

Examining the Impact of Simultaneous Alcohol and Cannabis Use on Alcohol Consumption and Consequences: Protocol for an Observational Ambulatory Assessment Study in Young Adults

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Abstract

Background: There is significant conflicting evidence as to how using cannabis while drinking alcohol (i.e., simultaneous alcohol and cannabis use) impacts alcohol volume consumed, patterns of drinking, and alcohol-related consequences. The impact of simultaneous use on drinking outcomes may be influenced by several within- (e.g., contextual) and between-person (individual) factors.

Objective: The current study was designed to examine naturalistic patterns of alcohol and cannabis use in a sample of non-treatment seeking young adults who report simultaneous use alcohol and cannabis to understand how simultaneous use may impact drinking outcomes. The primary aims were to understand: 1) if simultaneous use is associated with increased alcohol consumption and riskier patterns of drinking; 2) if simultaneous use leads to increased alcohol consequences; and 3) how contextual circumstances moderate the impact of simultaneous use on consumption and consequences.

Methods: Data collection involves a 28-day ambulatory assessment protocol in which participants complete ecological momentary assessments (EMA: random, event-contingent, and time-contingent surveys) of alcohol and cannabis use, contexts, motives, and consequences on their personal smartphones while continuously wearing an alcohol biosensor bracelet. Participants also complete a baseline assessment and brief virtual 14-day check-in and 28-day final sessions.

Results: The project aimed to enroll 95 participants to obtain a target sample of 80 accounting for attrition. Recruitment and data collection began in May 2021 and is expected to continue through June 2024. Initial results for primary aims are expected in October 2024. As of March 2024, the project has recruited 118 eligible participants, 94 who have completed the study, exceeding initial projections in the study timeframe. Remaining recruitment will provide capacity to probe cross-level interactions that were not initially statistically powered. Strengths of the project include rigorous data collection, good retention and compliance rates, faster than expected enrollment procedures, use of a novel alcohol biosensor, and successful adaptation of recruitment and data collection procedures during the COVID-19 pandemic.

Conclusions: This is the first investigation to assess the key momentary predictors and outcomes of simultaneous use as well as self-reported and objective (via alcohol biosensor) measures of alcohol consumption and patterns. The results of this study will inform prevention efforts and studies of individuals who use cannabis who are engaged in alcohol treatment. Clinical Trial: <https://doi.org/10.17605/OSF.IO/S4BYZ>

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Original Manuscript

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Abstract

Background: There is significant conflicting evidence as to how using cannabis while drinking alcohol (i.e., simultaneous alcohol and cannabis use) impacts alcohol volume consumed, patterns of

drinking, and alcohol-related consequences. The impact of simultaneous use on drinking outcomes may be influenced by several within- (e.g., contextual) and between-person (individual) factors.

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Results: Recruitment and data collection began in May 2021 and is expected to continue through June 2024. Initial results for primary aims are expected in October 2024. As of March 2024, the project has recruited 118 eligible participants, 94 who have completed the study, exceeding initial projections in the study timeframe. Remaining recruitment will provide capacity to probe cross-level interactions that were not initially statistically powered. Strengths of the project include rigorous data collection, good retention and compliance rates, faster than expected enrollment procedures, use of a novel alcohol biosensor, and successful adaptation of recruitment and data collection procedures during the COVID-19 pandemic.

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simultaneous use as well as self-reported and objective (via alcohol biosensor) measures of alcohol consumption and patterns. The results of this study will inform prevention efforts and studies of individuals who use cannabis who are engaged in alcohol treatment.

International Registered Report Identifier: <https://doi.org/10.17605/OSF.IO/S4BYZ>

Data Availability: All data, including acknowledgement of missing data, will be made available at study completion at pre-registration site.

Keywords: Ecological momentary assessment, alcohol, cannabis, consequences, transdermal alcohol biosensors, ambulatory assessment.

Abbreviations: EMA: Ecological Momentary Assessment, TAC: Transdermal Alcohol Concentration, THC: delta-9 tetrahydrocannabinol, AA: Ambulatory Assessment, SCID-5-RV : Structured Clinical Interview for DSM-5 Research Version, TLFB: Timeline Follow-back, LME: linear mixed effects, FIML: Full-information Maximum Likelihood

Introduction

Alcohol and cannabis use are among the most commonly used substances in the U.S. Rates of using both substances are particularly high among young adults[1], who also report the highest rates of simultaneous alcohol and cannabis use (i.e., using alcohol and cannabis at the same time so that the effects overlap)[2]. Young adults (i.e., ages 18-26) are the only age group for whom rates of cannabis use increased following legalization of cannabis[3]. Co-use of alcohol and cannabis (i.e., use of both substances but not necessarily so that the effects overlap), and particularly simultaneous use (i.e., use of both alcohol and cannabis so that the effects overlap[4]), are associated with

increased risky behaviors and negative consequences, including driving under the influence, alcohol-related injuries, and other legal, academic, interpersonal, physical, and mental health problems relative to alcohol or cannabis use only[1,5–9]. Despite the increased risks associated with co-use, findings as to whether or not cannabis use leads to momentary increases in alcohol consumption or consequences remain mixed[10] and our understanding of how co-use confers liability for alcohol problems remains poorly understood. It is critical to understand the impact of cannabis use on alcohol use and consequences, as alcohol use is the third-leading cause of preventable death in the U.S.[11,12] and alcohol misuse cost the \$249 billion in 2010[13] and 5.1% of the global burden of disease and injury[14]. Globally, alcohol misuse was the leading risk factor for death and disability among those aged 15-49 in 2016[15]. The present work was designed to use ambulatory assessment methods to closely examine the momentary impact of simultaneous use on alcohol consumption, patterns, and consequences, as well as the social and contextual factors that may moderate those effects.

