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Association of Alcohol Use Biomarkers and Cognitive Performance in Veterans with Problematic Alcohol Use and Posttraumatic Stress Disorder: Data from the Mind Your Heart Study

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Abstract

We conducted a study of alcohol use biomarkers and cognitive performance among 85 veterans with problematic alcohol use and posttraumatic stress disorder (PTSD). All analyses were adjusted for demographics, depression, anxiety, and PTSD symptoms. Elevated levels of aspartate aminotransferase (AST) were associated with worse performance on the Trail Making Test Part A and Hopkins Verbal Learning Test. Two other biomarkers were not associated with any neurocognitive measures. Indirect alcohol use biomarkers (e.g., AST) may have a specific role in identifying those veterans with problematic alcohol use and PTSD who show a change in psychomotor speed and immediate verbal memory performance.

Keywords

alcohol use biomarkers; cognitive performance; problematic alcohol use; posttraumatic stress disorder

INTRODUCTION

Cognition is a key area of focus in the field of clinical alcohol research[1, 2]. Individuals with alcohol use disorders demonstrate impairments in multiple cognitive domains[3–5]. Cognitive impairment, in turn, can impact a range of alcohol-related clinical outcomes, including response to treatment and rates of relapse and abstinence[6–9]. Despite the importance of cognition, screening for cognitive impairment in patients with alcohol use disorders remains

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Conflicts of Interest
The authors report no conflicts of interest.

challenging[10–14], as neurocognitive evaluations are typically time-consuming and may not be feasibly in busy primary care settings[15, 16]. Therefore, we must identify clinical measures that can be quickly collected and provide information on cognitive domains in patients with alcohol use disorders.

Biomarkers of alcohol use may fulfill this role, as many are collected as part of routine laboratory testing. If biomarkers are associated with cognitive performance, they could serve as useful clinical tools to identify patients that may benefit from more detailed cognitive screening. Alcohol use biomarkers are generally divided into indirect and direct biomarkers[17, 18]. The indirect biomarkers include alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), mean corpuscular volume (MCV), and carbohydrate-deficient transferrin (CDT). Previous research has shown that several indirect alcohol use biomarkers correlate with cognitive performance in individuals with alcohol use disorders: ALT[19], AST[20], GGT[21], and MCV[22].

However, existing research on the association of these biomarkers and cognitive performance is limited. A particular area of concern is how they will perform in the setting of mental health disorders, such as posttraumatic stress disorder (PTSD), that are common among patients with problematic alcohol use and can lead to particularly poor clinical outcomes[23–26]. Problematic alcohol use, defined as consuming 5 or more drinks for men (or 4 or more drinks for women) on any occasion in the past year[27, 28], is a significant area of concern for veterans. For example, one study of 88,235 veterans returning from Operation Iraqi Freedom found that 12–15% of veterans endorsed problematic alcohol use in the 3 to 6 months following their return from combat[29]. Problematic alcohol use is well known to be associated with PTSD. For example, in another study of 287 Iraq and Afghanistan war veterans, veterans who screened positive for PTSD or depression were 2 times more likely to report problematic alcohol use compared to veterans who did not screen positive for these disorders[30]. Thus, exploring the relationship between alcohol use biomarkers and cognitive performance is relevant to a significant number of veterans who suffer from problematic alcohol use and comorbid PTSD.

The relationship between alcohol use biomarkers and cognitive performance in veterans with PTSD has only been previously explored in one other study, specifically among veterans with alcohol dependence[31]. This study found AST and GGT (gamma-glutamyltransferase) to predict performance on the Hopkins Verbal Learning Test—Revised %Retention, and GGT predicted performance on the Trails Making Test Part A. To our knowledge, in veterans with *problematic alcohol use* and PTSD, no studies have explored the relationship between alcohol use biomarkers and cognitive performance. In order to address this concern, we examined data from 85 veterans with comorbid PTSD and problematic alcohol use that were participating in a larger cohort study. At baseline, this study included indirect alcohol use biomarkers (MCV, AST, ALT) and several neurocognitive measures, which allowed us to explore the relationship between biomarkers and cognitive performance. We hypothesized that elevated levels of the indirect biomarkers (MCV, AST, ALT) would be associated with worse baseline cognitive performance in several domains.

