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Dose-dependent Relationships of Same-day and Typical Substance Use to Sleep Duration in College Cannabis and Alcohol Users: A Multilevel Modeling Approach Using Daily Diary Data

Neel Muzumdar[1,2], Kristina M. Jackson[3], Jennifer F. Buckman[1,2], Andrea M. Spaeth[1], Alexander W. Sokolovsky[3], Anthony P. Pawlak[2], Helene R. White[2]

[1]Department of Kinesiology and Health, Rutgers University – New Brunswick
[2]Center for Alcohol and Substance Use Studies, Rutgers University – New Brunswick
[3]Center for Alcohol and Addiction Studies, Brown University, School of Public Health

ABSTRACT

This study characterized how quantities of cannabis and alcohol use affect sleep. Single-day and typical cannabis and alcohol use patterns were considered to assess acute-chronic use interactions. Linear and non-linear associations assessed dose-dependence. College students (n=337; 52% female) provided 11,417 days of data, with up to five time points per day. Daily self-reported sleep duration, cannabis use quantity, and alcohol use quantity were subjected to linear mixed modeling to capture linear and curvilinear associations between single-day and typical use on same-night and typical sleep. Sleep duration (difference between bedtime and waketime) was the outcome. Quantity of cannabis used each day andtypical quantity used across all days were predictors in the cannabis models. Parallel single-day and typical alcohol variables were predictors in the alcohol models. Follow-up analyses excluded days with alcohol-cannabis co-use. Main effects of single-day and typical cannabis quantity on sleep duration were observed when all cannabis-use days were modeled. Higher than typical doses of single-day and typical cannabis were associated with longer sleep durations, but only to a point; at the highest doses, cannabis shortened sleep. A main effect of single-day alcohol quantity and two interactions (single-day use with both linear and curvilinear typical use) on sleep duration were observed when all alcohol-use days were modeled. Greater alcohol consumption on a given day led to shorter same-night sleep, but typically heavier drinkers required higher doses than typically lighter drinkers to experience these adverse effects. Follow-up models suggested alcohol co-use may contribute to the purported sleep-promoting effects of cannabis.

Key words: = Co-use; Marijuana; Drinking; Emerging adults; Non-linear; Sleep behavior

Insufficient sleep, difficulty falling asleep, and poor quality sleep have been widely reported in college samples for more than a decade (Hershner & Chervin, 2014; Lund et al., 2010; Owens et al., 2017). In 2022, 42% of college students reported average sleep durations of less than 7 hours per night on weeknights (American College Health Association, 2022) – a particularly troubling statistic considering that sleep problems elevate risk for a variety of mental and physical health

Corresponding Author: Kristina M. Jackson, Ph.D., Center for Alcohol and Addiction Studies, Brown University, Box G-S121-4, Providence, RI 02912. Phone: (401) 863-6617. Email: kristina_jackson@brown.edu

issues (Watson et al., 2015). Prevalence of cannabis and alcohol use in the college context is also high (American College Health Association, 2022; Goodhines et al., 2019), and these substance use behaviors, while touted to promote sleep, may adversely impact sleep quantity and quality (Babson et al., 2017; Sharma et al., 2022a). Experimental and ecological studies that capture substance use patterns and sleep at both day-level (single-day use behaviors and same-night sleep, to approximate acute effects) and person-level (typical use behaviors and typical sleep habits, to approximate chronic effects) are needed to untangle the impacts of cannabis and alcohol on sleep, particularly in the college context where insufficient sleep and frequent cannabis and alcohol use are endemic.

A relationship between cannabis use and sleep has long been speculated. Early, small-scale cannabis administration studies reported reduced sleep onset latency (Cousens & DiMascio, 1973; Nicholson et al., 2004) and altered sleep architecture (Feinberg et al., 1975) at varying doses; however, the higher potency products of today raise questions about the generalizability of these findings. Evidence from well-powered, high-quality studies remains limited (Babson et al., 2017; Maddison et al., 2022), and the majority of recent research on cannabis and sleep comes from survey-based studies that do not parse the effects of frequency or quantity of cannabis use on sleep. Instead, these studies emphasize the relationship of sleep on the development of substance use disorders or the relationship of substance use on the development of sleep disorders. While important, these studies cannot address whether this cannabis-sleep relationship is due to the direct pharmacological actions of cannabis on body and brain processes. Epidemiological studies also fail to contribute to understanding the potential biological mechanisms at play; one recent study of >21,000 participants reported that *any* past 30-day use of cannabis was associated with both low and high extremes of sleep duration (Diep et al., 2022). Such findings are hard to reconcile with other physiological and behavioral differences that are observed between infrequent/light users and chronic/heavy users.

Outside the sleep research field, pharmacological studies of cannabis effects on brain and cardiovascular responses suggest complex, nonlinear dose-response relationships (Latif & Garg, 2020; Strougo et al., 2008), which parallel the extensive and complex endocannabinoid system upon which it acts. Recent literature suggests that cannabis can alter systems that play an important role in sleep physiology; for example, acute use is linked to increased cortisol concentration (Glodosky et al., 2021) and disrupted autonomic nervous activity (Latif & Garg, 2020). Modulation of the cannabinoid receptor type 1 (CB1) activity by Δ9-THC (delta-9-tetrahydrocannabinol, the primary psychoactive ingredient in cannabis) may also play a pivotal role in altering the maintenance of sleep architecture (Kesner & Lovinger, 2020). Such dose-response relationships could further be affected by chronic use behaviors; for example, repeated use can reduce availability of CB1 receptors (Ramaekers et al., 2020), which would adversely impact sleep homeostasis (Murillo-Rodríguez, 2008). These observations support investigation of both linear and non-linear cannabis-sleep associations as well as interactions between acute and chronic use behaviors.

