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ORIGINAL ARTICLE

Co-Use of Tobacco and Alcohol Is Associated With Blunted Blood Pressure Responses During Stress: A Prospective Examination 9–14 Years Later

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ABSTRACT

Tobacco smoking has been described as a gateway to substances, such as alcohol during adolescence, and both are often used in times of stress. While the effects of smoking on cardiovascular stress responses are well documented, alcohol use is generally restricted for an arbitrary time period or covaried. Additionally, how tobacco and alcohol co-users respond to acute psychological stress has yet to be determined. The present study sought to examine prospective associations between baseline substance use and cardiovascular reactivity 9–14 years later. Specifically, we examined the impact of tobacco-only use, alcohol-only use, co-use, and non-use on cardiac activity in response to acute stress. Data were drawn from a sample of 774 participants from the Midlife Development in the United States (MIDUS) series. Participants had their blood pressure and heart rate monitored during a standardized laboratory protocol where they completed self-report questionnaires and mental arithmetic and Stroop tasks. Results showed that co-users had lower diastolic blood pressure responses during stress compared to alcohol-only users. Co-users also reported lower positive affect and higher negative affect. They reported an earlier age of onset for both tobacco and alcohol, a greater number of cigarettes smoked, and more alcohol-related problems. The findings extend earlier observations of blunted stress responses in substance users and indicate the need to examine their implication in predicting relapse.

1 | Introduction

Alcohol use disorder (AUD) reportedly impacted 28.9 million people living in the United States in 2022 (National Institute Health [NIH] 2024) with the equivalent purported for current smokers (VanFrank et al. 2024). Tobacco and alcohol independently affect health outcomes, with smoking linked to increased risk of hypertension in males (Halperin et al. 2008) and females (Bowman et al. 2007), as well as premature cardiac disease and mortality (Hahad et al. 2023; Zhang et al. 2023). Alcohol-related illnesses include cardiovascular disease (CVD), sleep disorders, and cirrhosis of the liver (McKee and Weinberger 2013). Global reports estimate over 2 billion people consume alcohol and 1 billion continue to smoke, and the global economic burden attributed to smoking and alcohol related diseases is substantial (Goodchild et al. 2018; World Health Organization [WHO] 2018), placing a heavy toll on health care systems. While tobacco smoking and alcohol consumption can lead to increased susceptibility to disease outcomes, both are modifiable behaviors.

However, tobacco and alcohol are considered gateway drugs, with 40% of heavy smokers meeting criteria for AUD, suggesting concurrent use is common (WHO 2018). In addition, tobacco and alcohol co-use has been linked to all-cause mortality in men (Hart et al. 2010), preterm labor in women (Odendaal et al. 2009), and a greater susceptibility to hypertension in men and women (Singh et al. 2022). One common factor implicated in the development, maintenance and risk of relapse for tobacco and alcohol use disorders is stress.

Stress can indirectly impact health through harmful behaviors such as smoking and drinking alcohol. Both are used as coping mechanisms to alleviate feeling anxious or depressed (Mensch and Kandel 1988), though mood deterioration between cigarette use has been reported (Parrott 2003), and this can make cessation more difficult. Increases in tobacco use and alcohol consumption were noted during COVID-19 as a means of coping with the pandemic (Kosendiak et al. 2021). In addition, stress has been linked to earlier initiation, higher intake of both substances, and less successful quit attempts (Krueger and Chang 2008). Stress response profiles are proposed as biomarkers for substance use disorders (Evans et al. 2015; Milivojevic and Sinha 2018).