Simultaneous Alcohol and Cannabis Use

Laboratory work examining acute effects of simultaneous use suggests that cannabis enhances subjective effects of alcohol[16–18], increases motivation to drink alcohol[19,20], and leads to synergistic cognitive impairment[21–23], relative to when alcohol is used alone. Although these studies provide ideally controlled conditions for examining the acute effects of combined cannabis and alcohol, they are less ideally suited to examine complex contextual factors (e.g., location, activity, social) and naturalistic patterns of consumption. Observational studies of simultaneous use in which participants self-report their patterns of alcohol and cannabis use yield a naturalistic observation of cannabis' impact on alcohol outcomes. In particular, the use of repeated measurement, including the timeline follow-back (calendar-assisted method using anchoring dates to gather substance use estimates at the day level)[24] and ambulatory assessment methods, including ecological momentary assessment (EMA) are increasingly utilized to measure fine-grained patterns

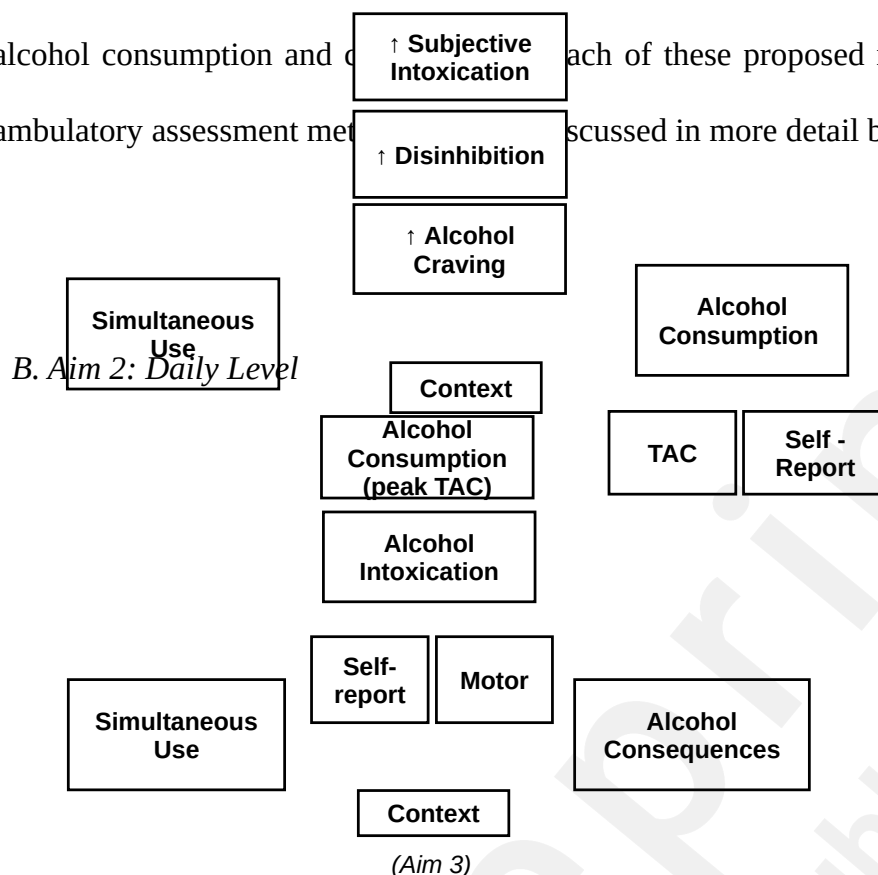
and correlates of co-use at the event-level[25]. Initial research suggests simultaneous use is associated with higher levels of alcohol and cannabis consumption, relative to when either substance is used alone[26–29]. However, competing findings exist in an observational study of primarily college students who provided 14 days of daily diaries, suggesting no increased risk of consumption[30]. With regards to alcohol-related consequences, there is a body of literature suggesting higher risk of consequences on simultaneous or co-use days relative to alcohol only days (see review by Lee and colleagues [31]). Despite these significant findings, several studies found no significant association between simultaneous use and consequences, especially when alcohol or cannabis quantity is controlled[27,32–34].

These conflicting results about the effects of simultaneous use have given way to two competing theories, namely whether cannabis acts as a substitute (i.e., replacing the effects of alcohol, resulting in decreased use) or a complement (i.e., used to enhance the effects of alcohol, resulting in increased use) [10,35,36]. The extant empirical literature provides compelling evidence for both substitution and complementary effects, in addition to nuanced findings based on population and mechanisms, including patterns (e.g., order of use in a day) and contexts (e.g., social settings) of use. These seemingly conflicting findings highlight that simultaneous use is at times complementary and at other times reflects substitution patterns (i.e., within-person effects). There is need for additional research examining fine-grained details of simultaneous use events, including mechanisms and contexts of simultaneous use, to isolate the conditions in which simultaneous use may lead to increased consumption and consequences.

Proposed Mechanisms of the Impact of Simultaneous Use on Alcohol Outcomes

Incentive-sensitization theory posits that addiction results from foundational characteristics of “drug liking” and “drug wanting”[37]. Expansion of this theory suggests that incentive sensitization paired with loss of inhibitory control (i.e. disinhibition) leads to increased motivation to use substances[38,39]. We can test whether this theory applies to how simultaneous use events confer

risk for increased alcohol consumption by examining whether simultaneous use indeed leads to increased alcohol consumption. Each of these proposed mechanisms can be assessed with ambulatory assessment methods discussed in more detail below (See Figure 1, Aim 1).



Intoxication. There is mixed evidence regarding the impact of simultaneous use on subjective intoxication in naturalistic settings, with some studies suggesting increased subjective intoxication during co-use occasions relative to alcohol only occasions[4], and other studies failing to find these effects[30]. While conflicting findings exist among the limited ambulatory assessment studies, participants consistently report increased intoxication during simultaneous use occasions, often referred to as “cross-fading,”[40,41] and laboratory work under controlled conditions suggest synergistic effects of a single low dose of alcohol with a low dose of cannabis compared to an alcohol-only dose[16,42–44]. Individuals may engage in simultaneous use to enhance these experiences of positive subjective intoxication through increased alcohol consumption. Alternately, alcohol may alleviate negative affect states or reduce feelings of anxiety/physiological arousal experienced at higher levels of intoxication from delta-9 tetrahydrocannabinol (the primary

psychoactive cannabinoid in cannabis, THC)[45]. Importantly, increased intoxication associated with higher rates of alcohol consumption is a robust predictor of risk for experiencing alcohol consequences[4,46–49], and may explain the link between simultaneous use and alcohol consequences such as drinking more than intended, experiencing nausea/vomiting, or neglecting responsibilities (See Figure 1, Aim 2).