Similarly, the effects of acute alcohol intoxication on sleep are complex (Koob & Colrain, 2020) and consistent with disruptions in sleep homeostasis and sleep architecture (Borbély & Achermann, 1999; Thakkar et al., 2015) in ways that are not yet fully elucidated. Alcohol use has long been acutely associated with shorter sleep onset latency (Sharma et al., 2022b; Stein & Friedmann, 2005). In addition, sleep disruptions occur mainly during the second half of the night (Chakravorty et al., 2016; Ebrahim et al., 2013). Therefore, there may be differential effects of alcohol on slow wave sleep, which is more prominent in the first half of the night, and rapid eye movement (REM) sleep, which is more prominent in the second half (Carskadon & Dement, 2011). Different alcohol-sleep relationships may also exist on the ascending versus descending limb of the blood alcohol curve, a biphasic relationship such as that seen on the cardiovascular system (Kajander et al., 2001; Oshita et al., 1993; Puddey et al., 2001). Finally, like with cannabis, the acute effects of alcohol on sleep are likely to be complicated by chronic alcohol use behaviors (Grotenhermen, 2003; Most et al., 2014), such that a heavy drinking episode could differentially influence sleep in typically heavy versus light drinkers (Brower, 2003). These observations suggest a need to characterize both

linear and non-linear alcohol-sleep associations as well as interactions between acute and chronic use behaviors.

The aim of the present study was to examine linear and curvilinear associations of cannabis quantity and alcohol quantity with sleep duration in college students at both the day-level (same-day) and person-level (typical). Data were leveraged from a parent study wherein daily self-reported sleep duration, cannabis use, and alcohol use from two 28-day intensive longitudinal survey bursts were collected. We hypothesized non-linear relationships between single-day cannabis use quantity and same-night sleep as well as between typical cannabis use quantity and typical sleep duration, consistent with a saturable, receptor-mediated effect. Further, we anticipated that the quantity of alcohol use on a given day would disrupt same-night sleep; a linear effect was predicted due to a lack of research into non-linear effects. Cross-level interactions were exploratory; we expected that both alcohol and cannabis effects on same-night sleep would be dependent on typical use behaviors, but such interactions could reflect tolerance (i.e., dampened negative effects on sleep among individuals with higher typical use patterns) and/or sensitization (i.e., exaggerated negative effects on sleep among those with higher typical use patterns).

METHODS

Design and Participants

Undergraduate students were recruited to participate in a two-burst longitudinal study on alcohol and cannabis co-use. Recruitment targeted three state universities in states with different recreational cannabis use laws (i.e., illegal, decriminalized, legal for adults 21+); medical use of cannabis was legal in all states. Undergraduate students were randomly selected from each university's database (N=8,000 at each university) to receive online screening survey invitations. Of these, a total of 7,000 completed the screening survey. Participants were incentivized with a lottery to win a $100 Amazon.com gift card (10 per campus). Eligibility criteria for the baseline survey included: (1) full-time enrollment at one of the universities; (2) age 18–24 years; (3) past-year alcohol and cannabis use, and (4) verified e-mail address (details on recruitment and representativeness were previously published (White et al., 2019)). Past-month alcohol and cannabis users were oversampled to ensure eligibility for the subsequent daily survey phase. Eligible students (n=2,501) were e-mailed invitations to participate in the baseline survey; 1,610 enrolled and provided consent to participate. After screening for individuals who proved ineligible on the baseline survey or who encountered technical issues, the final sample was 1,390; demographic data have been published (Jackson et al., 2021). Compensation for the baseline survey was a $25 Amazon gift card.

Students who reported past-month use of alcohol and cannabis "at the same time so their effects overlapped" at baseline were eligible for the daily diary phase of the study. These potential participants were stratified by frequency of past-month co-use occasions (i.e., 1–2 times versus 3+ times representing infrequent and frequent co-use, respectively) and sex (assigned at birth), with males and frequent co-users oversampled to ensure heterogeneity relative to the larger study sample; a generally equal number of students were invited from each school. Across schools, 343 of 379 invitees agreed to participate (90.5%); two students discontinued data collection during the first two days and were excluded from further analyses.Thus, 341 completed the daily surveys. A flowchart depicting screening into the daily surveys has been previously published (Gunn et al., 2021). Participants completed a 26-day (the first two days were deleted due to technical issues) burst of intensive longitudinal experience sampling comprising five daily surveys delivered via a custom-developed smartphone application. Three months later, 316 students (92.7% of the first burst) completed a repeated 28-day burst. Participants were compensated $1 for each completed survey (up to $5 per day/$35 per week) with potential bonuses of $10 each week for 85% survey compliance that week and $20 at the end of 4 weeks for 90% compliance, totaling $200 maximum (Amazon gift cards) per burst.

Daily surveys were predictably scheduled (9:00am; 2:00pm; 5:00pm; 8:00pm; 11:00pm). Surveys remained active for two hours (four hours for 9:00am survey). Each survey asked about behavior from the exact time that the last survey was completed until the completion time for the current survey, except when two consecutive

surveys were missed, in which case the current survey used the scheduled time of the previous survey as the anchor. Previously published supplemental materials (Stevens et al., 2020) offer full details on missed surveys. Afternoon and evening survey completion took approximately 2 minutes. Morning survey completion took approximately 5 minutes and contained two parts: (1) a similar survey to the others assessing prior-day substance use behavior between the time of the last completed survey and bedtime, and (2) items about bedtime (prior night) and wake time, as well as consequences from the prior day's alcohol and cannabis use behaviors from wake time through bedtime. All procedures were approved by the Institutional Review Board of Brown University and a Certificate of Confidentiality was obtained from NIDA.

