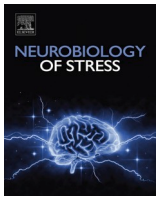
Neurobiology of Stress 29 (2024) 100602

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr



Subjective stress and any drinking during alcohol treatment: Disentangling within and between person autoregressive effects

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ARTICLE INFO

Handling Editor: Rita Valentino

Keywords:
Perceived stress
Alcohol use disorder
Random intercept cross-lagged panel models
Bayesian analyses
Sex differences

ABSTRACT

Alcohol use has been shown to increase stress, and there is some evidence that stress predicts subsequent alcohol use during treatment for alcohol use disorder (AUD), particularly among females who are more likely to report coping-motivated drinking. Gaining a better understanding of the processes by which stress and alcohol use are linked during treatment could potentially inform AUD treatment planning. The current study aimed to characterize the association between stress and drinking during the course of AUD treatment and whether there were sex differences in these associations. Secondary data analyses of the COMBINE study (N = 1375; 69% male, 76.3% non-Hispanic and white, average age of 44.4 years) were conducted to examine self-reported perceived stress and alcohol consumption across 16 weeks of treatment for AUD using a Bayesian random-intercept cross-lagged panel model. There was stronger evidence for any alcohol use predicting greater than typical stress in subsequent weeks and less strong evidence for stress increasing the subsequent probability of alcohol use, particularly among males. For females, greater stress predicted subsequent drinking earlier in the treatment period, and a lower probability of subsequent drinking in the last week of treatment. Interventions might specifically focus on targeting reductions in stress following drinking occasions.

1. Introduction

Alcohol use disorder (AUD) causes significant morbidity and mortality, and leads to immense human suffering (World Health Organization, 2018). Although many effective treatments are available for AUD, many individuals who receive treatment for AUD will return to some level of drinking during the course of treatment (Witkiewitz et al., 2019). Considerable research on AUD treatment has attempted to identify those factors that may predict a return to drinking, which could be used to inform additional treatment needs, as well as to ultimately prevent a return to drinking (Brownell et al., 1986; Sliedrecht et al., 2019; Witkiewitz and Marlatt, 2004). Among the many risk factors for returning to drinking that have been examined over the past several decades, stress is among one of the most widely studied in both non-human animal (Becker, 2017) and human studies of AUD (Blaine and Sinha, 2017). Stress can be defined as physical, psychological, or social harmful experiences or circumstances that activate physiological and neurobiological stress systems, and are perceived as causing physical or psychological strain.

1.1. Epidemiology of AUD and stress

AUD is one of the most prevalent of all psychiatric disorders, with a lifetime incidence globally estimated to be 8.6% (range of 3.8%–97.1%; Glantz et al., 2020). Beyond meeting the criteria for an AUD, it has been estimated that alcohol has a global burden of disease of 5.1% and at least 3 million people die annually of alcohol-attributable causes (World Health Organization, 2018). From 2019 to 2020, the United States saw a 26% increase in alcohol-induced deaths (from 10.4 per 100,000 standard population in 2019 to 13.1 in 2020; Spencer et al., 2022). A systematic review and meta-analysis estimated the global prevalence of stress as 29.6% (95% confidence interval of 24.3%–35.4%; (Salari et al., 2020). Further, the prevalence of stress has also increased globally, with the World Health Organization estimating a 25% increase in depression and anxiety during the COVID-19 pandemic.

1.2. Bidirectional associations between alcohol use and stress

There are several models that have been developed and tested to

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https://doi.org/10.1016/j.ynstr.2023.100602
Received 27 October 2023; Received in revised form 26 November 2023; Accepted 15 December 2023
Available online 16 December 2023

explain the robust association between alcohol use and stress. In popular culture throughout millennia, it has been assumed that alcohol consumption reduces stress (Sayette, 1999; Sher et al., 2007). Early work by Conger (1956) was the first to propose, based on learning and drive-reduction theories, that alcohol use may reduce stress. The motivational model of alcohol use (Cooper and Russell, 1995; Cox and Klinger, 1988), the stress-response dampening model (Sher et al., 2007), self-medication models (Brower et al., 2001; Khantzian, 1997; Weiss et al., 1992), the three psychobiological pathways of craving model (Verheul et al., 1999), and the three-stage model of addiction, called the addiction cycle (Koob and Volkow, 2016), all propose that alcohol is commonly consumed to relieve negative affective states and stress. Empirical human studies over the past six decades have provided compelling evidence that alcohol and stress are associated (Becker, 2017; Blaine and Sinha, 2017; Keyes et al., 2012) and that exposure to stress predicts subsequent craving for alcohol (Bach et al., 2023; Blaine et al., 2019; Fox et al., 2007; Higley et al., 2011; Wemm et al., 2022; Wemm and Sinha, 2019). Importantly, research has been mixed on whether increases in stress directly predict increases in alcohol consumption in studies of humans (Anthenelli and Grandison, 2012; Dora et al., 2023; Votaw and Witkiewitz, 2021) and non-human animals (Becker, 2017; Noori et al., 2014).

There is far more compelling evidence from experimental studies in humans and non-human animals that alcohol consumption increases subsequent stress via adaptations of the hypothalamic-pituitary-adrenal (HPA) axis and dysregulation of the brain reward and stress systems (Becker, 2017; Blaine and Sinha, 2017). Persistent alcohol use and greater alcohol exposure leads to several neuroadaptations, including changes in reward processing, extra-hypothalamic stress systems, and the autonomic nervous system. These changes may ultimately result in compromised nervous system functioning that creates a state of persistent alcohol seeking, heightened reactivity to alcohol- and stress cues, and attenuated ability to respond to subsequent stressors (Bach et al., 2023; Becker, 2017; Blaine et al., 2019; Higley et al., 2011; Koob and Le Moal, 2008; Koob and Volkow, 2016; Sinha, 2008; Spanagel et al., 2014).