Extreme stress responses, be they exaggerated or blunted, indicate poorer health outcomes and have been linked to hypertension (Brindle et al. 2016), carotid intima-media thickness (Ginty et al. 2016), and premature mortality (Carroll et al. 2012). The reactivity hypothesis postulates that the magnitude of the individual stress response is a relatively stable trait, whereby a person's tendency to be high or low on reactivity is reliable across time (Manuck 1994). Although research shows that alcohol consumption and tobacco use can independently elevate blood pressure (BP) and heart rate (HR) (Grassi et al. 1994; Tasnim et al. 2020), chronic use has also been generally associated with blunted responses to acute stress. Moreover, alcohol use is commonly restricted or controlled for when examining associations between smoking behaviors and stress reactivity. Research shows that smokers display blunted neuroendocrine (al'Absi et al. 2003; Ginty et al. 2014) and cardiovascular (Keogh et al. 2024; Phillips et al. 2009; Roy et al. 1994) responses compared to non-smokers. Similarly, alcohol use has also been linked to blunted cortisol (Lovallo et al. 2000) and HR responses (Panknin et al. 2002). Another research study reported that habitual alcohol consumption was associated with lower HR responses but higher cortisol responses to stress (Jones et al. 2013). Moreover, these lower stress responses are observed in those at risk of relapse for alcohol (Junghanns et al. 2003), cocaine (Back et al. 2010), and smoking (al'Absi et al. 2005). These effects have also been observed at a younger age, with adolescent smokers demonstrating blunted HR responses to stress, while those who consumed moderate to high alcohol exhibited low HR responses in general across the procedure compared to those who consumed less alcohol (Evans et al. 2012). Carroll et al. (2017) suggest that blunted reactivity may reflect altered functioning within the fronto-limbic brain systems implicated in motivated behavior. Associations between markers of motivational deficits (e.g., smoking, alcohol dependence) and blunted responses to stress are well established. Therefore, neural alterations in brain regions linked to motivation regulation may underlie both diminished responses to stress and a greater propensity for substance use. While the additive impact of tobacco and alcohol co-use on health outcomes is established, how this co-use impacts cardiovascular responses to psychological challenge is unknown. Previous work from our lab examined the effects of co-use relating to other substances and found that tobacco-khat co-use was associated with increased negative affect (NA) and blunted cardiovascular responses to stress (al'Absi et al. 2014), and tobacco-cannabis co-use was associated with enhanced craving for cannabis (al'Absi et al. 2022). Additionally, elevated NA has been linked to AUD and risk of relapse (Stasiewicz and Maisto 1993). While recent work has begun to address the effects of co-use on subjective mood and stress responses, the psychophysiological effects of tobacco and alcohol co-use have yet to be determined.

With this in mind and given the independent effects of both substances on the stress response, the current study sought to address this gap by examining blood pressure and heart rate responses in tobacco-only users, alcohol-only users, co-users, and non-users. Below we report a prospective analysis from the MIDUS series, where associations between substance use and cardiovascular reactivity 9–14 years later were examined. In line with the above evidence, we hypothesized that responses to stress would be blunted in those who use tobacco, alcohol or both substances compared to non-users. Moreover, given the known additive impact of co-use, we expect the dysregulation in cardiovascular responses to be most pronounced in co-users compared to tobacco-only users, alcohol-only users and non-users.

2 | Method

2.1 | Participants

Data for the current study were drawn from the main MIDUS (1995–1996) longitudinal survey and MIDUS 2 biomarker project (2004–2009) 9–14 years later, with an average period of 11.17 (SD = 1.18) years. Data was merged using a key identifiable (M21D) variable. The main MIDUS project consisted of 7108 respondents who provided information on mental and physical well-being through adult life in order to assess psychosocial factors in age-related health differences. The biomarker project followed up with the original MIDUS sample and consisted of 1255 participants who attended a clinic visit and underwent psychobiological assessment. Inclusion was limited to those ($n = 1155$) who completed the biomarker project (Ryff et al. 2019). Similar to previous research (Keogh et al. 2022; O'Riordan and Costello 2024), a subset of twins ($n = 356$) were removed due to the assumption of independence in analyses and the possible confounding nature of genetic determinants of reactivity (Carmelli et al. 1985). In addition, 25 participants were removed, 16 who completed an extended version of the stress task and 9 who had a pacemaker implant. This left a total sample of 774 for analyses. At the time of the longitudinal survey (MIDUS 1), participants were on average 46.63 (SD = 11.64) years of age ($_{range}$25–74), with a mean body mass index (BMI) = 26.74 kg/m^2 (SD = 5.09). The sample was predominantly Caucasian ($n = 526$; 68.0%) and there was a similar gender split between females ($n = 311$; 40.2%) and males ($n = 281$; 40.2%). The sample consisted of tobacco-only users ($n = 35$), alcohol-only users ($n = 187$), co-users ($n = 57$) and non-users ($n = 289$). Excluded cases pairwise was used for missing data, whereby participants were included in analyses for which data was available. The biomarker data (MIDUS 2) provided follow-up analyses to determine the impact of tobacco and alcohol co-use on CVR to acute psychological stress. Informed consent was obtained prior to study procedures.