Measures

From the daily diary data, sleep duration was calculated as the time difference between bedtime each night and wake time the next day. Sleep durations above 15 hours were considered physiologically improbable and more likely associated with user error (e.g., reporting p.m. instead of a.m.) and excluded. Substance use behaviors were captured from survey items that asked whether the participant used alcohol, cannabis, both, or neither for each time interval: "What did you use between [time X] and [time Y]?" If alcohol and/or cannabis were endorsed, participants were presented with a timeline overlaid on a grid with time anchors (in minutes) and were instructed to tap on the screen at points corresponding to times when they used cannabis or had a drink (Gunn et al., 2021). Instructions were: "Tap your finger in the blue box each time you had a drink/used marijuana at the corresponding time"). Day-level cannabis and alcohol use quantity were indexed as the sum of the number of cannabis uses (taps) and drinks (taps), respectively, across all surveys in a given day; screenshots have been previously published (Jackson et al., 2021).

Analyses

The design of the study was multilevel in nature, i.e., days were nested within participants, and thus a linear mixed model (LMM) analytical approach was used with sleep duration as the outcome variable and subjects specified as a random effect. All analyses were conducted using SAS Software, Version 9.4 from the SAS Institute, Cary, NC.

An initial null LMM (i.e., no predictors specified) was fitted using maximum likelihood estimation to compute the intraclass correlation coefficient (ICC) (proportion of variance in sleep duration explained by the random effect of subject). Two subsequent sets of LMMs were conducted: one with measures of acute and typical cannabis use, and one with measures of alcohol use, each specified as continuous fixed effect predictors. Only days with complete coverage of the 24-hour period were included; incomplete coverage was defined as missing two consecutive surveys in a 24-hour period or missing the morning survey. There was a total of 11,417 out of 15,863 (72%) days of data with complete cases: 48% (n=5510) were no-use days, 26% (n=2,915) were cannabis-only use days, 13% (n = 1,464) were alcohol-only use days, and 13% (n=1,527) were alcohol- and cannabis-use days. Data from four individuals were excluded by the model for having no complete coverage days, resulting in a final N=337. We disaggregated the substance use variables into within-person (mean-centered daily number of cannabis uses or drinks) and between-person (mean number of cannabis uses or drinks per person aggregated across all assessment days). Squared person-mean-centered daily number of cannabis uses or drinks and squared mean number of cannabis uses or drinks were entered into the model to capture the curvilinear effects of those variables. All possible two-way cross level interactions (within-person by between-person effects) between the linear and curvilinear daily and mean use variables were specified in each model based on prior research and current hypotheses. Details of analysis methods are included in supplemental materials (S1). Follow-up models were tested to isolate the effects of cannabis (versus cannabis and alcohol co-use) and alcohol (versus alcohol and cannabis co-use) on sleep, with only days during which cannabis use, but not alcohol use, was reported and days when alcohol use, but not cannabis use, was reported.

The significant results of each LMM model were graphed using mathematical interpolation of the final regression equation in smoothed function plots in SAS PROC PLM. For each model, only the

specific main and/or interaction effects that were statistically significant, $p < .05$, were considered for graphical interpolation. The 95% confidence intervals for the interpolated functions were also computed and graphed.

RESULTS

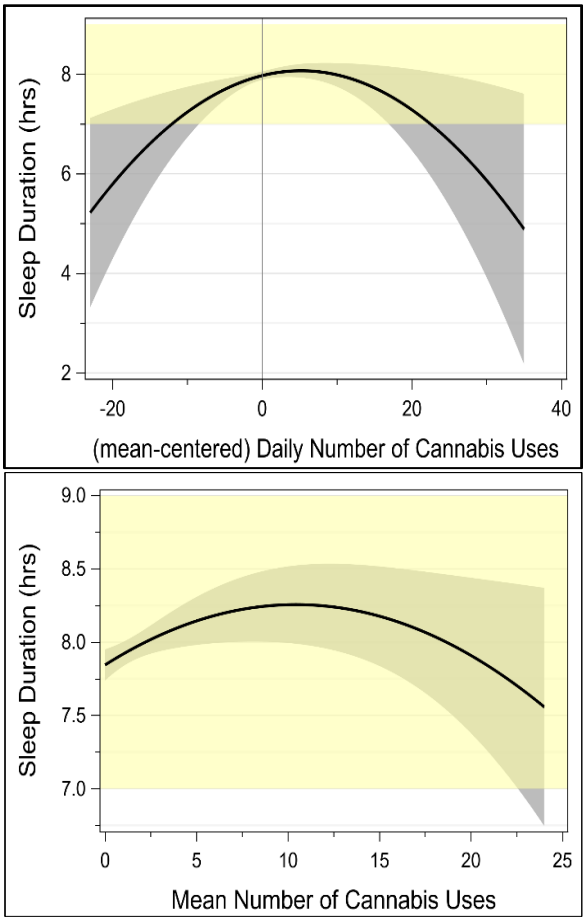
Average reported sleep per person from the daily surveys was 7.9 ± 0.9 hours per night. Although all participants invited into the daily survey stage reported cannabis and/or alcohol use on the baseline survey, 23 (6.7%) students did not report cannabis use and another 10 (2.9%) students did not report alcohol use during the daily survey stage. The null LMM indicated that the random effect of subjects explained a statistically significant amount of the sleep duration variance (13.1%).

