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The association between alcohol abuse and neuroendocrine system dysregulation: Race differences in a national sample

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Objectives

Health outcomes, including chronic disease and mortality, attributed to or associated with alcohol abuse are discrepant between African Americans and Whites. To date, the topic is not fully understood and few studies conducted have used biomarker indicators of health. We investigated whether the association between alcohol abuse and biomarkers of the neuroendocrine system vary between black or African American and White respondents aged 34 to 84 from the Midlife in the United States Study (MIDUS) II (2004–2006) (n =1,129). Alcohol abuse was assessed with a modified version of the Michigan Alcohol Screening Test. Ordinary least squared (OLS) regression was used to evaluate whether race moderated the associations between alcohol abuse and four biomarkers—urinary cortisol and serum dehydroepiandrosterone sulfate (DHEA-S), epinephrine and norepinephrine—and two composite summary scores, each consisting of two components that characterize the hypothalamic pituitary adrenal (HPA)-axis and sympathetic nervous systems (SNS), respectively. Covariates included age, sex, education, income, current drinking, smoking, exercise, fast food consumption, heart disease, blood pressure, diabetes, body mass index, medication use, anxiety/depression, sleep duration, and cholesterol markers. Race significantly moderated the associations between alcohol abuse and norepinephrine concentration (χ^2 [1] = 4.48, p=0.034) and the SNS composite score (χ^2 [1] = 5.83, p=0.016). Alcohol abuse was associated with higher mean norepinephrine levels (b=0.26, standard error (SE)=0.12, p=0.034) and SNS composite score (b=0.23, SE=0.11, p=0.016) for African Americans compared to Whites. Interestingly, for Whites a paradoxical association between alcohol abuse, norepinephrine and SNS levels was observed; those who abused alcohol had lower mean norepinephrine levels than non-abusers. Race differences in neuroendocrine response could be biological pathways that contribute the excess risk of chronic disease and mortality attributed to alcohol abuse among African Americans compared to Whites. Replication of these analyses in

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larger cohorts are warranted in addition to further studies of underlying mechanisms among Blacks and Whites separately.

Keywords

alcohol abuse; neuroendocrine system; biological markers; race/ethnicity; chronic disease; MIDUS

1. Introduction

Alcohol abuse contributes to 5% of the global burden of disease (World Health Organization, 2011) and it is the third lifestyle-attributed cause of preventable mortality in the United States (US) (Centers for Disease Control and Prevention, 2011). Alcohol abuse is a major causal factor in over 60 chronic diseases (Bauer et al., 2014; Connor et al., 2015), including diabetes, hypertension, cirrhosis of the liver, breast and liver cancer, and early mortality (Boffetta and Hashibe, 2006; Centers for Disease Control and Prevention, 2011; Chen et al., 2011; Rehm et al., 2010; Rehm et al., 2014). Alcohol abuse acts a chronic stressor that can result in dysfunction of the neuroendocrine system, which drives poor physical and mental health, chronic diseases, and early mortality (Clarke et al., 2008; Cui et al., 2011; Dees et al., 2015; Yakovleva et al., 2011).

Blacks/African Americans compared to Whites have higher rates of many of the physical and chronic health outcomes, injury, and mortality that are, in part, attributed to alcohol abuse, dependence or excessive alcohol use (Polednak, 2008; Keyes et al., 2012; Stahre and Simon, 2010). That Black-White pattern in alcohol-related health outcomes is evident even after adjustment for socioeconomic status, social, and environmental covariates (Kerr et al., 2011; Chartier et al., 2013; Mulia et al., 2009), and ethanol concentrations in different alcoholic beverages (Witbrodt et al., 2014). Drinking patterns among African Americans are characterized by higher frequency of heavy drinking occassions (Sempos et al., 2003) while clinical-based assessments of alcohol use disorder—which include abuse—reveal small to no statistical differences in 12-month prevalence of alcohol abuse and/or dependence (Hasin et al., 2007; Grant et al., 2015).

In light of race differences in chronic disease and mortality, it is possible that the impact of alcohol abuse and diseases will differ between Blacks and Whites (Zapolski et al., 2014). For example, some studies found that for Blacks compared to Whites, alcohol abuse, dependence or excessive alcohol use had a stronger negative impact on cardiovascular-related diseases (Fuchs et al., 2004; Fuchs et al., 2001), breast cancer (Park et al., 2014), years of potential life lost (Shield et al., 2013), and mortality (Jackson et al., 2015; Williams et al., 2012).

However, one major gap in this topic of research so far is that little is known about racial differences the association between alcohol abuse and biological markers of health systems that underly disease and mortality. Environmental, psychosocial, and behavioral exposures drive race differences in chronic disease and mortality through complex interplays on multiple bio-physiological pathways that include the cardiovascular, immune, and metabolic

systems, which can be represented through a measure of cumulative burden called allostatic load (Geronimus et al., 2006; Seeman et al., 2010). Despite the fact that multiple physiological systems contribute to health disparities, the scope of this study concerns the neuroendocrine system given the links to numerous diseases. Additionally, the topic is under-researched despite some evidence of Black-White differences in several hormones within this system, such as cortisol and norepinephrine (Cohen et al., 2006a; Ziegler et al., 1991).