2.2 | Procedure

Respondents from the main MIDUS longitudinal survey were eligible for the biomarker project if they completed the MIDUS

2 survey. These participants were invited to attend a clinical research center for 24-h where they underwent comprehensive psychophysiological assessment and completed standardized stress tasks while having their blood pressure and heart rate monitored throughout. Day 1 consisted of obtaining medical history, completion of self-administered questionnaires and urine analysis. Day 2 consisted of the psychophysiology experimental protocol. Data collection for the MIDUS series is reviewed and approved by the Education and Social/Behavioral Sciences and the Health Sciences Institutional Review Boards at the University of Wisconsin-Madison.

3 | Measures

3.1 | Substance Use

Tobacco and alcohol use were determined in the main MIDUS survey through a series of questions on history and habits, such as the age initial use began, previous quit attempts, and the number of cigarettes smoked during the heaviest period of smoking. Current smokers responded yes/no, while alcohol consumption was defined as a period where participants had at least one drink 3 or more days a week (yes/no). A 5-item alcohol screening test was also used to determine the negative effects of alcohol experienced in the previous 12-month period. Examples of items include "Did you ever, during the past 12 months, have any emotional or psychological problems from using alcohol—such as feeling depressed, being suspicious of people, or having strange ideas?" to "Did you ever, during the past 12 months, have such a strong desire or urge to use alcohol that you could not resist it or could not think of anything else?" A total score of the 5-items was computed with higher scores indicating a greater number of alcohol problems experienced.

3.2 | Subjective State

In line with similar research (al'Absi et al. 2021; Keogh et al. 2024), mood ratings of positive affect (PA) and NA were measured using a 12-item scale (Mroczek and Kolarz 1998). The PA scale was comprised of an average of 6 items: cheerfulness, happiness, satisfaction, calmness, full of life, and in good spirits. The NA scale consisted of an average of 6 items: nervousness, hopelessness, restlessness, worthlessness, and effort. Participants rated how they felt during the previous 30 days on a 5-point scale ranging from 1 (all of the time) to 5 (none of the time). Items were recoded so that higher scores indicate greater levels of PA and NA. Earlier research has demonstrated acceptable psychometric properties for both subscales (Mroczek and Kolarz 1998). In the current study, Cronbach's α values for positive affect (0.91) and negative affect (0.87) indicate acceptable internal consistency.

3.3 | Psychological Stress Task

The cognitive stressors consisted of the Stroop task and Morgan and Turner Hewitt (MATH) mental arithmetic task (Turner et al. 1986). Each task was 6-min duration and tasks were presented in random order. For the Stroop task, one of four color name words (i.e., red, blue, green, yellow) were presented to participants in a font that was either congruent or incongruent to the word name presented on screen (e.g., red presented in red font compared to red presented in green font). Using a keypad, participants selected the font color of the letters but not the color name. The presentation rate was performance-adaptive; incorrect responses led to slower rates of presentation. For the computerized mental arithmetic task, participants were presented with a number of addition and subtraction problems along with proposed answers, and they were asked to determine if the presentation was correct/incorrect by pressing one of two keys (corresponds to yes or no). The task included five difficulty levels ranging from level 1 (two 1-digit numbers) to level 5 (two 3-digit numbers). Task difficulty was dependent on participant performance, with the level of difficulty increasing with more correct responses.

3.3.1 | Stress Task Measures

On a 10-point Likert scale ranging from 1 (not at all) to 10 (extremely), participants rated the level of psychological stress experienced before undertaking the stress tasks and then after each stress task. As with previous research, the average score across the tasks was calculated, and changes in stress before and after the tasks were used to determine if the stress tasks were perceived as stressful (O'Riordan and Costello 2024).

3.4 | Physiological Assessment

Beat-to-beat systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed using a Finometer cardiovascular monitor (Finapres Medical Systems). Using the volume clamp method (Penaz 1973), continuous non-invasive measures of finger arterial pressure were taken. A finger cuff was placed on the middle finger of the non-dominant arm and a blood pressure cuff attached above the brachial artery was used for calibration of intrabrachial pressure measurements. HR was assessed using electrocardiogram (ECG), where beat-to-beat signals were measured and digitized at 500 Hz. R waves were detected using automated software and subsequently inspected by trained research staff to correct any detection errors. For each period in the psychophysiology session, data from 300 s epoch duration were analyzed. For the 11-min baseline, the mean of two epochs was computed. In line with earlier work (Keogh et al. 2023), the average of two epochs, one from each of the stress tasks, was used to derive stress reactivity values.