Importantly, sex differences in stress reactivity, alcohol use, alcohol-related harm, and stress-alcohol associations have been identified in both human and non-human animal studies (Mineur et al., 2022; Peltier et al., 2019). In general, females tend to exhibit heightened stress reactivity compared to males. This heightened stress reactivity has been attributed to hormonal factors, including fluctuations in estrogen and progesterone, which can modulate the activity of the HPA axis (Bale and Epperson, 2015; Flores-Bonilla, 2020; Mineur et al., 2022; Taylor et al., 2000). Socialization processes and societal expectations may also contribute to these sex differences, with women being more likely to seek emotional support and express stress (Taylor et al., 2000).

Moreover, males consume larger quantities of alcohol, are more likely to engage in heavy drinking, and have a higher prevalence of AUD, while females are more prone to experience certain alcohol-related health problems, such as liver damage and cardiovascular issues (Erol and Karpyak, 2015; Flores-Bonilla, 2020; Radke et al., 2021). Psychologically, these differences can be attributed to variations in motivations for alcohol use, social norms/societal expectations, and the effects of alcohol on cognitive and emotional functioning (Nixon et al., 2023; Nolen-Hoeksema, 2004; Taylor et al., 2000). Further, females often report using alcohol as a means of coping with stress, which can lead to different patterns of alcohol use and related consequences (Flores-Bonilla, 2020; Peltier et al., 2019).

Prior work examining alcohol and stress related processes have often been conducted in laboratory settings and studies in treatment seeking populations have largely failed to consider potential bidirectional processes, whereby stress may lead to greater drinking, but that greater drinking may also exacerbate stress. Gaining a better understanding of the processes by which stress, and alcohol use are linked during treatment could potentially inform treatment planning and lead to the development of novel interventions to intervene in the addiction cycle processes and support recovery from AUD.

1.3. Current study

Aims of the current exploratory secondary data analysis study were two-fold. First, we aimed to characterize the association between subjective stress and any drinking during the course of AUD treatment, and how that association changed over the course of treatment. Second, we aimed to examine the bidirectional and autoregressive effects of subjective stress on any drinking over time. To test this aim we used a random intercept cross-lagged panel model, which explicitly disaggregates between person (inter-individual, stable differences) and within person (intra-individual, time varying and dynamic) effects. Based on the several prior studies of alcohol and stress associations, we hypothesized a strong between persons association between stress and any drinking over time. Given findings from non-human animal investigations of stress and drinking, we hypothesized that any drinking during treatment would be strongly associated with subsequent subjective stress across time at the within person level; but that stress would be less strongly associated with subsequent drinking at the within person level. We also hypothesized, a priori, sex differences in the within person associations between stress and alcohol use. Specifically, we hypothesized that stress would be more strongly associated with subsequent drinking among females, but not among males.

2. Methods

2.1. Participants and procedures

The current study is a secondary analysis of data collected from participants (N = 1383) in the COMBINE study (Anton et al., 2006) who were recruited from 11 research sites between 2001 and 2004. All participants met Diagnostic and Statistical Manual, fourth edition (DSM-IV) (American Psychiatric Association, 1994) criteria for alcohol dependence and all participants consumed more than 14 drinks (females) or 21 drinks (males) per week and reported at least 2 heavy drinking (4+ drinks for females and 5+ drinks for males) occasions during a 30-day period within a three-month window prior to enrolling in the trial. Main exclusion criteria included the presence of another substance use disorder (other than nicotine or cannabis), a psychiatric disorder requiring medication, or unstable medical conditions, including serum liver enzyme levels that were more than 3 times the upper limit of normal.

Participants (n = 1383) were randomized using a 2 × 2 x 2 design in which they received: (1) active naltrexone (100 mg/day) or placebo naltrexone, (2) active acamprosate (3000 mg/day) or placebo acamprosate, (3) medication management with a combined behavioral intervention (CBI) or medication management (MM) alone, and an additional group received the CBI intervention without MM or pills. Participants completed assessments 8 timepoints during treatment (weeks 1, 2, 4, 6, 8, 10, 12, 16) and follow-up assessments at the end of treatment (week 16) and at 3 post-treatment follow-ups: 10 weeks (week 26 after baseline), 36 weeks (week 52 after baseline), and 1 year following treatment (week 68 after baseline). Results from the primary trial indicated that naltrexone without CBI, naltrexone with CBI, or CBI with MM were most effective at reducing any drinking (Anton et al., 2006). Given differences by treatment condition in the parent trial, treatment condition was included as a covariate in the current study.

Participants in COMBINE were mostly male (69%), non-Hispanic and white (76.3%), with at least 12 years of education (71%) and an average age of 44.4 years (SD = 10.2). The sample was also 11.6% Hispanic, 7.8% African American, and 4.1% “other”. At baseline, participants in COMBINE were drinking on 78.6% of days (SD = 22.5%), with most days heavy drinking days (Mean = 67.8%; SD = 28.0%), and an average of 10.95 drinks per drinking day (SD = 6.82).

