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Cardiovascular disease risks in adult Native and Mexican Americans with a history of alcohol use disorders: association with cardiovascular autonomic control

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Abstract

Hypertension and obesity are serious health problems that have been associated with an increased risk of cardiovascular disease (CVD). We recently showed a relationship between hypertension, obesity and cardiovagal control in a sample of Native and Mexican Americans at high risk of alcohol use disorders (AUD). While studies have shown that Native and Mexican Americans exhibit high rates of AUD, the consequences of AUD on CVD risk factors and their relationship with cardiovascular autonomic control is not well understood in these ethnic groups. This study investigated whether an association could be demonstrated between cardiovascular autonomic control and several CVD risk factors in Native and Mexican American men and women ($n = 228$) who are literate in English and are residing legally in San Diego County. Participants with lifetime history of AUD showed higher rates of systolic and diastolic hypertension and obesity than participants without lifetime AUD. Lifetime AUD was significantly associated with reduced HR response to deep breathing (HR_{DB}) measure of cardiovagal control, higher current drinking quantity, and obesity. Reduced HR_{DB} was also associated with increased systolic pre-hypertension or hypertension (pre-/hypertension) and with higher diastolic blood pressure in a linear regression model that included several diagnostic and demographic variables. HR_{DB} and time- and frequency-domain measures of cardiovagal control were significantly reduced in participants with diastolic pre-/hypertension. These data suggest that lower cardiovagal control may play a role in the prevalence of systolic and diastolic pre-/hypertension in a community sample with a history of alcohol and substance use disorders.

Keywords

Alcohol use disorders; Native Americans; Autonomic nervous system; Hypertension; Mexican Americans; Obesity

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Introduction

Alcohol dependence affects 4 percent of the adult population and is one of the leading causes of preventable death in the United States [1]. Epidemiological studies and results of several meta-analyses have shown that heavy alcohol consumption is associated with an increased risk of cardiovascular disease (CVD) and hypertension [2]. We have previously reported the presence of several CVD risk factors including hypertension and obesity in a community sample of Native and Mexican Americans at a high risk of developing an alcohol use disorder (AUD) e.g., 3–5. Studies have shown evidence of higher prevalence of CVD risk factors in both Native and Mexican Americans. Relative to other ethnic groups, Native Americans exhibit high rates of CVD, stroke, and substance dependence [6–8]. There is also evidence that Mexican Americans have a higher incidence of stroke than non-Hispanic whites [8, 9] and being Mexican American is a risk factor for alcohol dependence among Hispanic groups [10]. While we have shown that obesity and being male increases the risk for CVD in this sample of Native and Mexican Americans [3], the consequences of lifetime AUD on the risk of CVD and its comorbidities in these groups is of significant concern in order to address health disparities.

The autonomic nervous system (ANS) plays an important modulatory role by controlling blood pressure at rest and in response to environmental stimuli [11]. Time- and frequency-domain measures of heart rate variability (HRV), the beat-to-beat variation in heart rate (HR), obtained from short- (e.g., 2–5 min) or long-term (e.g., 24 h) recordings have been used to measure fluctuations in autonomic inputs to the Sino-Atrial node of the heart [12, 13]. Studies have shown that reductions in the amplitude of overall HRV and cardiovagal control may precede the development of hypertension and increase the risk of CVD [14]. Recent reviews assessing the effects of alcohol dependence on several time- and frequency-domain metrics of HRV have shown that alcohol-dependent participants consistently exhibit a reduction in the cardiovagal component of HRV [15, 16]. While there is evidence that reduced cardiovagal control may be associated with alcohol craving and relapse in alcohol dependence [17, 18], it has also been associated with a higher risk of CVD [16, 19]. Moreover, an increase in sympathetic nerve activity and an attenuation of cardiovagal control had been also associated with the generation and maintenance of hypertension [11, 20]. However, there is also evidence that current heavy alcohol use, but not current or lifetime AUD, was associated with an increase in cardiac sympathetic control and hyperactivity of the hypothalamic–pituitary–adrenal (HPA)-axis [21]. These findings suggest that current drinking quantity may also play an important role when assessing the consequences of AUD on cardiovascular autonomic control and CVD. Understanding the relationship among these CVD risk factors may provide important insight into the prevention and treatment of these conditions.

