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Article

Patients with AUD exhibit dampened heart rate variability during sleep as compared to social drinkers

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Abstract

Chronic heavy alcohol use profoundly affects the cardiovascular system, contributing to several life-threatening cardiovascular diseases. Heart rate variability (HRV), or the fluctuations in heart rate, reflects dynamic autonomic nervous system processes that change to meet biological demands and environmental challenges. In the current study, we examined whether HRV metrics are altered in alcohol use disorder (AUD) during waking and sleeping with passive biomonitoring as participants went about their daily lives. Social drinkers (standard deviation: $n = 10$, 5 female) and treatment-seeking individuals with moderate to severe AUD ($n = 16$, 7 female) provided continuous, real-world heart rate monitoring for 5 days of monitoring on average ($M = 5.27 \pm 2.22$). Five indices of respiration and HRV—respiratory sinus arrhythmia (RSA) amplitude, high frequency (HF), low frequency (LF), HF/LF ratio, root-mean-square standard deviation (RMSSD), and standard deviation of the *N–N* intervals (SDNN)—were analyzed separately for waking and sleeping hours. Both RMSSD and SDNN decreased the longer the participants were awake ($Ps < .013$). During sleeping hours, HF, RSA amplitude, RMSSD, and SDNN were significantly higher in light social drinkers as compared to patients with AUD (all $Ps < .009$), indicating higher parasympathetic activation during sleep in the SD versus AUD group. Sleep and waking HRV measures were significantly correlated with patient-reported symptoms of depression and sleep difficulties in the AUD group ($Ps < .05$). This natural observational study utilizing continuous autonomic biomonitoring in the real world indicates parasympathetic dysfunction that is clearly detectable during sleep in AUD and HRV measures, which are also related to clinical, patient-related symptoms of AUD.

Keywords: heart rate variability; alcohol; alcohol use disorder; autonomic nervous system

Introduction

Alcohol use disorder (AUD) is widespread throughout the USA and worldwide, with ∼29% of individuals meeting the criteria for AUD at some point in their lifetime (Grant et al. 2015). Of those individuals, only 19.8% of respondents who report meeting criteria for AUD are treated for this disorder, putting them at risk for chronic alcohol-related consequences, including mental and physical health problems. Both acute and chronic heavy consumption of alcohol has been linked to ∼60 acute and chronic diseases, including several chronic cardiovascular diseases such as hypertension, conduction disorder, and ischemic and hemorrhagic stroke (Rehm et al. 2003; Ezzati et al. 2006; Shield et al. 2014). Acute binge alcohol episodes (or four or more drinks in one sitting for women and five or more in men) are associated with temporary increases in blood pressure (Aranha Rosito et al. 1999; Seppä and Sillanaukee 1999). Daily alcohol use is associated with significant alterations in blood pressure which are sustained at binge/heavy levels, and alterations are also documented at moderate levels of alcohol use (about one to two drinks for women, and about three to four drinks for men), suggesting the possibility of alcohol drinking severity effects (Briasoulis et al. 2012; Tasnim et al. 2020). Identifying cardiovascular system alterations resulting from chronic alcohol use, especially those discernible in the real world, could provide a biological marker for identifying individuals with AUD for prevention efforts and improvement during treatment to address alcohol pathophysiology as well as risk for alcohol-related cardiovascular diseases.

One potential mechanism for the acute and chronic health effects of alcohol use might be alcohol's effect on the autonomic nervous system (ANS). The ANS regulates the heart rate in response to internal states and contextual stimuli, allowing individuals to effectively respond to and recover from events that occur in their day-to-day life (Drew and Sinoway 2011). Specifically, heart rate is accelerated by the sympathetic branch of the ANS in response to internal and external challenges and is decelerated by the parasympathetic branch to return to homeostasis. This dynamic of acceleration and deceleration of heartbeat, or the heart rate variability (HRV), serves as an index of the integrity of the two branches of the ANS (Vaillancourt and Newell 2002). Although there are many ways of quantifying HRV, the most used measurements rely on time domain or frequency domain measurements (Shaffer et al. 2014; Shaffer and Ginsberg 2017). Time domain measures of HRV quantify the variation in time from one heartbeat to the next, or the interbeat interval. These metrics include, in the time domain, the standard deviation of the *N–N* intervals (SDNN) and the root mean square of successive differences [root-mean-square standard deviation (RMSSD)]. The SDNN is influenced by both the sympathetic and parasympathetic activities and, when measured over a

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long period, provides data about cardiac reactions to environmental stimulation (Umetani et al. 1998). The RMSSD is an index of the interbeat variation in heart rate and is used as a metric of the vagally mediated, or parasympathetic, changes in HRV. Frequency domain measurements use linear time series analysis to decompose the variation in heart rate into separate spectral components. Low (LF) and high frequency (HF) HRV are the two oft-used frequency domain measurements of HRV. LF is influenced by both the parasympathetic and sympathetic nervous system, whereas the HF band is thought to reflect parasympathetic activity (Shaffer and Ginsberg 2017). The HF/LF has traditionally been assumed to reflect sympathetic versus parasympathetic dominance, although this assumption has been challenged (Billman 2013). Respiratory sinus arrhythmia (RSA) amplitude, or the peak-to-peak variations in heart rate caused by respiration, provides another metric of parasympathetic cardiac control. Collectively, these metrics can provide a window into the cardiovascular system's ability to shift in response to contextual cues and any potential disruption in its dynamic responses.