2.2. Measures

The variables of interest for the current secondary data analysis were subjective stress, as measured by the Perceived Stress Scale (Cohen et al., 1983), and any drinking assessed via the Form 90 (Miller, 1996) across the 16 weeks of treatment. The Perceived Stress Scale includes four items measured on a Likert-type scale from 0 ("Never") to 4 ("Very Often") with each item assessing one's ability to tolerate situations over the past week (e.g., "How often have you felt that you were unable to control the important things in your life?"; "How often have you felt difficulties piling up so high that you could not overcome them?"). Total scores were calculated by reverse scoring the two items that were written with higher scores indicating less stress, and then summing the four items (score range of 0–16).

The Form 90 is a calendar-based, self-report method to measure daily alcohol use over the past 90 days and continuous alcohol use data were collection from 90 days prior to baseline to one year following treatment. For both the stress and drinking measures we focused on the weeks during treatment with available measurements of stress (week 1, week 2, week 4, week 6, week 8, week 10, week 12, week 16). As shown in Table 1, Perceived Stress Scale scores decreased throughout treatment from a mean of 4.94 (SD = 2.94) at week 1 to a mean of 4.15 (SD = 3.13) at week 16. Internal consistency reliability of the 4-item Perceived Stress Scale was acceptable at all timepoints (lowest Ω = 0.73 at week 10 to highest Ω = 0.81 at week 2). The percent of individuals who engaged in any drinking increased across the weeks of treatment from 45.1% engaging in any drinking at week 1 and 50.7% engaging in any drinking at week 16.

2.3. Statistical analysis

First, we examined average association between subjective stress and any drinking during the course of AUD treatment, and how that association changed over the course of treatment using Pearson correlations of Perceived Stress Scale scores across time, tetrachoric correlations of any drinking across time, and the joint correlation between Perceived Stress Scale scores and any drinking at each time point over time. Second, we estimated a series of random intercept cross-lagged panel models (RI-CLPM) of stress scores and any drinking over time using a variety of different autoregressive and longitudinal growth structures via Bayesian estimation with a probit link function within Mplus version 8.10 (L. K. Muthén and Muthén, 2019). These models use a novel technique to handle the binary outcome, with methodological details described in recent papers (Asparouhov and Muthén, 2010; B. O. Muthén et al., 2023; B. O. Muthén and Asparouhov, 2023).

Models were estimated for each process separately and then combined into a single RI-CLPM, shown in Fig. 1. Given Bayesian estimation all effects are interpreted using 95% credible intervals: there is a 95% probability that the true population parameter value lies within the credible interval, given the observed data. When this interval does not contain 0, then there is a 95% probability that the true population parameter value does not equal 0, given the observed data. For example, if the estimated 95% credible interval for a correlation does not contain 0, then we could say with 95% probability that the correlation is non-zero, but if the 95% credible interval for a correlation does contain 0, then we would say there is a 95% probability that a zero correlation would lie within the interval.

Model fit was evaluated using the Bayesian positive predictive p-value, with values closer to 0.5 indicating excellent fit. Participant sex, treatment, and clinical research site included as covariates predicting the random intercepts. Sex was included as a covariate given sex differences in alcohol use and stress from prior studies (Mineur et al., 2022; Peltier et al., 2019). Treatment and clinical research site were included given the results from the primary trial indicating naltrexone or CBI were most effective at reducing any drinking and there were also main effects on drinking by research site (Anton et al., 2006). We also estimated a multiple group model with sex as a grouping factor to ascertain whether model parameters differed by biologically-assigned sex. Missing data were accommodated using Bayesian estimation under the assumption that data were missing at random and all individuals with any available data contributed to the analysis. Those individuals who were missing data on both the stress and the drinking outcome in all weeks were excluded from the analyses (n = 8; <1% of the sample).

Table 1
Perceived stress scale scores and any alcohol use over time during treatment.

Week	Any Alcohol Use	Perceived Stress Scale Scores (range 0–16)	Perceived Stress Scale Scores
	N (%)	Mean (SD)	Ω
1	619 (45.1%)	4.94 (2.94)	0.77
2	675 (49.5%)	4.68 (3.10)	0.81
4	672 (50.0%)	4.70 (3.15)	0.79
6	665 (50.3%)	4.45 (3.13)	0.76
8	651 (49.7%)	4.20 (3.18)	0.75
10	647 (49.9%)	4.18 (3.09)	0.73
12	644 (50.1%)	4.09 (3.16)	0.77
16	647 (50.7%)	4.15 (3.13)	0.77

3. Results

The associations between stress and any drinking over time were examined within each process and between processes over time. Table 2 provides the correlation matrix for the stress scores over time (below the diagonal) and any drinking over time (above the diagonal), and the bivariate association between stress and any drinking at each time point is provided on the diagonal. The correlations between stress and alcohol use were approximately .20 in each week, without much discernible change over time at the between person level.

Across both sets of processes, the random intercept model with a 2-lag autoregressive process provided a better fit to the data for both stress and alcohol use (Stress: AR1: posterior predictive p-value = .000; AR2: posterior predictive p-value = .116; Alcohol: AR1: posterior predictive p-value = .337; AR2: posterior predictive p-value = .414). The two 2-lag autoregressive models were then combined into a single cross-lag model with sex and treatment added as covariates. This model provided a reasonably good fit to the data (posterior predictive p-value = .319). Parameter estimates from the final model are shown in Table 3. The 95% credible interval (CI) for the variances of the random intercepts for both processes did not include 0, indicating large between person variability in stress and any drinking. Between person relations are captured by a positive correlation between the random intercepts (r = 0.23; 95% CI:0.14, 0.32), indicating an association between stress and any drinking at the between person level, which is consistent with the modest correlations between stress and drinking reported in Table 2.