Disinhibition. There is evidence that simultaneous use, compared to either substance alone, increases disinhibition (the ability to suppress an automatic behavioral or cognitive response), a core component of executive functioning[50]. Laboratory studies suggest that both cannabis[51–53] and alcohol[54–57] acutely impair inhibitory control (one indicator of disinhibition). In line with this, research and theory suggest that one's ability to moderate alcohol consumption is lower when inhibitory control is impaired[58,59]; this alcohol-induced impairment in inhibitory control increases ad libitum alcohol consumption[60]. Thus, simultaneous use could increase disinhibition, resulting in increases in alcohol use compared to non-simultaneous use situations. This possibility has not been well studied in real-time.

Craving. Cannabis and alcohol use both activate the endocannabinoid system[61] and in turn, the approach motivation system[62], therefore increasing approach to rewarding stimuli (e.g., alcohol)[63]. As alcohol and cannabis are commonly paired and known to increase pleasurable effects of both drugs[16,64], simultaneous use may trigger alcohol craving. Craving increases after exposure to alcohol cues and initiation[65–67], but only one laboratory study examined the effects of simultaneous use, finding an increase in “drug wanting”[67]. Active THC (versus placebo) alone has been shown to lower alcohol craving in a laboratory study[68], but no studies have examined the effect of simultaneous use on alcohol craving in the natural environment. Ambulatory assessment methods are ideal for examining direct effects of simultaneous use on the proposed mechanisms, as they can be assessed during the simultaneous use events.

Social Context in Simultaneous Use

Another critical consideration for understanding how simultaneous use affects alcohol outcomes is social contexts (e.g., number of people present, percent of people who are drinking), which are a consistent predictor of higher level of alcohol consumption[69–71]. Research on the context of alcohol consumption suggests that individual differences in motivation to drink predict drinking in certain contexts, but that social context is a consistent motivator for heavy drinking[72,73]. A recent EMA study of college students revealed that a majority of cannabis use episodes involved being with others, and found a positive association between using with others and amount of time spent using[74], suggesting using in social contexts may lead to higher levels of cannabis consumption as well. Recent work has also examined social contexts of simultaneous use episodes, revealing that among young adults, social events in private settings with a high percentage of people who are intoxicated resulted in increased likelihood of simultaneous use[75], and among adolescents in social contexts with greater number of underage individuals drinking was associated with increased likelihood of simultaneous use[46]. In daily or EMA data, social contexts were significantly associated with simultaneous use occasions (relative to alcohol or cannabis only) among college students[76] and young adult populations[77]. In qualitative work, young adults and adolescents suggest that they consider physical, social, and situational contextual factors when engaging in simultaneous use and that social characteristics are associated with simultaneous use[78,79]. Despite the converging evidence of the importance of social contexts for simultaneous use, no studies to date have examined whether context moderates the association between simultaneous use and alcohol consumption or consequences (See Figure 1, Aim 3).

Ambulatory Assessment of Simultaneous Use

Ambulatory Assessment (AA) methods include passive data collection (e.g., wearable biosensors) and ecological momentary assessments (EMA); they are ideal for studying substance use behavior and consequences as they allow for the assessment and control of contextual and social factors integral to substance use behaviors[25], as well as timing and direct effects as they naturally

occur[80,81]. AA also allows for the assessment of intoxication and impairment from self-administered doses of alcohol and cannabis, and with higher concentrations of THC than cannabis available for laboratory research. Recent advancements in AA also afford the opportunity to objectively assess substance use impairment via behavioral and cognitive tasks in the natural environment[82], expanding our ability to test these mechanisms in real time as they occur.

Transdermal alcohol biosensors provide a minimally invasive, objective, and passive method for continuously assessing alcohol consumption in the natural environment via transdermal alcohol concentration (TAC), a measurement derived from the small fraction (approximately 1%) of consumed alcohol excreted through the skin[83]. TAC sensors show robust correlations with breath alcohol sensors (BrAC) in the laboratory[84–86] and provide an objective, fine-grained indicator of alcohol use and specific high-risk patterns (e.g. rate of consumption) and are stable indicators of within-person variability[87,88], allowing for the examination of time-varying factors (e.g. cannabis use or context) on patterns of consumption. Three characteristics of drinking events that can be derived from TAC data and are of particular interest to our study aims are absorption rate (a function of physiological absorption rate and behavioral factors such as drinking pace and stomach contents), peak TAC (a proxy for maximum blood alcohol concentration or a marker of the peak intoxication), and area under the curve (including time and TAC values as an approximation of volume of alcohol consumed)[84,88]. TAC data mitigates the sole reliance on subjective self-report while reducing participant burden and circumventing issues with lower compliance with AA at higher drinking rates[89]. Taken together, pairing EMA with alcohol biosensors minimizes recall bias, maximizes external validity, and enhances the ability to more precisely model the influence of proximal factors linked with alcohol outcomes in the natural environment[90].

Study Aims and Hypotheses

This protocol aims to examine mechanisms by which simultaneous use leads to alcohol consumption and consequences utilizing naturalistic data collection. In addition to traditional self-

report EMA methods (e.g., assessing self-report craving and subjective impairment), the study will leverage technological advances in AA to assess motor impairment (gait and balance) and disinhibition (inhibitory control) with mobile app-based behavioral tasks in a participant's natural environment, as well as alcohol biosensors to passively and objectively measure patterns of alcohol consumption. This is the first study to directly examine mechanisms by which simultaneous use leads to increased alcohol consumption and consequences in the natural environment. Further, it is the first study to use transdermal alcohol biosensors and behavioral measures to assess objective impairment during simultaneous use events in the natural environment. The following specific aims and hypotheses will be examined:

Aim 1. Prospectively examine whether simultaneous use (vs alcohol only) is associated with increased alcohol consumption at the event level, as measured objectively and via self-report.

