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Authors

Richards, Veronica L
Sajdeya, Ruba
Villalba, Karina
et al.

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Secondary Aanalysis of a Randomized Clinical Trial of Naltrexone among Women Living with HIV: Correlations between Reductions in Self-Reported Alcohol Use and Changes in Phosphatidylethanol (PEth)

Veronica L. Richards, MPH[a], **Ruba Sajdeya, MD**[a], **Karina Villalba, PhD**[b], **Yan Wang, PhD**[a], **Vaughn Bryant, PhD**[a], **Babette Brumback, PhD**[c], **Kendall Bryant, PhD**[d], **Judith A. Hahn, PhD**[e], **Robert L. Cook, MD, MPH**[a]

[a.]Department of Epidemiology, University of Florida, Gainesville, FL

[b.]Robert Stempel College of Public Health & Social Work, Florida International University, Miami, FL

[c.]Department of Biostatistics, University of Florida, Gainesville, FL

[d.]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

[e.]Department of Medicine, University of California, San Francisco, CA

Abstract

Background: Direct biomarkers such as phosphatidylethanol (PEth) have the capability to detect heavy alcohol use, but it is unclear how strongly self-reported reduction in alcohol use correlates with reduction in PEth. We sought to explore the strength of correlation between reductions in self-reported alcohol use and change in PEth among a sample of women living with HIV (WLWH) who participated in a clinical trial to reduce heavy alcohol use. We also sought to determine whether this correlation was stronger in women with lower body mass index (BMI) and women without an alcohol use disorder (AUD).

Methods: 81 WLWH (mean age=48.7, 80% Black) engaging in a randomized trial of naltrexone versus placebo with a positive baseline PEth (≥8 ng/ml) and alcohol use data at baseline, two and seven months were included in this analysis. Spearman correlation coefficients were compared to measure the correlation between baseline PEth and number of drinks per week by demographic, biological, and alcohol use factors. Mini-International Neuropsychiatric Interview was used to screen for AUD. Further analyses were stratified by BMI and AUD. Spearman correlation coefficients were calculated for the change in PEth and the change in number of drinks per week over seven months, including three time-points: baseline, 2-months, and 7-months.

Results: At baseline, the correlation between baseline PEth and the number of drinks per week was significantly stronger for those with a body mass index (BMI) ≤25 compared to those with a BMI>25 (r=0.66; r=0.26, respectively). Similarly, the correlation between baseline PEth and

Corresponding author: Veronica L. Richards, 2055 Mowry Rd, PO Box 100009, Gainesville, FL, 32610, (561) 379-5273, vrichh@ufl.edu.

number of drinks was stronger for those who did not screen positive for AUD compared to those who did (r=0.66; r=0.25, respectively). When stratifying by BMI, a low-to-moderate correlation (r=0.32, p=0.02) was present for persons with a BMI>25; when stratifying by AUD, a moderate correlation (r=0.50, p<.01) was present for persons without an AUD between 0-2 months only.

Conclusions: In this sample of WLWH, BMI and AUD affected the strength of correlation between PEth and drinks per week. Future work examining changes in PEth over time in broader populations is needed, particularly to understand the differences in PEth due to sex differences.

Keywords

Phosphatidylethanol; alcohol; heavy drinking; HIV; women living with HIV

Introduction

Heavy alcohol use is common among people living with HIV (PLWH) and can lead to HIV transmission, and progression to severe disease (i.e., stage 3 [AIDS]), and complications, such as liver disease (Duko et al., 2019; Ganesan et al., 2018; Rehm et al., 2017). Direct and indirect alcohol biomarkers can serve as objective measures for estimating the severity of an individual's alcohol use and may assist clinicians in identifying persons who need intervention (Litten et al., 2010). For example, Eyawo and colleagues (2018) found that one biomarker, phosphatidylethanol (PEth), may be a better predictor of true harm compared to self-reported alcohol use.

