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Regional Cortical Brain Volumes at Treatment Entry Relates to Post Treatment WHO Risk Drinking Levels in Those with Alcohol Use Disorder

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Abstract

Background: Abstinence following treatment for alcohol use disorder (AUD) is associated with significant improvements in psychiatric and physical health, however, recent studies suggest resumption of low risk levels of alcohol use can also be beneficial. The present study assessed whether posttreatment levels of alcohol use were associated with neurobiological differences at treatment entry.

Methods: Individuals seeking treatment for AUD (n=75) and light/non-drinking controls (LN, n=51) underwent 1.5T magnetic resonance imaging. The volumes of 34 bilateral cortical regions of interest (ROIs) were quantitated via FreeSurfer. Individuals with AUD were classified according to post-treatment alcohol consumption using the WHO risk drinking levels (abstainers: AB; low risk: RL; or higher risk: RH). Regional volumes for AB, RL and RH, at treatment entry, were compared to LN.

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Contributors

Drs. Durazzo and Meyerhoff were responsible for study concept and design. Dr. Durazzo was responsible for conducting or supervising all participant recruitment and screening, administration or supervision of all clinical and behavioral assessments, execution of FreeSurfer processing and quality control, all statistical analyses, data interpretation and writing the manuscript. Dr. Meyerhoff, Dr. May, Ms. Stephens and Mr. Kraybill were involved in data interpretation, editing of all manuscript versions, and contributed significant intellectual content to all manuscript versions. All authors approved the final version of the manuscript.

Declaration of Competing Interest

No conflict declared.

Conflict of interest No conflicts declared.

Results: Relative to LN, AB demonstrated smaller volumes in 18/68 (26%), RL in 24/68 (35%) and RH in 34/68 (50%) ROIs with the largest magnitude volume differences observed between RH and LN. RH and RL reported a higher frequency of depressive disorders than AB. Among RH and RL, level of depressive and anxiety symptomatology were associated with daily number of drinks consumed after treatment.

Conclusions: Volumetric differences, at treatment entry, in brain regions implicated in executive function and salience networks corresponded with post-treatment alcohol consumption levels suggesting that preexisting differences in neural integrity may contribute to treatment outcomes. Depressive and anxiety symptomatology was also associated with brain morphometrics and alcohol use patterns, highlighting the importance of effectively targeting these conditions during AUD treatment.

Keywords

alcohol use disorder; WHO risk drinking levels; MRI; brain volumes; depression

1. INTRODUCTION

Multiple biopsychosocial factors contribute to the chronic relapse and remit cycle observed in those with alcohol use disorder (AUD) (Durazzo and Meyerhoff, 2017; Nguyen et al., 2020; Witkiewitz, 2011). Identification of the factors associated with successful treatment outcomes is necessary to develop interventions that effectively reduce the persistently high rates of resumption of hazardous levels of alcohol consumption posttreatment and the associated adverse psychosocial consequences (Witkiewitz, 2011; Witkiewitz and Marlatt, 2007). The biopsychosocial correlates of treatment outcome, however, are dependent on the operational definition of treatment success or relapse. The lack of consensus regarding the operational definition of relapse in the AUD field (Sliedrecht et al., 2022; Witkiewitz et al., 2020) has resulted in a wide range of findings for the biopsychosocial variables associated with treatment outcome.

Historically, consumption of any alcohol posttreatment frequently has been classified as a relapse and/or an unsuccessful clinical outcome, with at least 60% of individuals returning to hazardous levels of alcohol consumption after AUD treatment (Maisto et al., 2006; Nguyen et al., 2020). Sustained abstinence from alcohol over the first year following treatment is related to significant neurobiological, neurocognitive and postural stability recovery (Durazzo and Meyerhoff, 2020; Durazzo et al., 2015; Rosenbloom et al., 2007; Schmidt et al., 2014; Zou et al., 2018) as well as adaptive psychosocial functioning (Durazzo et al., 2008; Maisto et al., 2006). Magnetic resonance imaging (MRI) studies that investigated the morphological correlates of relapse found, at treatment entry, those who relapsed posttreatment had thinner cortices, smaller surface areas, and reduced volumes in multiple brain regions compared to those who maintained continuous abstinence for at least 3 months; these morphological differences were most consistently observed in anterior frontal regions (i.e., dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex) (Beck et al., 2012; Cardenas et al., 2011; Durazzo and Meyerhoff, 2017; Durazzo et al., 2011b; Rando et al., 2011; Seo et al., 2015). Additionally, higher frequency of major depressive/alcohol-induced mood disorder and greater anhedonic depressive

symptomatology were also significantly associated with increased relapse risk (Durazzo and Meyerhoff, 2017; Nguyen et al., 2020).

Although sustained post-treatment abstinence may be associated with optimal biopsychosocial outcomes, for some with AUD, maintenance of continuous abstinence may represent an unrealistic or undesirable objective and potentially discourage individuals from seeking or fully engaging in treatment (Witkiewitz et al., 2017). Accordingly, an increasing number of studies have investigated non-abstinent outcomes, involving variable levels of reduced alcohol consumption, and the associated biopsychosocial consequences (Witkiewitz, Montes, et al., 2020). Relative to pretreatment levels, moderate-to-large reductions in alcohol consumption after treatment were related to improved psychosocial, physical and psychological functioning (Charlet and Heinz, 2017; Gastfriend et al., 2007; Witkiewitz et al., 2018a; Witkiewitz et al., 2017b). This suggests that sustained abstinence following treatment may not be the lone adaptive/desirable treatment outcome or the only meaningful clinical trial outcome measure.