Cannabis use and sleep

Table 1 shows the results of the LMM that included all days during which cannabis was consumed. Significant linear day-level and person-level main effects both indicated a positive association between cannabis use and sleep. Significant curvilinear day- and person-level main effects appeared as concave-down associations between cannabis use and sleep (Figure 1), indicating that there was an optimal consumption quantity, below which cannabis showed a positive association with sleep duration and above which cannabis exhibited a negative relationship with sleep duration. Sample-wide cross-level interactions were not significant.

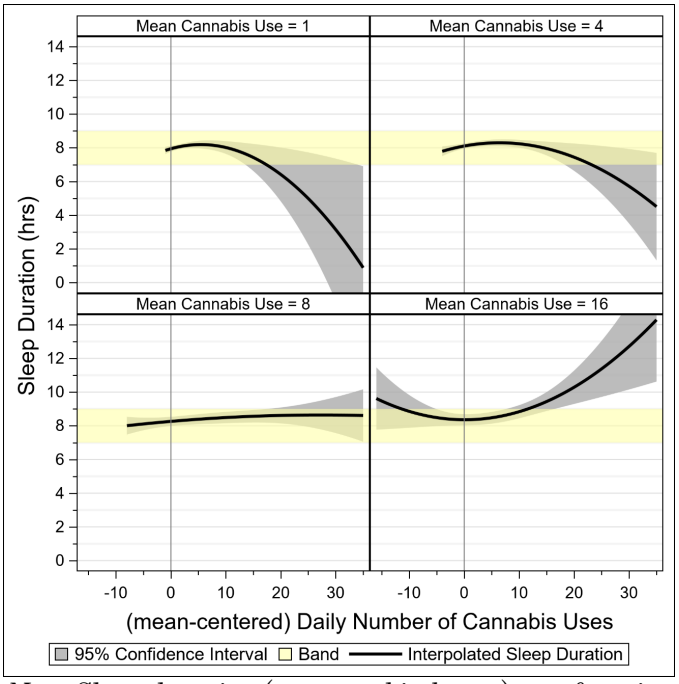
To isolate the effects of cannabis (versus alcohol and cannabis co-use) on sleep, a follow-up model was performed with data from days on which cannabis use, but not alcohol use, was reported. The linear and curvilinear main effects of person-level cannabis use were no longer significant, but a significant interaction was observed between curvilinear day-level and linear person-level cannabis use (Table 2). Figure 2 shows that on days when typical cannabis use quantities were exceeded, lighter average users demonstrate shorter sleep durations, whereas heavier average users demonstrated longer sleep durations.

Figure 1. *The Curvilinear Relationship Between Cannabis Use and Sleep duration at the Daily (Within-Person) and Average (Between-Person) Levels.*



Note. Sleep duration (measured in hours) as a function of person mean-centered daily number of cannabis uses (top panel) and average number of cannabis uses (bottom panel) across the assessment period. The function lines are smoothed regression lines that were mathematically interpolated from a LMM that showed only significant main effects for linear and curvilinear cannabis use. The 95% confidence intervals (shaded gray) were computed based on the results of the LMM. Data are mean centered; thus, 0 daily number of cannabis uses implies cannabis use at typical (person-mean-centered) levels. The yellow shaded band denotes the recommended sleep durations of 7-9 hours per night for young adults and is included to aid interpretation.

Figure 2. *The Interaction Effect of Daily and Average Cannabis Use on Sleep Duration for Days When Only Cannabis Was Used.*



Note. Sleep duration (measured in hours) as a function of person mean-centered daily number of cannabis uses and average number of cannabis uses across the assessment period. The function lines shown are smoothed regression lines that were mathematically interpolated from a LMM that showed a significant cross-level interaction between curvilinear daily cannabis use and linear average cannabis use when *only* cannabis was used. The 95% confidence intervals (shaded gray) were computed based on the results of the LMM. Data are mean centered; thus, 0 daily number of cannabis uses implies cannabis use at typical (person-mean-centered) levels. The yellow shaded band denotes the recommended sleep durations of 7-9 hours per night for young adults and is included to aid interpretation.

Alcohol use and sleep

Table 3 shows the results of the LMM that included all days during which alcohol was consumed. A significant linear day-level main effect indicated that more alcohol use on a given day was associated with lower same-night sleep duration. The curvilinear main effect was not significant, indicating that the dose-response relationship was the same at every dose. Neither the linear nor curvilinear person-level main effects were significant, indicating that typical alcohol use did not substantively affect average sleep duration.