A healthy heart's dynamic ability to meet the demands of the moment has been thought to represent an individual's ability to thrive in changing environments. However, heavy, chronic alcohol use may alter one's ability to meet the demands by disrupting the ability to shift between the branches of the autonomic system, thus resulting in altered HRV. Laboratory studies have demonstrated alterations in HRV, particularly reductions in resting HF-HRV and more reactive HF-HRV to challenges, with repeated alcohol exposure (Ralevski et al. 2019). For example, 1 week of daily low-dose drinking (approximately, two standard drinks) was associated with an increase in resting HF-HRV relative to abstinence (Flanagan et al. 2002). Previous research has also identified alterations in both resting and reactive HRV in individuals with AUD. AUD diagnosis is associated with lower resting HRV in both frequency and time domains (Murata et al. 1994; DePetrillo et al. 1999), particularly during sleep (Irwin et al. 2006). Individuals with AUD also have more reactive HF HRV to challenging physical, cognitive, or emotional situations (Ingjaldsson et al. 2003). Alterations in HRV reactivity have been prospectively associated with clinical outcomes, such as craving, negative affect, and relapse to alcohol (Hwang et al. 2021).

Much remains to be discovered in how HRV differs between those with AUD and those who socially drink and how HRV relates to clinical symptoms in individuals with AUD, particularly in the real-world setting outside of the laboratory. Researchers have begun to focus on studying HRV using wearable devices that measure variations in heartbeat throughout the day and across different real-world contexts. This 24/7 ambulatory measurement is a powerful tool for learning how chronic alcohol use impacts the ANS at baseline and how HRV correlates with clinical symptoms, sleep patterns, and general well-being in daily life.

In the current study, we investigated group differences in HRV indices between social drinkers (SD) and outpatient treatment-seeking patients with AUD as they went about their day-to-day lives. We chose to recruit social drinkers who had regular exposure to alcohol use relative to alcohol-naive individuals as we wanted to test the effects of disordered alcohol use over and above mere exposure to alcohol. Specifically, we examined the group differences in HRV metrics (i.e. HF, LF, HF/LF ratio, RSA amplitude, RMSSD, and SDNN) during waking hours and during sleep over up to 11 days. We hypothesized that social drinkers would display higher HRV, particularly during sleep, as compared to patients with AUD. We also conducted secondary correlation analyses within patients with AUD to examine the hypothesis that changes in HRV metrics would be associated with AUD-related clinical symptoms, including craving, alcohol withdrawal, self-reported sleep quality, depression, and anxiety.

Method

Participants

Individuals from the Greater New Haven community were recruited as part of a larger observational study through flyers, social media advertisements, online classifieds, local newspaper advertisements, and local addiction treatment facilities. All participants provided written informed consent as part of the research protocol approved by the Yale University Human Investigation Committee. Eligible individuals were between the ages of 18 and 50, could sign informed consent, read English, and complete the study evaluations. Participants were excluded if they met criteria for a substance use disorder other than alcohol or nicotine dependence as determined by the Structured Clinical Interview for the DSM-5 (SCID; First et al. 2015). Participants were excluded if they had significant underlying medical conditions, such as cardiovascular and heart and other somatic diseases, or reported regular use of anticonvulsants, sedatives/hypnotics, prescription analgesics, hypertensive, antiarrhythmic, antiretroviral medications, and tricyclic antidepressants. Individuals were also excluded if they were prescribed pharmacological treatments for AUD such as naltrexone or disulfram medications. Patients with AUD had to meet current DSM-5 criteria for AUD per the SCID. Social drinkers were individuals who did not meet DSM-5 current criteria for AUD based on the SCID interview. Individuals in the social drinking group had varied drinking history ranging from individuals who had not drunk in the past year to individuals who binge drank alcohol monthly. Twenty-seven demographically matched patients with AUD and social drinkers who were participating in the latter part of a larger study wore the heart rate monitor as they went about their daily lives for 2–11 days ($M = 5.27 \pm 2.22$, see Table 1). The groups did not differ in age, sex, race, education, marital status, employment status, smoker status, current psychiatric diagnoses, or baseline cardiovascular function (i.e. heart rate and systolic and diastolic blood pressure). One individual was dropped because they were participating in a pharmacotherapy clinical trial while in the study. The final sample consisted of 26 individuals.

Self-report and interview measurements

All participants provided sociodemographic information and completed the SCID-5. Only patients with AUD provided information about clinical symptoms. These clinical symptoms included depression and anxiety symptoms, sleep difficulties, alcohol craving and withdrawal, and harmful and hazardous alcohol use.

Sociodemographic information. Participants provided their demographic information, medical history, and family psychiatric history during intake interviews and completed questionnaires in a prestudy baseline period.

Table 1. Demographic and baseline characteristics.