3.5 | Data Analyses

Mean levels for baseline and task periods were calculated for cardiovascular parameters (i.e., SBP, DBP, HR) and cardiovascular reactivity was computed as the difference in change scores between baseline and task periods (Task—Baseline). Data were screened for normality and assumption of fit. One-way ANOVAs and Chi-square (χ^2) analyses were used to assess between group differences in participant characteristics for continuous and categorical variables respectively. A series of repeated-measures ANOVAs (baseline, task) were conducted to determine if the tasks were successful in eliciting psychological and physiological responses. One-way ANOVAs were performed to examine group differences in PA and NA. To examine associations between substance use and cardiovascular responses (SBP, DBP, HR) to stress, a series of 4 × 2 mixed factorial analyses of variance (ANOVAs) were performed, with substance use (tobacco-only, alcohol-only, co-use, non-use) as the between-subjects factor and time (baseline, task) as the within-subjects factor. Significant effects were followed up with mixed-factor analyses of covariance (ANCOVAs) controlling for confounds, age and sex. Post hoc Bonferroni corrections were applied for multiple comparisons and significant effects were followed with one-way ANOVAs. Greenhouse–Geisser corrections (ε) are reported where assumption of sphericity was violated. Due to missing data variations exist in sample size and degrees of freedom. Statistical analyses were performed using IBM SPSS version 28.0.1.1.

4 | Results

4.1 | Key Demographics

Thirty-five participants (10 Male, 25 female) were tobacco-only users, 187 (112 Male, 75 female) were alcohol-only users, 57 (37 Male, 20 female) were tobacco and alcohol co-users, and 289 (115 Male, 174 female) were non-users. With the groups unbalanced by sex and between-group differences observed, χ^2 (3) = 30.20, $p < 0.001$, sex was controlled for in all main analyses. No significant group differences were observed in current medication ($p = 0.090$). The average age of onset for alcohol consumption was 17.84 (SD = 4.01) and 15.49 (SD = 4.00) for tobacco smoking. Participants reported having experienced on average 8.52 (SD = 1.3; $_{\text{range}}$3–16) alcohol related problems in the previous 12 months and consumed on average 3.21 (SD = 2.74) drinks during the period where they drank the most. The average number of cigarettes smoked during the heaviest year of use was 28.47 (SD = 12.56). While co-users reported an earlier onset of smoking tobacco ($M = 15.30$; SD = 4.68) than tobacco-only users ($M = 16.69$; SD = 2.90), as well as smoking more cigarettes a day ($M = 29.32$; SD = 13.09) during their heaviest year of use compared to tobacco-only users ($M = 27.11$; SD = 13.60), this was non-significant ($ps > 0.05$). Alcohol co-users began drinking ($M = 16.46$; SD = 3.32) at a younger age compared to alcohol-only ($M = 17.10$; SD = 4.12; $p < 0.001$) users. They also reported experiencing more alcohol-related problems ($M = 9.56$; SD = 2.32) compared to alcohol-only users ($M = 8.78$; SD = 1.51; $F(3, 545) = 21.15$, $p < 0.001$, $\eta_p^2 = 0.104$) and consumed a greater number of drinks ($M = 5.98$; SD = 4.65; $F(3, 545) = 35.10$, $p < 0.001$, $\eta_p^2 = 0.162$). A summary of descriptive information is reported in Table 1.

4.2 | Manipulation Check

A series of repeated-measures ANOVAs confirmed the stress task increased cardiovascular responses for SBP, $F(1, 671) = 699.92$, $p < 0.001$, $\eta_p^2 = 0.511$, DBP, $F(1,671) = 1195.92$, $p < 0.001$, $\eta_p^2 = 0.641$, and HR, $F(1,739) = 780.52$, $p < 0.001$, $\eta_p^2 = 0.514$. In addition, there was an increase in self-reported stress, $F(1, 770) = 1588.35$, $p < 0.001$, $\eta_p^2 = 0.674$, indicating the stress task was both psychologically and physiologically stressful.

