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The Association Of Allostasis With Alcohol Use Disorders: A Case-Control Study

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Dedication

Dedicated to Carlos Portillo, Sr., Elma F. Portillo, Erin M. Portillo, and Estrella Soria.

Thank you for your love and support.

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by

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Abstract

Background. Allostatic load (AL) is defined as the wear and tear on the body and the brain that can predispose one to disease due to the effects of the prolonged and/or constant activation of biological systems over time. The primary aim of the current study was to determine the relationship between an index of AL with having been diagnosed with an alcohol use disorder.

Methods. The current study is a secondary data analysis of case control data obtained from a sample of men with alcohol use disorder (AUD; n = 48) who were abstinent for a period of two to four weeks and a sample of healthy participants (n = 17) with no previous substance use issues to examine potential mean score differences in AL. AUD was determined by meeting the Diagnostic and Statistical Manual of Mental Disorders-Version IV (DSM-IV) criteria for alcohol dependence. AL load was measured using a composite index of biological measures such as cortisol (neuroendocrine system); interluken-6 (IL-6), fibrinogen, tumor necrosis factor-alpha (TNFa), and C-reactive protein (CRP, immune system); glucose, insulin, and leptin (metabolic system); pulse, systolic blood pressure readings, and diastolic blood pressure readings (cardiovascular and circulatory system); and body mass index (BMI, anthropometric system). It was hypothesized that (H1) higher AL mean scores would be observed in men with an AUD compared to the healthy control group. Higher AL scores were also hypothesized to be associated with increased amounts of (H2) baseline lifetime drinks per drinking day and (H3) drinks per drinking day at 3-month follow-up. Lastly, it was hypothesized that (H4) higher AL scores would be positively correlated with a psychological cumulative stress score derived from stress measures including the Childhood Adversity Interview, the Childhood Trauma Questionnaire, the UCLA Life Stress Interview, and two questions from the PTSD section of the Diagnostic Interview Schedule for the DSM-IV.

Results. Overall, there were no mean score differences in AL between the two groups ($t(63) = .50$, $p = .618$), nor was the AL index positively associated with the two drinking outcomes (lifetime drinks per drinking day [$F(1, 44) = .20$, $p = .65$, $R^2 = .005$]; drinks per drinking day at 3-month follow-up [$F(1, 39) = .92$, $p = .345$, $R^2 = .024$]) or psychological cumulative stress score index ($r(62) = -.008$, $p = .951$). However, post-hoc analyses indicated statistically significant group mean differences between the two groups ($t(61) = 3.87$, $p < .001$) on the psychological cumulative stress score such that the healthy control participants had lower scores compared to their counterparts.

Conclusion. Overall, the hypotheses were not supported. Based on the results, it may be reasonable to infer that AL in the context of AUD or drinking patterns may not be applicable. Further, the method in which stress is captured warrants attention, given the differences observed in the psychological cumulative stress index but not the AL index.

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Chapter 1: Introduction

Background

Alcohol has been attributed to over 95,000 deaths annually, making alcohol one of the leading causes of death in the United States (CDC, 2019). National survey data also suggests that an estimated 14 million adults ages 18 and older are diagnoseable with alcohol use disorder (AUD) with less than eight percent of adults having received treatment in the past year (SAMHSA, 2019). Heavy drinking episodes have been suggested to be accompanied by more negative outcomes (Ritchie & Roser, 2018). The World Health Organization (WHO) reported that an excess of 200 diseases and injury-related health conditions were attributed to alcohol consumption (2014). One common disease associated with alcohol misuse is liver disease, in which recent data suggest that nearly 43% of the estimated 83,500 liver disease deaths were associated with alcohol (CDC, 2019). Strikingly, men contributed to nearly 63% (52,499) of all liver disease deaths with an estimated 45% (23,800) being related to alcohol (CDC, 2019). Bagnardi and colleagues (2015) also found evidence suggesting that alcohol consumption is associated with various types of cancers (i.e., mouth, throat, liver, and colorectal cancer). Other notable alcohol-related consequences include domestic violence perpetration (Field et al., 2004), emergency department admission due to an alcohol-related injury (Field et al., 2001), a compromised immune system (WHO, 2014), and cognitive impairments (i.e., dementia; WHO, 2014). Overall, evidence overwhelmingly suggests that alcohol consumption, and excessive alcohol consumption continue to impact health outcomes and often result in a plethora of consequences.

Stress

Stress has been categorized into two different types: acute stress and chronic stress. Acute stress is characterized as having resulted from an event that affects the sense of control (i.e., public speaking). Such events may elicit various responses such as rapid heart rate. Chronic stress differs from acute stress in that chronic stress results from repeated instances perceived as stress-inducing (Centre for Studies on Human Stress, n.d.). Chronic stress has also been associated with physiological dysregulation, poor mental and physical health, chronic disease, and has been associated with influencing life expectancy, particularly in vulnerable populations (Cohen et al., 2007; Groer et al., 2010).

From a psychosocial standpoint, stress has often been measured and assessed using self-reported measures as well as structured interviews administered by trained clinicians and have been created to account for various timepoints of one's life (i.e., childhood, lifetime, recent stressors, and daily hassles). The Adverse Childhood Experiences (ACEs) Questionnaire (Felitti et al., 1998), the Childhood Adversity Interview (CAI; Dienes et al., 2006), the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1998), the UCLA Life Stress Interview (Hammen et al., 1995), the Hassles and Uplifts Scale (HUS; Kanner et al., 1981), the Depression, Anxiety, and Stress Scale (DASS-21or 42; Lovibond & Lovibond 1995) and the Diagnostic Interview Schedule (DIS; Robins et al., 1981) are examples of stress measures. Previous research has observed associations between such stress measures and drinking during adulthood. For example, Dube and colleagues (2002) observed that those reporting a higher number of ACEs evidenced an increased chance of developing problematic alcohol patterns as adults – consistent with prior research suggesting that negative experiences during childhood are associated with alcohol

misuse (Kunitz et al., 1998). Moreover, these stressors experienced during childhood have been found to have lasting effects that develop over time into adulthood (Birn et al., 2017).

Taken together, the concept of cumulative stress is not a specific type of stressor, rather, it is the compounding effects of various stressors experienced over time that can be examined both biologically and psychologically.

Alcohol and Stress

Various domains of risk factors have been examined to understand how drinking habits may occur. Historically, self-reported reasons for drinking have primarily been to cope with stress (Conger, 1956) and due to social influences (Abbey et al., 1993). Previous findings have observed support for biological, environmental, and psychosocial risk factors. Being a male has been a well-documented risk factor for misusing alcohol due to the disproportionate consumption rates observed in comparison to females (i.e., Nolen-Hoeksema, 2004). Society's acceptance of alcohol consumption, outlets, and media advertisement of alcohol are some contributing environmental factors for drinking. The social learning theory of alcohol use and abuse suggests individuals drink as a coping response when other stress-relieving methods are not immediately available and also because an individual perceives the effects of alcohol as a removing agent of negative emotions (Abrams & Niaura's 1987). Moreover, there is a growing need to understand the importance of stress and how it impacts drinking patterns as stress accumulates over time. The concept of stress accumulating over time and its relationship with alcohol have been examined more in depth; it has been argued that as stress levels and drinking continue to impact a person's health, allostatic load (AL; "the wear and tear on the body") increases from a psychological and biological perspective (McEwen & Stellar, 1993).

Advances in AL Understanding

Homeostasis is defined as the ability for an organism to internally regulate and stabilize itself due to external stimuli (Cannon, 1929) and, in turn, allows for efficient physiologic functioning (Breed & Moore, 2016). McEwen (2016) added that the process in which the body regulates to return to a set state and function normally was essential for survival. The concept of homeostasis posits that through negative feedback loops, external triggers that cause a change activate the negative feedback loop response to counterbalance the effects. One common textbook example is the body's ability to change temperature by sweating to cool down the body in response to an increase in body temperature (Sadava et al., 2009). In this example, the body's response in lowering body temperature to its regular state is due to the negative feedback loop response. McEwen and Stellar (1993) highlight that the concept of homeostasis maintains that the body stays relatively constant. However, the conceptualization of homeostasis still contained gaps.