The World Health Organization risk drinking levels (WHO-RDL) is a taxonomy that designates sex-specific mortality risk associated with specific ranges of alcohol consumption. Categories are defined by the amount of alcohol consumed in grams per day (one standard drink contains 14g of pure ethanol), with sex-specific ranges: abstinent (0 g males/females), low risk (1 to 40g males/1 to 20g females), medium risk (41 to 60g males/21 to 40g females), high risk (61 to 100g males/41 to 60g females), or very high risk (101+ g males/61+ g females; (WHO, 2000). Assessment of the consequences associated with reduced alcohol consumption corresponding to WHO-RDLs are of increasing interest as a potentially clinically beneficial treatment outcome. Compared to pretreatment consumption levels, reductions in WHO-RDL during or after treatment were associated with significantly improved psychosocial functioning, physical health, and quality of life (Knox et al., 2020; Knox et al., 2018; Witkiewitz et al., 2018b), decreased depression/anxiety symptomatology (Knox et al., 2019) and fewer alcohol-related adverse consequences (Witkiewitz et al., 2019; Witkiewitz et al., 2017a). Additionally, individuals that decreased consumption to the WHO-RDL low risk level showed psychosocial functioning equivalent to those that maintained abstinence assessed over the same observation period (Witkiewitz et al., 2018a). The reduced alcohol-related consequences and improvements in physical/mental health associated with lower WHO-RDL alcohol consumption were enduring in some cohorts (Witkiewitz *et al.*, 2019; Witkiewitz, Heather, et al., 2020).

While several studies have reported the psychosocial, psychiatric and physical health benefits of reduced alcohol consumption corresponding to WHO-RDL, few studies considered the neurobiological correlates of WHO-RDL defined reductions in alcohol use. We previously reported that lobar brain volumes (e.g., total frontal lobe) of those who returned to WHO-RDL low-risk levels of alcohol use within approximately 8-months after AUD treatment were not significantly different from those who maintained complete abstinence over the same interval; participants who consumed alcohol at higher WHO-RDL levels (medium, high and very high levels combined), demonstrated significantly smaller volumes in frontal gray matter (GM) and thalamic regions than individuals who maintained complete abstinence; however, they also showed significantly smaller volumes than those

that consumed alcohol at low WHO-RDL levels (Meyerhoff and Durazzo, 2020). In a follow up study, examining brain volumes within 34 bilateral cortical regions of interest (May et al., 2023), we found individuals that consumed alcohol at higher rates (WHO-RDL medium, high, and very high risk levels combined) at 8-months post-treatment, demonstrated significant volume loss in cortical nodes of circuits involved in executive functions/cognitive control and positive and negative affect, relative to light/non-drinking controls. Those who resumed consumption at low WHO-RDL following treatment showed significant volume loss in cortical nodes corresponding to the executive function/cognitive control circuit. Low and higher WHO-RDL showed smaller volumes in executive functions/cognitive control cortical regions than abstainers. Furthermore, compared to controls, abstainers had smaller volumes in few cortical regions and these differences were of lower magnitude than those of WHO-RDL low and higher groups relative to controls; regions where abstainers differed from controls were largely in cortical nodes of the default mode network [see (Padula et al., 2022; Williams, 2016) for a review of the circuits described above]. WHO-RDL low and higher also reported greater depressive and anxiety symptomatology than abstainers. Collectively, our previous studies on regional brain volumes suggest resumption of low WHO-RDL alcohol consumption is associated with significantly better brain structural outcomes than consumption at higher WHO-RDL levels following AUD treatment.

Given the brain tissue volume and psychiatric symptomatology differences between the WHO-RDL post-treatment levels observed in our previous studies (May et al., 2023; Meyerhoff and Durazzo, 2020), the current study assessed for differences at treatment entry between healthy, non-smoking, light/non-drinking controls (LN) and individuals who later achieved abstinence or returned to WHO-RDL low or WHO RDL higher (medium, high and very high combined) levels of alcohol consumption following outpatient treatment. Participant assignment to the forgoing three AUD groups was based on their alcohol consumption over a minimum of 6 months post-treatment. Determining regional volume and psychiatric functioning differences between abstainers (AB), WHO-RDL low (RL), and WHO-RDL higher (RH) at the beginning of treatment is necessary to better understand the post-treatment morphological and clinical implications of the WHO-RDL classification. Additionally, assessment for regional brain volumetric differences, based on WHO-RDL classification, at treatment inception may serve as a potential biomarker for identification of individuals at differential risk to resume hazardous alcohol consumption post-treatment. Based on the previously described research, we predicted:

1. Relative to controls, the AUD groups show the following order of global (total left and right hemisphere) and regional volume loss at treatment entry: RH > RL > AB
2. RH demonstrate a higher frequency of depressive and anxiety disorders and higher severity of depressive and anxiety symptomatology than AB and RL.

2. MATERIALS AND METHODS

2.1. Participants

Individuals with an AUD (n = 75) were recruited from the San Francisco VA Medical Center (SFVAMC) Substance Abuse Day Hospital (85%) and the San Francisco Kaiser Permanente Chemical Dependence Recovery (15%) outpatient treatment clinics; data in this study was collected from 2001–2013. All AUD participants were actively in treatment at the time of study and met DSM-IV criteria for alcohol dependence. Treatment program duration typically ranged from 14–35 days and the average treatment length was 28 days [for additional information on the treatment program characteristics see (Durazzo et al., 2008)]. LN (n = 51; nine females) were primarily recruited from the local community via electronic billboards. All participants provided written informed consent prior to engaging in study procedures. Study procedures were approved by the University of California San Francisco and the SFVAMC and conformed to the ethical standards of the Declaration of Helsinki. All participants reported in May et al., 2023 and Meyerhoff and Durazzo, 2020, are included in the current study.