The present report is part of a larger study exploring risk factors for substance dependence among Native and Mexican American men and women residing in southwest California [3–5]. The overall objective of this study was to assess the relationship between cardiovagal control and CVD risk factors in a community sample of Native and Mexican American men and women with a high prevalence of lifetime AUD. This objective was accomplished

through two specific aims: The first aim determined the association of lifetime DSM-5 AUD on cardiovascular autonomic control and the rates of CVD risk factors. The second aim of the study determined the relationship among systolic and diastolic blood pressure (BP) and measures of cardiovascular autonomic control, lifetime AUD and demographics.

Methods

Participants and psychiatric diagnoses

The present study assessed Native and Mexican American men and women at high risk of addiction and cardiovascular disease (American Indians, $n = 52$; and, Mexican Americans, $n = 176$; total sample = 228). Native and Mexican American participants (18–30 years of age) who were mobile and without serious medical illness, were recruited as reported previously [4]. The protocol for the study was approved by two institutional internal review boards and also the Indian Health Council. All participants were asked to refrain from alcohol or any other substance use for 24 h before testing. Participants were compensated for their time spent in the study. Participants from both ethnic groups were included in the study if they resided in the United States legally and were able to read and write in English. Participants were excluded if they were pregnant or nursing, currently had a major medical or neurologic disorder, or a head injury, if they were taking psychoactive medication or had a positive breath alcohol test on the day of the evaluation. Participants were also excluded if they had an implanted cardiac pacemaker, were taking beta-blockers or if they had electrocardiogram (EKG) recordings with significant arrhythmia such as atrial fibrillation or excessive ectopic activity.

On the test day, after a complete description of the study to the participants, written informed consent was obtained using a protocol approved by The Institutional Review Board of The Scripps Research Institute. Participants also took an alcohol breathalyzer test to assess blood alcohol concentration. Participants responded to a screening questionnaire that was used to gather information on demographics, personal medical history, ethnicity and detailed measures of current and past substance abuse history. Each participant also completed an interview with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), as previously described [5]. Diagnoses of lifetime AUD were made on the basis of having 2 lifetime DSM-5 criteria. Diagnoses of lifetime nicotine dependence were made on the basis of DSM-IV criteria. A total of 116 participants were diagnosed with lifetime DSM-5 AUD [22]. The SSAGA interviews were administered by trained research assistants, and all best final diagnoses were made by a research psychiatrist/addiction specialist (DAG). Current alcohol consumption (at least 1 alcohol drink during the past week) and current drinking quantity (number of drinks during the past week) were determined.

General procedures and statistical analysis

Respiration rate and the EKG (sampled at 1024 Hz) were measured using a physiological monitoring system (Nexus-10, Mind Media, The Netherlands; or, the I-330-C2 + 12, J & J Engineering, Poulsbo, WA). The EKG was manually inspected for artifacts and ectopic heart beats and filtered using the Kubios HRV Analysis Software (Biosignal Analysis and Medical

Imaging Group (BSAMIG), Department of Physics, University of Kuopio, Finland; <http://kubios.uef.fi>).