Hormones such as epinephrine, norepinephrine, cortisol, and dehydroepiandrosterone sulfate (DHEA-S), play a central role in the pathogensis of physical and mental health, chronic disease, and premature death (Anand et al., 2003; Olff et al., 2006; Roggero et al., 2016; Schroeder and Jordan, 2012; Trivedi and Khaw, 2001; Zoccali et al., 2002). Specifically, epinephrine, norepinephrine, and cortisol are main effectors of the body's response to stress and trigger a fight-or-flight response. Excessively high levels of these hormones are associated with high blood pressure, cancer tumor progression, and insomnia (Chrousos, 2009; Yang et al., 2009; Zijderveld et al., 1999). For example, one study of patients with type-2 diabetes found that a norepinephrine level ≥ 333 pg/ml was associated with a five-fold higher risk of incident adverse cerebral and cardiovascular events (Yufu et al., 2014) compared to levels below that threshold. Low levels of hormones such as norepinephrine has been linked to higher depressive symptoms (Moret and Briley, 2011) and lower cortisol has been linked to stress-related disorders through weakening the availability of glucocorticoid signaling (Raison and Miller, 2003).

Next, the hypothalamic pituitary adrenal (HPA)-axis is a major neuroendocrine signaling system that regulates physiological responses to stress through the hypothalamic release of corticotropin-releasing hormone (Smith and Vale, 2006). Dysregulation in the HPA-axis is associated with post-traumatic stress disorder (Olff et al., 2006) and likely development of cancers, although the impact of cancer growth as a function of lower or higher production of hormones, including cortisol and epinephrine, depends on the type of cancer (Armaiz-Pena et al., 2009; Sood et al., 2006; Yehuda, 2003).

Finally, DHEA-S declines with age and lower levels are associated with frailty and higher risk of mortality (Ohlsson et al., 2015) while some evidence suggest higher levels are protective of cardiovascular diseases (Savineau et al., 2013).

The links between alcohol abuse and dysregulation of the neuroendocrine system has been demonstrated in both animal and human studies. For instance, one experimental study in rats demonstrated that alcohol exposure at levels that reflect dependence, was associated with significant impairment of the HPA-axis and dampened neuroendocrine function — e.g., lower ability to cope with stress and heightened cortisol release (Richardson et al., 2008). One longitudinal observational study in humans found significant reductions (approximately 45%) in serotonergic neurotransmission in alcohol dependent individuals compared to controls (Fahlke et al., 2012). In addition, a population-based longitudinal study of adults from the Netherlands showed that heavy alcohol use (men: >3, women: >2 drinks/day) relative to moderate use (men: ≤3, women: ≤2 drinks/day) was associated with higher mean evening cortisol and lower mean cardiac sympathetic control, adjusting for

sociodemographic, health and lifestyle, depression, and medication covariates (Boschloo et al., 2011).

To the best of our knowledge, no prior study has examined whether there are race differences in the association between alcohol abuse and physiological biomarkers of the neuroendocrine system. We hypothesize that dysregulation of the neuroendocrine system in association with alcohol abuse is pronounced among African Americans compared to Whites.

2. Methods

2.1. Sample

Data were from the second wave of the Midlife in the United States (MIDUS) biomarker sample. MIDUS is a longitudinal study designed to study social, psychological and behavioral factors in relation to physical and mental health (Radler and Ryff, 2010). MIDUS I enrolled 7108 individuals, including sibling and twins ages 25 to 74 years between January 1995 and September 1996 from a national sample of non-institutionalized adults living in 48 states, through random digit dialing (Love et al., 2010). Among the original sample, a second wave (MIDUS II) of (n = 4963, 70% response rate) was conducted between 2004 and 2006. At that time, an additional sample of (n = 592) African Americans was recruited from Milwaukee, WI to increase participation of African Americans in the study. Milwaukee is a highly segregated city, which was close to Madison, WI—one site where the biological data were collected. Respondents in the MIDUS II national sample and Milwaukee sample were eligible to participate in the biological assessments if they had completed the MIDUS II surveys, and lived in the contiguous US. Biomarker data were measured among individuals who stayed overnight at one of three General Clinical Research Centers (GCRC): the University of Wisconsin, Madison; University of California, LA; and Georgetown University. The institutional review boards at each university approved all data collection (Love et al., 2010). All participants provided informed consent. The final sample with biomarker data was 1,255 participants. The sample for this secondary analysis is (n = 1,129) black or African American and White respondents only, ages 35 to 84 years with no missing data on the exposure, outcomes, and covariates of interest below.

2.2. Measures

2.2.1. Neuroendocrine biomarkers—Urine cortisol adjusted for creatine, and DHEA-S were assayed using a Roche Modular Analytics E170 analyzer via an Elecsys kit (Roche Diagnostics, Indianapolis, IN). The intra-assay coefficient of variance was 2.9% for cortisol and between 0.8 to 6.5% for DHEA-S. Epinephrine and norepinephrine based on 12-hour overnight urine collections adjusted for urine creatine levels, were assayed using high-pressure liquid chromatography (HPLC). The intra-assay coefficient of variation was 7.9% for epinephrine and 6.0% for norepinephrine. In regression models, cortisol, DHEA-S, epinephrine and norepinephrine were modeled as continuous variables, and were log-transformed to correct a right-skewed distribution and satisfy normality assumptions for OLS regression. We also created composite scores to capture HPA-axis burden (consisting of cortisol and DHEA-S), and the SNS burden (consisting of epinephrine and

norepinephrine). For both composite measures the range was 0 to 1, which indicates the average # of high-risk indicators (i.e., in the top quartile for each of the variables within that composite score).

Further details on the methodology of the biomarkers and composite summary score creation are published elsewhere (Duncan et al., 2003; Gruenewald et al., 2012).