Inclusion/exclusion criteria: Primary inclusion criteria for the alcohol dependent participants were fluency in English, DSM-IV diagnosis of alcohol dependence or abuse at baseline (all met criteria for alcohol dependence), consumption of greater than 150 standard alcohol-containing drinks (i.e., 14 grams of pure ethanol) per month for at least 8 years prior to enrollment for males, and greater than 80 drinks per month for at least 6 years prior to enrollment for females. LN were never-smokers with no history of biomedical and/or psychiatric conditions known or suspected to influence brain neurobiology and neurocognition. LNs consumed less than or equal to an average of 60 standard alcohol-containing drinks per month over lifetime. See Table 1 for group demographic data. Exclusion criteria for alcohol dependent participants were history of: dependence on any substance other than alcohol or nicotine in the 5 years immediately prior to enrollment, any intravenous drug use in the 5 years prior to baseline study, opioid agonist/replacement therapy, HIV seropositivity, arteriovenous malformations, cerebral aneurysm, intrinsic cerebral masses, cerebrovascular accident, myocardial infarction, medically uncontrolled chronic hypertension, type-I diabetes, chronic obstructive pulmonary disease, non-alcohol related seizures, significant exposure to established neurotoxins, demyelinating and neurodegenerative diseases, documented Wernicke-Korsakoff syndrome, delirium, penetrating head injury, and closed head injury resulting in loss of consciousness > 10 minutes. Psychiatric exclusion criteria were history of schizophrenia-spectrum disorders, bipolar disorder, cyclothymia, PTSD, obsessive-compulsive disorder and panic disorder. Given their high rates of comorbidity in AUD (Gilman and Abraham, 2001; Stinson et al., 2005; Durazzo, Nguyen and Meyerhoff, 2020; Padula and Durazzo, 2022), diagnoses of Hepatitis C, type 2 diabetes, hypertension, unipolar mood disorders, and cigarette smoking were permitted for AUD participants. All participants were breathalyzed and urine-tested for illicit substances before assessment and no participant tested positive for alcohol or substances.

2.2. Clinical Measures

At treatment entry, participants completed the Clinical Interview for DSM-IV Axis I Disorders, Version 2.0 (SCID-I/P) and semi-structured interviews for lifetime alcohol consumption (Lifetime Drinking History) and substance use (in-house questionnaire assessing substance type, and quantity and frequency of use). From the Lifetime Drinking History, average number of alcoholic drinks per month over 1 year prior to enrollment and average number of drinks per month over lifetime were calculated. All participants also completed standardized questionnaires assessing depressive (Beck Depression Inventory, BDI) and anxiety symptomatology (State-Trait Anxiety Inventory, Trait form Y-2, STAI), as well as nicotine dependence via the Fagerstrom Tolerance Test for Nicotine Dependence (FTND). See (Pennington et al., 2013) for corresponding references to the above measures. Family history of alcohol-related problems and density was assessed following the procedures as previously described (Mann et al., 1985; Meyerhoff et al., 2004) and calculated only for biological parents and grandparents. Hollingshead Socioeconomic Scale (eight-point scale; lower scores are associated with higher status) was used to determine socioeconomic status at study entry (Nam and Powers, 1983).

WHO-RDL levels were assigned to AUD participants as previously described (e.g., Hasin et al., 2017; Meyerhoff and Durazzo, 2020) and determined from the Timeline Follow Back (Sobell and Sobell, 2000) over the AUD post-treatment follow-up period (a minimum of 6 months). This information was used to classify AUD as AB, RL, RH (combining medium, high, and very high; RH) levels of alcohol consumption. This classification resulted in 38 AB (four females), 20 RL (two females), and 17 RH (two females). Posttreatment alcohol consumption over the follow-up period in the AUD groups were verified by medical records and/or collateral sources (e.g., spouse, relative, close friend), when available.

2.3. Magnetic Resonance Acquisition and Processing

A volumetric magnetization-prepared rapid gradient echo (MPRAGE) was acquired at 1.5T with TR/TE/TI = 9.7/4/300ms, 15° flip angle, 1×1 mm^2 in-plane resolution, and 1.5-mm-thick coronal partitions oriented perpendicular to the main long axes of bilateral hippocampi as seen on sagittal scouts. See Gazdzinski and colleagues (Gazdzinski et al., 2005) for detailed information on MR acquisition methods. FreeSurfer (v4.5) segmentation and cortical surface reconstruction methods were used to obtain regional cortical measures of average volume (mm^3), surface area (mm^2), and thickness (mm) for 34 bilateral anatomical regions of interest (Fischl et al., 2004). Only cortical volumes were considered in this study. See Durazzo and colleagues (Durazzo et al., 2011a; Durazzo et al., 2011b) for FreeSurfer image processing quality control procedures.

2.4. Statistical Analyses

2.4.1. Demographic and Clinical Variables—Groups were compared on baseline demographic, clinical variables and FHD with univariate tests, Chi-square or Fisher's Exact Test, were indicated; $p < .05$ was considered statistically significant for these analyses. All analyses were conducted with Statistical Package for the Social Sciences (SPSS) version 29.

2.4.2. Regional Volumes—In final analyses, groups (AB, RL, RH and LN) were compared on bilateral ROI volumes with generalized linear (GENLIN) models with age and ICV included as covariates, followed by pairwise t-tests. One-year average or lifetime average drinks per month were also individually considered as covariates in pairwise comparisons between AB, RL, and RH. To correct for multiple comparisons, we employed false discovery rate (FDR) using the procedure specified by Benjamini and Hochberg (Benjamini and Hochberg, 1995) adjusting for 408 total pairwise comparisons (six pairwise comparisons for each of the 68 ROIs, resulting in 408 total pairwise comparisons); FDR adjusted pairwise comparisons with $p < .05$ were considered statistically significant. Cohen's *d* (Cohen, 1988) was used to calculate effect sizes (ES) for pairwise comparisons of mean volumes for each ROI. Group comparisons on total left and right hemisphere cortical volume were not corrected for multiple comparisons. Preliminary analyses indicated sex was not a significant predictor of volume in any ROI in comparisons between AB, RL, RH and LN. Females were also removed from all group volume analyses and the pattern of results was unchanged from those reported below. In preliminary analyses between AB, RL and RH, smoking status (current, former and never-smoker) was considered as a covariate, and this variable was not a significant predictor of volume in any ROI.

3. RESULTS

3.1. Participant demographics and clinical measures

Groups were equivalent on percent males and females. AB were older than LN, RL and RH. RH had a lower frequency of White race than all other groups; this difference was driven by a higher percentage of Black participants in the RH (24%) than the other groups. LN had a higher socioeconomic status than AB, RL and RH. AB, RL and RH did not differ on FHD, but FHD for these groups was significantly higher than LN. RH demonstrated a significantly higher duration of resumed drinking, number of drinks over the follow-up interval, and drinks per drinking day than RL. The ratio of average drinks consumed per day post-treatment to average drinks consumed per day over 1 year prior to treatment was significantly higher in RH than RL. RH showed higher depressive and anxiety symptomatology and frequency of current mood disorder diagnoses (most frequent mood disorder was major depression, recurrent) than AB and RL. Of note, none of the RH participants were taking antidepressants at treatment entry. See Table 1 for group comparisons on demographic and clinical variables. In RL and RH combined, higher BDI ($r = .49$; $p = .002$) and STAI scores ($r = .35$; $p = .04$) were associated with higher average drinks per drinking day after treatment (see Fig. 2a and 2b).