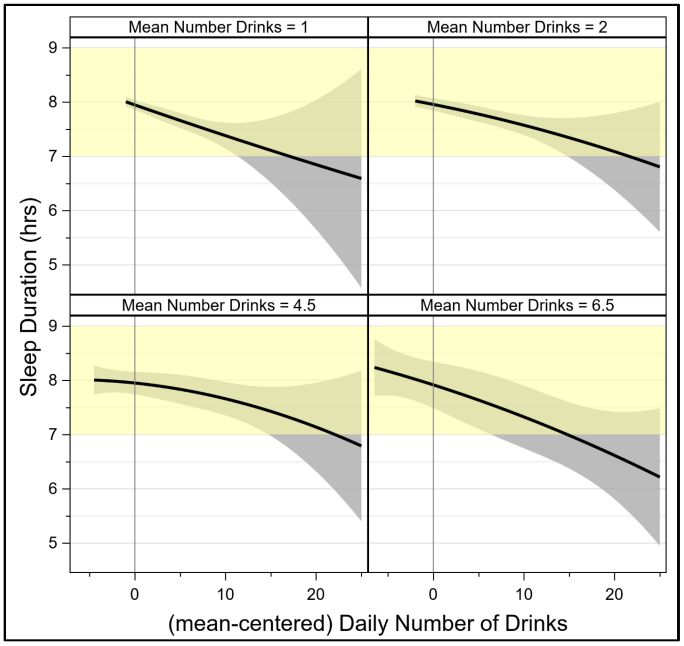
Interactions demonstrated that the effect of daily alcohol use on sleep duration changed as a function of an individual's mean alcohol consumption (Figure 3). A significant interaction of linear single-day alcohol use with linear typical alcohol use indicated that moderately heavier typical use (2-4.5 average drinks) attenuated the main effect of the negative relationship between alcohol use and same-night sleep. A significant interaction of linear single-day alcohol use with curvilinear typical alcohol use indicated that the attenuation of this relationship diminished with higher average amounts of daily drinks, i.e., typically heavy drinkers showed a more pronounced negative relationship between the number of daily drinks and sleep duration than typically moderate drinkers.

To isolate the effects of alcohol (versus alcohol and cannabis co-use) on sleep, a follow-up model was performed with only days during which alcohol use, but not cannabis use, was reported. The pattern of results changed such that only the interaction between curvilinear day-level and curvilinear person-level alcohol use was significant (Table 4). Figure 4 shows evidence for greater alcohol-related sleep reductions in all groups; this was most pronounced and curvilinear among those with the highest number of average daily drinks.

DISCUSSION

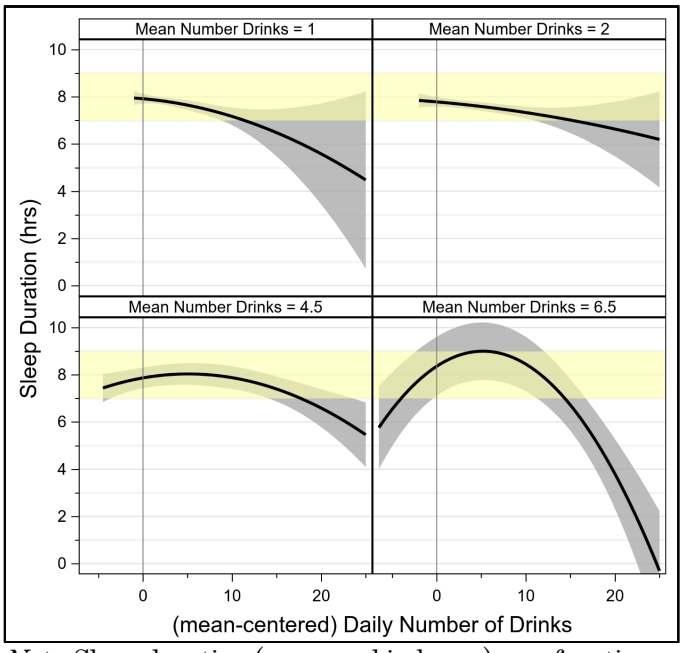
Using data from 11,417 days collected as part of a longitudinal study about alcohol and cannabis co-use among college students, this study provides a preliminary, fine-grained quantitative assessment of how substance use affects sleep. By considering factors such as interactions between acute and chronic use patterns and non-linear dose-response curves, this study reveals several novel observations related to cannabis and alcohol. Importantly non-linear relationships between cannabis use quantities and sleep duration were observed and suggested that moderate doses were associated with longest sleep duration; the left panel of Figure 1 suggests that using less than or more than usual on a given day shortens sleep. The right panel of Figure 1 further suggests that both typically light and typically heavy cannabis users show shorter average sleep durations than moderate cannabis users. The cross-level interaction in this model was

Figure 3. *The Interaction Effect of Same-Day and Typical Alcohol Use on Sleep Duration.*



Note. Sleep duration (measured in hours) as a function of person mean-centered daily number of drinks and average number of drinks aggregated across the assessment period. The function lines are smoothed regression lines that were mathematically interpolated from a LMM with significant cross-level interaction effects between linear daily and linear and curvilinear average effects of drinking. The 95% confidence intervals (shaded gray) were computed based on the results of the LMM. Data are mean centered; thus, 0 daily number of drinks implies drinking at typical (person-mean-centered) levels. The yellow shaded band denotes the recommended sleep durations of 7-9 hours per night for young adults and is included to aid interpretation.

Figure 4. *The Interaction Effect of Daily and Average Alcohol Use on Sleep Duration for Days When Only Alcohol Was Used.*



Note. Sleep duration (measured in hours) as a function of person mean-centered daily number of drinks and average number of drinks aggregated across the assessment period. The function lines shown are smoothed regression lines that were mathematically interpolated from a LMM that showed a significant cross-level interaction between curvilinear daily and curvilinear average drinking when *only* alcohol was used. Data are mean centered; thus, 0 daily number of drinks implies drinking at typical (person-mean-centered) levels. The 95% confidence intervals (shaded gray) were computed based on the results of the LMM. The yellow shaded band denotes the recommended sleep durations of 7-9 hours per night for young adults and is included to aid interpretation.