2.2.2. Alcohol Abuse—was assessed using a modified version of the Michigan Alcoholism Screening Test (MAST), which showed adequate reliability and validity in population studies (Selzer et al., 1975; Shields et al., 2007). MAST is a diagnostic measure used in clinical settings and has demonstrated concurrent validity with other popular diagnostic indicators such as Alcohol Use Identification Test (AUDIT) and Cut-back, Annoyance by critics, Guilt about drinking, and Eye-opening morning drinking (CAGE) scale (Gibbs, 1983; Hays et al., 1995). The MAST questions were: (a) did you have any emotional or psychological problems from using alcohol, such as feeling depressed, being suspicious of people, or having strange ideas? (b) did you have such a strong desire or urge to use alcohol that you could not resist or could not think of anything else? (c) did you have a period of a month or more when you spent a great deal of time using alcohol or getting over its effects? (d) did you find that you had to use more alcohol than usual to get the same effect or that the same amount had less effect on you than before? The fifth question was not available in MIDUS II questionnaire: (e) were you ever, during the past 12 months, under the effects of alcohol or feeling its after-effects in a situation which increased your chances of getting hurt- such as when driving a car or boat, or using knives or guns or machinery? The response option for each question is yes or no.

The four MAST items were summed and dichotomized to 0 = no alcohol abuse and 1 = alcohol abuse if a participant responds positively to at least one of the four questions. The variable was only computed for cases that have at least one valid response to the four questions in the summary variable. The internal consistency coefficient (Cronbach's α) for the 5-item MAST based on MIDUS I was 0.67 for African Americans and 0.75 for Whites. The Cronbach's α in MIDUS I for the four items (a to d) was 0.68 for African Americans and 0.73 for Whites. The Cronbach's α in MIDUS II for the four items was 0.76 for African Americans and 0.70 for Whites.

2.2.3. Race—was operationalized via self-reported identification (black or African American vs. White, only).

2.2.4. Sociodemographic Covariates—included sex (men vs. women); mean centered age in years, and educational attainment in years, and household income categorized into three equal groups and a fourth group assigned for missing responses.

2.2.5. Health Status and Behavior Covariates—were selected based on their association with race, alcohol use, and with physiological and neuroendocrine biomarkers (Beulens et al., 2008; Boschloo et al., 2011; Cohen et al., 2006b; Galán et al., 2014; Thayer et al., 2006; Volpato et al., 2004). Current drinking (consuming at least one alcoholic beverage in the past month), smoking history (yes, ever smoked regularly—that is, a few

cigarettes every day vs. no); exercise (defined as greater than or equal to 20 minutes three times per week vs. other exercise); body mass index (BMI) was calculated using height and weight measured by the GCRC staff (continuous variable, kg/m^2); and fast food consumption (eating fast food greater than or equal to once per week vs. once per week vs. never).

Positive responses to self-reported physician-diagnosed history of diabetes mellitus, cardiovasular disease (CVD) (stroke, heart attack, angina, and chest pain), high blood pressure, and medications (anti-hypertensive, lipid-lowering, corticosteroid, and antidepressant) were included as dummy indicators. Anxiety and depression in the past 12 months were defined in accordance with criteria specified in the Diagnostic and Statistical Manual of Mental Disorders-third edition-revised (DSM-III-R), average sleep duration (seven hours or more vs. less than or equal to six hours) and cholesterol measures (high-density and low- density lipoprotein, and triglycerides) were also controlled for in analyses.

2.3. Statistical Analyses

STATA 14.0 software (StataCorp, 2015) was used to analyze the data. Means and standard deviations were calculated for continuous variables and number and percent for binary or categorical variables. A series of ordinary least square (OLS) regression models were computed to examine the independent association of race and alcohol abuse on each neuroendocrine biomarker and the HPA and SNS composite scores within the pooled African American and White sample. Effect modification by race was assessed via an interaction term and the significance of any interaction was assessed using test of contrasts that reports a Chi-Square value with one degree of freedom.

There were two effect modification models. The first adjusted for age, sex, education, income, current drinking, smoking, exercise, fast food consumption, medication use (blood pressure, cholesterol, steroid, and anti-depressant medications), anxiety/depressive symptoms, and average sleep duration (Model 2). The next model adds the following health variables to the prior model: body mass index, diabetes, heart disease, high blood pressure, high density lipoprotein, low density lipoprotein, and triglycerides. The purpose of adding those variables in a subsequent step was to examine whether any potential race differences in neuroendocrine dysregulation from the prior model operates through health status (Model 3).

For those interactions that were statistically significant, marginal mean scores and 95 % confidence intervals for the association between alcohol abuse and the biomarkers for African Americans and Whites were obtained and plotted on their untransformed metric. For all models, bootstrapped estimates (stratified by alcohol abuse) of the standard errors and confidence intervals were computed by generating 500 iterations using the bias corrected and accelerated (bca) method (Carpenter and Bithell, 2000). Robust standard errors were also obtained. Bootstrapping addresses potential non-normality of the error term and heteroscedasticity in OLS regression, which potentially may occur with the small sample size of African Americans compared to Whites with alcohol abuse. Although MIDUS II contained twins, we did not account for clustering with methods such as General Estimating Equations (GEE). This is because there were too few twin pairs among the African

American sample, which caused the multivariable models to skip iterations and not converge during the bootstrapping.

3.0. Results

Supplement Table 1 shows the distribution of exposures and covariates between the analytic sample used in multivariable analysis and those excluded because of missing data on one or more covariates ($N = 75$). Ninety-four percent of the sample were included (i.e., $N = 1,129$). Respondents included were not statistically different from those excluded (i.e., $p > 0.05$) for alcohol abuse, nor any of the neuroendocrine markers except DHEA-S, nor any of the sociodemographic variables except age, nor any of the health status and behavior covariates except high blood pressure diagnosis and medication use. Moreover, among those excluded, there were no race differences in age, blood pressure diagnosis and medication use (all $p > 0.10$, results not displayed but available upon request).