	Social, $n = 11$	AUD, $n = 15$	Test, χ^2 or t	P
Demographic				
Gender—female (%)	5 (45.5%)	7 (46.7%)	0.000	1.000
Age (in years)	34.6 ± 12.4	35.5 ± 10.9	0.197	.846
Race			3.887	.274
White, non-Hispanic	6 (54.5%)	7 (46.7%)		
Black, non-Hispanic	2 (18.2%)	6 (40.0%)		
Other	3 (27.3%)	2 (13.3%)		
Years of education	15.6 ± 3.2	14.6 ± 2.4	−1.123	.276
Income				
$0	2 (18.2%)	2 (13.3%)	5.801	.325
$1–25,000	2 (18.2%)	5 (20.0%)		
$25,001–50,000	5 (45.5%)	1 (6.7%)		
$75,001–100,000	2 (18.2%)	1 (6.7%)		
$100,001–150,000	2 (18.2%)	2 (13.3%)		
$150,001–200,000	2 (18.2%)	0 (0%)		
>$200,000	0 (0%)	0 (0%)		
Marital status			1.145	.766
Divorced	2 (18.2%)	4 (26.7%)		
Married	2 (18.2%)	2 (13.3%)		
Never married	7 (63.6%)	8 (53.3%)		
Separated	0 (0%)	1 (6.7%)		
Employment				
Full time	3 (27.3%)	6 (40%)	4.662	.324
Part-time	2 (18.2%)	0 (0%)		
Student/homemaker	3 (27.3%)	5 (20.0%)		
Unemployed <1 month	1 (9.1%)	0 (0%)		
Unemployed >1 month	2 (18.2%)	4 (26.7)		
Current mood disorder	1 (9.1%)	1 (6.7%)	0.000	1.000
Current anxiety disorder (including PTSD)	1 (9.1%)	5 (33.3%)	0.957	.328
Smoker	2 (18.2%)	8 (53.3%)	1.994	.158
Baseline cardiovascular measures				
Heart Rate	68.0 ± 11.68	71.5 ± 8.14	0.911	.371
Systolic Blood Pressure	130.8 ± 15.9	132.4 ± 16.4	0.246	.808
Diastolic Blood Pressure	70.6 ± 9.9	79.0 ± 14.1	1.681	.106
Alcohol involvement				
Years of regular alcohol use (3×/week)	3.7 ± 3.7	10.4 ± 8.76	**2.370**	**.026**
Baseline drinking days (past 30 days)	8.7 ± 6.3	19.0 ± 7.8	**0.370**	**.001**
Baseline amount per drinking episode	2.9 ± 3.3	4.8 ± 3.2	1.504	.147
AUDIT total score	6.4 ± 4.6	18.9 ± 6.6	**5.195**	**<.001**
Clinical symptoms (AUD only)				
Withdrawal (CIWA)		5.7 ± 3.7		
Craving (AUQ)		2.6 ± 1.6		
Depression (BDI)		10.9 ± 11.2		
Sleep problems (PSQI)		9.5 ± 4.9		
Anxiety (HAM-A)		13.5 ± 7.2		
Real-world HRV measurement				
Number of days	4.82 ± 2.71	5.60 ± 1.80	0.83	.418
Waking hours per day	14.87 ± 4.46	7.79 ± 2.27	**−10.71**	**<.001**
Sleep hours per day	4.47 ± 3.59	4.30 ± 3.66	−0.27	.784

Note. Standard deviation values are presented following ±, and parentheses indicate the percentage. Results in bold typeface indicate a significant result. AUDIT = alcohol use disorder identification test, PTSD = Post-Traumatic Stress Disorder.

Depression symptoms. Depression symptoms were measured via self-report on the Beck Depression Inventory (BDI; Beck 1978), a widely used 21-item inventory of depression. Overall scores were used to measure current levels of depression. The internal consistency for this measure was $\alpha = 0.92$ (Cronbach's).

Anxiety symptoms. Anxiety symptoms were measured using the Hamilton Anxiety Rating Scale (HAM-A Hamilton 1959), which was completed by observation and interview with research staff. All items are scored on a scale ranging from 0 (not present) to 4 (severe), from which all items were scored to create a total score. The internal consistency for this measure was $\alpha = 0.83$ (Cronbach's).

Sleep difficulties. The Pittsburgh Sleep Quality Index (PSQI) was administered via self-report to assess patients with AUD sleep quality over the past week at intake (Buysse et al. 1989). The PSQI is scored in seven components, from which a summed total score is derived. The internal consistency for the PSQI in the present study was $\alpha = 0.83$ (Cronbach's).

Alcohol craving. Participants self-reported their alcohol craving on the Alcohol Urge Questionnaire (AUQ; Bohn et al. 1995). This eight-item questionnaire measures participants' desire to drink, their positive expectations of drinking, and the degree to which they believe drinking is unavoidable on a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree). A total score was derived by taking an average of

all eight items. The internal consistency for the AUQ was $\alpha = 0.81$ (Cronbach's).

Alcohol withdrawal. Alcohol withdrawal was measured by administering the 13-item observer-rated Clinical Institute Withdrawal Assessment—Alcohol Revised (CIWA; Sullivan et al. 1989), which measures alcohol withdrawal signs and symptoms. Trained clinical research staff administered this interview at intake to patients with AUD. Item responses range from 0 (no evidence of symptom) to 4 (highest severity), with possible total scores ranging from 0 to 67. The Cronbach's alpha for this scale was 0.37, consistent with prior literature on individual symptom correlations (Sullivan et al. 1989).

The Alcohol Use Disorders Identification Test (Saunders et al. 1993; AUDIT; Babor et al. 2001) was administered at intake to both social drinkers and patients with AUD to determine the level of problematic drinking. The Cronbach's alpha for this scale was $\alpha = 0.79$.