MATERIALS AND METHODS

Participants

Full details of the primary study used for this analysis have already been published[32, 33]. Briefly, the Mind Your Heart Study (MYHS) is a prospective cohort study designed to understand the long-term health effects of PTSD, particularly why veterans with PTSD are at increased risk for developing cardiovascular disease. Between 2/2008 and 6/2010, 746 outpatients recruited from two San Francisco Bay Area Veterans Affairs medical centers were enrolled in the cohort and completed a comprehensive baseline health assessment. Analyses for the present study were restricted to 86 participants who met criteria for PTSD and problematic alcohol use as described below; one participant with a dementia diagnosis was also excluded, resulting in the final sample size of 85. All participants provided informed consent. The study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF), and the Research and Development Committee at the San Francisco Veterans Affairs Medical Center (SFVAMC).

Procedures

All participants completed a baseline visit that included a detailed clinical interview, demographic history, a comprehensive medical history that included assessment of substance use, a fasting blood draw and neurocognitive testing.

Measures

Blood samples were obtained, and MCV, AST, and ALT levels were measured at the San Francisco VA Medical Center clinical laboratory. PTSD diagnostic status and current PTSD symptoms score were assessed with the Clinician-Administered PTSD Scale[34] (CAPS; a structured interview for diagnosing PTSD) and the PTSD Checklist-Civilian Version (PCL-C)[35, 36]. Measures of depression and anxiety included the 9-item Patient Health Questionnaire[37] (PHQ-9) and the Hospital Anxiety and Depression Scale[38] (HADS). The 10-item physical functioning subscale of the Short Form Health Survey[39] assessed functional status. A standardized questionnaire was used to assess demographics and medical history[32].

Alcohol use was measured with the Alcohol Use Disorder Identification Test-C[40] (AUDIT-C). Only female participants with a score of 3 or greater, and only male participants with a score of 4 or greater, were included in this analysis. These screening cut-offs, which approximate a frequency of consuming 5 or more drinks for men (or 4 or more drinks for women) on any occasion in the past year, have previously been used to define problematic alcohol use[40].

A neurocognitive battery was administered by trained research personnel to assess psychomotor speed, simple visual attention, task switching, cognitive flexibility, verbal fluency, category fluency and verbal memory. The Digit Symbol Coding subtest[41] of the Wechsler Adult Intelligence Scale-Revised assessed psychomotor speed, based on the total number of correctly coded number-symbol pairs. Performance time on the Trail Making Test[42] (TMT) Part A assessed psychomotor speed and simple visual attention and Part B

assessed task switching and cognitive flexibility. The Benton Controlled Oral Word Association Test[43] (COWAT) assessed verbal fluency. Participants were given 1 minute to name as many words as possible beginning with L or F, and the mean number of valid L and F words was used as the outcome. Category fluency[44] was assessed by asking participants to name as many words as possible in the categories of animals and vegetables in 1 minute. The mean number of valid animals and vegetables was used as the outcome. The Hopkins Verbal Learning Test-Revised[45] (HVLT-R) assessed verbal memory. Scores from Trial 1 (form #5) were used as a measure of immediate verbal recall.

Statistical Analysis

We conducted all analyses using IBM SPSS Statistics version 22 (Armonk, NY). We used *z*-scores to assess continuous variables for extreme values (> 3.29 or < −3.29); we adjusted any extreme values to the next highest value. We initially conducted descriptive analyses on all variables. For the primary analyses examining the association of biomarkers and cognitive performance, we used the General Linear Model function in SPSS, where we selected each neurocognitive measure as the dependent variable and each alcohol use biomarker (MCV, AST, ALT) as the independent variable. Since this was an exploratory secondary analysis, we considered p-values < 0.05 as significant. We first conducted an analysis adjusting for potentially confounding demographic factors: age, sex, education, and ethnicity. We then conducted a fully-adjusted analysis, which adjusted for: demographics, PHQ-9 score, HADS score and CAPS score. Since mood symptoms[46] and PTSD symptoms[47] and alcohol intake can affect cognition, we felt these were important variables to include in the fully-adjusted analyses.