PEth, a phospholipid metabolite formed on the surface of red blood cells (RBCs) in the presence of ethanol, is a direct biomarker that offers a promising capability to detect recent alcohol use (i.e., past 2-3 weeks) (Hahn et al., 2016a). PEth has been shown to be more sensitive and specific than other medium-term alcohol biomarkers (i.e., biomarkers that are present for weeks to months, for example-- alanine transaminase [ALT] and aspartate transaminase [AST]; Hahn et al., 2012, 2016a; Helander et al., 2019a, 2019b; Litten et al., 2010). However, identifying a specific period of abstinence that produces a negative PEth result and the amount of alcohol that produces a positive PEth result has been hindered by the observed substantial individual differences in formation and elimination of the biomarker, thus limiting its clinical applicability (Aradottir et al., 2006; Helander et al., 2019a, 2019b; Stewart et al., 2014; Ulwelling and Smith, 2018). Regardless of the large inter-person variability, PEth may still be helpful for detecting alcohol use, which is often under- or over-reported, whether purposefully or not (Hahn et al., 2016b; Papas et al., 2016; Wang et al., 2018).

PEth levels have been associated with levels of total alcohol consumption over the prior 2-3 weeks (Hahn et al., 2016a). However, to date, it remains unclear how PEth changes within individuals as they reduce alcohol use over extended time-periods. By understanding this relationship, clinicians would be able to give feedback to patients relating to changes in their alcohol use, while researchers could better evaluate the efficacy of alcohol interventions without solely relying on self-report. Most studies investigating PEth thus far have been cross-sectional and few studies have examined individual-level changes in PEth relative to changes in self-reported alcohol use habits over extended time-periods (Viel et al., 2012).

Helander and colleagues found that over a two-week period, PEth levels were correlated with individual change in self-reported alcohol use among 36 patients (69% male) at an outpatient treatment facility for alcohol reduction; that is, as patients decreased their self-reported alcohol use, PEth also decreased (Helander et al., 2019b). Self-reported alcohol use in the Helander et al. (2019b) study was measured using daily diaries and change in alcohol use was calculated using absolute change.

In order to study whether PEth changes over time relative to changes in self-reported alcohol use, we also need to consider other individual factors that can influence PEth. In addition to timing and patterns of alcohol use that impact the detection of PEth (Hahn et al., 2012; Helander et al., 2019b), individual differences in alcohol metabolism may also be a critical factor affecting PEth levels, as the rate of alcohol absorption in the small intestine varies across individuals (Hahn et al., 2016a; Javors et al., 2016). Such factors include age, sex, race, percent body fat, alcohol use disorders, HIV, and genetically determined levels of alcohol and acetaldehyde dehydrogenase (Hahn et al., 2016a; Javors et al., 2016; Jorgenson et al., 2017; Meier and Seitz, 2008; Zakhari and Li, 2007). Furthermore, PEth is examined using blood, so anemia may result in lower PEth levels (Hahn et al., 2016a; Isaksson et al., 2018). Papas et al. (2016) found a weaker correlation between PEth and self-reported alcohol consumtion in women than in men, and two studies have found similarly weak correlations in women (Littlefield et al., 2017; Wang et al., 2018), however other studies have found no sex differences in associations between PEth and self-reported measures (Hill-Kapturczak et al., 2018; Stewart et al., 2009; Wurst et al., 2010). Higher body mass index (BMI) has been associated with decreased PEth detection in some cases (Wang et al., 2018), but in other cases BMI was not significantly associated with PEth (Hahn et al., 2012; Wurst et al., 2010). Given the limited and mixed data on the relationship between factors that may influence alcohol metabolism and PEth, further investigation into such factors is warranted.

To expand on the existing literature, this study reports on longitudinal data from a trial of a pharmacologic intervention for women living with HIV (WLWH). The aims of the present study are, (1) to explore how the correlation between baseline PEth and number of drinks per week varies by individual differences including demographic (age, race/ethnicity), biological (BMI, anemia, HIV viral suppression), and alcohol use (alcohol use disorder [AUD], number of drinks/week at baseline); (2) to examine the strength of the relationship between individual-level self-reported change in alcohol use and change in PEth between 0-2 months, 2-7 months, and 0-7 months; and (3) to identify if the strength of the relationship between individual-level self-reported change in alcohol use and change in PEth is moderated by BMI and AUD.