Table 1. *Linear Mixed Regression Model of Cannabis Use on Sleep Duration for All Days When Cannabis Was Consumed.*

	B	*SE*	*t*	*p*
Constant	7.8417	0.05401	145.20	<.0001
Daily # Can Use	**0.04468**	**0.02006**	**2.23**	**0.0260**
(Daily # Can Use)^2	**-0.00446**	**0.001894**	**-2.36**	**0.0184**
Mean # Can Use	**0.07921**	**0.02812**	**2.82**	**0.0049**
(Mean # Can Use)^2	**-0.00379**	**0.001515**	**-2.50**	**0.0123**
Daily # Can Use x Mean # Can Use	-0.00432	0.004002	-1.08	0.2808
(Daily # Can Use)^2 x Mean # Can Use	0.000484	0.000360	1.34	0.1795
Daily # Can Use x (Mean # Can Use)^2	0.000116	0.000141	0.83	0.4082
(Daily # Can Use)^2 x (Mean # Can Use)^2	4.219E-6	0.000018	0.24	0.8137

Note. # = Number; Can Use = Cannabis uses; Daily # Can Use = individual person-mean-centered daily cannabis use; Mean # Can Use = Mean cannabis use per person across all days of bursts 1 and 2; (Daily # Can Use)^2 = Curvilinear effect of Daily # Can; (Mean # Can Use)^2 = Curvilinear effect of Mean # Can. Bolded text denotes statistical significance. $df_{constant} = 333$; $df_{non\text{-}constant\ parameters} \approx 1E4$

Table 2. *Linear Mixed Regression Model of Cannabis Use on Sleep Duration for Days When Only Cannabis Was Consumed.*

	B	*SE*	*t*	*p*
Constant	7.8822	0.1107	71.19	<.0001
Daily # Can Use	**0.1030**	**0.04587**	**2.25**	**0.0248**
(Daily # Can Use)^2	**-0.00973**	**0.003977**	**-2.45**	**0.0145**
Mean # Can Use	0.06486	0.03967	1.63	0.1022
(Mean # Can Use)^2	-0.00219	0.001731	-1.27	0.2052
Daily # Can Use x Mean # Can Use	-0.01228	0.008764	-1.40	0.1613
(Daily # Can Use)^2 x Mean # Can Use	**0.001392**	**0.000684**	**2.03**	**0.0420**
Daily # Can Use x (Mean # Can Use)^2	0.000361	0.000291	1.24	0.2152
(Daily # Can Use)^2 x (Mean # Can Use)^2	-0.00003	0.000024	-1.23	0.2189

Note. # = Number; Can Use = Cannabis uses; Daily # Can Use = individual person-mean-centered daily cannabis use; Mean # Can Use = Mean cannabis use per person across all days of bursts 1 and 2; (Daily # Can Use)^2 = Curvilinear effect of Daily # Can; (Mean # Can Use)^2 = Curvilinear effect of Mean # Can. Bolded text denotes statistical significance. $df_{constant}$ = 258; $df_{non\text{-}constant\ parameters}$ = 2490

Table 3. *Linear Mixed Regression Model of Alcohol Use on Sleep Duration for All Days When Alcohol Was Consumed.*

	B	*SE*	*t*	*p*
Constant	7.9308	0.07982	99.36	<.0001
Daily # Drinks	**-0.09396**	**0.03340**	**-2.81**	**0.0049**
(Daily # Drinks)^2	0.001076	0.003807	0.28	0.7776
Mean # Drinks	0.01883	0.07393	0.25	0.7990
(Mean # Drinks)^2	-0.00326	0.01246	-0.26	0.7933
Daily # Drinks x Mean # Drinks	**0.04115**	**0.02000**	**2.06**	**0.0397**
(Daily # Drinks)^2 x Mean # Drinks	-0.00104	0.001996	-0.52	0.6037
Daily # Drinks x (Mean # Drinks)^2	**-0.00537**	**0.002374**	**-2.26**	**0.0238**
(Daily # Drinks)^2 x (Mean # Drinks)^2	0.000120	0.000209	0.57	0.5668

Note. # = Number; Daily # Drinks = individual person-mean-centered daily alcohol use; (Daily # Drinks)^2 = Curvilinear effect of Daily # Drinks; Mean # Drinks = Mean alcohol use per person across all days of bursts 1 and 2; (Mean # Drinks)^2 = Curvilinear effect of Mean # Drinks. Bolded text denotes statistical significance. $df_{constant}$ = 333; $df_{non\text{-}constant\ parameters} \approx$ 1E4

Table 4. *Linear Mixed Regression Model of Alcohol Use on Sleep Duration for Days When Only Alcohol Was Consumed.*

	B	*SE*	*t*	*p*
Constant	8.1513	0.2108	38.67	<.0001
Daily # Drinks	-0.01112	0.09399	-0.12	0.9058
(Daily # Drinks)^2	-0.01002	0.008453	-1.19	0.2359
Mean # Drinks	-0.2763	0.1825	-1.51	0.1304
(Mean # Drinks)^2	0.04757	0.03559	1.34	0.1816
Daily # Drinks x Mean # Drinks	-0.03331	0.05938	-0.56	0.5750
(Daily # Drinks)^2 x Mean # Drinks	0.007285	0.004790	1.52	0.1286
Daily # Drinks x (Mean # Drinks)^2	0.01121	0.008158	1.37	0.1698
(Daily # Drinks)^2 x (Mean # Drinks)^2	**-0.00144**	**0.000619**	**-2.34**	**0.0197**

Note. # = Number; Daily # Drinks = individual person-mean-centered daily alcohol use; (Daily # Drinks)^2 = Curvilinear effect of Daily # Drinks; Mean # Drinks = Mean alcohol use per person across all days of bursts 1 and 2; (Mean # Drinks)^2 = Curvilinear effect of Mean # Drinks. Bolded text denotes statistical significance. $df_{constant}$ = 253; $df_{non\text{-}constant\ parameters}$ = 1129

non-significant, suggesting that chronic cannabis use shifts, but does not distort, the dose-response curve for sleep duration.Interestingly, when cannabis use days that also included alcohol use were excluded from the model (Figure 2), the cross-level interaction became significant. This suggests that, in the absence of alcohol, the sleep-promoting versus sleep-disrupting effects of cannabis were dependent on typical use quantities and that cannabis affects the heaviest users qualitatively differently than lighter users.