Heart rate variability measurements

Continuous HRV was collected using a Firstbeat Bodyguard 2 (Firstbeat Inc., Finland), a noninvasive monitor that connects to the chest underneath clothing via two electrodes. Participants were instructed to wear the device continuously and to remove it during showering or swimming. The instrument is well tolerated for continuous measurement spanning several days in previous studies (Partala et al. 2019) and demonstrates reliability comparable to the gold-standard laboratory electrocardiogram (Palmer et al. 2021). Once the device was returned to the laboratory, the data were uploaded to the Firstbeat Lifestyle Assessment Software (Firstbeat Technologies 2014). The Firstbeat Lifestyle Assessment software applies an artifact correction feature for ectopic heartbeats and signal noise (Saalasti et al. 2004). To obtain equidistant time series, the *R–R* intervals were resampled at a rate of 5 Hz using linear interpolation. The Firstbeat Wellbeing software then applies a polynomial filter and digital FIR band-pass (0.03–1.2 Hz) filter. From this filtered data, the package calculates the HF (0.15–0.4 Hz) and LF (0.04–0.15 Hz) power at each 5-min interval during which they wore the device. Data were visually examined prior to download from the Firstbeat Wellbeing software for outliers, which were then manually corrected. If sleep was detected for >50% of that hour, we classified that hour as a sleep hour. If <50% of the data for that hour were available, we dropped that hour from further analysis. Two outliers were detected in LF Power (>7090.442, 0.1% of total data); thus, a Winsorized transformation was applied to these two data points. The HF and LF power for each 5-min interval was then averaged across the hour to provide a summary of each index for that hour. The HF/LF ratio was calculated by dividing the averaged HF power by the LF power for that hour. RSA amplitude was derived by taking the averaged RSA amplitude for that hour. In addition to these HRV indices, we also calculated the RMSSD and SDNN for each hour from the exported artifact-corrected interbeat *R–R* interval data.

Procedures

All participants completed an initial phone screen to determine the preliminary eligibility. Eligible participants were invited to the center, where they provided their written informed consent and completed baseline intake measures. During the in-person appointments, participants provided urine samples for toxicology screens to verify their recent alcohol and drug use history. After completing the intake process, participants were provided with the mobile heartbeat-recording device, trained on its use, and set up for real-world passive biomonitoring over a minimum of 2 days and for up to 11 days (see Table 1). A subset of patients with AUD wore the device for an additional 2–3 days at the end of the study. The groups did not differ in the number of days that they wore the monitor.

Data analytic plan

Descriptive statistics (Wickham et al. 2015; dplyr and psych packages; Revelle 2017) and graphs ('ggplot2' and 'ggeffects' packages; Wickham 2016; Hallquist and Wiley 2018; Lüdecke 2018; Garnier et al. 2021) were generated in R v3.6.0. Statistical analyses were completed using R v3.6.0 (performance and lmer packages; Bates et al. 2014; Lüdecke et al. 2021). *T*-tests and chi-squares were used to determine whether the individuals who socially drink and patients with AUD differed on any demographic and alcohol use characteristics. The change in HRV over the day and during sleep at night were modeled using linear mixed models, specifying a random intercept and random for hour and varying by participant crossed with a random intercept varying by day. The structure for the random effects allowed heterogeneous variances and covariances between crossed random effects. Satterthwaite-approximated denominator degrees of freedom were used. The main effects of drinking group (AUD and SD) and hour (0–23) were included as fixed effects. We also examined the interactive effect of drinking group and time, but the interactive effects were not significant in any model (Supplemental Tables S1 and S2) and were therefore removed from the models. Hour was centered on its mean. Relevant demographic variables were included as covariates in all models [i.e. sex, marital status, socioeconomic status (average of standardized income and education), smoker status, and employment status]. Pearson zero-order correlations were used for the exploratory analyses examining the relationship between the HRV indices and clinical outcomes.

An exploratory *post hoc* analysis was conducted for patients with AUD to determine if there was a sex main effect or sex-by-time interactive effects in the HRV metrics separately during waking and sleeping hours. The same analytic strategy described for examining the change in HRV during the day was used for these exploratory analyses. We chose not to explore sex differences in the correlation models as we would be underpowered to detect a large effect based on an *a priori* power analysis.

Results

Demographic and continuous monitoring characteristics

Baseline drinking behavior and participants' demographic and clinical characteristics are included in Table 1. No differences in demographic characteristics or baseline cardiovascular function were found between SD and patients with AUD. As expected, however, we found differences in alcohol involvement between groups: patients with AUD had more years of regular alcohol use (≥3 drinking days per week; $P = .026$), more drinking days in the 30 days prior to starting the study ($P = .001$), and a higher AUDIT score ($P < .001$) as compared to SD The number of drinks consumed in a drinking episode was not statistically significant between the

Table 2. Linear mixed effects models for the main effect of group and time on HRV metrics during waking hours.