4.3 | Positive and Negative Affect

Results from one-way ANOVAs revealed significant between-group differences for PA, $F(3, 547) = 3.78$, $p = 0.010$, $\eta_p^2 = 0.020$, and NA, $F(3, 550) = 6.16$, $p < 0.001$, $\eta_p^2 = 0.033$. Co-users had higher levels of NA ($M = 1.77$; SD = 0.749) compared to non-users ($M = 1.43$; SD = 0.552, $p < 0.001$), and alcohol-only users ($M = 1.53$; SD = 0.582, $p = 0.040$). Additionally, co-users reported significantly lower levels of PA ($M = 3.20$; SD = 0.774), compared to non-users ($M = 3.48$; SD = 0.623, $p = 0.040$).

4.4 | Substance Use and Cardiovascular Reactivity

Mixed factorial ANOVAs were conducted to assess the prospective association between substance use and cardiovascular responses to stress 9–14 years later. As seen in Table 2, significant main effects of time were observed on all cardiovascular parameters confirming the stress task successfully perturbed cardiovascular activity. In addition, there was a significant main effect of substance use on SBP activity, $F(3,491) = 6.67$, $p < 0.001$, $\eta_p^2 = 0.039$. Post hoc simple effects

TABLE 1 | Participant characteristics.

	Tobacco-only user ($n = 35$; 6.2%)	Alcohol-only user ($n = 187$; 32.9%)	Co-user ($n = 57$; 10.0%)	Non-user ($n = 289$; 50.9%)
Sex (% Female)	71.4	40.1	35.1	60.2
Age (Mean/SD)	42.60 (8.72)	47.40 (11.81)	43.82 (10.50)	46.70 (11.99)
BMI (Mean/SD)	26.41 (5.26)	27.22 (5.02)	25.23 (4.82)	26.80 (5.17)
Race (% Caucasian)	85.7%	90.4%	82.5%	90.0%
Education (%)				
High School	45.7	25.0	31.7	25.2
College	51.5	67.4	68.5	70.8
Professional/Doctorate	2.9	7.5	—	3.8

TABLE 2 | Mean and standard deviations (SD) values for baseline and stress task responses in cardiovascular parameters.

	Baseline mean (SD)	Stress task mean (SD)
SBP (mmHg)	124.69 (18.67)	136.74 (22.04)[a]
DBP (mmHg)	61.58 (12.07)	67.48 (12.55)[a]
HR (bbp)	72.65 (10.76)	76.17 (11.14)[a]

[a]Statistically significant difference from respective baseline at $p < 0.001$.

follow-up showed that alcohol-only users demonstrated greater responses compared to co-users (*M*ean difference = 12.23; SE = 3.16, $p = 0.001$, 95% CI [4.08;20.39]) non-users (*M*ean difference = 5.08; SE = 1.92, $p = 0.041$, 95% CI [0.139;10.03]) and tobacco-only users (*M*ean difference = 10.37; SE = 3.69, $p = 0.027$, 95% CI [0.845;19.90]). As can be seen in Figure 1, alcohol-only users had significantly greater baseline and task SBP responses compared to the other groups. No significant time × substance use group interaction was observed across cardiovascular parameters or main effect of substance use on DBP and HR.

When controlling for covariates (age, sex), the main effects of substance use on SBP activity, $F(3, 489) = 5.33$, $p = 0.001$, $\eta_p^2 = 0.032$ remained statistically significant. Co-users demonstrated blunted SBP responses compared to non-users (*M*ean difference = −8.40; SE = 2.96, $p = 0.029$, 95% CI [−16.25; −0.544]) and alcohol-only users (*M*ean difference = −11.66; SE = 3.06, $p < 0.001$, 95% CI [−19.75;-3.56]). However, a follow-up one-way ANOVA revealed no significant difference in SBP reactivity as determined by change score values (i.e., Task—Baseline), suggesting findings reflect carryover effects.

In addition, a main effect of substance use on DBP activity, $F(3, 489) = 2.94$, $p = 0.033$, $\eta_p^2 = 0.018$ was also observed. A follow-up one-way ANOVA revealed significant group differences during the stress task ($F(3, 504) = 3.90$, $p = 0.009$, $\eta_p^2 = 0.023$), in that alcohol-only users had greater DBP responses to stress compared to co-users (Mean difference = 5.87; SE = 2.01, $p = 0.019$, 95% CI [0.688; 11.05]). However, similar to SBP reactivity, there were no significant differences for DBP reactivity, suggesting that these groups differed during task engagement, though the magnitude of change from baseline to task was not captured by change scores (please see Figure 2).