The 95% CIs for the within person associations between stress and any drinking at each time point also did not include 0 (residual correlations ranged from $r = 0.17$ in week 1 to as high as $r = 0.32$ in week 12), indicating strong associations between stress and any drinking at the within person level. Effects were in the positive direction, indicating that

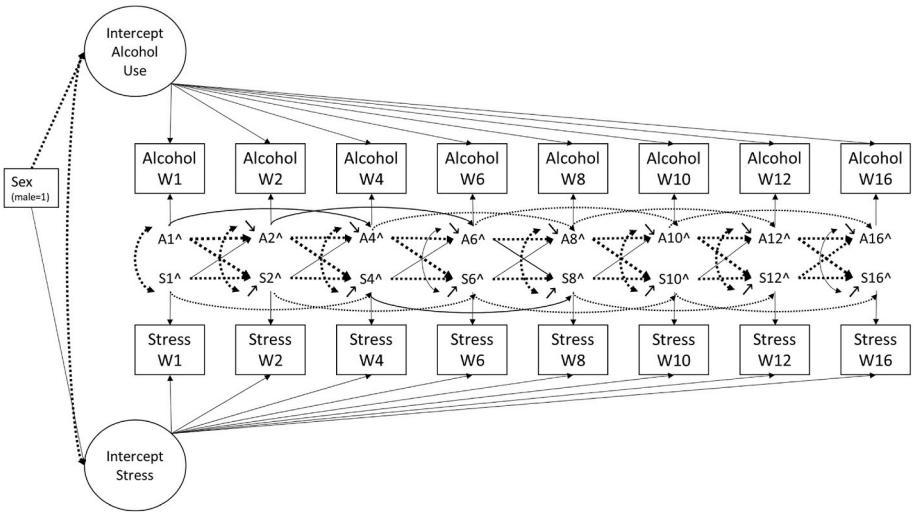

Fig. 1. Random Intercept Cross-Lag Panel Model with Autoregressive-2 Process
Note. Dashed bolded lines indicate parameter estimates that did not contain 0 in the 95% credible interval, suggesting strong associations between variables for those paths.

Table 2
Correlations between perceived stress scale scores and any alcohol use over time during treatment.

	Alcohol w1/ Stress w1	Alcohol w2/ Stress w2	Alcohol w4/ Stress w4	Alcohol w6/ Stress w6	Alcohol w8/ Stress w8	Alcohol w10/ Stress w10	Alcohol w12/ Stress w12	Alcohol w16/ Stress w16
Stress w1/ Alcohol w1	0.204	0.900	0.840	0.753	0.699	0.657	0.626	0.567
Stress w2/ Alcohol w2	0.735	0.258	0.876	0.781	0.714	0.675	0.647	0.570
Stress w4/ Alcohol w4	0.681	0.722	0.257	0.846	0.793	0.741	0.714	0.629
Stress w6/ Alcohol w6	0.618	0.653	0.687	0.238	0.813	0.810	0.761	0.676
Stress w8/ Alcohol w8	0.588	0.588	0.621	0.653	0.208	0.838	0.843	0.735
Stress w10/ Alcohol w10	0.574	0.571	0.589	0.625	0.662	0.243	0.882	0.794
Stress w12/ Alcohol w12	0.567	0.561	0.579	0.593	0.650	0.710	0.278	0.837
Stress w16/ Alcohol w16	0.577	0.569	0.583	0.587	0.604	0.643	0.669	0.258

Note. Perceived Stress Scale score correlations below the diagonal, any drinking tetrachoric correlations above the diagonal, and the correlation between Perceived Stress Scale scores and any drinking within each week on the diagonal.

individuals who positively deviated from their predicted level of stress at a given wave were more likely to drink during the same wave. Sex predicted the random intercept of any alcohol use ($r = -0.13$; 95% CI: −0.19, −0.06), such that males (coded 1) had a lower probability of any drinking over time. Sex was not related to the random intercept of stress ($r = -0.02$, 95% CI: −0.08, 0.04). Treatment condition was associated with any alcohol use, such that naltrexone with MM, naltrexone + acamprosate with MM, and CBI with placebo each predicted the random intercept of alcohol use (naltrexone + MM: $r = -0.11$; 95% CI: −0.20, −0.02; naltrexone + acamprosate + MM: $r = -0.12$; 95% CI: −0.20, −0.03; CBI + placebo: $r = -0.09$; 95% CI: −0.18, −0.002), such that these treatments were associated with lower probability of any drinking over time, on average. Receiving CBI only (without pills) was associated with the random intercept of stress ($r = 0.08$; 95% CI: 0.002, 0.16), such that individuals who received the behavioral treatment without medications in the context of a medication trial had higher average levels of

Table 3
Parameter estimates from the random intercept cross-lag panel model with order 2 autoregressive process.