Table 1 shows that the prevalence of 12-month alcohol abuse was higher for African Americans than Whites (7.9% vs. 4.4%, $p = 0.03$). The race-difference was significant among current drinkers ($p = 0.008$) but not among non-drinkers ($p = 0.443$), (results not displayed). For all neuroendocrine biomarkers, African American respondents had a lower mean value than Whites (all p values < 0.05). African Americans were younger, had lower mean levels of educational attainment and income, and vigorous exercise; however, African American respondents were more likely than White respondents to be women, smoke, consume fast-food, and have less than six hours of sleep (all $p < 0.05$). A lower proportion of African Americans compared to Whites had consumed alcohol in the past month and used medication for cholesterol, corticosteroid, and antidepressant medications (all $p < 0.05$).

Table 2 presents OLS regression results for the interaction between race and alcohol abuse with the biomarkers, adjusted for covariates. Model 1 shows the main effect for the independent associations of race and alcohol abuse on the neuroendocrine system markers and the composite scores, adjusted for basic covariates including age, gender, education and income. African American compared to White respondents had lower levels of cortisol ($p < 0.001$), epinephrine and norepinephrine, and SNS composite summary score ($p < 0.001$). Alcohol abuse, independently from race, was not statistically associated with any of the outcomes.

Model 2 builds on Model 1 to additionally include the interaction between race and alcohol abuse. Race moderated the associations between alcohol abuse and norepinephrine (χ^2 [1] = 3.69, $p = 0.054$) and the sympathetic system composite summary score (χ^2 [1] = 3.90, $p = 0.048$); we found no evidence of a significant interaction for the other outcomes.

Model 3 builds on Model 2 to add the health variables, including body mass index, diabetes, heart disease, high blood pressure, high density lipoprotein, low density lipoprotein, and triglycerides. The directions, point estimates and statistical significance of the outcomes were not materially altered by addition of those variables. Race significantly moderated the associations between alcohol abuse and norepinephrine (χ^2 [1] = 4.48, $p = 0.034$) and the sympathetic system composite summary score (χ^2 [1] = 5.83, $p = 0.016$).

Alcohol abuse was associated with higher mean levels of norepinephrine (b = 0.26, standard error (SE) = 0.12, $p = 0.034$) and SNS composite summary score (b = 0.23, SE = 0.11, $p = 0.016$) for African Americans compared to Whites.

Figure 1 shows the marginal predicted means of norepinephrine and SNS composite score, respectively, from Model 3. Among African Americans, alcohol abuse compared to no abuse was associated with higher mean levels of norepinephrine (27.75 vs 24.94 ug/dL) and overall SNS composite score (0.27 vs 0.16 average # of high-risk indicators). Paradoxically, among Whites, alcohol abuse compared to no abuse was associated with lower mean levels of norepinephrine (23.95 vs 27.95 ug/dL) and SNS (0.13 vs 0.25 average # of high-risk indicators). Hormone levels between African Americans who abused alcohol and White non-abusers did not significantly differ.

4.0. Discussion

Examining the role of alcohol abuse in the dysregulation of biomarkers within the neuroendocrine organ system can potentially elucidate the physiobiological mechanisms that can be intervened on within clinical settings (Freeman and Vrana, 2010; Schuckit, 2009). To the best of our knowledge, this is the first study to examine whether there were race differences in the association between alcohol abuse and biomarkers of the neuroendocrine organ system. As such, it would also be the first to show that alcohol abuse has an upregulating association of serum in norepinephrine and SNS composite for African Americans but downregulating association for Whites. Our findings contribute to the evidence of divergent health racial patterns in the association between alcohol use (abuse and disorders) and self-reported physical health and mortality (Chartier et al., 2013; Williams et al., 2012).

The main function of the sympathetic hormone norepinephrine is to mobilize the brain and body for action by increases in alertness, heart rate and blood pressure, and trigger release of glucose from energy stores. Higher norepinephrine is associated, at least partially, with high blood pressure, cardiovascular disease, depression, anxiety and other chronic diseases including diabetes (Montoya et al., 2016; Schroeder and Jordan, 2012; Thomas and Marks, 1978).

In this study, the levels of dysregulation in norepinephrine associated with alcohol abuse were not clinically significant given that normal range can span 15ug to 100ug/24hr (American Board of Internal Medicine, 2017). Nevertheless, our evidence suggest that dysregulation of norepinephrine and SNS could be components, which along with dysregulation of other serums from other biological systems, could contribute to a higher prevalence of chronic diseases and mortality for African Americans (Jackson et al., 2010; Williams, 2012). Although we focused on the neuroendocrine system for this study, it is well documented that multiple physiological systems interact in non-linear patterns in ways that underlie racial disparities in health (Geronimus et al., 2006; Seeman et al., 2010). Therefore, research on the topic going forward should examine measures such as allostatic load, which represents a more comprehensive view of bio-physiological risk profiles (Juster et al., 2010).

Given that we use cross-sectional data, it is plausible that poorer health profiles of African Americans drive the dysregulation between alcohol abuse and the outcome. For example, bivariate results showed that African Americans in this sample had higher prevalence of diabetes and blood pressure, and subsequently had higher medication use for blood pressure and cholesterol than Whites. However, our findings suggest that net of socioeconomic status and medication use, adding health variables including BMI, diabetes, and cardiovascular disease does not materially alter race differences in the association between alcohol abuse and norepinephrine and SNS serum.

Plasma norepinephrine levels reflect the spillover or clearance of the hormone from the system into the bloodstream (Goldstein et al., 2003). Previous experimental evidence showed race differences in the neuroendocrine system such that Blacks cleared infused norepinephrine from their plasma faster than Whites (Ziegler et al., 1991). A recent study showed that, adjusted for covariates, Black race predicted had higher plasma norepinephrine levels than Whites (Saxena et al., 2014). Other recent studies have also indicated that elderly African Americans had higher SNS control and responsiveness compared to Whites (Okada et al., 2012; Okada et al., 2016). Intriguingly, our results revealed that the norepinephrine levels are higher among White non-abusers compared to Black non-abusers as well as White persons who abuse alcohol. At the same time, there was no difference in serum levels between Black abusers and White non-abusers, which is equally perplexing.