Parameter	HF	LF	HF/LF Ratio	RSA Amplitude	RMSSD	SDNN
Waking hours						
Hour since waking	3.531	−8.584	0.005	0.722	−2.748[b]	−1.673[b]
	(10.289)	(7.704)	(0.005)	(1.084)	(0.840)	(0.512)
SD (1) versus AUD (0)	−68.183	−164.094	−0.060	−1.366	11.981	5.738
	(254.732)	(419.812)	(0.124)	(22.512)	(14.956)	(7.995)
Intercept	−262.834	719.562	0.525	−15.382	81.547[a]	77.328[c]
	(535.907)	(622.784)	(0.257)	(47.146)	(31.333)	(16.722)
Fit statistics						
Log likelihood	−10 807.580	−11 558.130	−132.104	−7687.180	−7841.536	−7313.833
Akaike Inf. Crit.	21 651.160	23 146.270	300.208	15 410.360	15 719.070	14 663.670
Bayesian Inf. Crit.	21 745.290	23 225.380	394.345	15 504.500	15 813.990	14 758.580
Sleep hours						
Hour since falling asleep	97.701[b]	120.411[a]	−0.046[a]	9.252[a]	1.825	4.268[c]
	(36.737)	(57.631)	(0.019)	(3.940)	(0.960)	(0.980)
SD (1) versus AUD (0)	1824.243[a]	466.117	0.511	242.740[a]	26.241[b]	27.032[b]
	(666.512)	(357.338)	(0.417)	(88.414)	(9.898)	(7.416)
Intercept	−2062.663	−342.194[a]	0.131	−345.345	6.224	9.251
	(1438.631)	(772.793)	(0.881)	(189.376)	(20.340)	(15.791)
Fit statistics						
Log Likelihood	−4866.321	−4901.468	−615.948	−3683.394	−2807.338	−2796.661
Akaike Inf. Crit.	9768.643	9842.936	1267.896	7402.789	5650.677	5629.322
Bayesian Inf. Crit.	9847.576	9930.808	1346.829	7481.722	5729.761	5708.407

Note. Standard error of the estimate is included in parentheses underneath its corresponding variable. All models, except for the LF models, included a random slope for hour elapsed since waking up and used a crossed random effect design. Model covariates include sex, marital status, employment status, socioeconomic status, and smoking status. [a]$P < .05$. [b]$P < .01$. [c]$P < .001$.

two groups ($P = .147$) but tended to be lower in social drinkers SD.

Both groups provided up to 11 days' worth of real-world HRV monitoring with no differences between groups, $t(16.31) = 0.83$, $P = .418$, and a comparable volume of data on their sleep hours each night, $t(17.00) = 0.53$, $P = .600$. Patients with AUD provided fewer waking hours of HRV monitoring than SD, $t(12.34) = -2.31$, $P < .001$.

Heart rate variability changes during waking

Time since waking was the only significant predictor of RMSSD and SDNN (Table 2). RMSSD and SDNN decreased the longer a person was awake, RMSSD: $F(1, 18.10) = 10.70$, $Est = -2.75$, $P = .004$; SDNN: $F(1, 13.86) = 10.69$, $Est = -1.67$, $P = .006$ (Fig. 1A and E). Time since waking and drinking group were not significant predictors in any other model.

Heart rate variability changes during sleeping and group differences

The time since falling asleep predicted HF, $F(1, 16.49) = 7.07$, $Est = 97.70$, $P = .017$; LF, $F(1, 22.89) = 4.37$, $Est = 120.41$, $P = .048$; HF/LF ratio, $F(1, 17.75) = 6.03$, $Est = -0.046$, $P = .025$; RSA amplitude, $F(1, 13.11) = 5.51$, $Est = 9.25$, $P = .034$, and SDNN, $F(1, 18.12) = 18.96$, $Est = 4.27$, $P < .001$ (Table 2). HF, LF, RSA amplitude, RMSSD, and SDNN (Fig. 1B–D, G, and H) increased the longer the participant slept, whereas HF/LF ratio decreased over time spent asleep (Fig. 1F). Individuals who social drank had higher HF, $F(1, 13.22) = 7.49$, $Est = 1824.24$, $P = .017$, RSA amplitude, $F(1, 13.07) = 7.54$, $Est = 242.74$ $P = .017$, RMSSD, $F(1, 12.92) = 7.03$, $Est = 26.24$, $P = .008$, and SDNN, $F(1, 13.05) = 13.29$, $Est = 27.03$, $P = .003$, as compared to patients with AUD (Fig. 1B, D, G, and H, respectively). That is, patients with AUD displayed markedly lower levels of parasympathetic activity during sleep when contrasted against SD.

Exploratory results for association of heart rate variability indices and clinical outcomes in alcohol use disorder

We then examined the correlations of these averaged HRV metrics during both waking and sleeping hours with alcohol-related clinical outcomes (Table 3). Waking RMSSD was positively correlated with sleep difficulties, $r = 0.71$, $P = .003$, alcohol withdrawal, $r = 0.61$, $P = .016$, depression, $r = 0.55$, $P = .034$, and hazardous and harmful drinking, $r = 0.52$, $P = .046$ (Fig. 2A–D). Sleep difficulties were negatively associated with sleeping LF, $r = 0.52$, $P = .035$, and were positively associated with sleeping HF/LF Ratio, $r = 0.52$, $P = .049$ (Fig. 2E and F).