McEwen and Stellar (1993) argue that homeostasis is insufficient at explaining how chronic stress may affect the body over time due to the continuous changes in various bodily functions, such as blood pressure, heart rate, endocrine output, and neural activity in response to various types of stressors accumulated over time. That is, in response to changes in the physiologic state due to factors such as stress, fluctuations in these bodily functions occur. More specifically, they argue that the chronic stress that the body undergoes to maintain stability fails to account for the "hidden tolls," such as changes to the brain associated with neuronal damage and imbalances to the neuroendocrine system, that result from the chronic stress and posit that chronic stress associated with maintaining stability results in "wear and tear" of the body. Indeed, McEwen and Stellar credited an advancement in the understanding of stress and homeostasis to

Sterling and Eyer (1988) in their development and conceptualization of allostasis, which would be further expanded later by McEwen.

Allostasis refers to how physiologic systems adapt to maintain constancy within the body due to internal and external demands (Sterling & Eyer, 1988). For example, Goldstein and McEwen (2002) use the example of glucose, blood pressure, body temperature, and metabolism regulation to help regulate and stabilize the body due to external demands. In response to physiological changes such as glucose and blood pressure, neurochemical responses are activated and secreted. These chemical messengers allow for adaptation in response to stress. McEwen (2005) suggests that these chemicals also contribute to allostatic overload. However, with high stress levels and the constant neurochemical activation in response to stress, Korte and colleagues (2005) suggest that biological systems (i.e., neuroendocrine system and immune system) may eventually overcompensate and, in turn, result in system failures, changes to the brain functioning, and increased susceptibility to stress-related diseases. One key distinction made between homeostasis and allostasis, according to Tsigos et al., (2020), is that the dysregulation that is associated with chronic stress can negatively impact the body's homeostasis that can lead to allostasis. McEwen (1998) adds that allostasis is a component of maintaining homeostasis. However, McEwen and Stellar (1993) also argue that allostasis does not account for some of the long-term effects of the wear and tear on the body that may increase disease vulnerability because of its more immediate/short-term focus, and, alternatively, McEwen and Stellar propose the concept of AL.

AL is defined as the "wear and tear on the body and the brain that can predispose one to disease," (McEwen and Stellar, 1993). Moreover, Goldstein and McEwen (2002) stated that the effects of the prolonged and/or constant activation of biological systems (i.e., neuroendocrine

system, immune system, etc.) in allostasis was an additional way of understanding AL with the difference being that AL takes into account the build-up over time. McEwen's definition of AL posits that chronic stress is the driving force in the wear and tear of the body and brain and may be a new method of conceptualizing biological cumulative stress (Seeman et al., 2001). By understanding the effects of both acute and chronic stress, Goldstein and McEwen (2002) suggest that AL can improve the understanding of the relationship with negative health outcomes. In general, McEwen (2004) argues that while stress may promote and facilitate in adaptation, stress has been overly and inappropriately used and argues that allostasis and AL are more precise at describing the physiological response that occurs when changes to the body occur due to external demands (or better known as "stress"). More specifically, Sterling and Eyer, as well as Goldstein and McEwen's conceptualization of allostasis extends on homeostasis by capturing how the physiologic systems adapt to maintain constancy within the body due to internal and external demands. Logan and Barksdale (2008) further add that the complex feedback loops that are defined by previous conceptualizations of homeostasis ultimately reduce variability in maintaining constancy but state that the variability is actually more favorable and is captured in the concept of allostasis (Carlson & Chamberlain, 2005). AL captures how the constant activation of the systems and the resulting wear and tear on the body due to the acute and chronic stress and the results from the activation may lead to disease susceptibility and vulnerability.

The AL model suggests that various physiological measures related to health outcomes be used to derive an overall index (McEwen & Stellar, 1993). Karlamangla and colleagues (2002) highlighted how some of their previous work with data collected from the MacArthur Studies used 10 markers that were associated with disease susceptibility (see Seeman et al., 1997), to create an index of AL. More specifically, Seeman and colleagues used measures of cortisol,

norepinephrine, epinephrine, DHEA-S, systolic and diastolic blood pressure readings, ratio of waist-to-hip circumference, high density lipid (HDL) cholesterol, the ratio of total-to-HDL cholesterol, and blood glycosylated hemoglobin. Then, individual measures that were deemed to be in the low or high-risk quartile, determined by distributions, were given a one and summed together (range of total score was 0 to 10) with higher scores indicating higher AL. Results from this secondary data analysis found that while the individual markers generally had no associations with health outcomes reported earlier by Berkman and colleagues (1993), the index created following McEwen's model yielded significant findings, such that higher index scores were associated with negative health outcomes, declines in cognitive and physical functioning, and increased mortality rates. In general, stress and physiological dysregulation have been believed to serve as risk factors (Epel et al., 2004) and negatively impact aging and affect disease onset (Seeman et al., 1997; Juster et al., 2010). However, research acknowledges that these impacts on aging and disease are subject to brain and bodily function and response to stress (McEwen, 1998, 2009), but can be negatively altered by chronic stress over time and have been previously described. The MacArthur Foundation Research Network on Successful Aging collected data from older adults (ages 70-79) to examine both psychological and physiological correlates of aging, cognitive decline, and other health-related outcomes (Berkman et al., 1993). Data from this study would later shed light on how stress should be conceptualized. Participants were characterized as either low, medium, or high functioning categories based on cognitive and physical performance. In this study, various measures were collected such as lung and brain functioning, as well as biological measures (urine and blood to measure cortisol, dopamine, cholesterol levels, etc.) related to health outcomes. In subsequent analyses of the data conducted by Seeman and colleagues (2001), results suggested that the AL index that had been initially

calculated was associated with mortality such that higher AL scores were related to increased risks of mortality. Furthermore, the authors reported a marginally significant association between AL scores and cardiovascular disease incidents (i.e., heart attacks) such that as AL scores increased, cardiovascular disease events also increased. Thus, researchers identified another example of how allostasis may be related to cardiovascular outcomes in addition to cognitive outcomes. Related to physical functioning, Seeman and colleagues (2001) concluded that increased AL scores were associated with greater declines in physical functioning. Finally, results indicated that those with higher AL scores were associated lower cognitive functioning.

Based on Suvarna and colleagues' 2020 review, substance use (collapsing alcohol, smoking, and drug use altogether) was related to AL, such that increased substance use was positively associated with higher AL. Notably, one of the four studies included in the 2020 systematic review that examined the relationship between alcohol and AL identified that Japanese men with higher AL scores drank more (see Kusano et al., 2016). Further, it was also reported that heavy drinking men also had higher AL scores in comparison to moderate drinkers (see Petrovic et al., 2016). Taken altogether, the support of using a cumulative measure of AL to examine the relationship with health outcomes is evident.

McEwen argues that various biological markers are associated with a number of health outcomes and are essential in calculating the AL index to ultimately examine potential associations. Juster and colleagues (2010) previously detailed biological markers and the corresponding biological systems that have been commonly used to calculate AL levels across various studies (see Appendix 1). More recently, Suvarna and colleagues (2020) conducted a systematic review in which they examined health risk behaviors associated with AL levels. In their review, they examined findings from human participant studies that looked at health

behaviors such as alcohol use, drug use, smoking, and sleeping among others and the relationship with AL measures. Suvarna and colleagues noted the various biological markers used in each of the studies in their review that were used in calculating the AL index. Given the work conducted by Juster and colleagues, the selection of biological markers for the present study will be informed by their conclusion of biological markers, depicted in Appendix 1, given the detailed information provided for each biological marker that corresponds to each biological system.

Biomarkers Associated with Health Outcomes and Alcohol Consumption

The AL model suggests using biological markers from various physiological systems to create an index of AL (McEwen & Stellar, 1993). Karlamangla and colleagues (2002) highlighted the 10 biological markers (cortisol, norepinephrine, epinephrine, DHEA-S, systolic and diastolic blood pressure readings, ratio of waist-to-hip circumference, high density lipid (HDL) cholesterol, the ratio of total-to-HDL cholesterol, and blood glycosylated hemoglobin) to create an index of AL. This index was then used to predict health outcomes and has been used to predict a wide range of health outcomes (i.e., sleep disorders; Chen et al., 2014; physical activity; Upchurch et al., 2015). The neuroendocrine system is responsible for the production of hormones and acts as a "control and regulatory center" to ensure other systems of the body receive hormones to function and react properly (Nishiyama & Katsura, 2015). Moreover, the neuroendocrine system and the circulatory system work together such that the circulatory system transports the chemicals released by the neuroendocrine system throughout the body (Van der Horst, 2003). The hormones produced and excreted, for example, aid the metabolic system in metabolism and energy production (Cornejo et al., 2016). The metabolic system has been linked with the immune system with Medzhitov (2008) stating that anomalies in the metabolic system may trigger the immune system to produce inflammatory responses. Poorer circulatory system functioning has been

associated with cardiovascular diseases, and it has been found that high body mass indices (an anthropomorphic system measure) are associated risk factors of cardiovascular diseases (Wormser et al., 2011). These relationships highlight how the biological systems are interconnected and perform various functions. However, when an individual responds to stress, hormones are produced and released (neuroendocrine system) in response to the stressor, which in turn, can increase heartrate and blood pressure (cardiovascular/respiratory system), increase glucose production which can increase type-2 diabetes risk (metabolic system), and weaken the immune system which can increase infection (immune system; Pietrangelo & Legg, 2020).