5 | Discussion

The current study sought to examine the extent to which substance use (i.e., tobacco-only users, alcohol-only users, co-users, and non-users) is linked with cardiovascular responses to acute psychological stress 9–14 years later. To the best of our knowledge this is the first study to investigate prospective associations between tobacco and alcohol co-use and blood pressure and heart rate reactivity.

As predicted, co-users had lower blood pressure (i.e., DBP) responses during stress over a decade later compared to alcohol-only users, that withstood adjustment for confounds (i.e., sex and age). These results extend previous research examining the impact of tobacco and cannabis co-use on the hypothalamic–pituitary–adrenal (HPA) axis system that found co-users demonstrated blunted cortisol stress responses during withdrawal (al'Absi et al. 2024). While the current study extends on research to report on the impact of tobacco and alcohol co-use on the cardiovascular system, future research may benefit from extending on our findings to examine differences between periods of use

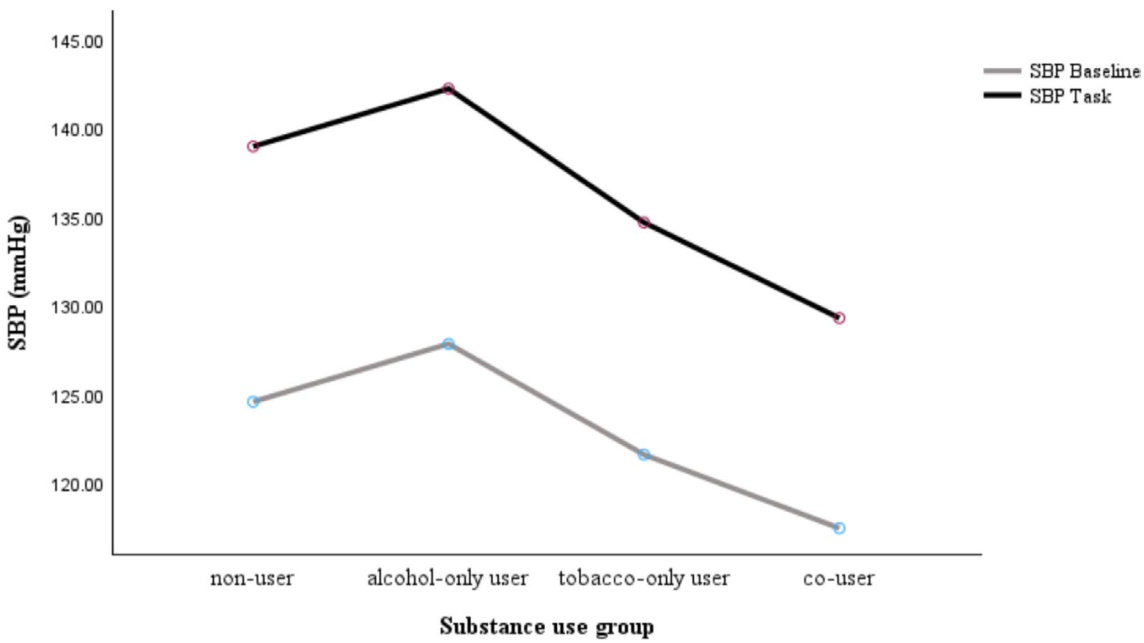

FIGURE 1 | Plot of systolic blood pressure activity at resting baseline and during stress measured in millimeters of mercury (mmHg), while controlling for covariates age and sex. Significant differences observed between co-users and alcohol-only users ($p < 0.001$) and non-users ($p = 0.029$) for baseline and stress task responses.