Post hoc exploratory sex difference analyses

We conducted an exploratory analysis to determine if there were any sex differences within the AUD group on HRV metrics. Tables and figures are provided for reference in the supplemental section of this paper. For the waking models, SDNN, RMSSD, and RSA amplitude models during waking hours failed to converge and thus are not reported. During waking hours, LF HRV was overall higher in men, $F(1, 6.03) = 14.22$, $Est = 1290.81$, $P = .009$ (Table S3 and Fig. S1A). Sex was not a significant predictor of any other HRV metrics during waking hours. During sleep, there was also a significant main effect of sex on HF HRV, $F(1, 5.87) = 28.92$, $Est = 1628.89$, $P = .002$; RSA amplitude, $F(1, 5.14) = 33.86$, $Est = 188.95$, $P = .002$; RMSSD, $F(1, 6.68) = 7.84$, $Est = 25.29$, $P = .028$; and SDNN, $F(1, 5.68) = 25.43$, $Est = 35.901$, $P = .003$; where men with AUD had a higher HRV metrics during sleep as compared to women with AUD (Fig. S1B, D–E, respectively; Table S4).

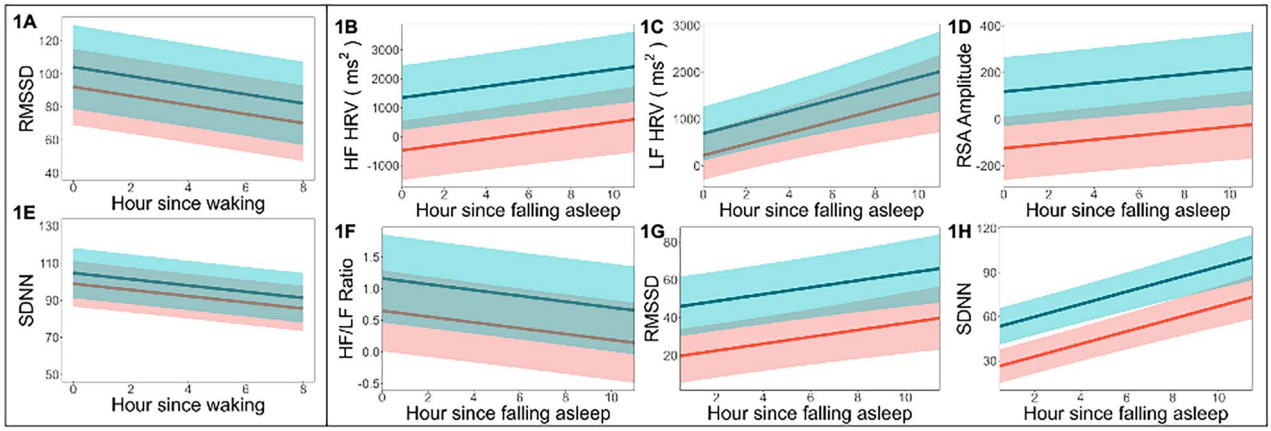

Figure 1. Waking HRV (1A, 1E) and Sleeping HRV (1B-D, 1F-H) with time by drinking group. Both RMSSD (1A) and SDNN (1E) levels reduced over time spent awake, which did not differ by group. During sleep, all HRV metrics, except for HF/LF (1D) and RMSSD (1F), significantly increased over time spent asleep. HF/LF ratio decreased as more time was spent asleep (1D). HF (1C), LF (1E), RSA amplitude (1G), RMSSD (1F), and SDNN (1H) were all higher during sleep in social drinkers as compared to individuals with AUD.

Table 3. HRV metrics correlations with clinical variables in individuals with AUD.

	HF	LF	HF/LF Ratio	RMSSD	RSA	SDNN
Waking						
BDI	0.20	−0.13	0.35	**0.55**[a]	0.17	0.20
PSQI	−0.10	−0.31	0.29	**0.71**[b]	−0.01	0.28
HAM-A	0.10	0.46	0.46	0.46	0.07	0.13
Alcohol quantity	−0.30	−0.25	−0.22	0.23	−0.34	−0.04
Alcohol frequency	0.17	−0.11	0.33	0.14	0.16	−0.09
Years of regular alcohol use	0.32	0.04	0.16	0.03	0.29	0.07
Years of any alcohol use	−0.27	−0.51	−0.16	0.10	−0.32	−0.35
AUDIT	−0.08	−0.23	0.22	**0.52**[a]	−0.05	0.17
AUQ	0.09	0.02	0.42	0.16	0.21	0.10
CIWA	−0.31	−0.41	0.09	**0.61**[a]	−0.32	0.12
Sleeping						
BDI	−0.03	−0.17	0.25	0.10	−0.10	−0.14
PSQI	−0.18	**−0.55**[a]	**0.52**[a]	−0.08	−0.05	−0.38
HAM-A	−0.11	−0.22	0.33	−0.09	−0.16	−0.32
Alcohol quantity	−0.20	−0.02	−0.20	−0.17	−0.23	−0.12
Alcohol frequency	0.08	−0.03	−0.14	0.12	0.06	0.03
Years of regular use	0.39	0.14	0.09	0.43	0.32	0.20
Years of any alcohol use	−0.19	−0.24	−0.12	−0.25	−0.25	−0.32
AUDIT	−0.05	−0.26	0.38	−0.09	0.02	−0.22
AUQ	−0.06	−0.32	0.26	−0.13	0.12	−0.21
CIWA	−0.36	−0.20	0.08	−0.15	−0.38	−0.30

[a]$P < .05$. [b]$P < .01$. Bold values indicate significant results.

