9.12]). Moreover, males using any alcohol on a given day were significantly more likely to use cannabis than males not using any alcohol on a given day ($b = 1.55$, SE=0.311, t(955)=4.98, $p=<0.001$, OR=4.718, 95 % CI [2.561, 8.693]). Observed marginal probabilities of males and females co-using alcohol and cannabis on a given day are reported in Fig. 1.

3.3. Effect of amount of alcohol used on probability of same day cannabis use

Amount of alcohol consumed on a given day was associated with a significant increase in the likelihood of same-day cannabis use ($b = 0.083$, SE=0.033, $t(955)=2.51$ $p = 0.012$, OR=1.09, 95 % CI [1.02,

Table 1

Sample Demographics.

Variable	Total		Male		Female	
	M	*SD*	*M*	*SD*	*M*	*SD*
Demographic Characteristics						
Sex (no., %)	–	–	19 (57.60)	–	14 (42.40)	–
Age	32.97	9.93	32.37	10.77	33.79	8.99
Race (no., %)						
White	16 (48.50)	–	11 (33.33)	–	5 (15.15)	–
Black/ African American	7 (21.20)	–	3 (9.09)	–	4 (12.12)	–
American Indian/Alaskan Native	0 (0.00)	–	0 (0.00)	–	0 (0.00)	–
Asian/ Asian American	2 (6.10)	–	1 (3.03)	–	1 (3.03)	–
Mixed Race	3 (9.10)	–	1 (3.03)	–	2 (6.06)	–
Other	5 (15.20)	–	3 (9.09)	–	2 (6.06)	–
Hispanic/Latinx (no., %)						
Yes	13 (39.40)	–	9 (27.27)	–	4 (12.12)	–
No	20 (60.60)	–	10 (30.30)	–	10 (30.30)	–
Education (no., %)						
High school/GED equivalent	10 (30.30)	–	4 (12.12)	–	6 (18.18)	–
2-Year College (i.e., associate's degree)	7 (21.20)	–	5 (15.15)	–	2 (6.06)	–
4-Year College (i.e., bachelor's degree)	13 (39.40)	–	9 (27.27)	–	4 (12.12)	–
Master's degree	3 (9.10)	–	1 (3.03)	–	2 (6.06)	–
Employment (no., %)						
Unemployed, disabled, retired, or other	6 (18.20)	–	3 (9.09)	–	3 (9.09)	–
Part-time, odd jobs, or full-time student	14 (42.40)	–	8 (24.24)	–	6 (18.18)	–
Full-time	13 (39.40)	–	8 (24.24)	–	5 (15.15)	–
Drinking Characteristics						
Heavy drinking days in past 30 days	5.55	5.71	5.26	6.51	5.93	4.63
Drinking days in past 30 days (range)	12.79 (3–30)	6.36	12.95 (3–30)	7.56	12.57 (7–23)	4.50
DPDD in past 30 days	4.20	2.13	4.47	2.43	3.82	1.63
AUDIT	13.52	6.38	12.47	4.89	14.93	7.97
Cannabis Use Characteristics						
Cannabis use days in past 30 days (range)	17.06 (2–30)	10.51	17.21 (2–30)	12.12	16.86 (7–30)	8.28
CUDIT-R	13.39	5.15	14.21	5.45	12.29	4.68

Note. GED = General Educational Development; DPDD = drinks per drinking day; AUDIT = Alcohol. Use Disorders Identification Test; CUDIT-R = Cannabis Use Disorders Identification Test–Revised; Heavy drinking days = days with binge drinking episode; Assessed by the Timeline Follow-Back interview for the past 30 days.

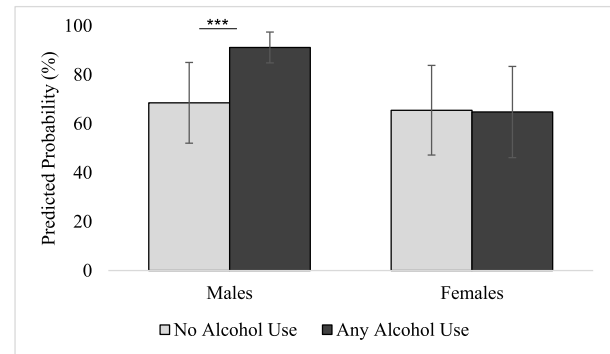**Predicted Probability of Same Day Alcohol and Cannabis Use by Sex**

Fig. 1. Predicted Probability of Same Day Alcohol and Cannabis Use by Sex. Significant effect of sex by any alcohol use interaction on probability of same-day cannabis use. The probability of males co-using any alcohol and cannabis on a given day was 91.13 %, reaching statistical significance, while the probability of females co-using any alcohol and cannabis on a given day was 64.76 %. Males using any alcohol on a given day were significantly more likely to use cannabis than males not using any alcohol on a given day ($b = 1.55$, SE=0.311, $t(955)$=4.98, p=<0.001, OR=4.718, 95 % CI [2.561, 8.693]). Plotted probabilities are computed based on the final logistic model including main effects and interaction. Error bars represent standard error of mean values. *** $p < 0.001$.