Materials and Methods

Overview

This study analyzed data from the WHAT-IF? (Will Having Alcohol Treatment Improve my Functioning?) study, a double-blinded randomized clinical trial of naltrexone vs. placebo for women with HIV and heavy alcohol consumption (Cook et al., 2019). The methods of this study have already been published. In summary, eligible women were randomized to receive

either daily oral naltrexone (50mg) or a placebo for four months. The study consisted of a baseline visit along with 2-month, 4-month, and 7-month follow-up visits, with PEth levels obtained at baseline, 2-months, and 7-months. In this paper, we analyzed data from baseline, 2- and 7-months since PEth was measured at these time-points. WLWH were eligible to participate in this study if they were 18 years of age or older, met past-month criteria for heavy alcohol use (>7 drinks/week or >3 drinks/occasion) (Office of Disease Prevention and Health Promotion, 2015) and did not have contraindications for taking naltrexone (e.g., opioid use). The study was approved by all involved Institutional Review Boards and was registered on ClinicalTrials.gov (NCT01625091). All participants provided informed consent.

Participants

A total of 194 participants participated in the WHAT-IF? Study. This analysis included 81 WLWH (51% 50 years or older, 80% Black). Individuals were excluded from this analysis if they were negative for PEth at baseline (<8 ng/ml; n=102), reported extremely high levels of alcohol use (≥ 350 drinks per week; n=3) or low levels of alcohol use (<7 drinks per week; n=2), or had missing alcohol use or PEth data at both follow-up visits (n=6) (Helian et al., 2017). By excluding those with negative PEth at baseline, we ensured including only actual heavy drinkers, as PEth is only formed in the presence of alcohol (Hahn et al., 2016a)

Study Procedures

Demographics.—The participants completed questionnaires using an audio computer-assisted self-interview (ACASI) program at each visit, and a demographic questionnaire was completed at baseline to collect information such as age and race/ethnicity.

Labs.—Blood samples were collected at each visit to obtain PEth levels, HIV viral loads, CD4+ counts, hemoglobin levels, liver enzymes (via ALT and AST) and kidney function (creatinine). Other variables were measured at baseline only. HIV viral suppression was defined as ≤200 copies/mL because this was the lower limit of detection. Anemia was defined as hemoglobin <12.0g/100mL (Mayo Clinic, 2005). Height and weight were measured at baseline to calculate body mass index (BMI).

PEth.—PEth was collected at baseline and the 2- and 7-month follow-up visits. Standard protocols were used to prepare the PEth sample. Blood was collected venously and dried blood spots (DBS) were prepared and sent to the United States Drug Laboratory (USDTL, Des Plaines, IL) to be analyzed using mass spectrometry. The most common PEth homologue (16:0/18:1) was detected using a lower limit of quantification of 8 ng/mL.

TLFB.—Trained research assistants obtained alcohol use data using a Timeline Followback (TLFB) (Sobell and Sobell, 1992) using a set of plastic glassware and lists of specific types of alcoholic beverages to help with self-report. At baseline, a 90-day TLFB was collected and at each follow-up visit, a TLFB dating to the previous visit was completed to ensure that there was 30 days of TLFB data at each timepoint. The TLFB was used to calculate the average number of drinks per week in the 30 days prior to the study visit.

Alcohol Use Disorder.—Participants were screened for AUD at baseline using a computerized-version of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

Statistical Analysis

To determine which TLFB period (1, 2, 3, or 4 weeks) would be best to calculate change in alcohol use, we examined the correlation between each period and baseline PEth calculated; the Spearman correlation coefficient comparing mean drinks per week for each time-period and PEth ranged between 0.31-0.36 and was significant ($p<0.01$) for all time periods. However, the 2-week TLFB had the strongest correlation of the four ($r=0.36$, $p<0.01$) and was used for all further analysis. We calculated the mean baseline PEth and number of drinks per week at baseline by each variable level. We also calculated the Spearman's rank correlation coefficients for baseline PEth and number of drinks per week within each variable. Variables that appeared to have different correlation coefficients by variable level (BMI and AUD) were used to stratify the final analysis.

To examine the strength of the relationship between change in reported drinks per week and change in PEth over three defined time periods over seven months, we calculated relative and absolute change (within-person) in number of drinks per week and PEth, from 0-2 months, 2-7 months, and 0-7 months. For example, to calculate the average relative change in PEth from 0 to 2 months, we subtracted the PEth at baseline from PEth at 2 months and divided by PEth at baseline. We stratified by AUD and BMI using Spearman's rank correlations to examine the relationship between average changes in alcohol use and average relative changes in PEth, by duration of the time difference (i.e., 0-2 months, 2-7 months, 0-7 months). All statistical analyses were conducted in SAS 9.4 statistical software.