1a. Evaluate mechanisms by which simultaneous use may be associated with increased alcohol consumption. We hypothesize that simultaneous use will be associated with: 1) increased disinhibition, 2) increased subjective intoxication, and 3) increased alcohol craving, and in turn increased alcohol consumption (self-report).

1b. Examine whether simultaneous use is associated with high-risk patterns of alcohol use (e.g. increased rate of consumption), as measured objectively (transdermal alcohol concentration [TAC]).

Aim 2. Prospectively examine whether simultaneous use is associated with increased alcohol consequences at the daily level.

2a. Evaluate mechanisms that may explain the association between simultaneous use and alcohol-related consequences. We hypothesize that simultaneous use will result in increased alcohol intoxication, as measured by: 1) motor impairment (gait and balance) and 2) subjective impairment, leading to greater number of alcohol consequences.

2b. Examine whether simultaneous use leads to increased alcohol consequences via increased alcohol consumption, as measured objectively (TAC).

Aim 3. Examine event-level contextual moderators of the association between simultaneous use and alcohol consumption and consequences. We hypothesize that simultaneous use in social contexts (e.g. locations where there are others drinking) relative to non-social contexts will result in 1) increased alcohol consumption and 2) more alcohol-related consequences.

Method

Design Overview

Young adult participants (18-30 years) complete a baseline session, 28 consecutive days of AA, including daily EMA and continuous wear of the BACtrack Skyn transdermal alcohol biosensor bracelet, and two virtual sessions during the AA period (a mid-point check-in at 14 days and a final session at 28 days). Data collection assesses characteristics of alcohol and cannabis use events, in addition to hypothesized mechanisms and moderators of the association between simultaneous use events and alcohol outcomes (consumption and consequences).

Ethical Considerations. Human subjects ethics review was completed and approved by the University IRB (IRB # 1911002571). All participants completed informed consent, where all aspects of the study protocol were reviewed by a research assistant and knowledge checks were completed before a participant was consented. All study data are de-identified. Monetary compensation (described above) was provided and deemed to be commensurate with time to complete study procedures.

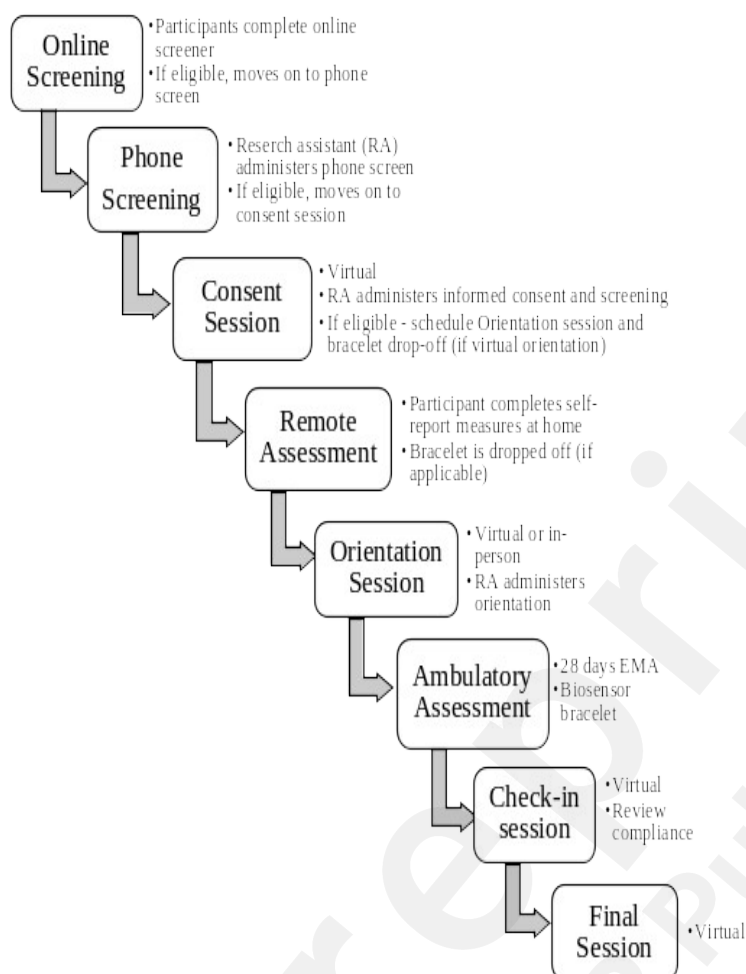
Participants

Up to 150 young adult participants will be recruited to achieve a final sample of 115 participants (accounting for up to 20% attrition) who complete the full study. Eligibility criteria include: 1) age 18-30 years; 2) ability to read and speak English; 3) drink alcohol on average twice per week (or 16 times) and drink heavily (>5 drinks for men and >4 drinks for women per occasion) on average once per week (or 8 times) over the last 60 days; 4) use cannabis on average of at least once weekly (or 8 times) for the past 60 days; 5) report recent (at least once in the past 30 days)

simultaneous alcohol and cannabis use (defined as using both alcohol and cannabis at the same time so that their effects overlap); 6) no recent use (past 30 days) of substances other than alcohol, cannabis, or tobacco; 7) not currently in or seeking treatment for cannabis or alcohol use; 8) not experiencing suicidal ideation (i.e., current intent) or symptoms of psychosis or mania in the past 30 days; 9) own a smartphone; 10) live within 10-mile radius of study location site or willing to drive within this radius to pick up study materials; 11) not colorblind; 12) not currently working overnight (i.e., third shift).