Cortisol has commonly been used as a biological measure of chronic stress (see Schulz et al., 1998). Previous research has examined the relationship between prolonged exposure to stressors and cortisol. Szabo and colleagues (2020) believe that cortisol may have a strong association with stress and alcohol intake due to elevated stress levels based on the accumulating research exploring this association. In all, the authors conclude in their review and proposed framework that cortisol may be indicative of developing an AUD and may also provide insight to relapse risk. In large, findings have concluded that prolonged stressor exposure was associated with elevated cortisol levels (i.e., Härenstam & Theorell, 1990; Rahe et al., 1990; Arnetz et al., 1991). Heightened levels of cortisol has been associated with negative health outcomes such as hypertension, immune function impairment, and changes to one's metabolism (Plat et al., 1999; Spiegel et al., 1999; Whitworth et al., 2005).

As related to alcohol misuse, research conducted by Adinoff and colleagues (2003) found that chronic alcohol dependent participants displayed heightened levels of cortisol when intoxicated. Further, the participants' cortisol levels increased more while withdrawing from alcohol. Adinoff et al., (2005) have also found support suggesting chronic alcohol consumption

impacts the hypothalamic-pituitary-adrenal (HPA) axis reactivity to stress, supporting the notion that altered HPA axis regulation is associated with alcohol misuse and alcohol use dependence. More recent evidence has found an association between heightened cortisol levels and alcohol misuse (Blaine et al., 2019), and, taking this and findings by Adinoff et al., altogether, may suggest that the neuroendocrine system may be experiencing dysregulation when alcohol is being consumed in excessive amounts.

Aldosterone is another hormone produced by the adrenal glands, as part of the neuroendocrine system. Evidence suggests a positive correlation exists between aldosterone levels and alcohol craving measures among abstinent participants (Leggio et al., 2008), which may have carryover effects leading to alcohol misuse. Moreover, Leggio et al. suggest that the neuroendocrine pathway associated with aldosterone is associated with anxiety, stress, and stress-induced drinking. Aoun and colleagues (2018) recently found a positive correlation between aldosterone levels and alcohol consumption, as well as alcohol craving. Other health outcomes have also been noted such that higher plasma aldosterone concentration has been linked with cardiovascular disease mortality (Tomaschitz et al., 2010). Moreover, those with higher aldosterone concentration and impaired kidney function have been associated with increased chances of cardiovascular-related deaths (Tomaschitz et al., 2011). Few, if any, studies have examined the relationship between chronic alcohol consumption, kidney functioning, and aldosterone levels. However, previous research has reported (1) a relationship between alcohol consumption and impaired kidney functioning such that heavy drinking was associated with 1.99 greater odds of kidney disease (Shankar et al., 2006), (2) a relationship between alcohol consumption and aldosterone levels such that aldosterone levels were positively correlated (r = .62) with the number of drinks consumed (Aoun et al., 2018), and (3) a relationship between

aldosterone levels and impaired kidney functioning such that heightened aldosterone levels were associated with 1.17 greater odds of chronic kidney disease incidence (Fox et al., 2010), it may be reasonable to speculate that a chronic alcohol consumption may be associated with both heightened aldosterone levels and impaired kidney functioning. Thus, aldosterone has shown promise in terms of predicting other health outcomes.

The Immune System. The immune system serves as the body's defense system against germs and allows for the body to build immunity (U.S. National Library of Medicine, 2020b). However, weakened immune systems may provide opportunities for negative health outcomes to take effect. Moreover, the immune system and the neuroendocrine system play a vital role together in the maintenance and functioning of the human body with evidence suggesting that both systems have an intricate communication network (Steinman, 2004). Notably, excessive alcohol consumption has been associated with weakened immune systems and increased susceptibility to illnesses (Schmidt & De Lint, 1972). Molina and colleagues (2010) also support that excessive alcohol consumption may suppress immune response and can heighten the risk for infections and draw to the relationships observed in alcohol misusers with pathological infections such as HIV/AIDS and hepatitis. The role of excessive alcohol consumption may weaken the immune system and, in turn, blunt the functioning of the neuroendocrine system (King et al, 2006). Thus, it is important to understand biological markers of the immune system in addition to those of the endocrine system, such as C-reactive protein (CRP) and Interleukin-6 (IL-6) as they may be indicative of other health outcomes that may be associated with problematic drinking.

C-reactive protein (CRP) is biological marker from the immune system. CRP levels are measured through blood samples, and when elevated, may indicate inflammation present in the body (Mayo Clinic, 2017). Relative to alcohol consumption, evidence suggests that elevated CRP

levels are positively associated in patients with cirrhosis of the liver due to prolonged alcohol consumption and, in turn, increased chances of having hypertension and decreasing overall survival of such patients (Mortensen et al., 2012).

Interleukin-6 (IL-6) is also an inflammatory marker. Research by Pederson et al., (2004) suggests that acute alcohol consumption is associated with increased IL-6 levels. Moreover, earlier research has also found an association between IL-6 and alcoholic liver disease (see Hill et al., 1992). Longitudinal data analyzed by Bell et al., (2017) suggests that heavy drinkers also have heightened levels of IL-6 which may impact disease risk and onset. Taken altogether, excessive alcohol consumption may dampen the immune system and increase susceptibility to disease due to the body's weakened response to fight off infections.

The Metabolic System. The metabolic system helps convert the nutrients obtained from food to energy for the body. However, metabolic disorders may have adverse health effects that may impact the liver or pancreas (U.S. National Library of Medicine, 2020c). Research suggests that individuals with chronic alcohol misuse have suppressed metabolisms which prevent the nutrients to be broken down and, in turn, may lead to deficiencies (Lieber, 2003). More recent research examining young adults has also suggested that problematic alcohol consumption is associated with a complex metabolic breakdown pattern (Würtz et al., 2016). As a result, examining metabolic markers such as glucose and insulin may provide insight to their respective relationships with alcohol, given that both markers play a vital role in metabolism.

Glucose, a metabolic marker, is a carbohydrate obtained from various foods and is used for energy. Elevated glucose levels measured through blood sugar monitors are often seen in people with diabetes and can have negative health outcomes if proper dieting is not practiced (U.S. National Library of Medicine, 2020d). Athyros and colleagues (2008) suggest that heavy

drinking is associated with higher glucose levels and may also contribute to heightened risk for developing diabetes.

Insulin, another metabolic marker, is produced in the pancreas and is responsible for allowing glucose to enter and be used by the body. Further, insulin is responsible for regulating blood sugar levels and storing excess glucose. A study found that higher insulin levels observed in nondiabetic patients was associated with faster cognitive decline in older women aged 70 – 75 years old (van Oijen et al.,2008). However, mixed evidence surrounds the relationship between alcohol consumption and insulin levels. More specifically, meta-analytic findings suggest that moderate consumption may decrease insulin levels in those that are fasting in nondiabetic patients and may even improve insulin sensitivity in women (Schrieks et al., 2015). McEwen (2008), however, suggests that stress and elevated AL are associated with dysregulation and metabolic syndrome which may increase susceptibility to type 2 diabetes. Thus, more research is warranted to help elucidate the relationship between alcohol consumption levels and insulin levels.

Cardiovascular/Circulatory System. The cardiovascular system is primarily responsible for pumping and supplying blood throughout the body. By doing so, the circulation of nutrients obtained from consumption travel through the blood and allow for bodily functioning. However, the relationship between alcohol consumption and this system remains complex. Previous meta-analytic findings have found beneficial associations between moderate drinking and coronary heart disease such that moderate alcohol consumption was associated with reduced risk of developing coronary heart disease (Rimm et al., 1999). In contrast, when alcohol is consumed in excess amounts, studies suggest that there is an increase in developing coronary heart disease and other health issues (Djoussé et al., 2002). Thus, those dependent on alcohol may have dampened cardiovascular functioning in part by the excessive alcohol consumption patterns. To further

explore the effects of excessive alcohol consumption on the cardiovascular system, heart rate variability may help shed information on the relationship.