Results

Sample Characteristics

Eighty-one WLWH (Mean age=48.7, SD=7.6) with self-reported heavy alcohol use and a detectable PEth at baseline were included in this analysis (Table 1). The majority of women identified as Non-Hispanic Black (80%), were unemployed (90%), had a high school education or less (79%) used tobacco in the past 30 days (74%), and screened positive for an AUD (60%) at baseline. Furthermore, many women had a BMI greater than 25 (64%), were anemic (25%), and were not HIV virally suppressed (40%) at baseline. Drinks per week at baseline varied, but the majority (68%) of participants reported alcohol use >35 drinks per week (Mean drinks per week=59.2, SD=43.8). The mean PEth at baseline was 76.7 ng/mL (SD=79.5).

Correlations Between PEth and Number of Drinks per Week at Baseline

The overall correlation between PEth and number of drinks per week at baseline was 0.40 ($r<.01$), but the strength of correlation varied significantly by AUD (yes: $r=0.25$ vs no: $r=0.66$) and BMI (specifically for comparing BMI ≤25.0: $r=0.66$ vs BMI >25 – ≤35: $r=0.26$). Correlations did not vary by age, race/ethnicity, anemia, or viral suppression (Table 1).

Relationship Between Relative Change in Drinks per Week and PEth

By the 2- month follow-up, approximately half of the participants reported heavy alcohol use and by 7-month follow-up, only one-third of participants reported continuing heavy alcohol use (>7 drinks per week; Table 2). Despite a reported reduction in alcohol use, PEth remained detectable in the majority of participants at both 2- and 7-months, ranging from undetectable to 702 ng/ml at 2-months and 876 ng/ml at 7-months (Table 2). The greatest reported change in alcohol use occurred between 0-7 months and the greatest change in PEth occurred between 2-7 or 0-7 months, depending on whether relative or absolute change was used (Table 3). Overall, the relationship between relative change in self-reported alcohol use and relative change in PEth was weak, with a Spearman's correlation coefficient ranging from 0.14 – 0.25 and no significant findings. However moderate correlations were present among persons without an AUD ($r=0.50, p<0.01$) and persons with a BMI > 25 between 0-2 months ($r=0.32, p=0.02$; Table 4a). The relationship between absolute change in self-reported alcohol use and absolute change in PEth were weaker among all AUD and BMI levels, with a the Spearman's correlation coefficient ranging from −0.14 – 0.34 and no significant findings (Table 4b).

Discussion

We examined the within-person changes in PEth and self-reported alcohol use longitudinally among WLWH participating in a treatment study. Results from this study indicate that the correlation between PEth and drinks per week varied significantly by BMI and AUD but not by age, race/ethnicity, anemia, or HIV viral suppression at baseline. Over time, the relative change in alcohol use and relative change in PEth were weakly correlated with each other with high variability, though, for the most part, not statistically significant.

This study was among one of the first studies to examine the relationship between within-person changes in reported alcohol use levels and PEth longitudinally. PEth is unique from other alcohol biomarkers in that it has a half-life of approximately 4 days (Hahn et al., 2016a), compared to other biomarkers with much shorter half-lives, such as ethyl glucuronide (EtG) and ethyl sulphate (EtS), with half-lives of approximately 2-3 hours (Høiseth et al., 2009, 2007), and 4 hours (Høiseth et al., 2009), respectively. PEth is one, if not the only, direct alcohol biomarker that allows for longitudinal assessment of within-person changes in alcohol use over weeks or months.

The correlation between change in drinks per week and change in PEth was weak, which is inconsistent with Helander and colleague's (2019b) findings, which found a stronger relationship ($r=0.46, p=<0.01$) between change in number of drinks and PEth. However, between baseline and two months, we did find a similarly strong correlation between change in PEth and change in alcohol use among persons without an AUD, though this relationship was only apparent for relative change, not absolute change. Still, we did observe that PEth tended to decrease as alcohol use decreased, thus offering a potential tool for clinicians to detect and monitor at-risk patients and their clinical progress. Data from the Veterans Aging Cohort Study (VACS) demonstrated the utility of using PEth in conjunction with AUDIT-C scores for detecting persons at increased risk of harm from alcohol use; persons who reported AUDIT-C scores of zero but had a detectable PEth value (i.e., ≥ 8 ng/ml) had the

highest risk of mortality (Eyawo et al., 2018). As such, PEth remains a promising biomarker that can predict alcohol-associated outcomes in clinical settings.