Procedures

Recruitment and Screening. Advertisements targeting individuals who use alcohol and cannabis include print and online media, social media, flyers, and handouts posted in the local community as well as “snowball” recruitment[91] (i.e., participant referrals). Participants who respond to advertisements complete an online screener, followed by a telephone screener to assess initial eligibility. Following initial remote screening, participants are scheduled for a virtual session in which they complete informed consent, followed by the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV)[92] interview to rule out those with current psychosis, mania, or suicidal intent and a Timeline Followback (TLFB)[24] interview to confirm eligibility on past 60-day alcohol, cannabis, and other substance use. Eligible participants complete a demographics and substance use history questionnaire and are scheduled for the baseline orientation session. See Figure 2 for study flow.



Baseli

ne Orientation Session. The baseline orientation occurs in-person or virtually. The decision to conduct the session in-person or virtually via Zoom depends on participant preference and the status of university policies around the COVID-19 pandemic. If virtual, research staff deliver the Skyn biosensor to the participant in advance of the orientation session. Prior to the session (regardless of it occurring in-person or virtual), participants complete an online assessment consisting of questionnaires to assess various mental health, personality, and substance use constructs (see Appendix A for full list of non-EMA self-report measures). During the orientation session, participants train in the use of the survey application (TigerAware[93]), including how and when to initiate surveys, answer different survey types, how to estimate standard drink and cannabis quantity

reporting, and when to reach out to staff during data collection. They are trained on the use of the Skyn biosensor for AA data collection, including when and how to sync and charge the bracelet and when to remove it (e.g., to avoid water damage). They also receive study-related handouts detailing reminders of the study protocol, Skyn biosensor operating procedures, and personalized standard alcohol and cannabis quantity estimates.

Ambulatory Assessment (AA)

Ecological Momentary Assessments. Immediately following the baseline orientation session, participants begin the AA data collection phase which consists of using their personal smartphones to answer daily surveys (EMA) and wearing the Skyn biosensor in daily life. The EMA protocol (see Appendix B for full EMA survey details) will instruct participants to self-initiate event-contingent surveys when they begin drinking alcohol or using cannabis (“Start” survey) and when they finish drinking or using cannabis (“Finish” survey) during each day of the AA data collection period. Participants are instructed to complete a Finish survey if they are done using cannabis or drinking, but forgot to initiate the Start survey. “Follow-up” surveys at 30, 60, 90, and 120 minutes are pushed after the initiation of a Start survey to capture additional use, intoxication, affect, craving, and contextual changes. Follow-up surveys assess hypothesized mechanisms (disinhibition, subjective intoxication, and craving) and social context moderators (see Data Analysis for more details).

In addition to event-contingent surveys, participants receive signal-contingent surveys (i.e., random prompts) to capture substance use periods that were not self-initiated and social contexts during non-use moments. Random prompts occur once within each 3-hour block during the afternoon, evening, and night (Block 1: 3:00 pm – 6:00pm; Block 2: 6:00pm -9:00pm; and Block 3: 9:00pm -12:00am). Prompts for these Random surveys are not sent if they would occur during the follow-up period of a Start survey. When substance use is reported on a Random survey, Follow-up surveys identical to those following the Start surveys are prompted.

Finally, a time-contingent “Morning” survey is available to be self-initiated every morning,

and prompted by two reminders (9:00 and 11:00 am). Morning surveys assess the prior days' alcohol and cannabis use, alcohol and cannabis-related consequences, other substance use, reasons for non-use, and intentions for use in the present day. All surveys are designed to be short (< 3 minutes) and participants may suspend prompts at any time to avoid interrupting their sleep or tasks (e.g., employment or education activities).

Passive Alcohol Consumption Assessment. The Skyn biosensor is worn continuously on the non-dominant wrist of each participant to passively collect TAC during the AA data collection period (see Figure 3). The application used to transmit data collected via Bluetooth from the Skyn biosensor is not supported on Android devices, therefore study iPhones are provided for syncing the Skyn biosensor only (no data/cell service required) for participants who own Android phones; study-provided phones are not used for EMA data collection. Participants are instructed to open the Skyn application and sync the app once a day, which they are compensated to complete (see Table 1). Participants are also instructed to wear the bracelet at all times, but are told that it is not waterproof, so to only remove it when charging, swimming, showering, or doing any other activities where the bracelet may be submerged in water. The charging protocol varies based on bracelet version. In September 2021, BACTrack Skyn released a new bracelet, which has a prolonged battery life (average of 13 days), relative for the previous version (48-72 hours). Protocol for charging instructions is adapted to these versions. It is emphasized during orientation to wear the bracelet while drinking and overnight, as drinking often occurs in evening hours and removing the bracelet prior to full metabolism of alcohol consumption would result in missing data. Therefore, we suggest to participants that they charge the bracelet while bathing to reduce the number of removals. Participants are instructed to avoid exposure to alcohol-based products (e.g., using hand sanitizer) when possible as this can cause a temporary elevation in TAC (that does not resemble a consumed alcohol episode but is troublesome during data cleaning so should be minimized).

Check-in and Final Sessions. Participants complete a virtual check-in session via Zoom

videoconference after two weeks of AA data collection to review compliance and allow for troubleshooting of any technical aspects of the study. Finally, participants complete a final session via Zoom after coordinating the bracelet return with research staff. In the final session, research staff review the final compensation earned and administer a brief interview to receive feedback on the protocol. The interview requests general feedback on the study protocol, comfort wearing the bracelet, usability of the TigerAware application, and the study compensation.

Compensation. Participants are paid \$30 for the orientation session, \$25 for completing the remote baseline assessment, up to \$40 for completing the first two AA weeks, up to \$50 for completing the second two AA weeks (compliance details described in Table 1), \$15 each for the check-in and final session, and a \$50 completion bonus (contingent on completing all sessions and remaining active in all four weeks of AA). Compliance will be maximized in the AA study phase by compensating participants increasing dollar amounts based on compliance rates each week (see Table 1). Compliance is also incentivized for wearing the Skyn biosensor bracelet with a maximum of \$35 per week (\$5 per day for keeping the bracelet charged and synced). Total possible study payment is \$450. Payments are made on reloadable debit cards. Payments for orientation completion are given directly after those sessions, while total payments are given at study completion or at time of withdrawal (prorated).