The findings between White abusers and non-abusers, plausibly, may be due to lifestyle factors and socioeconomic status. For instance, some evidence show that alcohol abuse is associated with higher physical activity through pathways that appear to include common personality, biological, and social mechanisms (Lisha et al., 2013). Higher physical activity is in turn associated with reduced SNS and norepinephrine levels (Bote et al., 2014), although the extent of changes in the hormones varies by intensity of exercise (Greiwe et al., 1999). Higher socioeconomic status, specifically income, has also been associated with higher alcohol abuse (Keyes and Hasin, 2008) and with higher physical activity (Trost et al., 2002). Interestingly, in exploratory posthoc analyses (not shown), Whites with alcohol abuse had higher income than White non-alcohol abusers, but that income pattern was inverse among African Americans; and as shown in Table 1, Whites overall had higher physical activity rates than African Americans.

Race is a social construct that captures a set of social exposures environments including racism that influences gene-environment interactions (Jones, 2000; Lillie-Blanton and Laveist, 1996). Therefore, a combination of socioeconomic status and epigenetics could also plausibly explain why African Americans who abused alcohol had lower norepinephrine levels than White non-abusers. For instance, one population-based study showed that higher income-wealth ratio was associated with lower urinary cortisol and that inverse association was stronger among African Americans compared to Whites (Castro-Diehl et al., 2014). We adjusted for income and education and those measures did not account for race-differences in our study. However, it is possible that qualitative differences in effects of SES on health between Blacks and Whites (Williams et al., 2010) or other socioeconomic status markers such as wealth may play a greater role in health inequalities (Shapiro, 2004). In these data, we were not able to adjust for wealth.

One biologically plausible explanation for the paradoxical finding among Whites and compared to African Americans is racial/ethnic differences in genotypes of alcohol metabolizing enzymes (Chartier et al., 2014). For instance, ADH1B*3—the most widely replicated genetic variant of aldehyde dehydrogenase and primary enzyme responsible for metabolizing alcohol faster, is more prevalent among African Americans compared to Caucasians (Brennan et al., 2004; McCarthy et al., 2010).

However, evidence suggests that although ADH1B*3 is protective of alcoholism among African Americans; once they develop alcoholism, their health profile deteriorates dramatically because of higher risk for developing alanine and aspartate aminotransferase—biomarkers of liver disease (Ehlers et al., 2007). Higher risk for alcohol-related problems among African Americans has also been linked to higher sensitivity to the effects of alcohol compared to European Americans (Pedersen and McCarthy, 2013). On the basis of race differences in prevalence of ADH1B*3, ADH1C*1/2, ADH1B* 1/1, and the rapid health decline among African Americans with alcoholism; it is plausible to observe a lower overall norepinephrine level or no difference in SNS level between African Americans who abuse alcohol compared to White non-abusers. On that same basis discussed above, it is also possible to simultaneously observe higher norepinephrine and SNS level among African American abusers compared to Whites who abuse alcohol. Other, yet unknown, racial/ethnic differences in genetic expression and methylation of DNA (Zhang et al., 2011) may also play a role in our findings.

Despite the paradoxical association between alcohol abuse and norepinephrine and SNS among Whites, the association between race and alcohol abuse with health found in our study is consistent with the wider body of evidence on the topic. Two previous studies found that current alcohol use was associated with elevated levels of alanine and aspartate aminotransferase—biomarkers of liver disease among Black compared to their non-Hispanic White counterparts (Stewart, 2002; Stranges et al., 2004). One other study examined alcohol consumption in relation to breast cancer diagnosis using tumor biomarkers—e.g., estrogen receptor (ER) and human epidermal growth factor receptor 2—and found that African American women who drank greater than seven drinks per week had about 35% higher risk of breast cancer than their White counterparts (Williams et al., 2016). That study also found that the elevated risk of heavy alcohol use on ER negative and triple-negative breast cancers was significant for African American but not White women. Those studies differ from ours as they examined alcohol consumption and not alcohol abuse based on diagnostic indicators such as MAST.

We found that African Americans compared to Whites in MIDUS II had a higher 12-month prevalence of alcohol abuse. However, the higher prevalence was only significant among current drinkers. The higher prevalence of alcohol abuse in these data are in contrast to results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC wave 2, 2004–2005), which is one of the largest population-based studies in the United States and closest to the MIDUS time frame. NESARC data indicate that, *in the general population*, African Americans compared to Whites have lower 12-month prevalence of alcohol abuse (3.3% vs. 5.1%), however, NESARC assesses abuse using the Diagnostic Statistical Manual-IV (DSM-IV) criteria (Hasin et al., 2007). NESARC also sampled,

especially among African Americans, from a more geographically diverse population, which is another plausible reason why prevalence estimates were different in our sample.

Our findings of higher alcohol abuse prevalence, however, is consistent with complementary evidence on race differences such that, *among current drinkers*, African Americans experience a greater number of alcohol abuse and dependence symptoms than Whites (Chartier and Caetano, 2010; Mulia et al., 2009; Witbrodt et al., 2014)

Some limitations of this study include sample representativeness. The African American sample in MIDUS II biomarker study was recruited primarily from Milwaukee, WI. While Milwaukee is a highly segregated city that reflects the living conditions of a large portion of urban Blacks, our sample is not representative of all African Americans in the US. A related issue is the relatively low sample number of African Americans in the study. The sample size of African Americans with alcohol abuse was almost half that compared to Whites. We attempted to adjust statistically for small sample size through bootstrapping the standard errors. Nonetheless, findings based on this sample of African Americans may have diminished our ability to detect effect modification by race across biomarkers other than norepinephrine and the SNS composite summary score. Next, although there was an approximately one year delay between when the alcohol questions were assessed and the biomarker data collected, the data are essentially cross-sectional, thus we cannot draw causal inferences about the associations found.