A reason for the weak association found in this study may be due to the makeup of the study population, which consisted entirely of WLWH. Other studies have also found similarly weak correlations between PEth and alcohol use in WLWH, specifically, although it is not clear why (Littlefield et al., 2017; Papas et al., 2016; Wang et al., 2018), but it is possible that alcohol metabolism may be involved. Another likely explanation for the weak association between PEth and alcohol use is the possible underreporting of alcohol use, as many women who reported quitting heavy alcohol use still had detectable PEth values at follow-up several months later. The correlations we observed between PEth level and self-reported alcohol use cross-sectionally were substantially lower than in many previous studies (Asiimwe et al., 2015; Hahn et al., 2012; Helander et al., 2019a), however those studies included a wider range of alcohol use behavior (from no-alcohol use through heavy alcohol use), while this study included only heavy alcohol use. When we examined correlations of PEth with self-reported number of drinks within subgroups, we found correlations of 0.66 within the lower BMI (<25 kg/m^2) and non-AUD subgroups; these correlations are more consistent with those reported in previous literature (Aradottir et al., 2006; Ferguson et al., 2020; Hahn et al., 2012; Hartmann et al., 2007; Helander et al., 2019b; Kechagias et al., 2015; Piano et al., 2015; Schröck et al., 2017; Walther et al., 2015).

This study is limited in that neither self-report nor PEth are per se a “gold standard” measure of alcohol use; thus, it is difficult to say whether one is more accurate than the other. That the Spearman correlation coefecients between PEth and self-reported alcohol use at baseline were statistically significant but indicated a weak relationship, is cause for concern, though this does not seem to be an issue among those without an AUD and those with a BMI<25. Nevertheless, the weak correlation found in this study may be artificial, as any participant with an undetectable PEth at baseline was excluded from the analyses. Further, self-reported data is frequently associated with inaccuracy.

Conclusions

This was among one of the first studies to assess the association between within-person changes in PEth and alcohol use. Cross-sectionally, PEth was more strongly correlated with number of drinks per week among persons without an AUD and persons with a BMI≤25. Between baseline and two months, relative change in PEth and relative change in drinks per week was moderately correlated among persons without an AUD and perons with a BMI>25. Although the association between changes in PEth and changes in alcohol use was weak, overall, PEth may still be helpful to detect heavy alcohol use. Future work examining the changes in PEth over time is in broader populations is needed, especially to understand the differences in PEth due to sex differences.

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Table 1.

Characteristics of women living with HIV with detectable phosphatidylethanol (PEth) levels at baseline (N=81)

	Frequency	Drinks per week	PEth	Drinks per week and PEth	
	(%)	Mean (SD [a])	Mean (SD)	Correlation	95% CI [b]
Age					
18-49	40 (49%)	60.4 (44.2)	87.4 (76.6)	0.49	0.21-0.70
50+	41 (51%)	58.0 (44.0)	66.2 (81.8)	0.32	0.01-0.57
Race/ethnicity					
Black	65 (80%)	59.1 (41.0)	74.3 (70.1)	0.40	0.17-0.58
Other	16 (20%)	59.5 (55.3)	86.2 (110.2)	0.49	−0.01-0.79
BMI [c]					
≤25.0	29 (36%)	65.2 (50.2)	80.3 (82.7)	0.66	0.38-0.82
>25 – ≤35	28 (47%)	50.0 (34.5)	73.6 (72.0)	0.26	−0.06-0.54
>35	14 (17%)	71.9 (50.1)	77.5 (96.6)	0.29	−0.29-0.71
AUD [d]					
No	32 (40%)	51.0 (43.8)	73.5 (74.7)	0.66	0.40-0.82
Yes	49 (60%)	64.6 (43.5)	78.7 (83.2)	0.25	−0.03-0.50
Anemia [e]					
Yes	20 (25%)	53.2 (39.4)	61.8 (50.4)	0.40	0.16-0.59
No	61 (75%)	61.2 (45.3)	81.5 (86.7)	0.44	0.00-0.74
Viral Suppression [f]					
Yes	48 (60%)	58.5 (43.1)	71.1 (75.4)	0.40	0.13-0.61
No	32 (40%)	60.4 (43.2)	84.9 (87.0)	0.44	0.11-0.69
Assignment					
Naltrexone	41 (51%)	51.8 (33.2)	72.7 (75.4)	0.41	0.11-0.63
Placebo	40 (49%)	66.8 (51.9)	80.7 (84.2)	0.40	0.10-0.63