3.2. Regional cortical volumes

Relative to LN, AB demonstrated smaller volumes in 18/68 (26%), RL 24/68 (35%) and RH 34/68 (50%) regions. In regions significantly different from LN, AB showed large magnitude effect size (i.e., ES ≥ 0.80) differences in 3/18 (2%), RL 13/24 (54%) and RH 30/34 (88%) regions. In general, the regional volume differences between the AUD groups, and LH, were bilateral; see Fig. 1a–c for specific regional group differences, compared to LN, and associated ES. AB had greater volume than RL only in the right rostral middle frontal gyrus (ES = 0.89); by contrast, AB showed greater volume than RH in six ROIs;

see Table 2 for regions and associated ES. RL showed greater volume than RH in the right posterior cingulate gyrus (ES = 1.06). AB, RL and RH had significantly smaller total left and right hemisphere volumes than LN, where the magnitude of differences to LN were as follows: RH > RL > AB (see Table 3). Across AB, RL and RH, one-year and lifetime average drinks per month and FHD were not significantly related to volume in any ROI.

4. DISCUSSION

The main findings from this study of treatment-seeking, primarily male Veterans were as follows: (1) At treatment entry, a pattern of reduced volumes among AB, RL, and RH compared to LN was observed in regions implicated in executive/cognitive control and salience networks; (2) While the AUD group, as a whole, demonstrated significant volume loss in multiple brain regions at treatment entry, the number of ROIs showing volume loss was not equivalent across groups, and the magnitude of the differences was disparate; RH consistently showed the largest number and magnitude volume differences compared to LN; (3) Relative to AB, RH demonstrated smaller volumes in six ROIs, while RL exhibited smaller volumes in only one ROI; RH demonstrated smaller volumes than RL in one ROI; (4) frequency of depressive and anxiety disorders and associated symptom severities at treatment entry were significantly higher in RH than in AB and RL.

Consistent with our previous research assessing brain morphometrics at treatment entry (Cardenas et al., 2011; Durazzo et al., 2011), the AUD group, as a whole, demonstrated significant volume loss across the cortex. However, when grouped according to the WHO-RDL categories applied in this study, there were clear differences in the frequency and magnitude of regions showing volume loss relative to LN. Specifically, RH showed smaller volumes than LN in 50% of the 68 ROIs assessed with large magnitude differences in 88% of these regions. RL demonstrated smaller volumes than LN in 35% of ROIs with large magnitude differences in 50%, while AB had smaller volumes than LN in only 25% of ROIs, with large magnitude differences only apparent in 2%. The regions where AB, RL and RH showed at least moderate effect size mean differences from LN were generally bilateral. There were few differences in direct comparisons among AB, RL and RH, and the most notable were smaller volumes in RH compared to AB in anterior frontal regions. The limited number of differences among AB, RL and RH were likely related to the modest sample sizes of the RL and RH groups. Nevertheless, taken together, our results further support the importance of considering non-binary definitions of treatment outcome in the identification of potential biomarkers for severity of alcohol use following treatment (Maillard et al., 2022; May et al., 2023). Specifically, this study indicated regional gray matter volume loss in those with AUD, at treatment entry, were related to functionally relevant, non-binary measures of treatment outcome and not simply a consequence of long-term hazardous alcohol consumption.

RL and RH differed in their post-treatment level of alcohol consumption relative to their pre-treatment consumption. For RH, the average number of drinks consumed per day post-treatment was 64% of the average number of drinks consumed per day over 1 year prior to treatment, compared to 4% for RL. Although the magnitude of alcohol consumption

post-treatment in RH was markedly higher than RL, RH, as a group, did not return to their pre-treatment level of alcohol consumption following treatment.

An overall pattern of smaller regional volumes among the AUD groups compared to LN was observed, primarily in brain regions associated with executive function/cognitive control and salience networks. Relative to LN, the magnitude of volumetric differences in the foregoing circuits was substantially greater in the RL and RH groups than the AB group. This finding is consistent with previous work asserting that dysfunction in these networks plays a critical role in the maintenance of the chronic relapse-remit cycle that many individuals with AUD experience (Padula et al., 2022; Volkow et al., 2013). Given that morphological abnormalities in the executive/cognitive control and salience circuits are linked to abnormal decision making, impulse control and hedonic valence (Grodin et al., 2021; Paulus, 2022; Suk et al., 2021; Voon et al., 2020), volume loss in these circuits may affect the ability to effectively engage in, and integrate, cognitive-behavioral-based treatment interventions, and employ adaptive behaviors in the context of alcohol-related cues or stressors.

Baranger and colleagues (Baranger et al., 2023) proposed regional brain structural abnormalities in those with AUD correspond to predispositional risk factors (i.e., genetic or epigenetic) for the development of AUD, and/or causal consequences related to excessive alcohol consumption and related maladaptive lifestyles. Structural abnormalities in the frontal pole, middle and inferior temporal cortex, superior parietal cortex, and precuneus were suggested to reflect predispositional risk factors for developing AUD, while morphological abnormalities in the middle frontal gyrus, superior frontal gyrus and the insula represent both predispositional and causal effects. In the present study, RH showed bilaterally decreased cortical volumes, compared to LN, in most regions proposed by Baranger and colleagues to represent predispositional risk factors. RH, RL, and AB showed decreased cortical volume at varying magnitudes, compared to LN, bilaterally in the insula and superior frontal gyrus, regions suggested to exhibit both predispositional and causal effects. The numerous affected regions and large magnitude volume loss in RH compared to LN in the predispositional regions proposed by Baranger and colleagues suggests these individuals may have a pre-existing vulnerability to engage in problematic alcohol use and that the structural abnormalities observed in these individuals are not simply a consequence of excessive alcohol consumption. Further, given that pre-treatment alcohol consumption measures were not associated with volume in any region across AB, RL and RH, genetic, epigenetic, and/or lifestyle (e.g., nutrition, exercise) factors not considered in this study, may also be related to the cortical volumes observed in this cohort and may have independently influenced treatment outcomes.