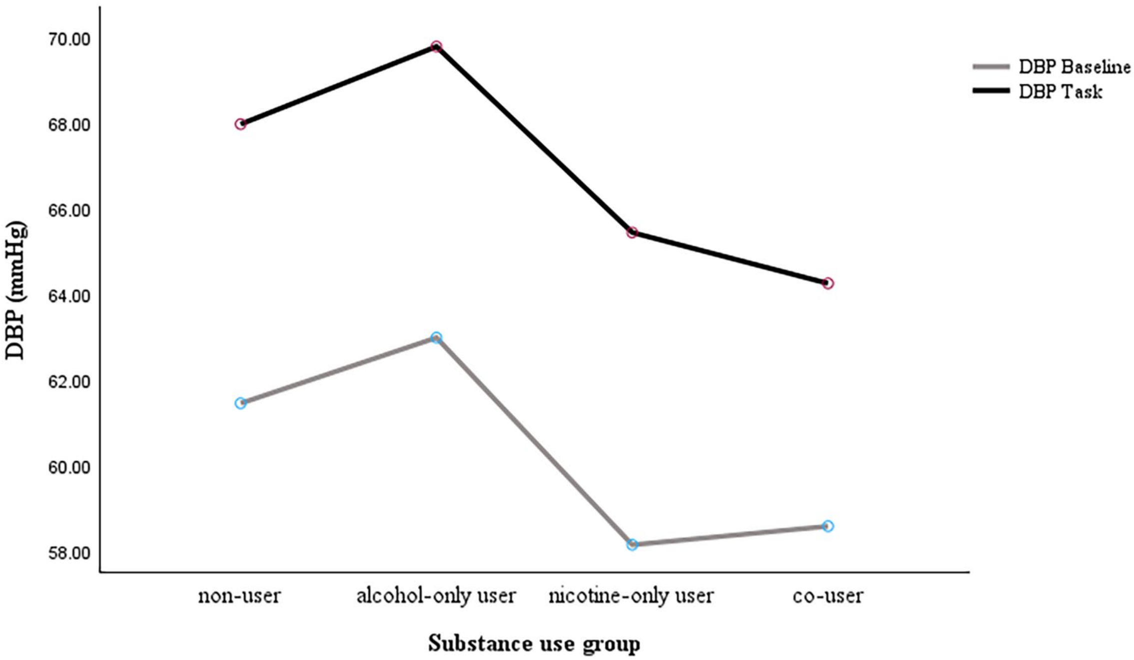

FIGURE 2 | Plot of diastolic blood pressure (DBP) activity at resting baseline and during stress measured as millimeters of mercury (mmHg) controlling for covariates age and sex. Significant differences observed between alcohol-only users and co-users responses during stress ($p = 0.019$).

and withdrawal as well as their implication on cessation and recovery.

We found that co-users initiated using alcohol at a younger age, consumed more alcohol and experienced more alcohol related problems compared to alcohol-only users. Consistent with previous research that found co-users (i.e., tobacco-khat) had blunted stress responses and increased NA (al'Absi et al. 2014), and earlier age of onset, greater intake and more severe dependence, as well as changes in affect (Keogh et al. 2025), in the present study co-users reported lower levels of PA, higher levels of NA and exhibited blunted DBP responses during stress compared to alcohol-only users. Thus, it appears that the depressogenic effects of alcohol (Brady 2006) are intensified in co-users. These effects may be related to dopaminergic neurons in the mesocorticolimbic system, which is central in addiction and implicated in the reinforcing effects of substance use (Tolu et al. 2017). Those with alterations in these neural circuits may not only be more susceptible to substance use but also exhibit attenuated responses to stressful challenges (Carroll et al. 2017).

In addition, alcohol only users had heightened blood pressure activity compared to the other groups which is consistent to reports linking alcohol to increased BP (Rosoff et al. 2020). Though some observed group differences (i.e., SBP) were a result of carryover effects, significant group differences (i.e., DBP) emerged during stress, not linked to differences in tonic baseline. Responses that deviate from the norm (i.e., exaggerated/blunted) are related to negative health and behavioral outcomes and may be indirect pathways linking substance use to CVDs. Research has shown that when drinking alcohol participants had a greater urge for hookah smoking, longer periods of use and increased inhalation depth (Leavens et al. 2020), which may enhance the risk of disease outcomes in co-users.