[a] SD – Standard Deviation

[b] CI – Confidence Interval

[c] BMI – Body Mass Index

[d] Alcohol use disorder (AUD) was measured using the Mini-International Neuropsychiatric Interview based on DSM-IV criteria; alcohol abuse and alcohol dependence were combined as a positive screen for AUD

[e] Anemia was defined as hemoglobin <12.0/100mL

[f] Viral suppression was defined as HIV viral load ≤200 copies/mL

Table 2.

Mean number of drinks per week and phosphatidylethanol (PEth) at 0, 2, and 7 months (N=81)

	Baseline	2 month follow-up	7 month follow-up
Mean number of drinks per week (SD [a])	59.2 (43.8)	22.6 (42.0)	12.6 (30.7)
Mean PEth (SD)	76.7 (79.5)	83.5 (113.2)	100.4 (141.9)
Heavy alcohol use reported [b] (%)	81 (100%)	38 (47%)	27 (37%)
Detectable PEth [c] (%)	81 (100%)	73 (90%)	60 (82%)

[a] SD – Standard Deviation

[b] Heavy Alcohol Use - >7 drinks/week or >3 drinks/occasion

[c] ≥8 ng/ml

Table 3.

Relative and absolute changes in drinks per week and phosphatidylethanol (PEth) from 0-2 months, 2-7 months, and 0-7 months (N=81)

	0 – 2 months	2 – 7 months	0 – 7 months
Mean relative change in drinks per week (SD [a])	−59.6% (61.9)	18.4% (237.0)	−78.4% (34.0)
Mean absolute change in drinks per week (SD)	−36.6 (44.7)	−7.7 (22.2)	−47.4 (39.5)
Mean relative change in PEth (SD)	14.4% (98.0)	60.2% (172.9)	29.5% (96.9)
Mean absolute change in PEth ng/mL (SD)	6.8 (82.8)	20.1 (126.2)	25.6 (99.3)

Table 4a.

Spearman correlation between relative change in phosphatidylethanol (PEth) and relative change in reported number of drinks per week over 7 months, stratified by alcohol use disorder (AUD) and body mass index (BMI)

	0 – 2 months		2 – 7 months		0 – 7 months	
	Correlation coefficient	**P-value**	**Correlation coefficient**	**P-value**	**Correlation coefficient**	**P-value**
Total sample	0.21	0.07	0.25	0.07	0.14	0.22
Persons with AUD (N=32)	0.05	0.69	0.32	0.08	0.05	0.77
Persons without AUD (N=49)	0.50	<0.01	0.17	0.43	0.29	0.12
Persons with BMI ≤25 (N=29)	0.03	0.88	0.32	0.19	0.12	0.55
Persons with BMI >25 (N=52)	0.32	0.02	0.20	0.23	0.13	0.37

Table 4b.

Spearman correlation between absolute change in phosphatidylethanol (PEth) and absolute change in reported number of drinks per week over 7 months, stratified by alcohol use disorder (AUD) and body mass index (BMI)

	0 – 2 months		2 – 7 months		0 – 7 months	
	Correlation coefficient	**P-value**	**Correlation coefficient**	**P-value**	**Correlation coefficient**	**P-value**
Total Sample	0.02	0.87	0.17	0.16	−0.03	0.80
Persons with AUD (N=32)	−0.04	0.79	0.12	0.46	−0.14	0.38
Persons without AUD (N=49)	0.15	0.42	0.26	0.17	0.20	0.29
Persons with BMI ≤25 (N=29)	−0.01	0.98	0.34	0.09	0.09	0.65
Persons with BMI >25 (N=52)	0.04	0.78	0.10	0.51	−0.13	0.39