	Estimate (Posterior SD)	95% Credible Interval	Standardized Estimate
Covariate Effects			
Covariates predicting Stress			
Sex (male = 1)	−0.10 (0.15)	−0.41, 0.20	−0.02
Naltrexone + MM	−0.03 (0.30)	−0.62, 0.54	0.003
Naltrexone + CBI	0.10 (0.29)	−0.48, 0.67	0.01
Acamprosate + MM	0.49 (0.30)	−0.11, 1.06	0.07
Acamprosate + CBI	0.34 (0.30)	−0.24, 0.91	0.05
Naltrexone + Acamprosate + MM	−0.04 (0.30)	−0.64, 0.54	−0.01
Naltrexone + Acamprosate + CBI	−0.11 (0.30)	−0.69, 0.48	−0.02
CBI + Placebo	0.48 (0.29)	−0.08, 1.05	0.06
CBI-only	0.58 (0.30)	0.02, 1.17*	0.08
Covariates predicting Any Alcohol Use			
Sex (male = 1)	−0.41 (0.11)	−0.63, −0.19*	−0.13
Naltrexone + MM	−0.51 (0.21)	−0.94, −0.11*	−0.11
Naltrexone + CBI	−0.21 (0.2)	−0.62, 0.21	−0.05
Acamprosate + MM	−0.30 (0.21)	−0.72, 0.11	−0.06
Acamprosate + CBI	−0.33 (0.21)	−0.75, 0.09	−0.07
Naltrexone + Acamprosate + MM	−0.55 (0.21)	−0.98, −0.15*	−0.12
Naltrexone + Acamprosate + CBI	−0.40 (0.21)	−0.82, 0.02	−0.09
CBI + Placebo	−0.42 (0.21)	−0.85, −0.01*	−0.09
CBI-only	0.14 (0.21)	−0.28, 0.55	0.03
Random Intercept (RI) Variance			
Stress	5.26 (0.27)	4.75, 5.81*	0.95
Any Alcohol Use	1.90 (0.33)	1.26, 2.58*	0.86
Residual Variance: Between			
Stress w1	3.89 (0.24)	3.45, 4.39*	1.00
Stress w2	3.57 (0.19)	3.20, 3.93*	0.81
Stress w4	3.55 (0.18)	3.20, 3.91*	0.82
Stress w6	3.78 (0.21)	3.38, 4.23*	0.88
Stress w8	3.96 (0.24)	3.51, 4.43*	0.93
Stress w10	4.09 (0.24)	3.64, 4.59*	0.90
Stress w12	3.85 (0.21)	3.47, 4.28*	0.80
Stress w16	3.73 (0.20)	3.34, 4.13*	0.86
Concurrent Association: Between			
Stress with Alcohol Use	0.73 (0.18)	0.39, 1.07*	0.23
Concurrent Associations: Within			
Stress w1 with Alcohol Use w1	0.34 (0.14)	0.06, 0.61*	0.17
Stress w2 with Alcohol Use w2	0.28 (0.11)	0.05, 0.50*	0.29
Stress w4 with Alcohol Use w4	0.39 (0.11)	0.05, 0.60*	0.29
Stress w6 with Alcohol Use w6	0.21 (0.12)	−0.01, 0.44	0.24
Stress w8 with Alcohol Use w8	0.27 (0.11)	0.05, 0.49*	0.22
Stress w10 with Alcohol Use w10	0.31 (0.13)	0.06, 0.55*	0.25
Stress w12 with Alcohol Use w12	0.34 (0.12)	0.09, 0.58*	0.32
Stress w16 with Alcohol Use w16	0.22 (0.11)	−0.001, 0.44	0.28
Autoregressive Paths: Within			
Stress w2 on Stress w1	0.38 (0.04)	0.29, 0.46*	0.36
Stress w4 on Stress w1	0.13 (0.04)	0.05, 0.21*	0.12
Stress w4 on Stress w2	0.28 (0.04)	0.20, 0.36*	0.28
Stress w6 on Stress w2	0.12 (0.04)	0.04, 0.19*	0.12
Stress w6 on Stress w4	0.20 (0.05)	0.11, 0.29*	0.20
Stress w8 on Stress w4	0.06 (0.04)	−0.03, 0.15	0.06
Stress w8 on Stress w6	0.16 (0.05)	0.08, 0.25*	0.16
Stress w10 on Stress w6	0.10 (0.05)	0.01, 0.19*	0.10
Stress w10 on Stress w8	0.20 (0.05)	0.11, 0.29*	0.19
Stress w12 on Stress w8	0.13 (0.04)	0.04, 0.21*	0.12
Stress w12 on Stress w10	0.30 (0.04)	0.22, 0.38*	0.30
Stress w16 on Stress w10	0.10 (0.04)	0.01, 0.18*	0.10
Stress w16 on Stress w12	0.16 (0.04)	0.08, 0.24*	0.17
Alcohol Use w2 on Alcohol Use w1	0.93 (0.14)	0.67, 1.23*	0.68
Alcohol Use w4 on Alcohol Use w1	0.25 (0.14)	−0.01, 0.54	0.18
Alcohol Use w4 on Alcohol Use w2	0.62 (0.09)	0.43, 0.81*	0.59
Alcohol Use w6 on Alcohol Use w2	0.02 (0.09)	−0.16, 0.19	0.02
Alcohol Use w6 on Alcohol Use w4	0.61 (0.09)	0.43, 0.78*	0.64
Alcohol Use w8 on Alcohol Use w4	0.24 (0.08)	0.07, 0.39*	0.26
Alcohol Use w8 on Alcohol Use w6	0.41 (0.09)	0.25, 0.58*	0.43
Alcohol Use w10 on Alcohol Use w6	0.34 (0.08)	0.20, 0.50*	0.32
Alcohol Use w10 on Alcohol Use w8	0.52 (0.09)	0.36, 0.69*	0.46
Alcohol Use w12 on Alcohol Use w8	0.41 (0.09)	0.23, 0.58*	0.31
Alcohol Use w12 on Alcohol Use w10	0.67 (0.08)	0.51, 0.83*	0.57
Alcohol Use w16 on Alcohol Use w10	0.16 (0.11)	−0.05, 0.37	0.15
Alcohol Use w16 on Alcohol Use w12	0.64 (0.09)	0.46, 0.83*	0.69
Cross-Lag Paths: Within			
Alcohol Use w2 on Stress w1	0.03 (0.03)	−0.03, 0.11	0.05
Alcohol Use w4 on Stress w2	−0.04 (0.03)	−0.10, 0.02	−0.06
Alcohol Use w6 on Stress w4	0.03 (0.03)	−0.03, 0.10	0.05
Alcohol Use w8 on Stress w6	0.01 (0.03)	−0.05, 0.07	0.01
Alcohol Use w10 on Stress w8	0.05 (0.03)	−0.01, 0.11	0.07
Alcohol Use w12 on Stress w10	0.00 (0.04)	−0.07, 0.07	0.000
Alcohol Use w16 on Stress w12	−0.07 (0.04)	−0.14, −0.001*	−0.09
Stress w2 on Alcohol Use w1	0.41 (0.13)	0.16, 0.66*	0.19
Stress w4 on Alcohol Use w2	0.22 (0.09)	0.05, 0.40*	0.15
Stress w6 on Alcohol Use w4	0.21 (0.09)	0.04, 0.38*	0.14
Stress w8 on Alcohol Use w6	0.19 (0.10)	−0.002, 0.38	0.12
Stress w10 on Alcohol Use w8	0.23 (0.10)	0.03, 0.43*	0.14
Stress w12 on Alcohol Use w10	0.28 (0.08)	0.13, 0.45*	0.19
Stress w16 on Alcohol Use w12	0.27 (0.07)	0.13, 0.41*	0.22