Anthropometry. By obtaining height and weight measurements, in general, a measure of body fat can be estimated and is often referred to as body mass index (BMI). On average, higher BMI measures are associated with obesity. In turn, this association can also be paired with other negative health outcomes. Meta-analytic findings suggest obesity is associated with poorer levels of both physical and mental health-related quality of life (Ul-Haq et al., 2013). In a large study, Cournot and colleagues (2006) found that higher baseline BMIs were associated with cognitive decline at follow-up in healthy men and women participants. Interestingly, it has been found that elevated BMI measures were associated with lower alcohol consumption (Kleiner et al., 2004) and the authors go on to speculate that there may be a reward discrepancy between food and alcohol.

Present Study

Based on initial findings by Berkman and colleagues (1993) on the MacArthur study, examining individual associations between biological markers and health outcomes may yield limited information. Given McEwen's conceptualization for calculating AL indices, using Juster et al's., (2010) and Suvarna et al's., (2020) summary of commonly used biological markers as a guide for selecting, the current study may contribute to the literature by constructing a well-informed index of AL used to predict AUD status. Furthermore, given the mixed findings surrounding AL and the relationship with alcohol use, suggested by Suvarna and colleagues' (2020) systematic review, further research is warranted examining this relationship. Thus, constructing an index of AL from baseline data gathered from a sample of men with an AUD and

healthy control men with no known substance-use issues may aid in filling the gap between AL levels and the association with AUD status and alcohol consumption.

Study Aims and Hypotheses

As such, the purpose of this secondary data analysis was to construct an index of biological cumulative stress utilizing the group AL index method as well as the z-Score AL index method derived from baseline measures of biological markers to examine group mean difference among men with an AUD and a group of healthy men. Additionally, a cumulative psychological score was created by obtaining the sum and then averaging the standardized subscales of the CTQ, CAI, DIS, and the two chronic stress total ratings from the UCLA Life Stress Interview researcher and participant ratings, potentially complementary of the AL index. It was hypothesized that:

1. (H1) Differences in AL mean scores would be observed between the healthy control group compared to the participants with an AUD such that men with an AUD would have higher AL scores.
2. (H2) Indices of AL would be positively associated in men with an AUD's lifetime drinks per drinking day prior to participating in the study such that higher AL scores would be associated with higher lifetime drinks per drinking day.
3. (H3) Among men with an AUD, higher baseline AL scores would be positively associated with total drinks per drinking day at the three-month follow-up timepoint such that higher AL scores would be associated with higher total drinks per drinking day.
4. (H4) The baseline AL scores would be positively correlated with the psychological cumulative stress scores derived from the psychological measures among men with an AUD.

Chapter 2: Method

The Parent Study

The present study is a secondary analysis of data obtained from Dr. Bryon Adinoff. The purpose of the initial study was to examine the impacts of psychological stressors on the HPA axis reactivity among men with an AUD and healthy men controls between the ages of 20 and 59 years old. The authors hypothesized that childhood adversity, lifetime trauma, and chronic stress would lessen the HPA axis response among those with an AUD compared to healthy controls. Zhang et al., (2020) analyzed data obtained from 26 healthy control men and 70 men with an AUD. Participants were administered ovine corticotropin-releasing hormone and psychological stressors to examine the effects on the HPA axis. Both adrenocorticotropin hormone and cortisol were periodically assessed. Participants were followed-up with every two weeks for six months. Results indicated among the healthy control men, higher levels of childhood adversity, lifetime trauma, and chronic stress was associated with decreased adrenocorticotropin hormone responses but not in men with an AUD. The authors suggested that among individuals diagnosed with an AUD, there may not be any biological or psychological protective factors from the impacts of life stress and further postulate that the lack of any type of stress effect on the HPA axis reactivity among those with an AUD may be attributed to the constant, heavy drinking and withdrawal.

Participants. To be eligible for the study, participants must have been between 18 and 60 years of age. Biological samples were collected from male participants prior to the administration of any psychological measures or ovine corticotropin-releasing hormone (baseline). Seventy men with an AUD who were abstinent for a period of two to four weeks were recruited from a residential treatment center in Texas and also from the VA North Texas Healthcare System. Twenty-six healthy control participants with no known histories of substance use disorder(s) were

recruited from a Texas community. Men with an AUD must have reported alcohol as the primary substance used, must have reported having consumed the equivalent of a six-pack of beer or more a day for at least two weeks before being admitted to the residential treatment facility, and must have reported drinking 90 consecutive days prior to treatment admission. The materials and methods have been described further elsewhere (Zhang et al., 2020).

For the purposes of the current study, data were analyzed for 48 men with an AUD and 17 abstinent men due to the limited/depleted biological samples available. Data from three participants were excluded as two participants were duplicates and one participant did not have the matching identifier.

Measures

Demographics. Participants provided demographic information such as age, marital status, racial identification, and educational background.

Biological measures. Participants provided blood samples at baseline to assess various biological markers via immunoassays. For the purpose of this study, the following 12 biological markers informed the index: cortisol (neuroendocrine system); interluken-6 (IL-6), fibrinogen, tumor necrosis factor-alpha (TNFa), and C-reactive protein (CRP, immune system); glucose, insulin, and leptin (metabolic system); pulse, systolic blood pressure readings, and diastolic blood pressure readings (cardiovascular and circulatory system); and body mass index (BMI, anthropometric system). Cortisol, pulse, systolic blood pressure, diastolic blood pressure, and BMI data was analyzed by Dr. Adinoff (see Zhang et al., 2020). Moreover, IL-6, fibrinogen, TNFa, CRP, glucose, insulin, and leptin analyses were conducted at the University of Texas at El Paso using enzyme-linked immunosorbent assays (ELISA-type assays) or MILLIPLEX Kits to

examine the levels of the various biological markers. Height and weight were recorded and subsequently used to calculate body mass index.

AL Index. Various methods for creating an index for AL have been previously described elsewhere (Juster et al., 2010). One common formulation is the group AL index in which the distribution of biological marker values are examined and given a value of one if values are in the upper (or lower; dehydroepiandrosterone) 25th percentile and summed (see Kusano et al., 2016 Pretovic et al., 2016; Seeman et al., 1997). Markers for each participant that do not meet these cutoff values are assigned a zero. Each biological marker is given equal weight in the index. This overall summation is bound by zero and the number of markers used to calculate the index. This method is consistent with initial calculations McEwen has used in earlier studies. Similarly, biological marker values can be standardized to create a subsequent AL index, consistent with the z-Score method. Values meeting the cutoff percentiles were assigned a zero or one and then be summed, similar to the group AL index method.

Psychological Cumulative Stress Index. To construct the cumulative psychological stress measure score, a similar calculation previously described by Zhang and colleagues (2020) using the same dataset previously described from the parent study was employed. In short, the subscales pertaining to the CTQ, CAI, and eight of the 10 subscale ratings from both the research and subject from the UCLA Life Stress Interview were standardized. Further, the two scores from the DIS (the total number of terrible, horrible, frightening events in life and total number of times the events happened) were also standardized. Then, the standardized subscale scores pertaining to the CTQ and CAI were averaged to form a childhood stress variable. Similarly, the standardized subscale ratings from the UCLA Life Stress Interview were averaged to form a chronic stress variable. Next, the standardized DIS scores were averaged to form a lifetime trauma score. The

three newly created standardized scores were then be averaged to create the cumulative psychological stress score derived from the psychological measures.

Psychological measures. Participants completed baselines psychological measures of stress. More specifically, participants completed the CAI, CTQ, UCLA Life Stress Interview, and the DIS.

Childhood Adversity Interview (CAI). The CAI, a semi-structured interview, was developed to assess early life stress one may have experienced during the first 13 years of life (Dienes et al., 2006). The semi-structured interview contains seven domains: physical neglect, emotional abuse or assault, physical abuse or assault, witnessing violence, sexual abuse or assault, separation and loss involving the primary caretaker(s), significant loss involving others and/or life-threatening illness or injury to others or self. Scores in each domain ranged from 1 "little to no adversity" to 5 "high adversity." Moreover, a total score could be derived by summing the scores from each domain with a range of 7 "little to no adversity" to 35 "high adversity."