Our previous study (May et al., 2023) found that RH, after resuming alcohol consumption following treatment, showed smaller volumes than LN in the bilateral inferior parietal lobule, insula, lateral orbitofrontal, middle temporal, pars orbitalis, precentral, rostral middle frontal and superior frontal cortex. RL had smaller volumes than LN in the inferior parietal, insula, middle temporal, pericalcarine, precentral, rostral middle frontal and superior frontal cortex. In the present study, RH and RL also differed significantly from LN in all of the foregoing regions at treatment entry. Many of these regions correspond with those identified by Baranger et al., 2023 as predispositional markers for the development of AUD.

Considering our cumulative findings, morphological variations within these regions may also represent a potential risk factor for resuming variable levels of alcohol consumption following treatment.

The volumetric findings from the current study also show some correspondence with those of Maillard and colleagues (Maillard et al., 2022), that compared GM volumes and clinical measures of treatment-seeking individuals with AUD at baseline (11±4 days after last drink), based on their post-treatment alcohol consumption. At 6-and-12 months post-treatment, males that consumed ≤ 140 grams and females that consumed ≤ 70 grams of ethanol per week, were classified as “low risk” and those who exceed these levels were classified as “relapsers.” Based on the alcohol consumption at 6 months posttreatment, relapsers showed higher baseline alexithymia symptoms and smaller gray matter volume in the midbrain than controls. Based on the alcohol consumption at 12 months post-treatment, compared to controls, relapsers showed smaller gray matter volume in the amygdala, ventromedial, prefrontal cortex and anterior cingulate at baseline. There were no significant baseline volume differences between controls and the low risk group or among the low risk group and relapsers.

The prevalence of depressive disorders was higher in RL and RH than AB. RH also reported a higher magnitude of anxiety and depressive symptomatology than AB and RL, however, no RH participant was actively taking an antidepressant at the time of study. Among RL and RH, self-reported depressive and anxiety symptoms were positively related to a higher average number of drinks per drinking day over the follow-up observation. These depressive and anxiety disorder-related findings correspond with greater cortical volume loss among RH and RL in regions implicated in depressive and anxiety disorders. Specifically, RH and RL showed smaller volumes in left rostral middle frontal gyrus than AB and LN (the volume of the rostral middle frontal gyrus comprises 71% of the middle frontal gyrus in this sample), a region in which decreased volume and cortical thinning has been observed among individuals with treatment-resistant depression (Klok et al., 2019). The middle frontal gyrus has previously been found to be an effective target for repetitive transcranial magnetic stimulation (rTMS) for individuals with depression, implicating the neurobiological integrity of this region in the development and maintenance of mood disorders (Batail et al., 2023; Mitra et al., 2023). Effective application of rTMS-induced brain stimulation requires consistent and accurate delivery of the magnetic pulse at a specific magnitude to the target tissue to initiate activation or inhibition (George, 2007). For rTMS, the distance from the treatment coil to the cortex influences the level of stimulation (excitatory or inhibitory) of the underlying tissue (Stokes et al., 2005). Considering the variations in brain volume among individuals, adjustments of the pulse magnitude may be required to effectively stimulate the target site and optimize rTMS treatment for individuals with AUD (Stokes et al., 2007). Thus, the pattern of volume loss demonstrated across the AUD group may have implications for rTMS and potentially other non-invasive neurostimulation methods.

This study has limitations that may affect the generalizability of the findings. First, this study utilized a predominantly male Veteran sample. Additionally, due to the limited number of females, potential sex effects could not be cogently examined. This study primarily relied on self-report of drinking history, substance use history, and psychiatric diagnoses

and severity; however, this information was verified by medical records and collateral sources, when available. The sample size of the RH precluded the ability to independently evaluate the medium, high, and very-high WHO-RDL groups. Lastly, this study focused specifically on cortical volumes; consideration of cortical thickness, surface area, and subcortical volumes among WHO-RDL groups at treatment entry is warranted.

5. CONCLUSIONS

This study demonstrated that regional brain volume, at initiation of treatment, corresponded to varying levels of alcohol consumption post-treatment consistent with WHO-RDL categories. Individuals who returned to low and higher-risk levels of alcohol consumption after treatment showed lower volumes at treatment entry than controls in brain regions involved in executive function/cognitive control and salience networks; this supports previous research indicating neurobiological abnormalities in these neural networks are associated with the chronic relapse-remit cycle of AUD. Specifically, the overall pattern of loss observed in the AUD groups may represent a predispositional risk for problematic alcohol use, particularly for the RH group, suggesting that pre-existing abnormalities in regional brain structural integrity may relate to treatment outcomes. Depressive and anxiety symptomatology and diagnoses were significantly higher in in RH, highlighting the importance of incorporating assessment and empirically supported pharmacological and/or cognitive behavioral interventions for these conditions during the early phase of AUD treatment. Overall, these findings suggest that regional cortical volumes observed at treatment entry are associated with alcohol use post-treatment and that the pattern of volume loss may serve as potential biomarkers of AUD intervention outcomes.