Participants were seated in a private room and indices of cardiovascular autonomic control were assessed by recording the EKG and the rate of respiration in two separate sessions: (1) during a 5 min rest period to assess time- and frequency-domain measures of cardiovascular autonomic control; and, (2) during assessment of HR_{DB} to determine respiratory sinus arrhythmia, a measure of cardiovagal control [24, 25]. These sessions were carried out as follow: (1) 5 min rest period: Time- [RMSSD (the square root of the mean squared successive differences between interbeat interval (IBIs))] and frequency-domain measures of HRV [LF-HRV (low-frequency HRV), HF-HRV (high-frequency HRV)] and the LF/HF ratio were estimated during the 5 min rest period. Fourier transform was performed on the IBI data to determine LF-HRV power (0.04–0.15 Hz), HF-HRV power (0.15–0.40 Hz) and LF-HRV/HF-HRV Ratio using the Kubios HRV Analysis Software. The unit for LF-HRV and HF-HRV power is ms². RMSSD (in ms) was determined using the CMetX software, as previously described [23]. The rate of respiration was measured during the 5 min rest when time- and frequency-domain measures of HRV were determined. It is recommended that respiration rate of participants to be within the frequency band used to define cardiovagal control (e.g., 0.15–0.40 Hz) [12]. (2) HR_{DB} assessment: HR_{DB} estimates cardiovagal control by determining the mean HR range (maximum–minimum) of the five consecutive largest responses, as described by Low and Sletten [24]. To determine HR_{DB} participants were asked to breathe eight times at 6 breaths per min (bpm) using the Pacer EZ-Air Plus (Biofeedback Foundation of Europe, London, UK). Body mass index (BMI) was calculated as body weight in pounds divided by height in inches squared $\times 703$ (lb/in² $\times 703$). Obesity was defined as BMI ≥ 30 . In addition, mean systolic BP (SBP) and diastolic BP (DBP) were determined as the average of 5–7 measures using a Digital Blood Pressure Monitor (HEM-907XL, Omron Healthcare, Bannock, IL) obtained during the experimental procedures. Hypertension was defined as mean systolic BP of at least 140 mm Hg or mean diastolic BP of at least 90 mm Hg [26]. Pre-hypertension was defined as systolic BP between 120 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg [27]. The standard deviation (SD) of mean SBP and DBP (SBPSD and DBP SD) was also calculated. Procedures were performed between 9:00 A.M. and 2:00 P.M.

IBM Statistics SPSS v.20 software (IBM Corp, Armonk, NY) was used for data analysis. The data analyses were based on the study aims. The first aim was to determine the association of lifetime DSM-5 AUD on cardiovascular autonomic control and the rates of CVD risk factors. The Kolmogorov–Smirnov normality test was used to test normality. Categorical variables were presented as number (%) and continuous variables as mean (SEM) when normally distributed or median value with interquartile range (IQR) when variables were not normally distributed. Comparisons of demographics, cardiovascular measures and CVD risk factors were conducted using the Mann–Whitney *U* test for continuous variables and the Fisher's Exact Test for dichotomous variables. The second aim of the study determined the relationship among BP (SBP and DBP), measures of cardiovascular autonomic control, lifetime AUD, and demographics. To accomplish this objective, participants were divided into two groups according to their mean SBP and DBP: a group with participants with either pre-hypertension or hypertension (pre-/hypertension

group) and a control group with participants with no prehypertension or hypertension (no pre-/hypertension group). Comparisons of demographics, cardiovascular measures and CVD risk factors were done as described in aim 1. This aim also determined whether deficits in cardiovascular autonomic control were significantly associated with mean SBD and DBD. A backward stepwise linear regression analysis for mean SBP and DBP as outcome variables in separate regressions was conducted while controlling for several independent variables: age, gender, obesity, current drinking quantity (number of drinks past week), resting HR (HR_{rest}), LF-HRV, HF-HRV, LF-HRV/HF-HRV Ratio, RMSSD, HR_{DB} , and lifetime AUD. The backward stepwise regression removes the independent variable which is least significant (defined as the independent variable with the highest p value >0.10) in explaining the outcome variable in steps. Statistical significance was set at probability level of $P < 0.05$ for all tests. Power analyses indicated that there was sufficient power (0.80) at $\alpha = 0.05$ to detect differences in our primary analyses, for a medium effect size [28].

Results

Lifetime AUD in Native and Mexican American participants: relation to cardiovascular autonomic control and CVD risk factors

Demographic data on the 228 participants are presented in Table 1. The sample contained more women participants ($n = 126$, 55 %) than men ($n = 102$, 45 %). There were no significant differences between AUD and no AUD groups in gender, years of education, income and rates of diabetes. However, AUD participants were more likely to be older have higher BMI and higher rates of obesity and lifetime nicotine dependence. Lifetime AUD participants were also more likely to be currently drinking alcohol and to consume greater number of drinks per week.