Childhood Trauma Questionnaire (CTQ). The CTQ is a self-report measure developed by Bernstein and Fink (1998) to assess emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect during the respondent's child or teenage years. This measure contains 28 items using a 5-point Likert-type scale ranging from 1 "Never True" to 5 "Very Often True," with higher scores associated with more severe maltreatment/abuse. Each subscale ranged from five (low severity) to 25 (high severity). Similarly, a total score could be computed by summing the subscale scores with a range of 25 (low severity) to 125 (high severity). Of the 28 items, 25 items contribute towards the five subscales while the remaining three items target potential false-negative responses. A factor analysis of the items indicated a five-factor structure each containing five items per factor, consistent with the initial development of the measure.

Internal consistency measurements for each of the five subscales indicated satisfactory to strong reliability (physical abuse α = .77, physical neglect α = .64, emotional abuse α = .90, emotional neglect α = .86, and sexual abuse α = .95).

UCLA Life Stress Interview. The UCLA Life Stress Interview, developed by Hammen and colleagues (1995), is also a semi-structured interview used to measure chronic and episodic stress in the last six months in which both the participant and the interview provide ratings in each of the domains. Originally, the interview tool focused on 10domains (family relationships, independence from family, close friendships, romantic relationships, social life, school, work, finances, health of subject, and health of family). A Likert-type scale was used ranging from 1 to 5 with higher scores associated with more sever chronic stress. A total chronic score rating can then be calculated with a range of 10 to 50, with higher scores indicative of more severe chronic stress. Consistent with previous research, independence from family and school were excluded as these domains pertain more towards a younger population rather than an adult population (see Zhang et al, 2020). Thus, total chronic stress score ratings ranged from 8 to 40.

Diagnostic Interview Schedule (DIS). Two questions from the PTSD section of the Diagnostic Interview Schedule for the DSM-IV (Robins et al., 2000) were used to assess the number of "terrible, frightening, or horrible" lifetime events and the number of times these events happened.

Timeline Follow Back (TLFB). The TFLB, developed by Sobell and Sobell (1992), was used to estimate lifetime drinking patterns as well as patterns three months prior to the study. Total drinks consumed and the number of drinking days were calculated and constituted the dependent variable of interest. Lifetime total drinks per drinking day and total drinks per drinking day at three-month follow-up were obtained and used as dependent variables.

Power Analysis

Petrovic and colleagues (2016) reported an odds ratio effect size = 2.28. Utilizing Kohn and Senyak's (2020) power calculator website used for designing clinical research, $\alpha = .05$, a .262/.738 group sample proportion, the current study was 81.5% powered to detect an effect.

Procedure

Missing Data. All data were analyzed using IBM Corporation's SPSS version 27.0 software package (2020). Thirteen imputations were conducted to allow the standard error estimates to be more replicable, consistent with von Hippel's formula for identifying the number of imputations needed (2018). More specifically, von Hippel (2018) suggests accounting for the fraction of missing data (24%, given that pulse yielded the highest missing data percentage) and the accepted standard error variations (5%). Using the following formula where *M* is the number of suggested imputations, *FMI* is the fraction of missing information, and *CV* is the coefficient of variation of the standard error:

$$M = 1 + \tfrac{1}{2}\,(FMI \,/\, CV\,(se))^2$$

Known acceptable/possible values of the various biological markers were accounted for in the imputed data to ensure no extraneous values were calculated. Moreover, biological values greater than Cook's distance of one were considered as "missing" and subsequently imputed. Two CRP values and one fibrinogen value exceeded Cook's D of one. Data were not imputed for psychological measures as missing data were less than five percent for each subscale. In sum, 47 (73.44%) participants had complete data for all biological variables. Fifty-eight (90.62%) participants had complete data for all psychological constructs. The following further describes the number of missing datapoints and percentage for the biological variables: IL-6 (2; 3.08%), TNFa (2; 3.08%), fibrinogen (1; 1.54%), CRP (1; 1.54%), glucose (1; 1.54%), pulse (15;

23.08%), systolic and diastolic blood pressure readings (14; 21.54%, respectively), and BMI (2; 3.08%). Cortisol, insulin, and leptin did not have any missing data points.

Approach to Analyses

Participant characteristics such as age, lifetime drinks per drinking day, racial identity, marital status, and educational backgrounds of the participants were examined using independent samples t-test to examine the mean differences in age among the two groups. A series of chi-square tests to examine the categorical variables and their relationships with the participants in the two distinct groups were also conducted. These analyses were for descriptive purposes.

Hypothesis 1 Analyses. An independent samples t-test was conducted to examine if the standardized and unstandardized mean AL scores were different among the two groups.

Hypothesis 2 Analyses. The AL index scores were entered in a linear regression model to examine the association among men with an AUD's lifetime drinks per drinking day.

Hypothesis 3 Analysis. The AL index scores were entered in a linear regression model to examine the association among men with an AUD's drinks per drinking day three months after participating in the treatment study.

Hypothesis 4 Analysis. A bivariate correlation was conducted to examine the relationship between the AL index scores with the cumulative psychological stress score.

Chapter 3: Results

Participant Characteristics

Across both groups, a total of 65 participants were analyzed in the current study. In examining racial makeup among the two groups, there was no association between group membership and race $X^2(1) = 4.63$, $p = .330$. However, there was an association between group status and marital status ($X^2(4) = 12.59$, $p = .013$); as well as group status and educational status ($X^2(4) = 26.97$, $p < .001$; see Table 1). The control group yielded an overall mean age equal to 41.41 ($SD = 10.74$) while the group of men with an AUD yielded a mean age equal to 42.85 ($SD = 10.06$). The mean ages among the two groups were not statistically different, ($t(61) = .49$, $p = .501$).

Table 1: Baseline characteristics of the study sample by group status

Categorical variables	Controls (n = 17) n (%)	Cases (n = 48) n (%)	
Race			$X^2(3) = .13$, $p = .988$
White	12 (70.6)	34 (73.9)	
Black	3 (17.6)	7 (15.2)	
Hispanic	1 (5.9)	2 (4.3)	
Other	1 (5.9)	3 (6.5)	
Marital Status			**$X^2(4) = 12.59$, $p = .013$**
Single	7 (41.2)	21 (45.8)	
Married	6 (35.3)	2 (4.3)	
Separated	0 (0.0)	5 (10.9)	
Divorced	3 (17.6)	16 (34.8)	
Widowed	0 (0.0)	0 (0.0)	
Living Together	1 (5.9)	2 (4.3)	
Educational Background			**$X^2(5) = 16.97$, $p < .001$**
None	0 (0.0)	6 (12.5)	
HS/GED	4 (23.5)	27 (56.3)	
Associates Degree	4 (23.5)	11 (22.9)	
Bachelor's Degree	9 (52.9)	1 (2.1)	
Graduate Degree	0 (0.0)	1 (2.1)	
Continuous variables	*M* (SD)	*M* (SD)	
Age	41.41 (10.74)	42.85 (10.06)	$t(61) = .49$, $p = .501$
Lifetime Drinks per Drinking Day	3.01 (2.11)	14.36 (7.94)	**$t(56.68) = 8.76$, $p < .001$**

3-Months Drinks per Drinking Day	.94 (.25)	3.63 (4.48)	***t*(39.60) = 3.79, *p* < .001**
AL Index	3.24 (2.28)	2.94 (2.05)	*t*(63) = -.50, *p* = .649

Hypothesis 1 Results

The overall AL index was bound between 0 and 12, with higher scores indicative of higher biological cumulative stress. AL scores ranged from 0 to 8 (see Table 2). The control group yielded an overall mean AL index equal to 3.24 (*SD* = 2.28) while the group of men with an AUD yielded a mean AL index equal to 2.94 (*SD* = 2.05). Moreover, the control group yielded an overall mean standardized AL index of 3.06 (*SD* = 2.33) while the group of men with an AUD yielded a mean standardized AL index of 2.94 (*SD* = 2.05) To evaluate Hypotheses 1, an independent samples t-test was conducted to examine any group differences in the two AL scores. Overall, there were no statistically significant group differences in the group AL scores (*t*(63) = .50, *p* = .618) or in the standardized AL scores (*t*(63) = .20, *p* = .840; table 3).