Table 1. Compliance Schedule

<i>Reimbursement for Sessions</i>				
Orientation Session	\$30			
Remote baseline assessment	\$25			
Check-in session	\$15			
Final Session	\$15			
Completion Bonus	\$50			
<i>Reimbursement for daily surveys</i>	<i>Week 1</i>	<i>Week 2</i>	<i>Week 3</i>	<i>Week 4</i>
Under 25% completion	\$5	\$5	\$5	\$5
25-49% completion	\$10	\$10	\$15	\$15
50-74% completion	\$25	\$25	\$30	\$30
75-89% completion	\$35	\$35	\$45	\$45

Over 90% completion	\$40	\$40	\$50	\$50
<i>Reimbursement for biosensor bracelet wearing</i>				
Full compliance \$5 per day	\$0 -35	\$0 -35	\$0 -35	\$0 -35
Total Possible Compliance	\$450			

Measures

Remote Baseline Assessments. Prior to the orientation session, participants complete a battery of self-report measures assessing various mental health, personality, and substance use constructs using an online Qualtrics survey, Version [May, 2021] (Qualtrics, Provo. UT) at home (see Appendix A for full list of self-report measures). This battery is expected to take approximately one hour to complete.

Baseline Demographics and Substance Use History. This survey assesses demographic information (e.g., sex at birth, gender, race, ethnicity) and substance use history information (e.g., age at first alcohol and cannabis use, history of use of substances other than alcohol and cannabis). In addition, a subset of items from the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU)[94] are included. The survey takes approximately 15 minutes to complete during the recruitment and screening session and completed using an online Qualtrics survey by the participant. Full scoring information is not described here, as a subset of items were included in this study, however this information is provided in the original citation for the DFAQ-CU[94].

Timeline Followback (TLFB). The TLFB[24] is a calendar-assisted interview administered by a research assistant to assess recent daily substance use. The TLFB uses a calendar to assist participants in remembering substance use with cues for personal events and dates to enhance accurate recall. The TLFB will be used to assess past 60-day alcohol (number of drinks), cannabis, tobacco, and other substance use to confirm eligibility and characterize substance use patterns. The TLFB has been found to be reliable and valid in a variety of prior studies with various substances and populations [95–99] and takes approximately 10-30 minutes to complete, depending on the

substance use patterns of the participant who is being interviewed.

The Structured Clinical Interview for DSM-5, Research Version (SCID5-RV). The SCID 5-RV[92] semi-structured interview administered by research staff includes a screening tool that is used to assess current symptoms of psychosis and mania. The SCID 5-RV screening tool for mania and psychosis takes approximately 10 minutes to complete and is scored based on DSM-5 criteria for each diagnosis. The SCID 5-RV has shown strong clinical validity and intra-rater and test-retest reliability[100].

Patient Health Questionnaire-9 (PHQ-9). The PHQ-9[101] is a self-report measure administered by the participant of current depressive symptoms, including suicidal ideation, and is used to screen for current suicidal intent. The PHQ-9 is administered using an online Qualtrics survey and takes approximately five minutes to complete. The PHQ-9 has shown strong reliability and validity as a self-report screening tool for major depressive disorder [102].

EMA Survey Items. Key constructs are assessed in EMA through event-contingent (begin- and end-use alcohol and cannabis surveys [i.e., Start and Finish], follow-ups, morning) and signal-contingent (Random) surveys using Tigeraware [93] software. Each construct assessed is included in Table 2 and exact items are included in Appendix B. Measures were selected based on hypothesized associations with primary dependent variables of alcohol consumption and consequences. Start and Finish surveys are always available and begin with assessment of whether the participant is reporting alcohol or cannabis use (or both) and continue to additional constructs, as relevant (see Appendix B). In addition, participants are instructed to complete a “Hand Sanitizer/Alcohol-based Product” survey anytime they encounter these products, which will simply ask them to enter the time they come in contact with the product. A modified version of the Stroop[103] task and a Gait and Balance task developed by Apple ResearchKit[104] are included in the 30- and 60- minute Follow-ups surveys to assess disinhibition and motor impairment, respectively. The Stroop Task asks participants to select the first letter of the name of the color that is presented (e.g., B for Blue), where the color of the text

is displayed in the opposing color for a proportion of the trials. The Gait and Balance task instructs participants to place their phones in their pockets and walk in a straight line for 20 steps.

Table 2. EMA Constructs Assessed

Construct	Delivery	Example item
Alcohol Use	ST, ED, FU, RM, MR	<i>Have you had any alcohol since your last report?</i>
Alcohol Type	ED, MR	<i>What type of alcoholic drinks did you have?</i>
Alcohol Start Time	ST, RM, MR	<i>Confirm the time you started drinking.</i>
Alcohol End Time	ED, MR	<i>What time did you finish drinking?</i>
Alcohol Quantity	ST, ED, FU, RM, MR	<i>How many total standard drinks did you have?</i>
Subjective Intoxication	ST, FU, ED, RM	<i>Rate how drunk/high you feel.</i>
Cannabis Type	ST, FU, ED, MR	<i>Are you using flower (i.e., plant, bud)?</i>
Cannabis Quantity	ST, FU, ED, MR	<i>How much flower (i.e., plant, bud) are you using?</i>
Cannabis Start Time	ST, RM, MR	<i>Confirm the time you started using flower.</i>
Cannabis End Time	ED, MR	<i>What time did you finish using flower yesterday?</i>
Cannabis Reasons	ST, RM	<i>Please select the reason(s) you are using cannabis.</i>
Cannabis Mode	ED, MR	<i>Which of the following modes did you use with flower?</i>
Context: Location	ST, RM, FU	<i>Where are you?</i>
Context: Activity	ST, RM, FU	<i>What are you doing?</i>
Context: Social	ST, RM, FU	<i>Are you by yourself or with others?</i>
Context: Social relationship	ST, RM, FU	<i>Who are you with?</i>
Context: Social use	ST, RM, FU	<i>Are the people (person) you are with drinking alcohol?</i>
Nicotine Use	ST, MR	<i>Are you using any of the following nicotine products?</i>
Craving	ST, FU, RM, ED, MR	<i>How strong is your urge to drink alcohol right now?</i>
Affect	ST, ED	<i>How much have you felt upset in the past 15 minutes?</i>
Impulsivity	ST	<i>I did something without really thinking it through.</i>
Disinhibition (Stroop task)	FU ^a	*
Motor Intoxication (Gait task)	FU ^b	*
Alcohol/Cannabis Consequences	MR	<i>Did you experience any of the following yesterday as a result of your alcohol use?</i>
Alcohol/Cannabis Intentions	MR	<i>Do you plan to drink alcohol today?</i>
Intoxication Intentions	MR	<i>How high do you plan to get today?</i>
Non-use reasons	MR	<i>Please select the reasons you did not use cannabis yesterday.</i>
Other substance use	MR	<i>Did you use substances other than alcohol or cannabis yesterday?</i>