RESULTS

The demographic characteristics of participants are presented in Table 1. Most of the participants in this analysis were men in their mid-50's, Caucasian, married, and had some college education. Table 2 describes the clinical features of the participants. A significant percentage of participants had comorbid hypertension, depression, and anxiety. Table 3 describes the substance use features of the participants. 31.8% of the participants drank 1–2 drinks/day when drinking, 60% of the participants drank alcohol 4–5 times/week in the past year, 35.3% of participants used marijuana in the past year, and 27.1% of participants currently smoked cigarettes.

Table 4 reports the raw scores of the 6 neurocognitive measures used for this analysis. Table 5 shows the association of biomarkers and neurocognitive measures from regression models. In models adjusted for demographics, elevated AST was associated with worse performance on the Trail Making Test Part A. In models adjusted for demographics and clinical variables, elevated AST was associated with worse performance on the Trail Making Test Part A and Trial 1 of the Hopkins Verbal Learning Test. Figures 1 and 2 illustrate the relationship of AST with Trail Making Test Part A and Trial 1 of the Hopkins Verbal Learning Test in scatterplot format. AST was not associated with any other neurocognitive measure. MCV and ALT were not associated with any neurocognitive measures.

DISCUSSION

In this study of veterans with problematic alcohol use and PTSD, we found that elevated levels of the indirect alcohol use biomarker AST was associated with worse performance on measures of psychomotor speed and immediate verbal memory. This association was independent of demographics, depression, anxiety, and PTSD. AST was not associated with any other neurocognitive measure. MCV and ALT were not associated with any neurocognitive measures.

AST may be linked with cognitive performance for several reasons. First, as a marker of heavy alcohol use, it may correlate with the neurotoxic effects of alcohol. Second, it may reflect the effects of hepatic dysfunction on cognition. The association of some neurocognitive measures with AST is consistent with previous research in those who meet criteria for a full alcohol use disorder[20], including in our own previous report[31]. This study examined individuals with *problematic alcohol use*, who may have earlier stages of liver dysfunction than patients with alcohol use disorders. In this setting, cognitive changes may be due to the liver starting to fail to catabolize circulating neurotoxins[48], and abnormal AST may help identify patients who could benefit from further testing for cognitive impairment and counseling about alcohol use.

ALT and MCV were not independently associated with cognitive performance. This may be due to their differential distribution in body tissues. Whereas ALT is predominantly of hepatic origin, AST can be found in tissues outside the liver, such as the brain[49]. Regarding MCV, though some studies show that erythrocyte volume may impact cognition[50], we were not able to replicate such a finding in this analysis.

This analysis suggests that one of the indirect alcohol use biomarkers, specifically AST, may serve as an indicator of a subset of patients with problematic alcohol use and PTSD who are at an increased risk for cognitive impairment. Alcohol use biomarkers are not a substitute for a comprehensive neurocognitive assessment. Rather, such biomarkers might be used to identify potential areas of cognitive concern, which would then warrant a referral for a more comprehensive neurocognitive assessment. One advantage of AST, compared to more sophisticated alcohol use biomarkers, is that it can be easily ordered in most clinical settings and is often checked by primary care physicians as a routine screening laboratory measure.

Our analysis of alcohol use biomarkers and cognitive performance has several strengths. First, we were able to analyze 5 different domains of cognition. Second, we were able to control for multiple demographic and clinical factors that can affect cognition. Third, the study sample was from a clinical cohort of outpatients rather than a highly-selected clinical trial population. Therefore, these findings may be generalizable to other veteran populations. Finally, this is the first known analysis to explore the relationship between alcohol use biomarkers and cognitive performance in veterans with comorbid problematic alcohol use and PTSD. Given several recent studies linking PTSD to cognitive dysfunction[51–53], this high risk group could benefit from improved cognitive screening measures.