Lifetime AUD participants showed higher systolic and diastolic mean BP and were also more likely to have systolic pre-hypertension (55 vs. 37 %) and systolic and diastolic hypertension (18 vs. 4 and 12 vs. 3 %, respectively) than no AUD participants (Table 2). Figure 1a, b displays the scatter plots for the relationships between systolic blood pressure and age across both AUD and no AUD participants in men and women. While lifetime AUD was associated with reduced HR_{DB} , AUD participants showed no significant changes in time- and frequency-domain measures of cardiovascular autonomic control (Table 2). The respiration rate assessed during a 5 min rest was not significantly different between AUD and no AUD participants (no AUD: 15.6 ± 0.3 breaths per min; AUD: 14.7 ± 0.3 breaths per min; $F(1, 196) = 3.3$, $p > 0.05$).

Systolic and diastolic pre-hypertension and hypertension in Native and Mexican American participants: relation to cardiovascular autonomic control and lifetime AUD

Participants with systolic pre-/hypertension were more likely to be older, male, and obese than participants without systolic pre-/hypertension (Table 3). Systolic pre-/hypertension was also associated with an increase in the standard deviation of systolic BP and LF/HF ratio and reduced HR_{DB} (Table 3). Participants with diastolic pre-/hypertension were more likely to be older, obese, show an increase in the standard deviation of diastolic SD, and

reduced frequency- and time-domain measures of cardiovagal control (HF-HRV and RMSSD) and HR_{DB} (Table 4).

Table 5 presents the results both for the full model and for the final model after backward stepwise regression. A higher systolic BP score in the final model revealed the following significant variables: male gender and obesity. While lifetime AUD associated with high systolic BP showed a non-significant trend ($p = 0.05$), no other variables were associated with a high systolic BP score in the final regression model (Table 5). A higher DBP score in the final model showed the following significant variables: higher HR_{rest} and DBP SD, lower HR_{DB} , male gender, obesity and lifetime AUD (Table 5). Thus, male gender and high obesity were significantly associated with mean SBP and DBP. However, lower HR_{DB} , higher DBP SD and HR_{rest} , and lifetime AUD were also significantly associated with higher mean DBP.

Discussion

The present study sought to determine the consequences of a lifetime history of AUD on CVD risk factors and measures of cardiovascular autonomic control in a sample of Native and Mexican American men and women. Participants with lifetime AUD showed increased rates of obesity, lifetime nicotine dependence, systolic, and diastolic hypertension and deficits in cardiovagal control defined by reduced HR_{DB} . This study also determined whether the increase in mean SBP and DBP were associated with deficits in cardiovascular autonomic control. Participants from the systolic pre-/hypertension group were more likely to be male, obese, older, showed higher SBP variability, lower HR_{DB} and higher LF/HF ratio, compared to controls. Participants from the diastolic pre-/hypertension group were more likely to be obese, older, showed higher DBP variability and a reduction on all measures of cardiovagal control (HF-HRV, RMSSD and HR_{DB}), compared to controls. While these findings are not surprising since these variables are considered important CVD risk factors in the general population [14], they underscore the high rates of CVD risk factors that are associated with lifetime AUD in these ethnic groups. Overall, these results suggest that a reduction in the cardiovagal measure HR_{DB} was consistently associated with CVD risk factors in this sample of Native and Mexican American young adults.

Previous studies have shown that alcohol-dependence is associated with an increase in LF-HRV and LF/HF ratio and a reduction in RMSSD and HF-HRV [15–18]. In this study a lifetime history of AUD had no effect on time- and frequency-domain measures of HRV in young adult participants. These findings are consistent with previous studies suggesting that current heavy drinking, but not current or remitted AUD, is associated to deficits in time- and frequency-domain measures of cardiac sympathetic and parasympathetic control [21]. While participants with lifetime AUD reported significantly higher current drinking quantity than participants without lifetime AUD (Table 1), the amount use was considerably lower than the group of current heavy drinking participants (2.8–4.0 drinks/day) reported by Boschloo et al. [21]. However, this study found that lifetime AUD was associated with HR_{DB} . HR_{DB} is considered a sensitive measure of parasympathetic cardiac function and an important component of the battery of cardiovascular autonomic function tests used in clinical autonomic laboratories [24, 25]. However, the clinical significance of reduced HR_{DB} on

CVD risk factors in this sample is not well understood. How these findings are related to evidence that this measure of cardiovagal control is a potential marker for self-regulation and relapse in alcohol-dependent patients is not known [15–18]. Studies with a larger sample are needed to assess the relationship between these metrics of cardiovagal control and current symptoms of AUD associated with an increased risk of CVD and alcohol-seeking behavior in participants with a lifetime history of AUD.