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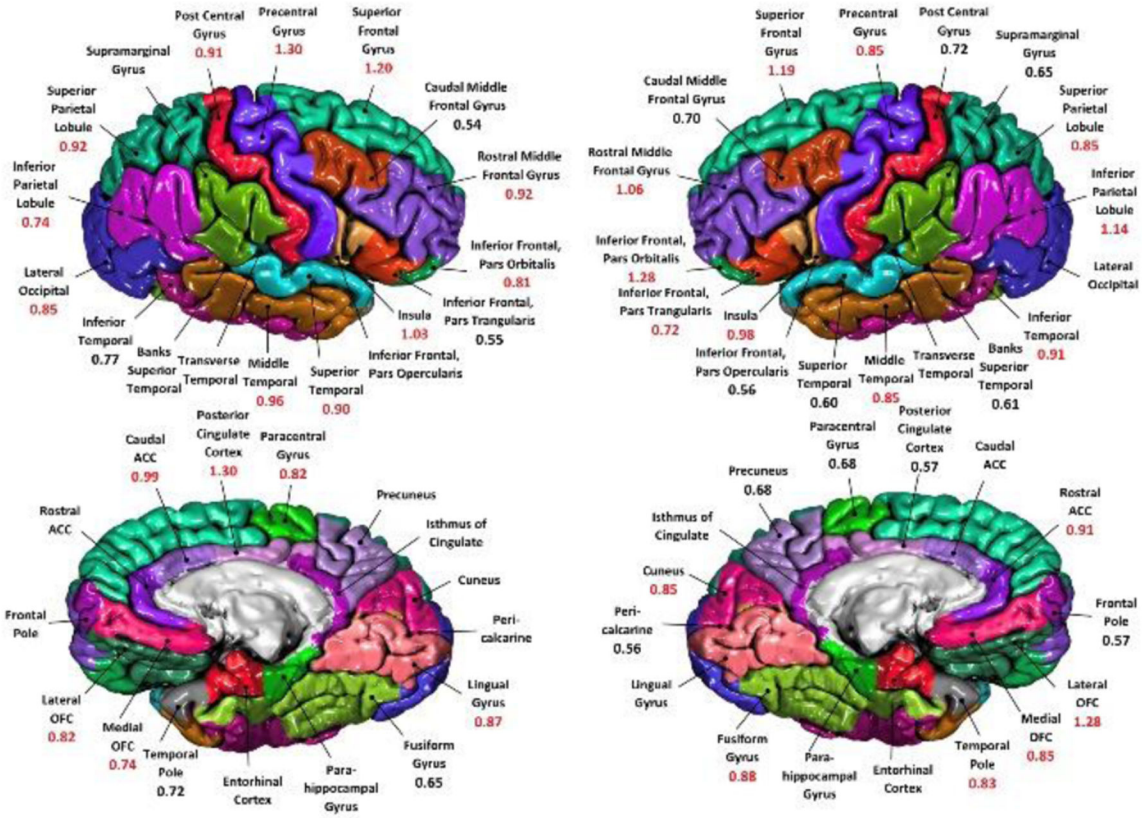
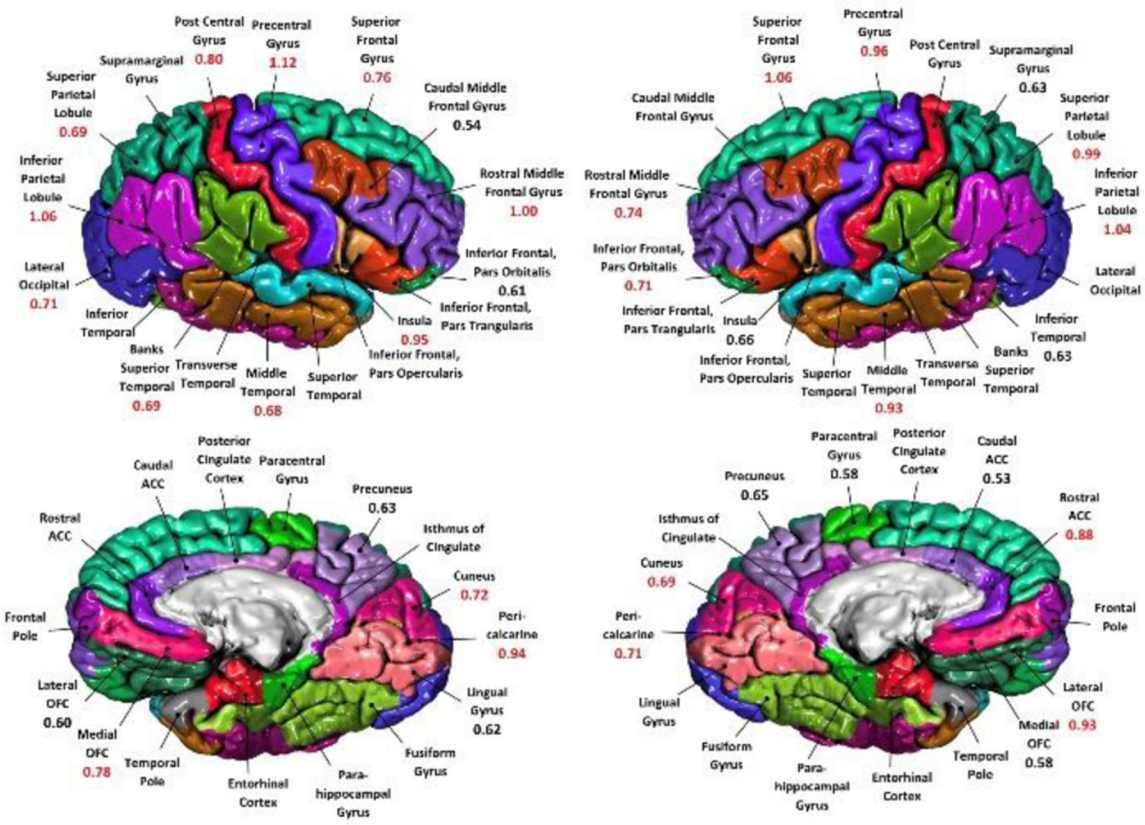
Highlights

- Those with alcohol use disorders (AUD) were assigned to WHO risk drinking levels.
- Abstainers, Low Risk and Higher Risk groups were formed from the AUD participants.
- Regional brain volumes of AUD groups were compared at treatment entry.
- Future abstainers showed the fewest and lowest magnitude cortical volume deficits.
- Results indicate volumes at treatment entry are associated with future alcohol use.