Table 2: AL score frequencies

	Frequency	Percent
0.0	6.0	9.2
1.0	11.0	16.9
2.0	14.0	21.5
3.0	10.0	15.4
4.0	10.0	15.4
5.0	4.0	6.2
6.0	5.0	7.7
7.0	3.0	4.6
8.0	2.0	3.1
Total	65.0	100.0

Table 3: AL index scores and cumulative psychological stress score group characteristics

	Control *M* (SD)	Cases *M* (SD)	
AL Index	3.23 (2.28)	2.94 (2.05)	*t*(63) = -.50, *p* = .649
z-AL Index	3.06 (2.33)	2.94 (2.05)	*t*(63) = -.20, *p* = .851
Cumulative Psych. Score	-.36 (.57)	.14 (.42)	***t*(61) = 3.87, *p* < .001**
	Control *M* (SD)	Cases *M* (SD)	

CAI and CTQ Average	-.21 (.55)	.08 (.61)	$t(61) = 1.70$, $p = .094$
DIS Average	-.45 (1.05)	.18 (.86)	**$t(61) = 2.40$, $p = .020$**
UCLA Average	-.43 (.36)	.16 (.43)	**$t(61) = 5.05$, $p < .001$**

Hypothesis 2 Results

To evaluate Hypothesis 2, the AL indices were entered into separate linear regressions to examine the association between the index scores and lifetime drinks per drinking day among men with an AUD, prior to participating in the parent study. The linear regression model using the AL index as a predictor was not statistically significant, ($F(1, 44) = .20$, $p = .65$, $R^2 = .005$; table 4). Moreover, the linear model predicting lifetime drinks per drinking day among men with an AUD using the z-score AL index was not statistically significant, ($F(1, 44) = .20$, $p = .65$, $R^2 = .005$; table 5).

Table 4: Regression summary for lifetime drinks per drinking day in men with an AUD

Variable	B	SE	95% CI	*t*	*p*
(Constant)	15.105	2.034	[11.00, 19.22]	3.77	< .001
AL index	-.261	.579	[-1.43, 0.91]	-.45	.654

Note: 95% CI is for B, $R^2 = 0.005$

Table 5: Regression summary for lifetime drinks per drinking day in men with an AUD

Variable	B	SE	95% CI	*t*	*p*
(Constant)	15.105	2.034	[11.00, 19.21]	7.43	< .001
z-AL index	-.261	.579	[-1.43, 0.91]	-.45	.654

Note: 95% CI is for B, $R^2 = 0.005$

Hypothesis 3 Results

In evaluating Hypothesis 3, two separate linear regressions were conducted to examine if the two distinct AL index scores were associated with AUD drinks per drinking day three months after participating in the parent study. The linear regression model using the AL index as a predictor was not statistically significant ($F(1, 39) = .92$, $p = .345$, $R^2 = .024$; table 6). Moreover,

the linear model predicting lifetime drinks per drinking day among men with an AUD using the z-score AL index was not statistically significant, ($F(1, 39) = .92$, $p = .345$, $R^2 = .024$; table 7).

Table 6: Regression summary for 3-month drinks per drinking day in men with an AUD

Variable	B	SE	95% CI	*t*	*p*
(Constant)	4.499	1.149	[2.08, 6.92]	3.77	< .001
AL index	-.295	.326	[-0.95, 0.37]	-.91	.371

Note: 95% CI is for B, $R^2 = 0.021$

Table 7: Regression summary for 3-month drinks per drinking day in men with an AUD

Variable	B	SE	95% CI	*t*	*p*
(Constant)	4.499	1.149	[2.08, 6.92]	3.77	< .001
z-AL index	-.295	.326	[-0.95, 0.37]	-.91	.371

Note: 95% CI is for B, $R^2 = 0.021$

Hypothesis 4 Results

To evaluate Hypothesis 4, a bivariate correlation examining the relationship between the AL indices with the cumulative psychological stress score among all participants was conducted. Results of the bivariate correlation indicated no statistically significant association between the AL index and the psychological cumulative stress score, ($r(62) = -.008$, $p = .951$). Moreover, the z-score AL index was not statistically significantly correlated with the psychological cumulative stress score, ($r(62) = .020$, $p = .878$; table 8).

Table 8: Pearson correlation of AL scores and cumulative psychological stress score

Variable	*M*	*SD*	1	2	3
1. AL index	3.02	2.09	-		
2. z-AL index	2.97	2.11	.995	-	
3. Cumulative Psych. Score	.01	.51	-.008	.020	-

Chapter 4: Discussion

The purpose of this secondary data analyses was to construct an index of AL and examine differences and associations related to drinking status and drinking patterns. Specifically, the present study investigated (1) mean group differences in the AL indices among the two groups, (2) the association between AL indices and lifetime drinks per drinking day among men with an AUD, (3) the association between AL indices and drinks per drinking day at three-month follow-up among men with an AUD, and (4) the correlation between AL indices with a psychological cumulative stress index score. Overall, the results did not support any of the proposed hypotheses. That is, the mean scores of AL were not statistically different between the healthy control group of men and the group of men with an AUD, the AL index was not associated with lifetime drinking patterns or drinking patterns at three-month follow-up, and the AL index was not correlated with the psychological cumulative stress score. Thus, biological stress captured by the index of AL may not be appropriate in the context of AUD and drinking patterns.

The findings from the current study may be attributed to multiple factors, such as the lack of a definitive list of biological markers in which to include when calculating AL. Additional factors include the lack of research focusing on AL and drinking status, which, in turn, may have impacted the power to detect the desired effect in the current study. Moreover, the method in which AL is calculated may also be a contributing factor. Further, a distinction between biological cumulative stress and psychological cumulative stress may exist. A final factor may be attributed to the lack of stress captured by the biological markers, which may be related to the overall relationship between AL and drinking.

While reviews have listed the most commonly used biomarkers, there is no standard list of biomarkers that should be definitively included in analyses and the subsequent creation of an

index of AL. Previous research in which AL is measured have used a variety of biomarkers differing in the number of biomarkers used. For example, as few as six biological markers have been used to calculate AL (i.e., Chen et al., 2015; Doan et al., 2014). In contrast, other studies have reported using as many as 24 biological markers in creating the AL index (Robinette et al., 2016; Vadlivello & Mattei, 2017). As McEwen suggested in earlier work, including more biological markers in the AL index would provide a stronger representation of the major biological systems and a stronger indication of overall biological cumulative stress. While additional systems exist within the human body (i.e., reproductive system, integumentary system), McEwen and Stellar (1993) suggest that effects of stress on health are largely associated with the autonomic (neuroendocrine), cardiovascular, gastrointestinal (metabolic and, more recently, the anthropometric system), and immune system pathologies that, in turn, increase susceptibility for disease. Moreover, McEwen (1998) suggests that when these systems are unable to function regularly due to the constant activation and, instead, cannot activate normally, the protection these systems provide are dampened. It remains unclear as to which biomarkers should be included in AL indices and whether a minimum quantifiable threshold of biomarkers are needed to accurately capture biological cumulative stress.

Second, given the relatively small number of studies that have examined the association of AL with drinking, there may be (1) an insufficient amount of evidence to definitively indicate an association, (2) AL may not be associated with drinking and AUD, or (3) AL may be negatively associated with drinking and AUD. Survarna and colleagues (2020) previously indicated that out of five studies that examined the association of AL with drinking, two studies reported a positive association (Kusano et al., 2016; Petrovic et al., 2016) while three other studies reported a negative relationship (Gallo et al., 2011; Hampson et al., 2009; Hu et al., 2007). While the current

study utilized the effect size reported by Petrovic and colleagues (despite differences in group characteristics), the current study may not have been adequately powered. More specifically, the effect size retrieved from Petrovic et al., (2016) may have been inaccurate to use in the current study due to the differences in which alcohol consumption was calculated in the study conducted by Petrovic and colleagues and the method employed in the parent (current) study. The magnitude of the effect in differences among the two groups reported by Petrovic et al. was the result of examining AL and the type of drinker (moderate and heavy drinkers). It is unknown whether the participants in the study met the criteria for AUD since Petrovic and colleagues categorized types of drinkers and not by AUD status. Thus, the magnitude of the relationship in which Petrovic et al. observed is not necessarily equivalent to the current study as it reflects the magnitude of differences observed in moderate and heavy drinkers, but not among healthy controls and men with an AUD. However, given the relatively few studies that have examined such associations and the lack of studies with a similar study design to the current study, it is difficult to infer whether the current study was appropriately powered to detect such an effect.