Discussion

The current study demonstrated that patients with AUD display dampened parasympathetic activity during sleep compared to social drinkers. Our results suggest that chronic, heavy alcohol use is associated with disruption in the ANS, particularly the rest-and-recovery processes that occur during sleep. These findings are consistent with laboratory studies that have found patients with AUD have lower resting HRV in both frequency and time domains during sleep (Murata et al. 1994; DePetrillo et al. 1999; Irwin et al. 2006). Our study extends this prior research by being the first to employ naturalistic, observational methods to continuously monitor autonomic responses in a naturalistic setting during both waking and sleeping periods and by comparing patients with AUD and social drinkers. Our results provide ecological evidence for dampened parasympathetic activity in AUD, consistent with previous laboratory research (Flanagan et al. 2002; Ralevski et al. 2019). The current study provides further evidence that autonomic disruption is characteristic of AUD, which may play a role in increasing vulnerability for patient-related AUD symptoms.

In general, we found that time domain HRV metrics (RMSSD and SDNN) decreased the longer a participant was awake. By contrast, time domain, frequency (HF and LF), and amplitude (RSA) metrics increased the longer a participant was asleep. During sleep, autonomic control fluctuates between parasympathetic and sympathetic controls depending on the sleep stage. Rapid eye movement (REM) sleep is associated with increased sympathetic activity, whereas non-REM sleep is associated with increased parasympathetic activity (Tobaldini et al. 2013). HRV metrics that are predominantly indices of parasympathetic control (i.e. HF, RSA amplitude, and RMSSD) were dampened in patients with AUD during sleep, indicating a shift toward sympathetic dominance during sleep in the autonomic control similar to individuals with sleep disorders (Vanninen et al. 1996).

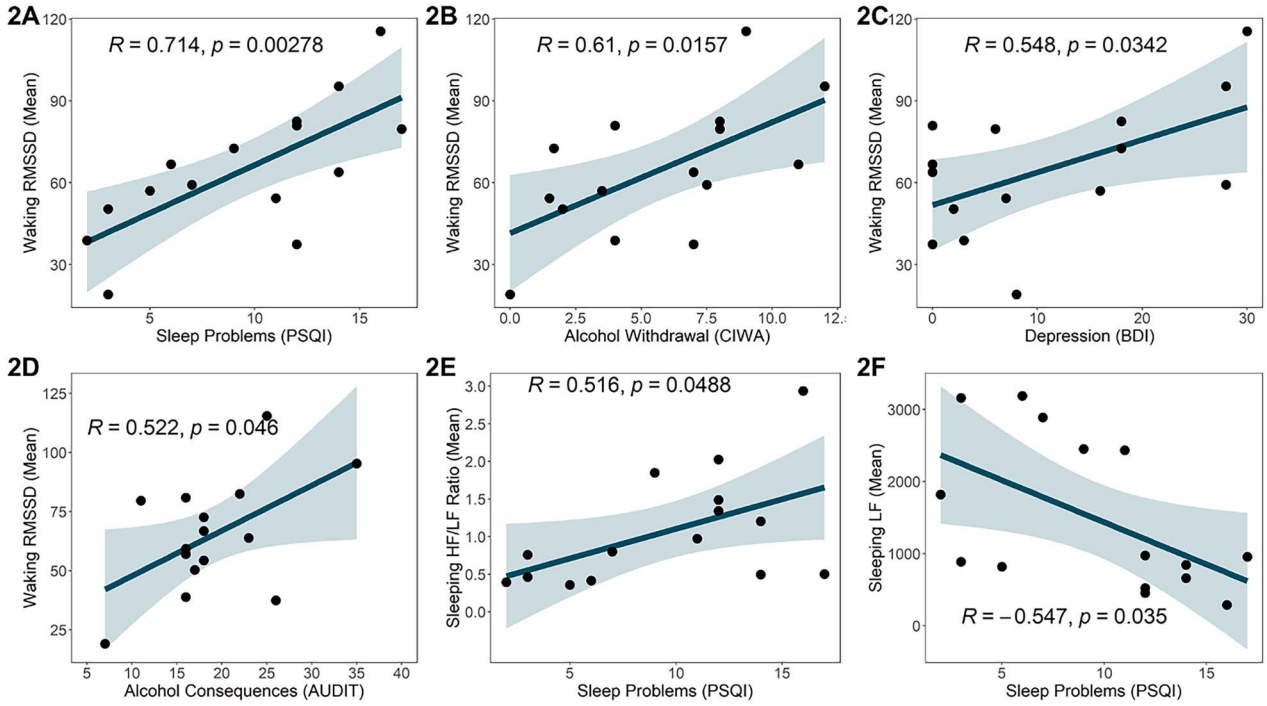

Figure 2. Correlations between HRV metrics and clinical symptoms at baseline in individuals with Alcohol Use Disorder.

We did not find differences between patients with AUD and social drinkers during waking hours, which is likely related to more variability in context and activities while participants were awake as compared to sleep. This additional variability limited our ability to detect broad group differences. However, our previous laboratory work during waking hours has shown that patients with AUD display heightened heart rate (Sinha et al. 2009; Seo et al. 2013) and irregular autonomic modulation during stress induction laboratory procedures compared to social drinkers (Hwang et al. 2021). Taken together, HRV metrics assessed in the real world may provide a useful index of early cardiovascular dysfunction in patients with AUD, particularly during sleep even before the development of cardiovascular disease.