Another limitation is the measure of alcohol abuse. One of the five standard MAST questions was not available in MIDUS II. Although there are no previously published studies on the reliability of the MAST for the remaining four items at the present time, our study found that the reliability for both African Americans and Whites based on the four-item MAST was good (i.e., Cronbach's α 0.70 to 0.76) considering a scale with four items (Cortina, 1993). It is also noteworthy that the reliability for the four items for alcohol abuse according to criteria set forth in the Diagnostic and Statistical Manual fourth edition (DSM-IV) was 0.73 (Grant et al., 1995), which is within the range of the reliability found with the four-item MAST measure in our study. Nevertheless, further research that seeks to replicate our findings with a more geographically diverse and representative sample of African Americans and evaluation with other diagnostic measures or biomarkers of alcohol abuse is warranted.

5.0. Conclusion

The present study found that alcohol abuse is associated with upregulated norepinephrine and the SNS composite serum for African Americans but downregulated serum for Whites. Future studies incorporating biological markers of alcohol abuse are warranted to understand potentially paradoxical relationships between alcohol abuse and neuroendocrine markers of health, among Black and White persons separately. Future research should also examine whether there are race differences in the association between alcohol abuse and biological markers for other organ systems, which can inform research and interventions to eliminate racial disparities in health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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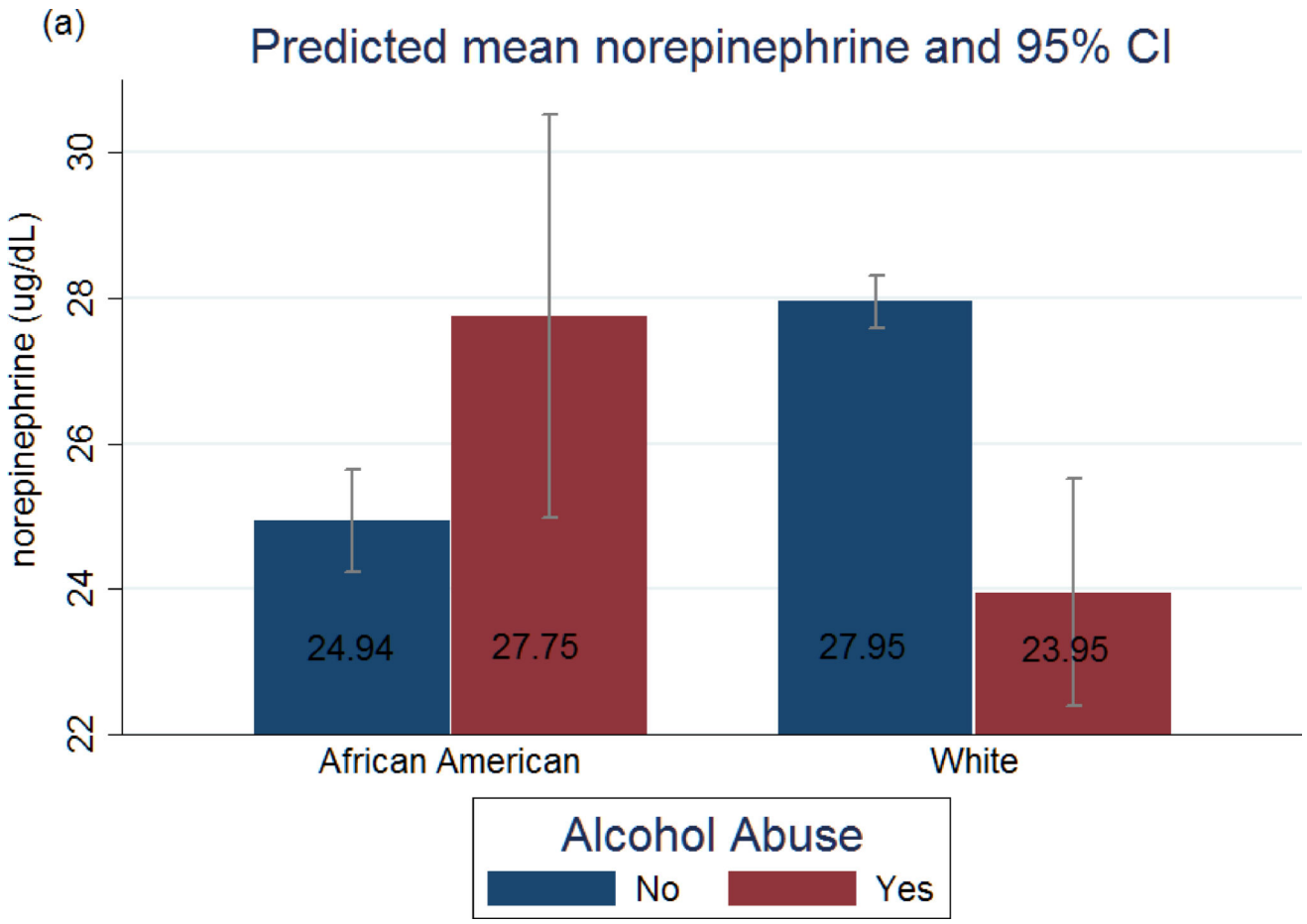
- We examined the interaction of race*alcohol abuse on neuroendocrine system biomarkers
- Blacks had lower mean cortisol, DHEA-S, epinephrine and norepinephrine than whites
- Race moderated the association between alcohol abuse and norepinephrine, and SNS
- Alcohol abuse upregulated norepinephrine and SNS for blacks compared to whites
- White alcohol abusers exhibited lower norepinephrine and SNS than white non-abusers