Related to calculating AL, the current study utilized the approach McEwen first proposed (and is also the most frequently used method), known as the group AL method. Each biomarker value among the study sample was classified into quartiles and each value that was in the 75^{th} percentile was deemed as being at the highest risk. Each biomarker value in the 75^{th} percentile then received a numerical value of one and summed to yield the overall AL score for each participant. Thus, AL was operationalized by the 12 biomarkers, with higher scores indicative of more biological stress. As indicated by the frequencies of AL scores for men with an AUD, 38 (79.2%) yielded an AL score of four or less. Similarly, 13 (76.5%) of the healthy control participants had an AL score of four or less. Collectively, nearly 79% of all participants were in

the same range. Given the multitude of evidence suggesting higher AL scores are associated with negative health outcomes, it was hypothesized that higher AL scores would be associated with the presence of an AUD diagnosis. While the current study employed the most common method in calculating AL by comparing biomarker values within the study sample, other approaches may be beneficial. For example, using normative data to compare biomarker values may yield a difference in AL and has been utilized by Petrovic and colleagues (2016). Moreover, other studies have used a slightly different approach to calculating AL in which values within the 25th percentile were considered as "extreme low" values and (indicative of physiological dysregulation) values in the 75th percentile were considered "extreme high" values (also indicative of physiological dysregulation; Hampson et al., 2009). Similarly, Hampson and colleagues also created an index based on cutoff values in the 10th percentile and 90th percentile range. Thus, other strategies in calculating AL may be justified.

A fifth explanation may be the existence of a distinction between perceived stress captured by psychological measures of stress and how biological systems capture stress (AL). Notably, Zhang and colleagues previously demonstrated that higher cumulative psychological stress scores were associated with men with an AUD. That is, the association between psychological stress and AUD has been clearly demonstrated in the sample of patients being used in the current study. Given the findings reported by Zhang and colleagues, a post-hoc independent samples t-test was conducted in the current study to examine potential group differences in the cumulative psychological stress score among the two groups, which may elucidate potential differences in stress captured by AL and stress captured by psychological measures. One distinction between the method in which Zhang and colleagues calculated cumulative psychological stress and the method reported in the current study was that alcohol consumption was not included in the

psychological scores. Zhang and colleagues included drinking rates as a type of stressor, and, therefore, included the drinking rates observed in their sample as part of the overall cumulative psychological stress score. In examining the association between AUD and the psychological measures of stress, Zhang and colleagues may have conflated psychological stress and drinking. Thus, drinking was more precisely delineated from the relationship between stress and drinking/drinking status. Similar to findings reported by Zhang et al., group differences were observed in the cumulative psychological stress variable in the expected direction ($t(61) = 3.87$, $p < .001$; table 4). That is, higher mean scores of psychological cumulative stress was observed in men with an AUD compared to the healthy control group. Given these post-hoc results, it may be reasonable to infer that, in the context of AUD status, biological cumulative stress as measured herein may not be sensitive enough to detect stress and/or the effects of stress in comparison to psychological measures of stress. Further, it may be that psychological stress may not have a large enough impact on biomarkers related to stress to effectively differentiate any group differences. Whether this would be a stable conclusion if the biological measures were expanded is not clear and merits future research.

The final factor may be the lack of stress captured by the biological markers. McEwen's model of AL posits that the effects of stress are associated with physiologic dysregulation in which physiologic dysregulation can be observed by examining the levels of each biological marker. However, biomarker level comparisons among the sample of participants were relatively similar. Overall, few participants in the current study yielded biological marker values that were above the 75^{th} percentile which would have been indicative of physiological dysregulation in comparison to other sample participants. The lack of variability in AL scores across both groups, in turn, did not support the hypothesis that AUD is associated with greater physiologic

dysregulation compared to healthy controls. In fact, the opposite may be occurring in which higher AL scores may be associated with less alcohol consumption.

Drinking and AL Literature

As previously mentioned, five studies have examined the relationship between AL and drinking with two showing positive relationships between AL with drinking and three showing negative relationships.

Related to the positive association, Kusano et al., (2016) employed the group AL method to calculate AL in which values in the 25th percentile and 75th percentile were used. However, to measure drinking in the Kusano et al. study, the Brief Diet History Questionnaire was used. Notably, alcohol consumption quantities, frequencies, and a description of a standard drink were not reported. Overall, higher AL scores were associated with alcohol consumption. Petrovic and colleagues (2016) also observed a positive relationship between AL and the type of drinker (moderate and heavy drinkers) in a sample of participants from Switzerland. Rather than utilizing the group AL method, the authors referred to clinical thresholds to categorize low and high values for each biomarker. The authors further dichotomized the AL scores into low versus high scores based on a median cutoff score. This study also reported using biomarkers not commonly used. Thus, grouping participants based on the type of drinker (i.e., moderate versus heavy drinkers) and utilizing clinical thresholds of the biomarkers used in the study represent the various ways in which drinkers and biomarkers can be characterized.

Contrary to the two findings suggesting a positive association between AL and drinking, Gallo et al., (2011), Hampson et al., (2009), and Hu et al., (2011) reported a negative association between AL and drinking. Gallo and colleagues (2011) aligned their AL calculation by using biomarkers reported in the MacArthur study, but excluded the use of DHEA, citing a difference

among men and women related to health disparities. Gallo and colleagues modified the "high risk" bounds exclusively for cortisol by using the lower and upper 12.5% ranges. Related to drinking, Gallo et al. grouped participants into four groups (0-1 drinks [per month], 2-5 drinks, 6-19, and 20 or more). The authors reported higher alcohol consumption was related to lower AL in their sample of Mexican-American women. Moreover, Hampson and colleagues (2009) also reported a negative association between AL and drinking. The authors created an index in which values in the 10^{th} and 90^{th} percentiles as well as values in the 25^{th} and 75^{th} percentiles were used. Drinking was measured by multiplying the number of days alcohol was consumed in the past month by number of drinks typically consumed on a single day. Overall, higher consumption rates were associated with less physiological dysregulation. Finally, Hu and colleagues (2011) reported using the same biomarkers first reported in the MacArthur study to calculate AL. The group AL method was used to derive the AL scores for participants using the 25^{th} and 75^{th} percentiles to compare values among the sample. However, alcohol status was categorized as either a participant being a current user or a non-user. Overall, Hu and colleagues (2011) reported current alcohol use (versus abstainers) being associated with lower AL.

Overall, there appears to be two significant characteristics warranting attention: the variability in deriving an index of AL and the variability in measuring drinking patterns. The scarcity of studies examining AL and drinking, the varying number of biomarkers used to calculate AL, the potential differences in which stress is captured (biologically or psychologically), the variations in measuring and characterizing alcohol consumption and type of drinker, and the method in which AL is calculated may be impacting the true nature of the relationship between AL and drinking.

Limitations

The current study is not without limitations. Due to the secondary nature, lack of available biological samples, and a relatively small sample size, additional biomarkers such as dehydroepiandrosterone, epinephrine, dopamine, aldosterone, and waist-to-hip ratio could not be calculated. The addition of these measurements may have contributed more information related to AL, consistent with McEwen's suggestion of incorporating more biomarkers to better assess AL. Moreover, other biological systems were not represented, such as the reproductive system. While examining the reproductive system has been less commonly used, chronic stress has been associated with impacting testosterone production, sperm production, and sperm motility (APA, 2018). Moreover, the compounding effects of stress may impact the reproductive system in men via the immune system if the immune system is weakened/compromised, thus increasing infection vulnerability to the testes, for example (APA, 2018).

Additionally, the cross-sectional and correlational nature of the current study is noteworthy. However, McEwen initially began a large part of his work on allostasis/AL examining cross-sectional associations and found support for his model utilizing longitudinal data from the MacArthur Study on Successful Aging. Thus, correlational research is foundational to understanding the initial relationship between AL and alcohol to inform future research. An additional limitation to the current study was the use of imputed data for some missing values among the biological markers. While it is widely accepted to impute data, inferences related to the results must be given further consideration related to validity.

Future Directions

Based on current findings and the differences reported in studies examining AL and drinking, future research is warranted. For example, examining a larger clinical sample of men

diagnosed with an AUD with regard to the relationship with AL to elucidate this relationship is warranted. Further, longitudinal designs are warranted to examine the stability of AL index scores and their associations with various health behaviors. More specifically, biological marker values have been observed to fluctuate over time (i.e., cortisol production, blood pressure readings, pulse readings, and body mass index can change if a person experiences any changes in weight, is a smoker, and/or is a chronic drinker). Thus, examining the impacts of these fluctuations and the potential relationship with health outcomes is warranted. Additionally, the exploration of a psychological equivalent of biological cumulative stress is warranted, given the lack of an available measures in which the various types of stress are represented in a single measure. Other future research may wish to compare biomarker values to normative data, in addition to making comparisons within the sample, to examine the differences in which AL is interpreted based on normative comparisons and group-informed AL comparisons. Finally, future research establishing a list of biological markers to use to calculate AL is warranted.