1.16]). The effect of amount of alcohol use in a given day on the probability of same-day cannabis use was moderated by sex. A significant interaction between sex and drinking alcohol on any given day was observed ($b = 0.14$, SE=0.0678, $t(955)$=2.02, $p = 0.044$, OR=1.15, 95 % CI [1.00, 1.31]). Upon probing this interaction at the mean value of drinks consumed and at standard deviations above and below that mean, it was observed that the interactive effects between sex were not significant. At the mean number of drinks (2 drinks), males were more likely than females to use same-day cannabis, although this did not reach significance ($b = 0.78$, SE=1.06, $t(955)$=0.74, $p = 0.458$, OR=2.91, 95 % CI [0.28, 17.45]).

3.4. Effect of binge drinking alcohol on probability of same day cannabis use

Binge drinking was not associated with a significant increase in the likelihood of same-day cannabis use ($p = 0.445$).

4. Discussion

The present study sought to examine the moderating effect of sex on relationships between alcohol and cannabis use in a sample of males and females who consume both alcohol and cannabis at high-risk levels. Consistent with previous work, we hypothesized that there would be associations among same-day cannabis use and measures of daily alcohol use and that these observed associations would be greater in males compared to females.

Our current findings revealed important sex differences. Any alcohol use and total number of drinks on a given day were associated with significantly higher probability of same-day cannabis use in male co-users but not in female co-users who use alcohol and cannabis at high risk levels. This finding is in line with previous work implicating important sex dependent effects (Roche et al., 2019; Venegas et al., 2020, 2021). Sex differences in pharmacological and subjective effects of co-use have been reported (Wright et al., 2021), such that females smoke less cannabis than males after consuming alcohol, but report similar acute pharmacological and subjective effects, indicating that cannabis and alcohol co-use may impact females more than males. These sex-dependent findings are aligned with a higher prevalence of males developing AUD, which may be associated with the observation that

males with AUD have smaller amygdala and basolateral nucleus volumes compared with females (Grace et al., 2021). In terms of cannabis use, there are not yet established findings of sex differences in brain structure or function (Calakos et al., 2017).

Notably, there was no significant effect of binge drinking on same-day cannabis use. Previous research has found that males are significantly more likely to binge drink on cannabis-use days compared to females (Karoly et al., 2021). However, these findings were observed in a sample who reported binge drinking on almost half of their drinking days (Karoly et al., 2021), while the present sample reported binge drinking episodes on less than a quarter of their drinking days.

Strengths of the study include that we identified sex-dependent relationships in participants with *high-risk* levels of both alcohol and cannabis use, approximating a co-user that may be indicative of what is seen in clinical practice. By using TLFB data to define co-use days, we were able to utilize a larger number of observations within a moderate sample size. Lastly, we defined alcohol use both dichotomously and continuously, providing a nuanced perspective of alcohol use patterns and their associations with cannabis co-use. However, limitations of this study include lack of temporal relationship between cannabis use and alcohol use within the same day, which could provide insight into the potential directionality of co-use. This study lacked information on the route of administration or quantity and content of cannabis consumed. Additionally, utilizing TLFB data is limited due to the issues with recall bias and under-reporting of past month substance use.

4.1. Conclusions

This study demonstrates that daily alcohol use variables are associated with same-day cannabis use in individuals who co-use at risky levels, with sex moderating these relationships. The sex-dependent nature of co-use identified in this study holds clinical utility in elucidating risk profiles. The finding that males are more susceptible than females to daily-level co-use patterns could aid in identifying at-risk individuals for harmful alcohol and cannabis co-use patterns, enabling early interventions to prevent avoidable negative outcomes of co-use.

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Contributors

All authors contributed in a significant way to the manuscript and have read and approved the final manuscript.

Declaration of Competing Interest

The authors report no relevant disclosures. Outside of this work, LAR is currently serving as a consultant for Alkermes and receives study medication from Pfizer and Medicinova.

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