Note: ST = event-contingent begin alcohol/cannabis use or “Start” survey, ED = event-contingent end alcohol/cannabis use or “Finish” survey, RM = signal-contingent “Random” survey, FU = event-contingent “Follow-up survey, MR = event-contingent morning report, ^aadministered in first follow-up only, ^badministered in second follow-up only, *see Appendix.

BACTrack Skyn Alcohol Biosensor. The Skyn biosensor uses fuel cell-based sensors to continuously measure TAC, body temperature, and movement in 20 second intervals. TAC data will be used to assess daily peak TAC and rate of consumption as reflected in rate of absorption (see Analytic Plan). Data are synced via Bluetooth on the Skyn iOS-based application by the participant, and a single csv file is downloaded at the completion of participation. Research staff also perform daily data tracking on the BACTrack online portal to check for participant compliance to the syncing and charging protocol and reach out to participants if any missing data is observed.

Data Analysis Plan

Data Cleaning and Aggregation. An event-level data set will be created to examine aims 1 and 2 and a day-level dataset will be created to test aim 3 hypotheses. Event rows will be derived from: 1) initiation of Start surveys paired with corresponding Follow-up and Finish surveys, 2) Random surveys and corresponding Follow-up surveys (when substance use is reported), 3) “Orphan” Finish surveys where participants complete a Finish survey but there is no corresponding Start or Random survey where substance use is reported or there is another preceding Finish survey. Finish surveys will be paired with Start or Random surveys with substance use if they are submitted 6 hours apart. A social day (6am-6am) will be used to aggregate event-level data and Morning surveys for a day-level dataset. Each row in the day-level dataset will encompass data from the Morning survey and an aggregate of relevant event-level variables.

Simultaneous use events will be defined by self-report of alcohol and cannabis use at any point in the initial survey (Start or Random surveys) and associated Follow-ups or Finish surveys. Drinking events from the Skyn biosensor will be identified and processed using the TASMAL 2.0 survey software[105]. Timestamps will be used to associate and merge TAC data with drinking events. Events with no self-reported drinking or cannabis-only use with unreported (i.e., missing) drinking that is indicated from TAC data will be flagged and removed from analyses when self-reported data is necessary for analyses. Social context will be defined as events where others are

around or being around others who are drinking alcohol (*“Are the people (person) you are with drinking alcohol?”*).

All variables will be examined descriptively and checked for assumptions of normality[106]; significantly skewed variables will be transformed or modeled appropriately. Analyses will be conducted to examine whether missing data, specifically on dependent variables, are associated with baseline characteristics (e.g. demographics; Alcohol Use Disorder). Sensitivity analyses will determine if findings are consistent in cases with significant missingness[107]. Full information maximum likelihood (FIML) estimation[108] will be used for data missing at random. FIML allows for the handling of missing data without compromising power of large intensive longitudinal data. After checking for missing data assumptions, FIML[109] or sequential modeling will be used in multilevel models to impute missing data using packages such as mdmb [110].

Aim 1: Examine the impact of simultaneous use on alcohol consumption. To determine if simultaneous use leads to increased alcohol consumption, data from alcohol-only and simultaneous use events (from both event- and signal-contingent surveys) will be analyzed. Two-level linear mixed effects (LME[111]) will be used and will include aggregated measures of level 1 (L1) predictors (random intercepts for individual) at level 2 (L2) to control for the effect of individual-level predictors (e.g. simultaneous use), allowing for the interpretation of other L1 predictors on outcomes as purely within-person associations (e.g., impact of simultaneous use on total alcohol consumption). Aim 1 models will control for subject-level covariates at L2 (sex, age, race, ethnicity) and time-varying covariates at L1 (time lag of cannabis use for simultaneous events, tobacco, day of the week, other substance use). Aim 1a will use mediation to examine the effects of hypothesized mechanisms (increased disinhibition, subjective intoxication, and craving measured in Follow-up surveys) between simultaneous use (versus alcohol only use) and alcohol consumption, measured via self-report (total number of drinks consumed). Aim 1b will use LME to test the association between simultaneous (versus alcohol only) events and drinking rate (measured via TAC absorption rate).

Peak TAC will be calculated as highest TAC recorded within an episode, area under the curve will be calculated as the sum of the area of trapezoids under the TAC curve, and absorption rate is calculated as peak TAC divided by time from last zero reading to peak TAC)[84,87,88].

Aim 2: Examine the impact of simultaneous use on alcohol consequences. To examine whether simultaneous use is associated with increased alcohol consequences, LMEs will again be used with day-level aggregate data where consequences are assessed in the Morning survey and simultaneous use is defined as incidence of simultaneous use in any event data form the prior day. The same subject- and time-varying covariates will be included as in aim 1 models. Mediation in LME will again be used to test effects of hypothesized mechanism: motor impairment (i.e., gait/balance data) and subjective impairment (self-report) measured from Follow-up surveys (2a) and total alcohol consumption measured via TAC (2b) between simultaneous use and alcohol consequences.