The present study showed that LF-HRV was not significantly different between participants with systolic or diastolic pre-/hypertension, compared to their respective controls. This study found a significant increase in LF/HF ratio in participants with systolic pre-/hypertension. However, the notion that LF-HRV provides an index of cardiac sympathetic control and LF/HF ratio provides an index of “sympathovagal balance” is controversial [see 29–31]. Research evidence supports the association of LF-HRV and LF/HF ratio with baroreflex modulation of autonomic outflow instead [30]. Since systolic pre-/hypertension was also associated with reduced HR_{DB} , further research is needed to determine the relationship between HR_{DB} and adrenergic baroreflex sensitivity in the development of systolic pre-/hypertension in these ethnic groups. In contrast, participants from the diastolic pre-/hypertension group showed a reduction on all measures of cardiovagal control (HF-HRV, RMSSD and HR_{DB}), compared to controls. Moreover, lower HR_{DB} was associated with higher mean DBP, but not with SBP, in a multiple regression model that controlled for several diagnostic and demographic variables. These results demonstrate a relationship between lower cardiovagal control and higher DBP in this sample of Native and Mexican Americans young adults at high risk of AUD and CVD.

The results of this study should be interpreted in the context of several limitations. First, only retrospective and crosssectional data on the lifetime AUD were assessed. Participants were of different ages and thus could be at different stages of their use disorders. Second, the study focused on Native and Mexican American adults legally residing in the U.S, and it may not be possible to generalize these results to other Native Americans, all Mexican Americans or all Hispanic Americans. The study used a combination of Native and Mexican Americans with differences in demographics, environmental and genetic factors that could have influenced the present findings. While the present study assessed several CVD risk factors such as lifetime history of nicotine dependence, obesity and self-reported current drinking quantity, factors known to influence BP and HRV such activity levels and exercise, meal intake, sleep patterns and a wide variety of drugs of abuse were not accounted in the present analysis. Despite these limitations, this report represents an important step in an ongoing investigation to determine genetic and environmental risk factors associated with substance use disorders and related psychiatric disorders in these high risk and understudied ethnic groups. Separate studies in this population with a larger sample are also needed to assess how cardiovascular autonomic control influences the development of co-morbid cardiovascular and neuropsychiatric disorders.

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Fig. 1. Scatter plots for the relationships between systolic blood pressure and age across both AUD and no AUD participants in women (a) and men (b)

Table 1
Demographic characteristics of participants as a function of lifetime AUD in Native and Mexican American adults ($n = 228$)

Variable	No lifetime AUD ($n = 112$)	Lifetime AUD ($n = 116$)
Age (years) ^a	22.0 (7)	24.0 (6) **
Gender (n)		
Men	46 (41 %)	56 (48 %)
Women	66 (59 %)	60 (52 %)
Years of education ^b	13.4 (0.2)	13.0 (0.2)
Income ^b	4.4 (0.2) [\$30,000–\$39,000/year]	4.6 (0.2) [\$30,000–\$39,000/year]
BMI ^a	26.5 (7.5)	28.1 (10.1) *
Obesity (n)		
No	84 (75 %)	67 (58 %) **
Yes	28 (25 %)	49 (42 %)
Diabetes (n)		
No	111 (100 %)	110 (97 %)
Yes	0 (0 %)	4 (3 %)
Lifetime nicotine dependence (n)		
No	109 (97 %)	81 (70 %) ***
Yes	3 (3 %)	35 (30 %)
Current alcohol use (n)		
No	70 (63 %)	49 (42 %) **
Yes	42 (37 %)	67 (58 %)
Current drinking quantity ^a (# of drinks past week)	0 (2.0)	1.5 (8) ***

Groups were compared using the Mann–Whitney U test for continuous variables and Fisher's Exact Test for dichotomous variables

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^a values are median (IQR)

^b values are mean (SEM)

Table 2
Cardiovascular and cardiovascular characteristics of participants as a function of lifetime AUD in Native and Mexican American adults ($n = 228$)