Further, quantity of alcohol consumed on a given day was negatively associated with same-night sleep in a dose-dependent manner, and this relationship was exponentially exacerbated by heavier typical alcohol use patterns. When days that potentially included cannabis co-use were excluded from the analyses, the relationship of acute and chronic alcohol use behaviors appeared more complex, particularly for those with heavier typical drinking patterns (Figure 3 versus Figure 4).

The effects of cannabis on sleep

A novel and important finding from this study was that cannabis-sleep relationships were non-linear. Up to a point, higher doses of cannabis were associated with longer sleep durations both at the day-level and the person-level, but, at the highest doses, cannabis shortened sleep. The inverted U-shaped dose-response curve of single-day cannabis quantities on same-night sleep suggests a 'diminishing returns' effect where, as doses approached the axis of symmetry (i.e., the dose corresponding to the curve's apex), the beneficial effect of cannabis on sleep waned. Also noteworthy is the fact that this vertex appeared just above the person-centered average use quantities, suggesting a consistent need to gradually increase dosing to optimize sleep benefits. Together, this is consistent with the concept of tolerance and may speak to diminishing returns of medicinal efficacy, at least if used as a sleep aid.

A similar curvilinear phenomenon was observed for typical use patterns. In this case, this inverted U-shaped graph can be interpreted as typically moderate cannabis users exhibited longer sleep durations than either lighter or heavier users; non-users were not included in these analyses. Across numerous scientific domains, non-linear cannabis dose-response curves have been observed (Calabrese & Rubio-Casillas, 2018; Childs et al., 2017; Hodges, Marshall, & Ashpole, 2020; Latif & Garg, 2020; Zuardi et al., 2017). For example, recent epidemiological studies (Corroon et al., 2017; Cuttler et al., 2018) and some administration research (Childs et al., 2017; Fusar-Poli et al., 2010) suggest that low-to-moderate cannabis consumption has some anxiolytic properties, but higher doses can be anxiogenic (Bossong et al., 2013; Karniol et al., 1974; Petrie et al., 2021; Sharpe et al., 2020). Much more rigorous human experimental research on cannabis is needed, but such observations are in keeping with current theories about a homeostatic role of the endocannabinoid system (Aizpurua-Olaizola et al., 2017; Huestis, 2007), the primary physiological target of phytocannabinoids.

Interestingly, follow-up analyses that explored cannabis-sleep relationships after data from days that included both alcohol and cannabis use were excluded found a significant interaction rather than significant main effects. Comparison of the graphs from these models (Figure 1 versus Figure 2) reveals that when the effects of alcohol are controlled, cannabis had only nominal sleep benefits for light and moderate users; sleep promotion is only observed among the heaviest cannabis users, who required substantially more than their typical dose to experience sleep promoting benefits. Unexpectedly, this increase in sleep duration occurred in excess of the 7-9 hour recommendations for this age group, making the clinical significance of this effect unclear. Taken together, the cannabis-sleep models raise the question of whether some of the purported sleep-promoting effects of cannabis are related to co-use of alcohol and cannabis, and whether the effects of cannabis on sleep are dependent on an individual's typical sleep behaviors. Such observations require further investigation, including experimental studies that can carefully control timing and dose of both drugs and objectively measure indicators of sleep.

The effects of alcohol on sleep

The current study identified a linear day-level dose-dependent main effect, wherein greater alcohol consumption on a given day led to shorter same-night sleep. In addition, typical drinking

behaviors appeared to impact sleep duration, but in such a way that two people consuming the same number of drinks on a given night could have different sleep disruptions. Specifically, sleep duration declined below eight hours (i.e., the sample mean), and outside the range of recommended sleep durations, only when an individual's average use quantities were exceeded. Thus, typically heavier drinkers require higher doses than typically lighter drinkers to experience adverse effects on sleep duration. It is also noteworthy that when average use quantities were exceeded, typically heavier drinkers showed a more precipitous reduction in sleep duration compared to typically lighter drinkers. Taken together, these results suggest a tolerance-like effect, wherein sleep habituates to the effects of alcohol over time, as well as a sensitization-like effect, wherein heavier drinkers appear increasingly vulnerable to greater alcohol-related sleep disruptions. The latter finding is also consistent with physiological tolerance interacting with the sedative properties of alcohol at higher doses (Hendler et al., 2013).

That alcohol reduces overall sleep duration on a drinking night is commonly reported, but supporting data are mainly from self-report studies that categorically compare drinking to non-drinking nights, often over a small number of nights (Arnedt et al., 2011; Goodhines et al., 2019; Stein & Friedmann, 2005). The current study meaningfully contributes to the research by suggesting that the sleep-alcohol relationship is dose dependent and that interactions exist between acute and chronic alcohol use behaviors. Future studies are needed to parse whether the reduced sleep duration is associated with pharmacological actions of alcohol on the brain or with other sleep-disrupting lifestyle factors, such as sociocultural tendencies of late-night drinking, elevated academic and social stress, or concomitant effects of other drug co-use. In addition, the low subjective accuracy of intoxication, particularly in college students, who are often new drinkers, can further elevate risk for compounding alcohol and sleep problems (Grant et al., 2012).