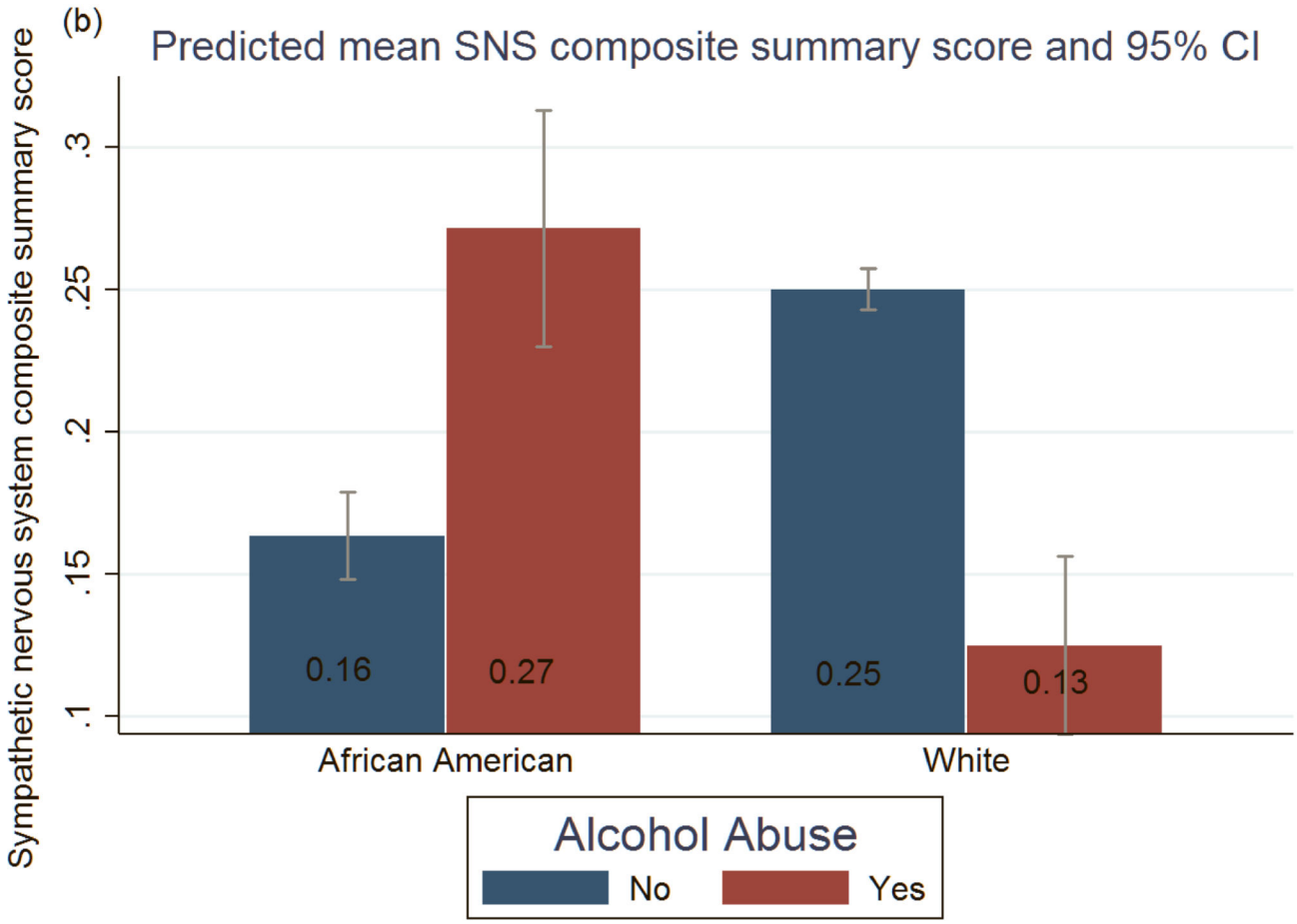


Figure 1.

Predicted mean and 95 % Confidence Intervals of (a) norepinephrine and (b) sympathetic nervous system (SNS) composite summary score, by alcohol abuse for African American and White Respondents. Estimates were derived from OLS regression model as described in the text and results (Table 2, Model 3), which was adjusted for: age, sex, education, income, current drinking, smoking, exercise, fast food consumption, medication use (blood pressure, cholesterol, steroid, and anti-depressant medications), anxiety/depression, average sleep duration + health variables (body mass index, cardiovascular disease, diabetes, blood pressure and cholesterol measures (HDL, LDL, and Triglycerides)). IQR= Interquartile range, *for the entire sample

Table 1

Characteristics of White and African American respondents (n = 1,129); Midlife in the United States (MIDUS) Biomarker Study