Our findings should also be interpreted in light of several limitations. First, the primary study was not specifically designed to assess the association of alcohol use biomarkers and

cognitive performance, and therefore it would be important to explore additional biomarkers in future studies. Second, the sample was naturalistic and included veterans with other psychiatric comorbidities. Though the inclusiveness of the study helps make the results more generalizable, it may have contributed to the non-significant findings in Table 5. More stringent inclusion/exclusion criteria for primary psychiatric disorders and substance use disorders may help clarify the relationship between alcohol use biomarkers and cognitive performance in veterans with problematic alcohol use and PTSD in the future. Finally, a more comprehensive neurocognitive battery evaluating other cognitive domains (e.g., attentional bias, impulsivity, decision-making, visuospatial memory) may add further information on the relationship between alcohol use biomarkers and other cognitive domains in this population of veterans.

CONCLUSION

This analysis of alcohol use biomarkers and cognitive performance in veterans with problematic alcohol use and PTSD found that AST may have a specific role in identifying patients who demonstrate changes in psychomotor speed and immediate verbal memory performance. Future directions to confirm or refute these findings include the use of a more complete neurocognitive battery and recruiting a sample with fewer psychiatric comorbidities.

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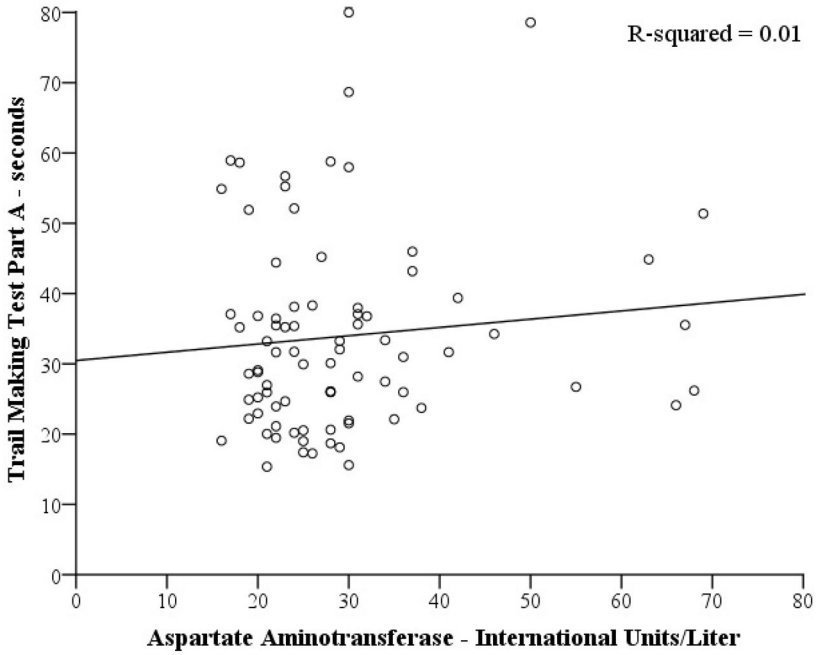

Figure 1.
Scatterplot of Trail Making Test Part A versus Aspartate Aminotransferase.