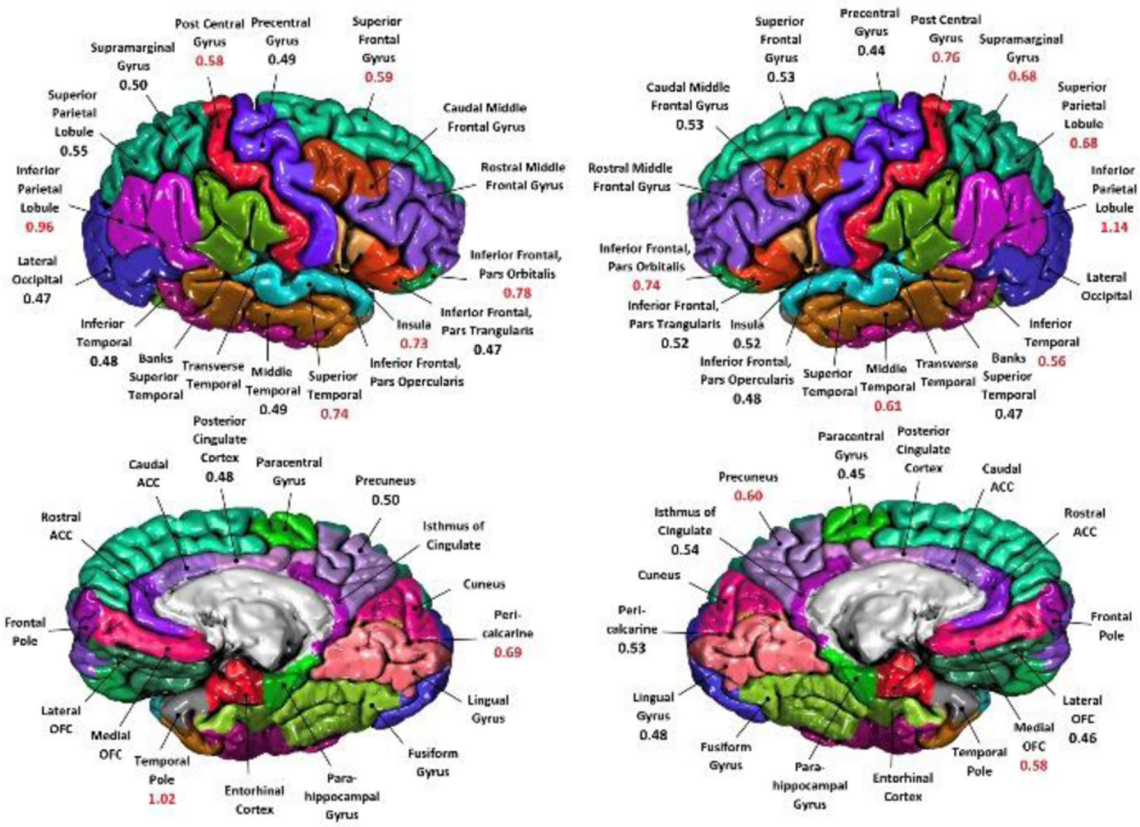


Figure 1.

a. Region of interest comparison for RH versus LN. Values for each region of interest represent effect sizes. Effect sizes in red font indicate statistically significant group differences; effect sizes in black font indicate moderate magnitude group differences that were not statistically significant after FDR correction. Regions with no listed effect size were weak (i.e., < 0.50) and statistically non-significant.

b. Region of interest comparison for RL versus LN. Values for each region of interest represent effect sizes. Effect sizes in red font indicate statistically significant group differences; effect sizes in black font indicate moderate magnitude group differences that were not statistically significant after FDR correction. Regions with no listed effect size were weak (i.e., < 0.50) and statistically non-significant.

c. Region of interest comparison for AB versus LN. Values for each region of interest represent effect sizes. Effect sizes in red font indicate statistically significant group differences; effect sizes in black font indicate moderate magnitude group differences that were not statistically significant after FDR correction. Regions with no listed effect size were weak (i.e., < 0.50) and statistically non-significant.