Note. MM = Medication Management; CBI = Combined Behavioral Intervention.
* indicate 95% credible intervals that do not contain 0.

stress.

The autoregression and cross-lag effects are shown in Table 3 and path estimates that did not include 0 in the CIs are indicated by bolded dashed lines in Fig. 1. Results indicated within person effects of any drinking in predicting subsequent drinking. Similarly, stress each week predicted subsequent stress. Cross lag paths indicated within person increases in any drinking had a strong *positive* relation on subsequent within person increase in stress across weeks all weeks, except week 6–8,

suggesting individuals who engaged in any drinking had higher than typical stress in subsequent weeks. The reverse was not true, and cross-lag paths indicated within person increases in stress did not predict within person increases in drinking, except week 12–16. From week 12–16, within person increases in stress had a strong negative relation in predicting within person drinking, such that greater stress than is typical in week 12 predicted a decreased probability of any drinking in week 16.

The multiple group model to examine potential sex differences in model parameters yielded similar results. Within person effects for females and males, presented in Table 4, indicated any drinking predicted

Table 4
Parameter Estimates from the Multiple Group Random Intercept Cross-Lag Panel Model with Order 2 Autoregressive Process Estimated Separately in Males and Females

Note. Parameters that were set to equality across males and females for identification purposes are not reported Table 4 and did not substantively differ from those reported in Table 3, including the random intercept variances, residual variances, and concurrent associations. See Table 3 for estimates of these parameters.