Tobacco use is associated with increased risk of alcohol use, and poorer drinking behaviors including higher alcohol consumption, binge drinking, greater alcohol dependence, withdrawal symptoms, and elevated rates of alcohol use disorders (McKee and Weinberger 2013). Moreover, tobacco and alcohol co-users are at greater risk of mortality than those who use either substance separately (Rosengren et al. 1988) as well as psychiatric co-morbidity (Le Strat et al. 2010). Considering the literature and our findings which signify that co-users have less favorable outcomes, with poorer mood and blunted blood pressure responses, as well as a host of negative health behaviors (e.g., greater consumption/use, earlier use), highlights the importance of tailoring interventions that integrate tobacco and alcohol cessation strategies. Given co-users have greater dependence and are more prone to relapse (Weinberger et al. 2015, 2023), adapting treatment programs that account for the additive impact of co-use may help reduce the negative effects related to both alcohol and tobacco and improve long term treatment outcomes. While testing associations between groups at baseline and at follow up resulted in some participants belonging to different groups, this may be promising from a health perspective, given ten smokers appeared to have quit smoking by the stress testing session approximately 11 years later. That said, without more comprehensive assessment of use (i.e., type of administration, dose), and continuity of measures across studies to test these differences further (i.e., alcohol) this is speculative.

The current study is not without limitations. First, with the use of self-report measures, clinical status on substance use disorders cannot be made. In addition, important details such inhalation depth, types of cigarettes smoked (i.e., dose) and types of alcohol consumed (i.e., alcohol percentage) were not measured. Future research should aim to include a more comprehensive assessment of substance use, such as the method of administration for nicotine (e.g., e-cigarettes, pipes). Given links between substance use and altered motivation, and the task-related differences in blood pressure responses observed in the current study, including measures of motivation or task engagement would have been beneficial. Second, given the prevalence and overlap with tobacco smoking and other substances (e.g., cannabis), and that alcohol and cannabis co-use is related to greater alcohol consumption (Ben Salah et al. 2022), it is recommended that future studies account for a broader range of polysubstance use. However, this is the first study to examine the additive impact of tobacco and alcohol co-use on cardiovascular responses to stress. Third, the sample was predominantly Caucasian. Considering documented racial disparities in both smokers (Trinidad et al. 2011) and alcohol use (Vaeth et al. 2017) future research should aim to recruit more diverse samples. Additional differences in participant characteristics that may have influenced the study findings include group differences in baseline values (e.g., carryover effects were observed in group differences on SBP), as well as substance use behaviors among co-users (e.g., greater alcohol-related problems), which given the links between co-use and an increased risk of psychiatric comorbidities, may help explain the observed changes in affect (Kar et al. 2023). Fourth, our sample consisted of middle aged adults and given that research shows nicotine use during adolescence plays a significant role in subsequent use of other substances, including alcohol (Cross et al. 2017), and that young adult smokers are more likely to meet criteria for AUD (Jackson et al. 2002), recruitment across a broader age spectrum is desirable. Fifth, it is worth noting that the substance use groups were characterized by sex imbalances, with more males in the alcohol-only and co-use groups, and females in the tobacco-only and non-use groups. Accordingly, sex was controlled for in all main analyses. That said, future studies would benefit from recruiting larger substance use samples and stratifying groups by sex or improving upon the study design (e.g., matched-subjects design) to account for such differences. Lastly, one important point for consideration is the potential influence that changes to these groupings over time could have on study findings. Grouping participants into substance use groups and then testing these associations 14 years later poses a limitation given some participants may belong to different groups at follow-up, as reported above for some smokers who belonged to a different group during the biomarker session. Some notable strengths include the sample size and the longitudinal design to establish associations between tobacco-alcohol co-use and cardiovascular responses.

In conclusion, this is the first study to the best of our knowledge that examines independent and additive effects of tobacco-only use, alcohol-only use, co-use and non-use on cardiovascular responses to stress over a decade later. While reactivity scores did not significantly differ between groups, differences were observed during task engagement. The findings extend on current research reporting separate effects of alcohol and tobacco on cardiac activity, by accounting for the compounded impact of co-use on the cardiovascular system. Co-use was negatively associated with cardiovascular responses at baseline and during stress and withstood adjustment for confounds. Co-users demonstrated blunted blood pressure responses (i.e., DBP) and a host of poor health behaviors (i.e., earlier age of onset, more alcohol-related issues and changes in affect). Given the compounded impact of tobacco-alcohol co-use, future research and intervention programs designed to address dependency to either tobacco or alcohol should account for polysubstance use and adapt intervention strategies accordingly.

Author Contributions

Tracey M. Keogh: conceptualization, writing – original draft, formal analysis, writing – review and editing. **Mustafa al'Absi:** conceptualization, funding acquisition, writing – review and editing, writing – original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Publicly available data from the MIDUS study was used for this research. The data supporting the study findings are openly accessible via the MIDUS Portal (https://midus.colectica.org/).

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