HRV during sleeping and waking hours were associated with alcohol-related clinical outcomes in patients with AUD. Higher parasympathetic activity during waking hours, as measured by RMSSD, was associated with AUD clinical symptoms, specifically increased harmful and hazardous drinking patterns, alcohol withdrawal, depression, and sleep difficulties. In addition, HRV metrics associated with sympathetic dominance during sleep (higher LF and lower HF/LF ratio) were related to less endorsement of sleep problems. These results indicate that within a clinical sample, the associations between HRV and clinical outcomes are complex and may be related to disruption in the overall autonomic function related to heavy alcohol use. Sympathetic and parasympathetic activities are not always reciprocal. A person's ability to shift between these two systems facilitates their capacity to meet various internal and external demands (Berntson et al. 1993); in patients with AUD, the reciprocity or balance between these two systems might be further disrupted. Individuals with higher vagal activity at baseline per polyvagal theory have a greater capacity for emotion regulation than those with lower vagal activity (Porges 2007). Prior work has demonstrated that individuals with lower baseline parasympathetic activity, similar to our sample of AUD, show lower reciprocal coupling between the parasympathetic and sympathetic activities and, therefore, less dynamic responding (Weissman and Mendes 2021). In our previous work, we found that alterations in autonomic responding were associated with *ad libitum* smoking and clinical symptoms of nicotine dependence (Ashare et al. 2012) as well as with greater alcohol involvement and disruptions in prefrontal-striatal brain function during stress exposure among patients with AUD (Hwang et al. 2021). Thus, the current finding of an association of clinical symptoms with higher parasympathetic activity in patients with AUD may reflect discoordination between the two branches of the ANS or inappropriate activation of the parasympathetic nervous system.

The relationship between alcohol use and cardiovascular disease is complex. The relationship between alcohol dose and physical health problems presents as a J-shaped curve (Day and Rudd 2019). Low-to-very low doses (~0.5–1 drink/day for women and 1–2 drinks/day for men) have been associated with lower mortality rates (Di Castelnuovo et al. 2006). However, even one drink more than that daily is associated with increased mortality rates (Di Castelnuovo et al. 2006). Heavy alcohol use has been associated with higher blood pressure, acute cardiac arrhythmia, atrial fibrillation, and nonischemic dilated cardiomyopathy (Day and Rudd 2019). Although patients with AUD in our sample were physically healthy, they had already begun to show altered cardiovascular function relative to a group of social drinkers with a similar demographic profile. Our findings suggest that shifts in parasympathetic functioning potentially underlie cardiovascular disease risk related to heavy alcohol use.

In exploratory analyses, we found that men with AUD tended to have higher HRV metrics as compared to women with AUD, particularly during sleep and when examining the LF HRV metrics. Our findings are consistent with prior studies in healthy men and women that found men have higher LF

HRV as compared to women; however, our findings contrast with prior studies that found women had higher HF HRV and other parasympathetic-related metrics. Our contrasting findings in women with AUD as compared to prior studies with healthy women may be a manifestation of the discoordination between the sympathetic and parasympathetic branches of the ANS related to chronic alcohol use, but these findings will need to be explored in a larger sample of men and women with AUD.

A strength of this current study was the use of an unobtrusive passive monitoring device that allowed participants to provide continuous monitoring over several days. This fine-grained monitoring procedure allowed us to examine the time course of various HRV metrics and how AUD diagnosis altered the diurnal pattern of these HRV metrics. Our data were collected over days rather than minutes and in a natural setting, thus providing a more stable estimate of parasympathetic functioning in these groups.

The results of this study should be considered within the context of its limitations. First, the sample size of this pilot study is small. This pilot study should be replicated with a larger sample of patients with AUD and social drinkers. We had less data during waking hours for patients with AUD as compared to social drinkers, which may have limited our ability to detect group differences in HRV. In addition, we could not collect information about the participants' contexts, emotional state, and daily activities throughout the day, which likely added noise to the waking HRV data. Future research should collect simultaneous self-reports to examine group differences in the HRV response to various activities (e.g. drinking alcohol and physical activity), contexts (e.g. location and alcohol cues), and emotional states (e.g. stress and negative affect) with a larger sample. Another limitation is that we only focused on certain frequency and time domain metrics of HRV. There are other metrics of HRV (e.g. NN50, pNN50, and entropy) that are not included in this paper and should be investigated in future research.

Despite these limitations, the current study is the first to report on passive biomonitoring of HRV with over 2087 h of monitoring of social drinkers and patients with AUD with evidence in support of alterations in the parasympathetic activity related to excessive alcohol intake, particularly during sleep. Our results suggest that higher levels of chronic alcohol use may be related to the allostatic shifts in the autonomic activity in AUD which relate to their clinical AUD symptomatology and which may also contribute to the long-term detrimental cardiovascular effects attributed to excessive alcohol use. The results of this study underscore the importance of investigating HRV as a biomarker of excessive alcohol use and as a possible target for novel interventions for AUD.

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Supplementary data

Supplementary data are available at *Alcohol and Alcoholism Journal* online.

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Data availability

Data available on request.

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