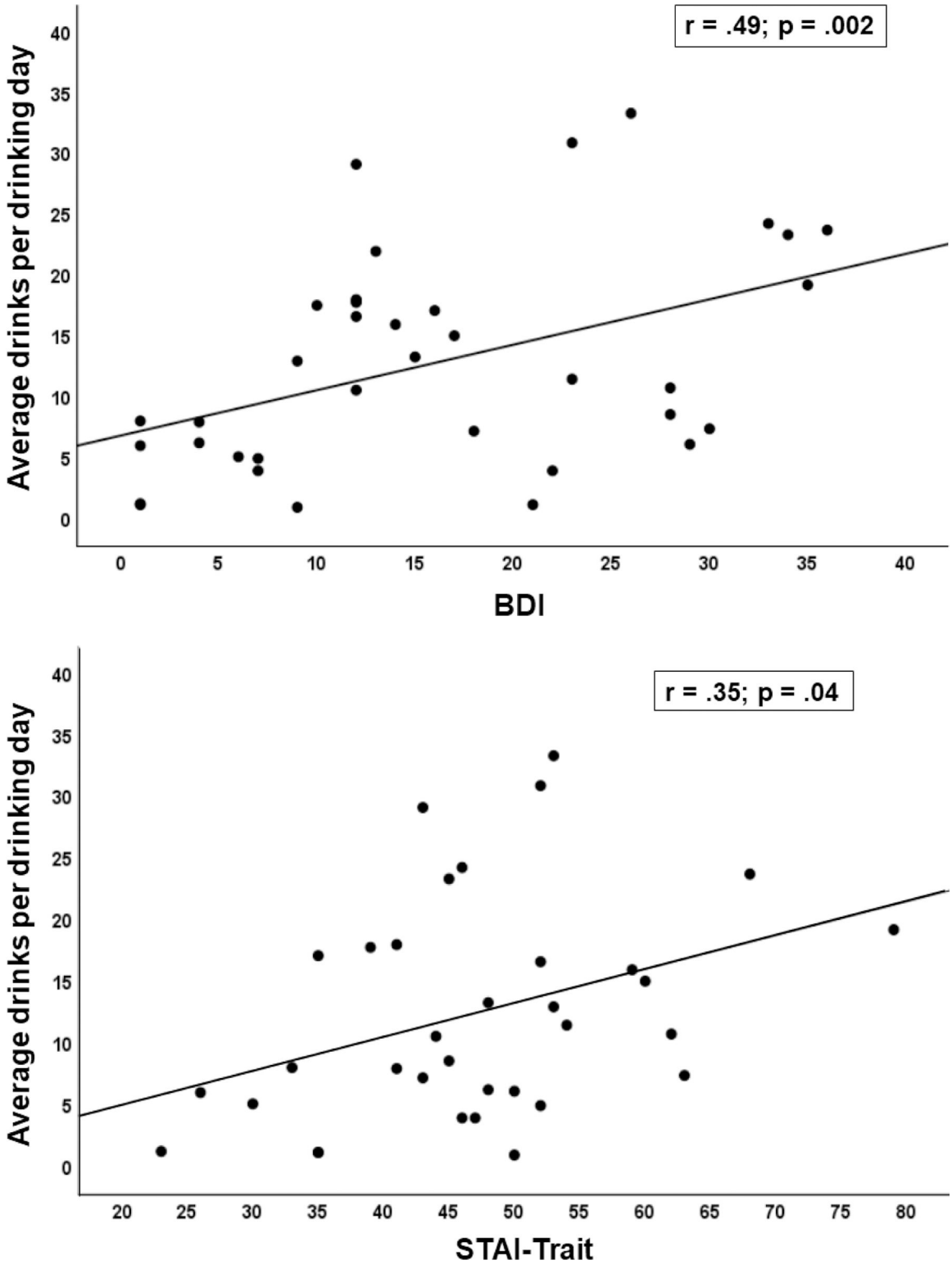


Figure 2.

a. Association between Beck Depression Inventory (BDI) at treatment entry and average number of drinks per drinking day post-treatment across RL and RH.

b. Association between State-Trait Anxiety Inventory-Trait (STAI) at treatment entry and average number of drinks per drinking day post-treatment across RL and RH.

Table 1.

Participant Demographics and Clinical Variables

Measure	LN (n = 51)	AB (n = 38)	RL (n = 20)	RH (n = 17)	Group[a] comparisons
Age	47.1 (8.6)	51.6 (11.1)	46.8 (8.1)	47.9 (5.2)	AB > LD, RL, RH
Education (years)	16.1 (2.5)	14.3 (2.1)	13.8 (2.0)	13.9 (1.6)	LD > AB, RL, RH
White (%)	76	79	80	52	LD, AB, RL > RH
Male (%)	82	90	90	88	
Hollingshead Socioeconomic Status (median)	3	7	7	7	LD > AB, RL, RH
Family history density of alcohol-related problems (median)	0.37	0.75	0.50	0.87	AB, RL, RH > LD
Number of previous formal inpatient or outpatient treatment programs (median/ mode)	NA	1/1 Min = 0 Max = 6	1/1 Min = 0 Max = 10	2/2 Min = 1 Max = 4	
Days abstinent from alcohol at study entry	NA	14.7 (12.0)	17.7 (17.0)	13.8 (11.5)	
1-year average drinks/month prior to study	13 (14)	405 (214)	394 (215)	344 (213)	AB, RL, RH > LD
Lifetime average drinks/month prior to study	13 (12)	218 (102)	233 (120)	254 (221)	AB, RL, RH > LD
Post-treatment follow-up interval (days; median)	NA	210	208	248	RH > AB, RL
Days abstinent until first alcohol consumption post treatment (median)	NA	NA	129 Min = 34 Max = 407	129 Min = 26 Max = 424	
Resumption of alcohol use duration (days; median)	NA	NA	15 Min = 1 Max = 208	128 Min = 35 Max = 448	RH > RL
Average drinks/day posttreatment as percentage of average drinks/day over 1 year prior to treatment	NA	NA	4 Min = .2 Max = 150	64 Min = 19 Max = 500	RH > RL
Drinks per day over follow-up interval (median)	NA	NA	0.51 Min = 0.1 Max = 2.3	5.51 Min = 2.3 Max = 30	RH > RL
Drinks per drinking day over follow-up interval (median)	NA	NA	7.5 Min = 1 Max = 33	15.1 Min = 6 Max = 30	RH > RL
Beck Depression Inventory (BDI)	3.7 (3.5)	11.5 (7.9)	12.2 (7.9)	20.5 (11.3)	AB, RL, RH > LD RH > AB, RL
State Trait Anxiety Inventory-Trait	32.8 (8.5)	44.3 (9.6)	43.4 (10.6)	50.8 (12.1)	AB, RL, RH > LD RH > AB, RL
Depressive disorders (%)	NA	21	50	71	RH, RL > AB
Anxiety disorder (%)	NA	0	5	18	RH > AB
Substance use disorder (%)	NA	21	25	24	
Antidepressant use (%)	NA	5	20	0	RL > RH
Never smoker (%)	NA	32	29	37	
Former smoker (%)	NA	11	11	13	
Current smoker (%)	NA	57	60	50	

Table 2.

Effect size for greater regional volumes in AB versus RDL-Higher

Region	Effect Size*
Right Caudal Anterior Cingulate	0.93
Left Rostral Middle Frontal	0.89
Left Lateral Orbitofrontal	0.81
Right Rostral Middle Frontal	0.81
Right Posterior Cingulate	0.81
Right Precentral	0.80

* = All effect sizes correspond to $p < .05$ FDR corrected

Table 3.

Hemispheric Cortical Volume Group Comparisons

	Group Comparison	p-value	Effect Size
Right Cerebral Cortex	LN > AB	<.001	1.05
	LN > RL	<.001	1.36
	LN > RH	<.001	2.13
	AB = RL	0.28	0.30
	AB > RH	<.001	1.07
	RL > RH	0.02	0.78
Left Cerebral Cortex	LN > AB	<.001	0.90
	LN > RL	<.001	1.28
	LN > RH	<.001	1.98
	AB = RL	0.18	0.37
	AB > RH	<.001	1.07
	RL > RH	0.03	0.70

Note: AB: Abstainer; LN: light-drinking non-smoking control; RH: WHO RDL higher; RL: WHO-RDL low. Equal sign (=) indicated no statistically significant differences between groups. P-value < .05 (not corrected for multiple comparisons) considered statistically significant.