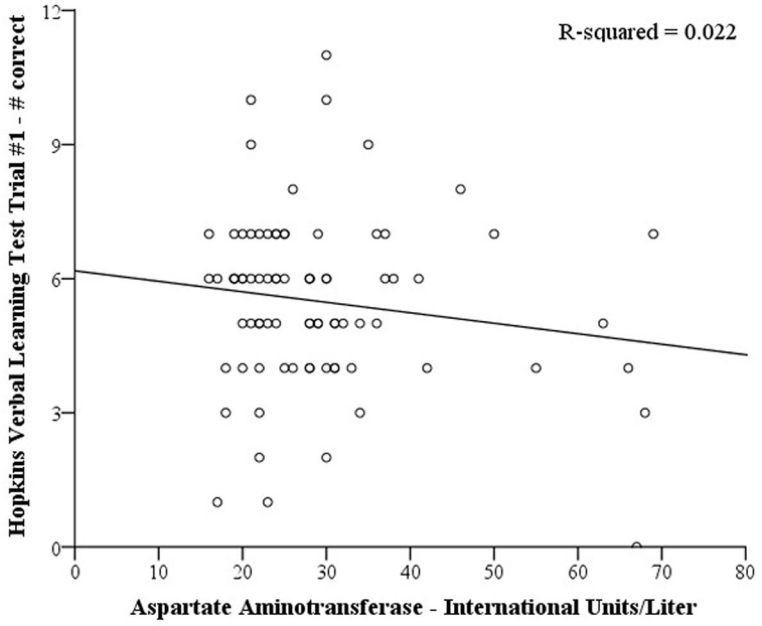

Figure 2.
Scatterplot of Hopkins Verbal Learning Test Trial #1 versus Aspartate Aminotransferase.

Table 1

Demographic Characteristics of Participants with Problematic Alcohol Use and Posttraumatic Stress Disorder (n = 85).

	Mean (S.D.) or %[a]
Age	56.9 (12.7)
Male	92.9%
Caucasian	58.8% [n = 83]
African-American	16.5% [n = 83]
Hispanic	16.5% [n = 84]
Married	47.1%
Divorced	18.8%
Never Married	24.7%
High school graduate	15.3%
Some college	49.4%
College degree	22.4%
Working in a paid job	27.1%
Living alone	29.4%

[a]Sample sizes in some cells vary due to missing data points.

Table 2

Clinical Features of Participants with Problematic Alcohol Use and Posttraumatic Stress Disorder (*n* = 85).

	Mean (S.D.) or %[a]
AUDIT-C summary score	6.3 (2.4)
Short Form Health Survey 36 physical limitation score	23.4 (5.4) [*n* = 84]
PTSD Checklist-Civilian total score	55.1 (14.2)
Clinician-Administered PTSD Scale symptom score	60.3 (21.5)
Depression symptom score	10.6 (5.6)
Anxiety symptom score	9.8 (3.5)
Hypertension	61.2%
Elevated cholesterol	56.5%
Stroke	3.5%
Diabetes	15.3%
Thyroid disease	3.5%
Seizures	5.9%
Parkinson's disease	1.2%
Liver disease	18.8%
Mean Corpuscular Volume (MCV)	92.4 (5.0)
Aspartate Aminotransferase (AST)	29.9 (15.1)
Alanine Aminotransferase (ALT)	32.0 (26.4)

[a]Sample sizes in some cells vary due to missing data points.

Table 3

Substance Use Features of Participants with Problematic Alcohol Use and Posttraumatic Stress Disorder (*n* = 85).

	Mean (S.D.) or %[a]
Currently smokes cigarettes	27.1%
1–10 years smoked cigarettes	23.5%
11–20 years smoked cigarettes	11.8%
21–30 years smoked cigarettes	12.9%
>30 years smoked cigarettes	24.7%
Drank alcohol monthly or less in past year	5.9%
Drank alcohol 2–4 times/month in past year	9.4%
Drank alcohol 2–3 times/week in past year	18.8%
Drank alcohol 4–5 times/week in past year	60%
1–2 alcoholic drinks/day when drinking	31.8%
3–4 alcoholic drinks/day when drinking	16.5%
5–6 alcoholic drinks/day when drinking	10.6%
7–9 alcoholic drinks/day when drinking	12.9%
Had 6+ alcoholic drinks <monthly in the past year	31.8%
Had 6+ alcoholic drinks monthly in the past year	12.9%
Had 6+ alcoholic drinks weekly in the past year	10.6%
Had 6+ alcoholic drinks daily/almost daily in the past year	16.5%
Past year use of illicit drugs	10.6%
Past year use of marijuana	35.3%
Days of Marijuana use in last 30 days	30 [*n* = 2]
Days of Methadone use in last 30 days	30 [*n* = 1]
Days of Other opiate use in last 30 days	24.5 (11) [*n* = 4]
Days of Sedative use in last 30 days	30 [*n* = 1]

[a]Sample sizes in some cells vary due to missing data points.