As demonstrated by studies examining AL and drinking relationships, future research is warranted to better understand whether there is a positive or negative association between AL and drinking. As suggested by the very few studies, the relationship is currently negative. Also, future research in which study designs that allow for causal inferences are warranted. More specifically, Hampson et al. and Hu et al. highlight the limitations of cross-sectional designs in which identifying whether alcohol use reduced AL or individuals with higher AL stop/limit their alcohol intake in response to health reasons. By designing a study in which causality can be inferred, identifying whether alcohol use influences AL or if individuals with higher AL respond by minimizing their drinking may provide stronger evidence of the relationship taking place between drinking and AL. Further, the method in which alcohol consumption is measured warrants

attention, given the variety of ways in which it was reported. A standard method for calculating alcohol use may allow for strong, consistent interpretation across studies. Studies examining AL and drinking also indicate the need for future work examining more diverse, western populations. Additionally, a broad range of drinkers should be utilized in future research given the findings suggesting differences among abstainers, moderate drinkers, and heavy drinkers. Finally, the inclusion of binge drinkers should also be examined, given the frequency of occurrence, associated costs, and deaths attributed to binge drinking in the U.S. (CDC, 2019).

Conclusions

The current findings of AL suggests that the relationship with drinking and AUD status is still not immediately clear. Studies examining the relationship between alcohol use and AL are scarce, as this topic remains in its infancy. Moreover, drinking in response to stress is not fully supported by the current findings and it may be reasonable to suspect that AL may not be applicable to drinking or may be negatively related to drinking, despite AL being related to substance use (in general), cardiovascular diseases, and cognitive functioning. The method in which stress is measured may be important to distinguish given the findings reported by Zhang and colleagues and the current findings of AL. Thus, understanding motives for heavy drinking may provide future guidance as to how stress may be driving this relationship.

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Appendix

Appendix 1: Biological systems, biomarkers, and function of biomarker as per Juster et al., (2010)

	Biomarker	Function
Neuroendocrine	Cortisol	Glucocorticoid produced by the adrenal glands. Functions include the conversion of stored fats and proteins into carbohydrates, anti-inflammatory and immuno-suppressive effects, increased blood pressure and heart rate, suppression of digestive, growth, and reproductive activities, and modulation of limbic and prefrontal regions upon traversing the blood–brain barrier.
	Dehydroepiandrosterone	Androgen produced by the adrenal glands. Known functions include its role as a HPA-axis antagonist and its ability to convert into androgens and estrogens. It also suppresses inflammatory cytokines, improves lipid metabolism and lean muscle mass, decreases insulin resistance, and reduces oxidative brain damage.
	Epinepherine	Catecholamine produced by the adrenal glands and the brain. As part of the ‘‘fight-or-flight’’ response, it increases heart rate and glucose levels while decreases digestive and immune functions.
	Norepinepherine	Catecholamine produced by the brain. As part of the ‘‘fight-or-flight’’ response, it increases blood pressure, constricts blood vessels, and modulates brain activities.
	Dopamine	Catecholamine produced primarily in the brain and adrenal glands. It is a well-characterized neurotransmitter involved in many neurological activities (motivation, voluntary movement, cognition) and also increases blood pressure and heart rate.
	Aldosterone	Minerocorticoid produced by the adrenal glands. Functions by reabsorbing sodium, retaining water, and excreting potassium in the kidneys in order to maintain blood acidity, as well as to decrease blood volume and blood pressure.
Immune	Interleukin-6	Cytokine produced by macrophages and T-cells. Functions in pro-inflammation and anti-inflammation by stimulating B cell and T cell

		differentiation that assist acute phase reactions to tissue damage.
	Tumor necrosis factor-alpha	Cytokine produced by macrophages. Functions in systemic inflammation by evoking mediators of acute phase reactions as well as in tumor apoptosis.
	C-reactive protein	Protein synthesized in the liver. Functions by enhancing phagocytosis during acute phase reactions that promote inflammation.
	Insulin-like growth factor-1	Polypeptide protein hormone produced primarily in the liver and pancreas. Functions as a stimulator of cell growth and as an inhibitor of cellular apoptosis.
	Fibrinogen	Protein that synthesizes into fibrin in the liver. Upon synthesis, functions as a blood clotting factor that promotes coagulation but when excessive increases risk of thrombosis.
Metabolic	High density lipoprotein cholesterol	Lipoprotein synthesized in the liver. Transports cholesterol from tissues to the liver. Commonly referred to as ‘‘good cholesterol’’, as its high protein/low cholesterol form is more easily removed by blood in the liver and excreted in bile.
	Low density lipoprotein cholesterol	Lipoprotein synthesized in the liver. Transports cholesterol to tissues that synthesize cell membranes and secretions. Commonly referred to as ‘‘bad cholesterol’’, as its low protein/high cholesterol form is more likely to be deposited in the walls of blood vessels and contribute to atherosclerosis.
	Triglycerides	Glyceride formed from glycerol and three chains of fatty acids. Functions as an important source of energy and as a transporter of dietary fat.
	Glycosylated hemoglobin	Hemoglobin used to index the average glucose concentration over many days, weeks and even months. This proportion represents the amount of glucose that the analyzed hemoglobin has been exposed to during its cell cycle.
	Glucose	Monosaccharide synthesized in the liver and kidneys. Functions as our main source of energy.
	Insulin	Protein hormone produced in the pancreas. Functions by lowering glucose levels and

		promoting energy storage in the form of glycogen.
	Albumin	Protein produced by the liver. Functions in the maintenance of blood volume regulation and as carrier for molecules of low water solubility.
	Creatinine	Nitrogeneous waste product of muscle creatine phosphate that is filtered and excreted by the liver. Creatinine clearance is a marker of glomerular filtration rate representing renal functioning.
	Homocysteine	Amino acid biosynthesized from methionine and can convert into cysteine. Functions in remethylation and transsulfuration pathways that are in part dependent on nutritional intake of folic acid and vitamin B12. Excessive homocysteine levels have been implicated in risk of cardiovascular disease.
Cardiovascular and Respiratory	Systolic blood pressure	Measured using a sphygmomanometer. Represents the maximal force exerted by blood against the blood vessel walls when the left ventricle is contracting during systole.
	Diastolic blood pressure	Measured using a sphygmomanometer. Represents the minimal force exerted by blood against the blood vessel walls when the left ventricle is relaxed during diastole.
	Peak expiratory flow	Measured using a peak flow meter. Represents the maximum speed of expiration and the degree of obstruction of airflow through the bronchi.
	Heart rate/pulse	Measured at sites where arterial pulsation can be felt. Represents the number of palpations made by the heart within a period of time.
Anthropometric	Waist-to-hip ratio	Measure of waist circumference and hip circumference using measuring tape values that are than calculated into a ratio by dividing waist by hip. Higher levels represent greater adipose fat distribution of concern for obese individuals. Body shapes that are commonly referred to as ‘‘apple shapes’’ (greater waist size) are considered to be at greater risk of health problems than ‘‘pear shapes’’ (greater hip size).

Body mass index	Measure of weight and height that is then calculated into an index by dividing weight by height2. Represents a proxy measure of an individual's relative body fat percentage ranging from severely underweight, underweight, normal, overweight, to three different classifications of obesity.

Vita

Carlos Portillo, Jr, was born and raised in El Paso, Texas. While at The University of Texas at El Paso, he was awarded the BUILDing SCHOLARS scholarship, funded by the National Institutes of Health, under the mentorship of Dr. Craig Field. He earned his bachelor's of science degree in Psychology from The University of Texas at El Paso. In the fall of 2017, he enrolled in the doctoral program in Psychology to pursue a master's degree in Clinical Psychology. He continued to work under the mentorship of Dr. Craig Field and also began conducting research under the mentorship of Dr. Theodore Cooper.

His first-year project was a secondary data analysis focusing on psychological cumulative stress in a sample of men diagnosed with an alcohol use disorder. Throughout his time working with Dr. Theodore Cooper, Carlos earned a publication as a second author published in the *Journal of Ethnicity in Substance Abuse*. He has also collaborated on numerous poster presentations.

Carlos will continue at The University of Texas at El Paso in pursuit of his Ph.D. in Psychology. He intends on continuing his work on stress and alcohol.

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