Variable	No lifetime AUD ($n = 112$)	Lifetime AUD ($n = 116$)
HR (bpm) ^b	68.9 (0.9)	69.4 (0.9)
Systolic BP (mmHg) ^a	117 (15.7)	123 (18.1) **
Systolic SD (mmHg) ^b	7.4 (0.3)	7.9 (0.3)
Diastolic BP (mmHg) ^a	71.2 (11.4)	75.0 (11.2) ***
Diastolic SD (mmHg) ^b	4.9 (0.2)	5.2 (0.2)
Systolic prehypertension (n)		
No	72 (66 %)	50 (48 %) *
Yes	37 (34 %)	55 (52 %)
Diastolic prehypertension (n)		
No	97 (89 %)	84 (80 %)
Yes	12 (11 %)	21 (20 %)
Systolic hypertension (n)		
No	72 (96 %)	50 (82 %) *
Yes	3 (4 %)	11 (18 %)
Diastolic hypertension (n)		
No	97 (97 %)	84 (88 %) *
Yes	3 (3 %)	11 (12 %)
LF-HRV (ms ²) ^b	1483 (210)	1286 (138)
HF-HRV (ms ²) ^b	1674 (194)	1491 (202)
LF/HF ratio ^b	1.6 (0.3)	1.7 (0.3)
RMSSD (ms) ^b	55.9 (2.9)	51.5 (2.4)
HR _{DB} (beats/min) ^a	25.7 (10.7)	22.9 (9.1) *

Participants with pre-hypertension or hypertension (Yes) were compared to participants with normal blood pressure (No). *HR_{DB}* the average of maximal inspiratory HR—minimal expiratory HR for each cycle of 5 breaths. Groups were compared using the Mann–Whitney *U* test for continuous variables and Fisher's Exact Test for dichotomous variables

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^a values are median (IQR)

^b values are mean (SEM)

Table 3
Comparison of variables entered into logistic regression to assess their association with systolic prehypertension and hypertension in this community sample of Native and Mexican Americans

Variables	No Systolic pre-/hypertension (<i>n</i> = 122)	Systolic pre-/hypertension (<i>n</i> = 106)
Age (years) ^{<i>b</i>}	23.0 (0.3)	24.2 (0.4) *
HR (bpm) ^{<i>b</i>}	69.6 (0.8)	68.3 (1.0)
LF-HRV (ms ²) ^{<i>b</i>}	1241 (123)	1552 (229)
HF-HRV (ms ²) ^{<i>b</i>}	1565 (144)	1601 (253)
LF/HF Ratio ^{<i>a</i>}	0.70 (1.3)	1.1 (1.4) *
RMSSD (ms) ^{<i>b</i>}	54.2 (2.3)	53.2 (3.1)
HR _{DB} (beats/min) ^{<i>b</i>}	25.3 (0.6)	23.3 (0.8) *
Systolic SD (mmHg) ^{<i>b</i>}	7.2 (0.2)	8.2 (0.4) *
Diastolic SD (mmHg) ^{<i>b</i>}	4.9 (0.2)	5.3 (0.2)
Current drinking quantity ^{<i>b</i>} (# of drinks past week)	2.5 (0.4)	5.6 (1.4)
Gender (n)		
Men	19 (16 %)	83 (78 %) ***
Women	103 (84 %)	23 (22 %)
Obesity (n)		
No	93 (76 %)	58 (55 %) **
Yes	29 (24 %)	48 (45 %)
Diabetes (n)	120 (99 %)	101 (97 %)
No	1 (1 %)	3 (3 %)
Yes		

HR_{DB} the average of maximal inspiratory HR—minimal expiratory HR for each cycle of 5 breaths. Groups were compared using the Mann–Whitney *U* test for continuous variables and Fisher's Exact Test for dichotomous variables

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^{*a*} values are median (IQR)

^{*b*} values are mean (SEM)

Table 4
Comparison of variables entered into logistic regression to assess their association with diastolic prehypertension and hypertension in this community sample of native and Mexican Americans