Table 4

Cognitive Performance of Participants with Problematic Alcohol Use and Posttraumatic Stress Disorder (*n* = 85).

Domain	Measure	Mean (S.D.)[a]
Processing Speed	Digit Symbol Coding, # of correct number-symbol pairs	56.5 (17.4) [*n* = 83]
	Trail Making Test Part A, seconds	34.3 (15.6) [*n* = 82]
Cognitive Flexibility	Trail Making Test Part B, seconds	89.1 (62.2) [*n* = 82]
Letter Fluency	Mean # of L words and F words in 1 minute	13.2 (3.7) [*n* = 82]
Category Fluency	Mean of # correct animals and # correct vegetables	18.6 (4.8) [*n* = 82]
Immediate Verbal Recall	Hopkins Verbal Learning Test Trial #1, # correct	5.5 (1.9) [*n* = 82]

[a]Sample sizes in some cells vary due to missing data points.

Table 5

Association of Cognitive Performance and Alcohol Use Biomarkers in Participants with Problematic Alcohol Use and Posttraumatic Stress Disorder (*n* = 85).

	Demographically-adjusted			Fully-adjusted		
	MCV	**AST**	**ALT**	**MCV**	**AST**	**ALT**
Processing Speed – Digit Symbol Coding	$F(62, 14) = 0.40$, $p = 0.99$	$F(32, 44) = 1.34$, $p = 0.18$	$F(39, 37) = 0.76$, $p = 0.80$	$F(62, 11) = 0.62$, $p = 0.88$	$F(32, 41) = 1.22$, $p = 0.27$	$F(39, 34) = 0.82$, $p = 0.73$
Processing Speed – Trail Making Test Part A	$F(62, 13) = 0.60$, $p = 0.91$	**$F(31, 44) = 2.57$, $p = 0.002$**	$F(39, 36) = 0.86$, $p = 0.68$	$F(62, 10) = 1.47$, $p = 0.26$	**$F(31, 41) = 2.40$, $p = 0.005$**	$F(39, 33) = 0.92$, $p = 0.60$
Cognitive Flexibility	$F(62, 13) = 1.96$, $p = 0.09$	$F(32, 43) = 1.19$, $p = 0.30$	$F(39, 36) = 0.86$, $p = 0.68$	$F(62, 10) = 1.58$, $p = 0.22$	$F(32, 40) = 1.65$, $p = 0.07$	$F(39, 33) = 0.93$, $p = 0.59$
Letter Fluency	$F(61, 14) = 0.95$, $p = 0.59$	$F(31, 44) = 0.90$, $p = 0.61$	$F(39, 36) = 0.94$, $p = 0.58$	$F(61, 11) = 1.07$, $p = 0.49$	$F(31, 41) = 1.14$, $p = 0.35$	$F(39, 33) = 0.94$, $p = 0.58$
Category Fluency	$F(61, 14) = 0.85$, $p = 0.69$	$F(31, 44) = 1.02$, $p = 0.47$	$F(39, 36) = 1.48$, $p = 0.12$	$F(61, 11) = 1.20$, $p = 0.40$	$F(31, 41) = 0.98$, $p = 0.52$	$F(39, 33) = 1.57$, $p = 0.09$
Immediate Verbal Recall	$F(61, 14) = 0.55$, $p = 0.95$	$F(31, 44) = 1.46$, $p = 0.12$	$F(39, 36) = 1.27$, $p = 0.24$	$F(61, 11) = 0.46$, $p = 0.97$	**$F(31, 41) = 1.99$, $p = 0.02$**	$F(39, 33) = 1.36$, $p = 0.19$