	White Respondents (n=914)[a] Mean (SD) or N (%)	African American Respondents (n=215)[a] Mean (SD) or N (%)	p-value
Alcohol Abuse			
Yes	40 (4.4)	17 (7.9)	=0.033
Neuroendocrine system markers			
Urine cortisol/creatine (ug/g)	16.4 (15.23)	10.4 (08.22)	<0.001
Blood DHEA (ug/dL)	104.7 (76.1)	100.7 (77.1)	=0.047
HPA-axis composite score[b]	0.25 (00.3)	0.18 (00.2)	=0.003
Urine epinephrine/ creatine (ug/g)	2.0 (01.3)	1.7 (01.3)	=0.001
Norepinephrine/ creatine (ug/g)	27.7 (13.2)	25.9 (16.7)	=0.007
Sympathetic system composite score[b]	0.24 (00.3)	0.17 (00.03)	=0.001
Age (years)	55.5 (11.9)	50.9 (10.6)	<0.001
Sex			
Men	416 (45.5)	72 (33.5)	0.001
Women	498 (54.5)	143 (66.5)	
Education (years)[c]	7.78 (2.43)	6.11 (2.48)	<0.001
Income (dollars)	$77,519 ($60,730)	$38,607 ($34,888)	<0.001
Health status and behaviors			
Currently consume alcohol (% yes)	622 (68.0)	118 (54.9)	<0.001
Smoked regularly (% yes)	404 (44.2)	131 (60.9)	<0.001
Vigorous exercise (20 mins) ≥3 times/week (% yes)	732 (80.9)	138 (64.2)	<0.001
Body mass index	29.1 (5.9)	32.8 (8.3)	<0.001
Eat fast food (%> once per week)	444 (48.6)	105 (48.8)	=0.417
CVD diagnosis (% yes)	104 (11.3)	25 (11.6)	=0.918
Diabetes diagnosis (% yes)	89 (09.7)	51 (23.7)	<0.001
High blood pressure diagnosis (% yes)	300 (32.8)	115 (53.5)	<0.001
Current medications (% yes)			
Blood pressure medication	312 (34.1)	100 (46.5)	=0.001
Cholesterol medication	268 (29.3)	43 (20.0)	=0.006
Corticosteroid medication[d]	115 (12.6)	19 (8.8)	=0.127
Anti-depressant medication	144 (15.8)	13 (06.0)	<0.001
Anxiety/depression (% yes)	175 (19.1)	43 (20.0)	=0.775
High-density lipoprotein	54.9 (19.4)	59.2 (19.4)	=0.002
Low-density lipoprotein	105.8 (34.9)	101.8 (35.3)	=0.120
Triglyceride	130.9 (79.7)	112.8 (73.3)	=0.001
Average sleep duration			
≤ Six hours (%)	232 (25.4)	94 (43.7)	<0.001

[a] Sample with no missing data on any of the covariates;

[b] the composite summary score ranges from 0 to 1, which indicates the average # of high-risk indicators (i.e., in the top quartile for each of the variables within that composite score);

[c] education (6=1 to 2 years of college no degree yet, 7= 3 or more years of college no degree yet;

[d] Corticosteroid medication includes adrenals, estrogens, antiestrogens and estrogen agonists-antagonists. HPA is hypothalamic pituitary adrenal. DHEA is dehydroepiandrosterone sulfate, SNS is sympathetic nervous system.

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Table 2

Ordinary least square regression assessing the main and interaction models of race and alcohol abuse in relation to biomarkers of the neuroendocrine system; Midlife in the United States (MIDUS) Biomarker Study (n=1,129)

	Log Cortisol b(SE)	Log DHEA-S b(SE)	HPA-axis composite[a] b(SE)	Log Epinephrine b(SE)	Log Norepinephrine b(SE)	Sympathetic nervous system composite[a] b(SE)
Model 1. Baseline Models[b]						
Alcohol Abuse:						
Yes	−0.14 (0.10)	0.05 (0.09)	−0.00 (0.03)	0.03 (0.07)	−0.03 (0.05)	−0.01 (0.04)
No (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Race:						
African American	−0.40 (0.07)***	−0.12 (0.06)	−0.04 (0.02)	−0.20 (0.05)***	−0.17 (0.04)***	−0.08 (0.03)**
White	1.0	1.0	1.0	1.0	1.0	1.0
Model 2. Including Interaction Term[b]						
Alcohol Abuse						
Yes	−0.16 (0.12)	0.11 (0.08)	−0.04 (.04)	0.00 (0.08)	−0.09 (0.05)	−0.07 (0.04)
No (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Race:						
African American	−0.42 (0.06)***	−0.10 (0.06)	−.07 (.02)**	−0.23 (0.05)***	−0.18 (0.04)***	−0.10 (0.03)***
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Alcohol Use Disorders × Race						
African American	−0.04 (0.25)	−0.23 (0.22)	0.14 (0.08)	0.21 (0.18)	0.23 (0.12)*	0.22 (0.11)*
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Model 3. Including Interaction Term + health variables[c]						
Alcohol Abuse						
Yes	−0.14 (0.12)	0.11 (0.08)	−0.04 (.04)	−0.02 (0.08)	−0.11 (0.05)	−0.08 (0.04)
No (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Race:						
African American	−0.43 (0.07)***	−0.12 (0.06)	−.06 (.02)*	−0.22 (0.05)***	−0.20 (0.04)***	−0.11 (0.03)***
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0

	Log Cortisol b(SE)	Log DHEA-S b(SE)	HPA-axis composite[a] b(SE)	Log Epinephrine b(SE)	Log Norepinephrine b(SE)	Sympathetic nervous system composite[a] b(SE)
Alcohol Use Disorders × Race						
African American	−0.01 (0.24)	−0.21 (0.22)	0.14 (0.07)	0.22 (0.16)	0.26 (0.12) *	0.23 (0.11) *
White (reference)	1.0	1.0	1.0	1.0	1.0	1.0

[a] The composite summary score ranges from 0 to 1, which indicates the average # of high-risk indicators (i.e., in the top quartile for each of the variables within that composite score).

[b] Models 1 and Model 2 include the covariates age, sex, education, income, current drinking, smoking, exercise, fast food consumption, medication use (blood pressure, cholesterol, steroid, and anti-depressant medications), anxiety/depressive symptoms, and average sleep duration.

[c] Model 3 is built upon Model 2 + health variables: body mass index, diabetes, heart disease, high blood pressure, high density lipoprotein, low density lipoprotein, and triglycerides. Unstandardized coefficients and bootstrapped standard errors from 500 iterations using the bias corrected and accelerated (bca) method are from separate linear regression models.

* $P < .05$;

** $P < .01$;

*** $P < .001$