Variables	No Diastolic pre-/hypertention (n = 181)	Diastolic pre-/hypertension (n = 47)
Age (years) ^a	23 (6)	26.0 (7) ***
HR (bpm) ^b	68.3 (0.7)	71.5 (1.5)
LF-HRV (ms ²) ^b	1433 (144)	1191 (242)
HF-HRV (ms ²) ^a	1011 (1496)	609 (1082) *
LF/HF Ratio ^b	1.7 (0.2)	1.8 (0.4)
RMSSD (ms) ^b	55.1 (2)	48.1 (4.5) *
HR _{DB} (beats/min) ^a	24.2 (9.5)	20.9 (11.0) **
Systolic SD (mmHg) ^b	7.5 (0.2)	8.0 (0.5)
Diastolic SD (mmHg) ^a	4.5 (2.4)	5.8 (3.1) **
Current drinking quantity ^b (# of drinks past week)	3.2 (0.6)	6.6 (2.5)
Gender (n)		
Men	75 (41 %)	27 (57 %)
Women	106 (59 %)	20 (43 %)
Obesity (n)		
No	134 (74 %)	17 (36 %) ***
Yes	47 (26 %)	30 (64 %)
Diabetes (n)		
No	176 (98 %)	45 (98 %)
Yes	3 (2 %)	1 (2 %)

HR_{DB} the average of maximal inspiratory HR—minimal expiratory HR for each cycle of 5 breaths. Groups were compared using the Mann–Whitney *U* test for continuous variables and Fisher's Exact Test for dichotomous variables

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$

^a values are median (IQR)

^b values are mean (SEM)

Table 5
Multiple linear regression results for the full model and final model of mean blood pressure outcome variables ($n = 228$)

	Full model			Variables retained in final model		
	<i>B</i>	<i>SE</i>	<i>t</i>	<i>p</i> value	<i>t</i>	<i>p</i> value
Systolic blood pressure						
Age	0.041	0.177	0.231	0.817		
HR _{rest}	0.058	0.100	0.577	0.565		
LF-HRV	0.000	0.000	-0.682	0.496		
HF-HRV	0.000	0.001	0.467	0.641		
LF/HF Ratio	0.066	0.264	0.249	0.804		
RMSSD	-0.041	0.060	-0.690	0.491		
HR _{DB}	-0.115	0.103	-1.116	0.266		
SBP SD	0.303	0.244	1.243	0.215		
DBP SD	0.440	0.344	1.279	0.202		
Current drinking quantity	-0.043	0.064	-0.674	0.501		
Male gender	16.916	1.402	12.063	0.000	12.951	0.000
Obesity	7.532	1.553	4.851	0.000	4.953	0.000
Lifetime AUD	2.411	1.375	1.753	0.081	1.971	0.050
Diastolic blood pressure						
Age	0.233	0.134	1.733	0.084		
HR _{rest}	0.207	0.076	2.732	0.007	4.272	0.000
LF-HRV	0.000	0.000	-0.074	0.941		
HF-HRV	0.000	0.000	0.658	0.511		
LF/HF Ratio	0.049	0.200	0.246	0.806		
RMSSD	-0.018	0.046	-0.395	0.693		
HR _{DB}	-0.161	0.078	-2.068	0.040	-2.312	0.022
SBP SD	-0.205	0.184	-1.113	0.267		
DBP SD	0.763	0.260	2.933	0.004	2.788	0.006
Current drinking quantity	0.015	0.049	0.299	0.765		
Male gender	5.146	1.061	4.851	0.000	5.031	0.000
Obesity	4.795	1.175	4.082	0.000	4.168	0.000

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Full model				Variables retained in final model			
	B	SE	t	p value	t	p value	
Lifetime AUD	2.028	1.041	1.948	0.053	2.038	0.043	

Multiple linear regression was used to assess the association of cardiovascular autonomic control and CVD risks with mean systolic and diastolic blood pressure (BP). The following independent variables were entered into the initial model for each regression: age at interview, mean resting heart rate (HR), low-frequency HRV (LF), high-frequency HRV (HF), LF/HF ratio, the square root of the mean squared successive differences between interbeat interval (RMSSD), HR response to deep breathing (HRDB), standard deviation (SD) of mean systolic BP (SBP SD), SD of mean diastolic BP (DBP SD), self-reported current drinking quantity (# of drinks during previous week), gender, obesity and lifetime AUD. Final models were determined using backward stepwise regression