	Males (n = 947)			Females (n = 428)		
	Estimate (Posterior SD)	95% Credible Interval	Standardized Estimate	Estimate (Posterior SD)	95% Credible Interval	Standardized Estimate
Autoregressive Paths						
Stress w2 on Stress w1	0.48 (0.05)	0.38, 0.57*	0.44	0.16 (0.07)	0.02, 0.30*	0.16
Stress w4 on Stress w1	0.16 (0.05)	0.06, 0.25*	0.15	0.07 (0.06)	−0.05, 0.19	0.07
Stress w4 on Stress w2	0.25 (0.05)	0.15, 0.34*	0.25	0.31 (0.07)	0.17, 0.43*	0.30
Stress w6 on Stress w2	0.13 (0.05)	0.04, 0.22*	0.14	0.07 (0.07)	−0.07, 0.20	0.07
Stress w6 on Stress w4	0.20 (0.05)	0.10, 0.30*	0.21	0.20 (0.08)	0.05, 0.34*	0.19
Stress w8 on Stress w4	0.04 (0.04)	−0.06, 0.14	0.04	0.09 (0.08)	−0.08, 0.25	0.09
Stress w8 on Stress w6	0.17 (0.05)	0.05, 0.27*	0.17	0.15 (0.07)	0.004, 0.29*	0.15
Stress w10 on Stress w6	0.08 (0.05)	−0.03, 0.19	0.08	0.14 (0.07)	−0.00, 0.28	0.13
Stress w10 on Stress w8	0.17 (0.06)	0.05, 0.28*	0.17	0.28 (0.08)	0.12, 0.42*	0.26
Stress w12 on Stress w8	0.14 (0.05)	0.05, 0.23*	0.13	0.10 (0.08)	−0.06, 0.25	0.10
Stress w12 on Stress w10	0.36 (0.05)	0.26, 0.46*	0.34	0.22 (0.07)	0.09, 0.35*	0.23
Stress w16 on Stress w10	0.09 (0.05)	−0.01, 0.19	0.09	0.11 (0.08)	−0.03, 0.24	0.12
Stress w16 on Stress w12	0.21 (0.05)	0.11, 0.31*	0.23	0.09 (0.07)	−0.05, 0.22	0.09
Alcohol Use w2 on Alcohol Use w1	0.90 (0.17)	0.61, 1.26*	0.66	0.71 (0.19)	0.39, 1.13*	0.58
Alcohol Use w4 on Alcohol Use w1	0.09 (0.16)	−0.23, 0.40	0.06	0.40 (0.22)	0.02, 0.87*	0.31
Alcohol Use w4 on Alcohol Use w2	0.66 (0.12)	0.44, 0.89*	0.65	0.42 (0.19)	0.06, 0.79*	0.40
Alcohol Use w6 on Alcohol Use w2	−0.03 (0.11)	−0.25, 0.17	−0.03	0.15 (0.19)	−0.20, 0.54	0.13
Alcohol Use w6 on Alcohol Use w4	0.54 (0.12)	0.31, 0.76*	0.60	0.66 (0.19)	0.31, 1.07*	0.58
Alcohol Use w8 on Alcohol Use w4	0.20 (0.09)	0.03, 0.34*	0.22	0.16 (0.21)	−0.29, 0.54	0.18
Alcohol Use w8 on Alcohol Use w6	0.43 (0.11)	0.23, 0.65*	0.43	0.31 (0.17)	−0.02, 0.64	0.37
Alcohol Use w10 on Alcohol Use w6	0.37 (0.12)	0.16, 0.61*	0.30	0.31 (0.10)	0.09, 0.53*	0.37
Alcohol Use w10 on Alcohol Use w8	0.65 (0.12)	0.43, 0.92*	0.54	0.30 (0.15)	−0.003, 0.58	0.28
Alcohol Use w12 on Alcohol Use w8	0.33 (0.13)	0.08, 0.56*	0.25	0.51 (0.17)	0.21, 0.89*	0.39
Alcohol Use w12 on Alcohol Use w10	0.67 (0.10)	0.49, 0.85*	0.61	0.64 (0.18)	0.34, 1.04*	0.52
Alcohol Use w16 on Alcohol Use w10	0.13 (0.13)	−0.14, 0.38	0.13	0.42 (0.27)	−0.06, 1.03	0.28
Alcohol Use w16 on Alcohol Use w12	0.56 (0.12)	0.33, 0.81*	0.63	0.81 (0.20)	0.49, 1.28*	0.67
Cross-Lag Paths						
Alcohol Use w2 on Stress w1	0.04 (0.04)	−0.04, 0.12	0.06	0.01 (0.05)	−0.09, 0.12	0.02
Alcohol Use w4 on Stress w2	−0.05 (0.04)	−0.13, 0.02	−0.08	−0.02 (0.07)	−0.15, 0.10	−0.04
Alcohol Use w6 on Stress w4	0.004 (0.04)	−0.08, 0.09	0.01	0.12 (0.07)	−0.01, 0.25	0.16
Alcohol Use w8 on Stress w6	−0.02 (0.04)	−0.10, 0.05	−0.04	0.04 (0.06)	−0.06, 0.16	0.07
Alcohol Use w10 on Stress w8	0.01 (0.04)	−0.07, 0.08	0.01	0.11 (0.05)	0.01, 0.22*	0.18
Alcohol Use w12 on Stress w10	−0.001 (0.04)	−0.09, 0.08	−0.001	0.004 (0.06)	−0.12, 0.12	0.006
Alcohol Use w16 on Stress w12	−0.003 (0.04)	−0.09, 0.08	−0.004	−0.20 (0.07)	−0.35, −0.06*	−0.21
Stress w2 on Alcohol Use w1	0.32 (0.14)	0.05, 0.58*	0.15	0.56 (0.24)	0.07, 1.003*	0.28
Stress w4 on Alcohol Use w2	0.25 (0.11)	0.03, 0.46*	0.16	0.12 (0.18)	−0.25, 0.46	0.08
Stress w6 on Alcohol Use w4	0.13 (0.11)	−0.12, 0.33	0.08	0.27 (0.19)	−0.09, 0.67	0.18
Stress w8 on Alcohol Use w6	0.21 (0.13)	−0.06, 0.33	0.13	0.12 (0.16)	−0.17, 0.46	0.09
Stress w10 on Alcohol Use w8	0.20 (0.13)	−0.05, 0.48	0.12	0.23 (0.21)	−0.23, 0.61	0.13
Stress w12 on Alcohol Use w10	0.24 (0.09)	0.07, 0.43*	0.17	0.23 (0.24)	−0.33, 0.64	0.15
Stress w16 on Alcohol Use w12	0.20 (0.08)	0.04, 0.36*	0.17	0.30 (0.13)	0.06, 0.58*	0.24

subsequent drinking and stress predicted subsequent stress. For both males and females, and consistent with models that did not examine sex differences, cross lag paths indicated within person variation in any drinking had a positive relation on subsequent within person variance in stress in most weeks. Similarly, cross-lag paths indicated within person variation in stress did not predict within person variation in drinking in subsequent weeks among males. For females, however, there were cross lag effects indicating within person increases in stress had a *positive* relation to subsequent within person increases in any drinking from weeks 8–10, but a *negative* relation to subsequent within person drinking from weeks 12–16.