Aim 3: Examine contextual moderators of the association between simultaneous use and alcohol consumption and consequences. To test whether social context moderates the impact of simultaneous use on increased consumption and consequences, an interaction of social context (from self-report event- and signal-contingent surveys) and type of substance use episode (simultaneous versus alcohol only) will be included as predictors on total alcohol consumption and consequence models, as defined above.

Results

The current protocol was funded in September 2019 and received Institutional Review Board approval in January 2020. A modified protocol to accommodate COVID-19 related disruptions in research, including a fully remote protocol, was approved in April 2021 and the first participant was enrolled in May 2021. Initial recruitment goals for the project[112] aimed to enroll 95 participants to obtain a target sample of 80 accounting for attrition. However, at the time of this submission, 118 eligible participants have been enrolled, of whom 94 (79.6%) have completed the full protocol. Of

the 20 who did not complete the protocol, 12 withdrew before participating in the AA and 8 withdrew during participation. Given the successful recruitment rate and remaining funding timeline, recruitment is ongoing at the time of this submission and is intended to continue until up to 115 total participants complete the protocol. These additional participants will allow for the probing of cross-level interactions that were underpowered based on initial budget and recruitment projections in the funding proposal (e.g., moderation of simultaneous use effects by frequency of cannabis use[113]). Data collection is expected to end by June 2024, and initial results for primary aims are expected in October 2024.

Discussion

The current paper describes a protocol aimed at understanding the impact of simultaneous alcohol and cannabis use on alcohol consumption and consequences among non-treatment seeking young adults in the natural environment. Given the high prevalence of simultaneous use among young adults[1–3] and its association with high-risk behaviors and alcohol-related consequences among those who use both substances[5–9], this investigation has critical public health impact for young adults. Further, although simultaneous use has been linked to alcohol-related risks, there is conflicting evidence as to the momentary impact of cannabis use on drinking[10,35]. The present study is the first naturalistic observational study that will comprehensively examine the mechanisms whereby simultaneous alcohol and cannabis use may confer alcohol-related risks in the moment and across contexts. With use of EMA and alcohol biosensors, this protocol will objectively identify how self-reported cannabis impacts patterns of drinking (e.g., rate of consumption). Further, the assessment of alcohol and cannabis use behaviors in the moment, while young adults are in their natural drinking environment, will allow for the direct measurement of the critical risk mechanisms under study; specifically: craving, subjective intoxication, motor impairment, disinhibition, and contextual influence.

Study Implications

The comprehensive study of these substance use patterns, and the identification of key hypothesized mechanisms, is critical to informing prevention and intervention efforts. In particular, this work will inform the next wave of technology-assisted treatment and intervention research, such as just-in-time adaptive interventions[114–117] and digital interventions[118]. There has been significant interest in this approach, specifically in the use of mobile apps to reduce alcohol use[119] and several effective trials, however no work yet has tested interventions for simultaneous use behaviors in young adults. To do this important prevention and intervention work, it is critical to understand the specific risk mechanisms of simultaneous use on alcohol outcomes. The current study will elucidate these mechanisms and clarify the competing literature (i.e., substitution versus complementary theories) on the momentary impact of simultaneous use on alcohol outcomes to inform these intervention approaches.

The current study will also pave the way for additional work aimed at integrating alcohol biosensor assessment within intensive longitudinal research protocols using EMA as well as for preventive interventions. While this is not the first study to utilize wrist-worn biosensors in naturalistic data collection[120,121], this is the first to align the use of additional substances within drinking events to understand how co-use may impact drinking patterns, such as rate of consumption. This work will not only elucidate the impact of cannabis use on drinking topography in naturalistic settings, thereby clarifying the role of simultaneous use in risky alcohol consumption patterns, but also establish the feasibility of complex polysubstance use assessment methods across levels of data analysis. This research has the potential to lead to important health policy recommendations, such as regulations on proximity of retail cannabis and alcohol placement and the distribution of products that include both alcohol and cannabis.

Limitations

Several limitations of the present protocol are worth identifying. First, while it is critical to understand etiology of simultaneous use in non-treatment samples to inform prevention and

developmental models of addiction, the current study implications are limited to non-treatment seeking young adults. Given that treatment status has been identified as a potential critical between-person moderator in the study of simultaneous use and the impact on alcohol outcomes[10], future work will be necessary to extend these findings to those with severe alcohol use disorder or who are seeking treatment for alcohol use. Second, recent use of substances other than nicotine or tobacco is an exclusion criterion in the current protocol. This exclusion criterion was necessary due to the limited resources of this funding mechanism that prohibit recruiting a sample large enough to power for variability from additional substance use that may greatly impact alcohol consumption patterns. Although it will be controlled for in the current analyses, future work that includes individuals who use a variety of additional substances is needed to understand the full range of polysubstance use and its impact on alcohol consumption and consequences. Finally, given there is no validated objective method for assessing cannabis use in naturalistic data collection, the current study is limited to self-report of cannabis use in the context of objective assessment of alcohol consumption. Objective measurement of both alcohol and cannabis use would further validate a rigorous approach to studying patterns of simultaneous use in the natural environment.

Conclusions

The current protocol describes the most comprehensive observational study to date of the impact of simultaneous alcohol and cannabis use on alcohol consumption and consequences in the natural environment among young adults. Data collected in the moment via self-report and passive alcohol sensing with a transdermal alcohol biosensor will elucidate competing theories as to how cannabis use while drinking impacts patterns of alcohol consumption and associated consequences. The study will also identify within- and between-person mechanisms and moderators of these key associations, such as subjective and objective measures of intoxication, via assessment during substance use events. Results will inform key prevention and intervention efforts to reduce the negative impact of simultaneous use among young adults who use alcohol and cannabis frequently

and set the groundwork for future work aiming to utilize these methods in expanded populations.

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Supplementary Files

Multimedia Appendixes

Peer-review reports.

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