Due to the nature of the sample used in these analyses, co-use of alcohol and cannabis was observed on 13% of days. Thus, the alcohol-sleep relationship was further explored in follow-up models that excluded data from days during which both cannabis and alcohol were used. The results of this model differed from that of the model that included all alcohol-use days, but, when graphed (Figures 3 and 4), several similarities were revealed: alcohol tends to disrupt sleep when average use quantities are exceeded, and this disruption is more pronounced in the heaviest drinkers. This observation appears exacerbated when cannabis using days were excluded, suggesting that co-use of cannabis may offset some of the negative effects of alcohol on sleep. The models mainly differ in relation to the heaviest drinkers who averaged 6.5 or more drinks per day (bottom right panels of Figures 3 and 4). When cannabis using days were excluded, these drinkers were more likely to sleep outside the recommended 7-9 hours – showing shorter–than-optimal sleep durations when less-than-average alcohol or greater-than-average alcohol was consumed and possibly longer-than-optimal durations when use quantities aligned with typical drinking habits. While this model was exploratory and requires confirmation, these results align with concepts of withdrawal and the development of adverse consequences from *not* using alcohol. Feed-forward reciprocal associations wherein sleep deprivation encourages continued and escalating alcohol use in an effort to "self-medicate" sleep, but ethanol's toxicity on sleep-related brain systems erodes sleep behavior and physiology, can potentially exacerbate dysregulated sleep and/or development of problematic alcohol use behaviors (Brower, 2003).

Limitations and Future Research

This study provides compelling novel evidence that cannabis and alcohol affect sleep in complex ways that are dependent on daily and typical use patterns. Nonetheless, this study should be considered in context of several limitations, most notably the sole reliance on self-reported sleep and substance use data. In terms of the sleep data, for example, we cannot verify whether participants remained asleep for the full time between bedtime and waketime, nor assess sleep quality. Future work would be strengthened by the inclusion of objective sleep behavior strategies (i.e., actigraphy) and measures of sleep quality, as well as physiological measures of alcohol and cannabis use.

In terms of cannabis use, we cannot verify the individual conceptualization of a 'dose' (e.g., a hit, a bowl, etc.); users themselves tend to be unaware of the dosage. This is further exacerbated by lack of phytochemical standardization across the sample. Cannabidiol (CBD) and THC are widely speculated to produce distinct and potentially competing physiological effects (de Almeida & Devi, 2020; Freeman et al., 2019; Fusar-Poli et al., 2010). With the vast variety of 'strains' available in the recreational market, it is difficult to control for differences in cannabinoid profiles. Nonetheless, because our analyses were primarily within-person, these issues of quantity and potency are less troublesome.

Although we performed follow-up analyses that focused exclusively on days that included cannabis, but not alcohol, use and alcohol, but not cannabis, use, future studies that can pharmacologically quantify cannabis and alcohol co-use are still needed. Cannabis and alcohol have potentially interacting pharmacokinetic profiles and, based on evidence that sleep physiology changes across a sleep epoch, understanding the biological ramifications of co-use is needed. However, the timing of cannabis and alcohol use in relation to each other is likely an important determinant of their effects on sleep. Alcohol exhibits different physiological actions on the ascending and descending limbs of the blood concentration curves. Less is known about the ascending and descending limbs of the blood cannabis curve. Likewise, examining co-use/poly-use of other drugs, including caffeine, tobacco/nicotine, cocaine, and psychedelics, warrants further analysis, as nearly all drugs can have effects on sleep behavior and physiology, especially if used proximally to bedtime. In addition, exam schedules, work and course schedules, and perceived stress, which all place pressure on sleep timing, are important considerations for assessing the specific relationship between substance use and sleep behaviors. Analyses that include these other factors will require complex modeling and large sample sizes to capture the dynamics of drug-drug interactions.

Future research also should include individuals with extremely heavy cannabis, alcohol, and co-use use patterns and/or who meet criteria for a substance use disorder. Studies should target older adults as well as young adults who are not enrolled in a four-year college, who may have different sleep patterns as well as different cannabis use habits and motivations (especially with respect to using cannabis as a sleep aid). Future research focused on individuals with dysregulated sleep is also needed; sleep deprivation is linked to dysregulation of neuroendocrine and autonomic reactivity (Meerlo et al., 2008), which may interact with cannabis and alcohol pharmacodynamics, and substance use is linked to neuroadaptations that may affect sleep regulatory systems (Bowers, 2003).

Like sleep research, cannabis research is a rapidly changing field and one that is garnering enormous public interest. Studies such as this continue to triangulate towards understanding the true impact of cannabis use on human health and behavior, but federal restrictions on conducting human experimental research with cannabis to date have severely limited our ability to establish accurate guidelines for safe recreational and medical doses. The present study was not designed as a rigorous pharmacological study, and thus cannabis doses most appropriate for sleep promotion cannot be determined. Nonetheless, this study adds to a growing consensus for harm reduction strategies that focus on moderating acute cannabis doses. These results suggest that a dosage guideline – that incorporates both acute dose as well as topographical use patterns that best support continued efficacy – may ultimately be possible.

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