4. Discussion

The current study examined bidirectional associations between alcohol use and perceived stress during the course of treatment among 1375 individuals with alcohol dependence who received treatment over 16 weeks. We tested these associations using a random intercept cross-lagged panel model, which disaggregated between person and within person effects. At the between person and within person levels, we found a strong positive association between stress and alcohol use, which is consistent with many prior human studies showing strong associations between stress and drinking (Bach et al., 2023; Blaine et al., 2019; Fox et al., 2007; Hien et al., 2023; Higley et al., 2011; Keyes et al., 2012; López-Castro et al., 2015; Wemm et al., 2022; Wemm and Sinha, 2019) At the within person level, results were consistent with prior research among non-human animals (Becker, 2017) in that there was stronger evidence for any alcohol use predicting greater than typical stress in subsequent weeks and less strong evidence for stress increasing the subsequent probability of alcohol use at the within person level.

The lack of evidence for within person stress predicting subsequent drinking among males in nearly all weeks and among females most weeks is consistent with equivocal findings in recent studies that have examined the role of stress and negative affect in predicting subsequent drinking using models that examine these relationships at the within person level among humans (Dora et al., 2023; Votaw and Witkiewitz, 2021). There is some evidence that stress may predict subsequent reinstatement in some non-human animal models (Noori et al., 2014; Spanagel et al., 2014) and that within day stress may predict subsequent drinking indirectly via increases in craving in human models (Wemm et al., 2022; Wemm and Sinha, 2019), however the findings from the current study only found support for stress predicting subsequent drinking among females across two of the seven cross-lags, and stress never predicted subsequent drinking among males. Importantly, the direction of this association flipped from being positive in the middle part of treatment, to being negative in the last week of treatment. This finding suggests that greater stress than typical predicted an increased probability of subsequent drinking during the middle stages of treatment, but that as females progressed through treatment greater stress than typical predicted decreased probability of any subsequent drinking in the last week of treatment. It could be the case that as treatment progressed females developed greater abilities to cope with stressors and were less likely to engage in subsequent drinking, even when stress was greater than typical at the within person level.

Treatment condition was also examined. Results indicated that individuals who received naltrexone with either placebo or acamprosate and those who received CBI with placebo had a lower probability of drinking at the between person level, which is largely consistent with the results of the parent study (Anton et al., 2006), which found that naltrexone and the behavioral intervention each predicted percent days abstinent over the course of the trial. Receiving CBI only was associated with greater stress across the treatment period, which is consistent with the results of prior studies showing that the CBI-only condition had the worst outcomes (Weiss et al., 2008). Weiss et al. (2008) speculated that enrolling in the COMBINE study, which was advertised as a medication study and being assigned to a condition that did not receive any pills could have had a "negative placebo effect" (p. 883), such these individuals fared worse because of dissatisfaction with the treatment assignment.

The current study has several limitations. Most notably, the measures of alcohol use and perceived stress relied on self-report. Alcohol use was corroborated with biomarkers in the COMBINE study and indicated high levels of agreement. The Perceived Stress Scale was based entirely on the subjective experience of stress, as assessed via four items. Importantly, prior research has found scores on the Perceived Stress Scale do correlate with serum cortisol levels, suggesting some correspondence between Perceived Stress Scale scores, on average, and other objective measures of stress responses (Pruessner et al., 1999; Wachholtz et al., 2011). The assessments across weeks was an additional limitation of the study design, particularly given recent work (Wemm et al., 2022; Wemm and Sinha, 2019) showing within day stress to be associated with subsequent drinking on the same day (albeit mediated by craving). Intensive longitudinal data examining associations between stress and drinking within the same day is critical for ascertaining the in-the-moment within person associations between stress and risk for drinking during the course of treatment.

Additional limitations of the COMBINE study include data being collected approximately two decades ago, the lack of racial, ethnic, and gender diversity in the sample, and the recruitment of individuals who were relatively high functioning. Future research should examine associations between stress and alcohol use in more contemporary samples that have greater racial, ethnic, and gender diversity, as well as among individuals who have more severe co-occurring psychopathology.

Overall, findings from the current study provide some support for bidirectional associations between stress and any drinking during treatment for alcohol use disorder. At within and between persons levels we found stress and drinking to be associated across time. When disaggregating between and within person effects, we found stronger evidence for within persons than between persons associations at most time points. The lagged associations at the within person level suggested strong autoregressive effects for both any drinking and stress, and cross-lagged associations provided more evidence for alcohol use predicting subsequent increases in stress, and less strong evidence of greater stress predicting subsequent increased probability of any drinking. The latter effect was only found among females at one of the time points, and in the last week of treatment greater stress predicted subsequent decreased probability of any drinking. Future research should continue to examine associations between stress and drinking, and to examine these associations at the within and between person levels in future alcohol clinical trials. If the findings of the current study are replicated, then interventions might specifically focus on targeting reductions in stress following drinking occasions. Research using intensive longitudinal designs would provide an opportunity to study the association between stress and risk of drinking within days across time and individuals and may provide more information regarding the stress-drinking associations, as well as the potential sex differences in these associations.

Funding and disclosure

This work was supported by the National Institutes of Health [R01AA022328; T32AA018108]. Bengt Muthén is the owner of the Mplus software that was used in this paper. The other authors declare no conflicts of interest.

Data sharing

Data from the COMBINE study are available from the National Institute on Alcohol Abuse and Alcoholism. Qualified researchers can received access to the data via a data access application and data use agreement, with more information available at this site: https://www.niaaa.nih.gov/combine-study.

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CRediT authorship contribution statement

Katie Witkiewitz: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **Christian C. Garcia:** Writing – review & editing. **Bengt O. Muthén:** Formal analysis, Methodology, Software, Writing – review & editing.

Declaration of competing interest

The other authors declare no conflicts of interest.

Data availability

Data are available from the National Institute on Alcohol Abuse and Alcoholism

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