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THE LONGITUDINAL RELATIONSHIP BETWEEN MODERATE ALCOHOL USE AND
COGNITIVE AGING AMONG OLDER ADULTS

by

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ABSTRACT

Cognitive aging appears inconsistent across cognitive domains, indicating that domains may not all decline at the same rate across individuals. Individual trajectories of cognitive aging can vary widely and are affected by numerous lifestyle and health factors. Alcohol use among older adults is known to confer both health risks, typically related to excessive use, and protective effects, often associated with moderate consumption. Moderate alcohol use has been linked with better cognitive functioning as well as a decrease in cardiovascular mortality and systemic inflammation, as compared to heavy or abstinent users. Given that extant research has identified C-reactive protein (CRP) as a mediator between the relationship of moderate alcohol use and cardiovascular disease mortality, this study examined the potential mediating role of CRP between moderate alcohol use and cognitive performance in later life. Therefore, the primary goals of this thesis were to: (1) examine the relationship between moderate alcohol use and cognitive aging over time in a demographically representative, longitudinal survey of Americans over the age of 65, and (2) examine a potential biological mechanisms by which this putative relationship functions. The sample utilized for this study consisted of the ADAMS sample of the Health and Retirement Study (HRS), a longitudinal, cohort-style study on health, retirement, and aging conducted by the University of Michigan and supported by the National Institute of Aging. In order to assess the effect of moderate alcohol use as related to the rate of change in cognitive performance over time, a series of slope-intercept models were run. Logistic regressions and Kaplan-Meier survival analysis were used to examine predictors of dementia risk and time-to-diagnosis. Results indicated that moderate alcohol use was significantly associated with better baseline functioning across cognitive measures ($p \leq .05$), but had no significant effect on rate of change over time. Next, structural equation models were employed to examine the

effect of alcohol use on cognitive performance as mediated by CRP within each domain. Ultimately, results from this study did not support the hypothesized models. Following this, a logistic regression and survival analysis were conducted in order to assess the effect of moderate alcohol use on dementia diagnosis. Results of these analyses indicated that moderate users of alcohol develop dementia at lower rates, and later in life, than do abstinent older adults. Lastly, a structural equation model was run to evaluate the effect of alcohol use on dementia diagnosis as mediated by CRP. Primary findings did not support the hypothesized model. Overall, findings from this study suggest that moderate alcohol use is associated with better cognitive functioning among community-dwelling older adults, and these relative benefits appear to persist throughout later life. Moderate alcohol use may also be related to a slower rate and onset of dementia development. Future research should investigate alternate biological mechanisms relating moderate alcohol use and cognitive functioning in later life.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Cognition

Changes in an individual's cognitive abilities can be seen across the lifespan. Broadly, cognitive abilities decline between one and two standard deviations between twenty and seventy years of age. Following this, cognitive abilities tend to decline at an average of about half of a standard deviation per decade (Anstey & Low, 2004; Salthouse, 2009, 2012). The extent of age-associated cognitive decline differs among individuals and can generally be delineated into normative, or non-pathological cognitive aging, and pathological cognitive aging (Deary & Der, 2005; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Raz et al., 2005). However, cognitive aging appears somewhat inconsistent across cognitive domains and it is vital to understand that domains may not all decline at the same rate across individuals (Anstey & Low, 2004; Park et al., 2001). Moreover, individual trajectories of cognitive aging can vary widely and are affected by numerous lifestyle and idiographic factors including components such as diet, neurobiological changes, genetics, overall general health, cerebrovascular factors such as atherosclerotic disease, and biological processes such as inflammation, and other medical factors (Deary et al., 2009). Moderate alcohol use has also been linked with better cognitive functioning as well as a decrease in cardiovascular mortality and systemic inflammation, as compared to heavy or abstinent consumers (Albert, 2003; Imhof et al., 2001; Lang, Wallace, Huppert, & Melzer, 2007). The relationship between moderate alcohol use and C-reactive protein (CRP), a marker of systemic inflammation, has also been explored (Albert, 2003; Imhof et al., 2001). As a result of the rapid demographic growth of the population of older adults, it will be imperative to better understand how these factors work both independently and in combination. Identification of accessible

protective factors, and elucidation of their mechanisms, will aid in advancing the public health of our aging population both in prevention and intervention strategies.

Although the amount and pattern of decline that is experienced can be highly idiosyncratic, there are also some important group level similarities that should be taken into account. The average adult's cognition declines between one and two standard deviations between twenty and seventy years of age (Anstey & Low, 2004); however, the rate of change over time is variable between cognitive domains. For example, there are typically greater declines in the domains of processing speed, memory, and some facets of executive functioning while verbal functioning tends to show smaller differences (Anstey & Low, 2004; Christensen, 2001; Craik & Bialystok, 2006; Hartshorne & Germine, 2015). Age-related changes in cognition have been broadly related to changes in brain morphology. As the brain ages, there is a decrease in brain size and volume, an increase in ventricular spaces and cerebrospinal fluid, and loss of neuronal bodies in the neocortex, hippocampus, and cerebellum (Deary et al., 2009; Raz & Rodrigue, 2006). The brain is one of the most heavily vascularized systems in the body and utilizes approximately 20% of the oxygen and calories consumed by the body. This high rate of metabolism is consistent through later life, even when taking broadly varying motoric and mental activity into account (Raichle & Gusnard, 2002). Hence, neural health is closely related to vascular health.

Consistent with this thesis, significant work has identified cerebrovascular disease, as well as associated cerebrovascular components, as principle risk factors for cognitive decline in late-life. Cerebrovascular risk factors that have been implicated include diabetes, hypercholesterolemia, atherosclerosis, peripheral arterial disease, hypertension, and elevated levels of lipids and fasting blood glucose (Deary et al., 2009; Jefferson, 2014; Raz, Rodrigue,

Kennedy, & Acker, 2007; Yaffe et al., 2014). In general, primary health interventions improve aging outcomes by reducing factors associated with disease risk such as diabetes, obesity, hypertension, diet, and other lifestyle factors that can affect cerebrovascular health (Anstey & Low, 2004; Deary et al., 2009; Warsch & Wright, 2010; Yaffe et al., 2014).

Dementia

When considering non-pathological and pathological cognitive aging with regard to dementias, it is important to note that dementias differ both quantitatively, in terms of degree of cognitive change, as well as qualitatively, in the pattern of decline across cognitive domains (Deary et al., 2009; Salmon & Bondi, 2009). While decline can be seen across many of the cognitive domains, it is particularly noticeable in episodic memory, semantic knowledge, and portions of executive functioning (Salmon & Bondi, 2009). Outside of cognitive decline, behavioral changes as well as decline in performing activities of daily living are also likely to be observed (Deary et al., 2009). The four most predominant types of dementia are Alzheimer's disease, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia.

The most common form of dementia is Alzheimer's disease (Salmon & Bondi, 2009). In 2005, it was estimated that 24.2 million people worldwide had dementia and that approximately 70% of these cases were established as AD (Reitz, Brayne, & Mayeux, 2011). AD usually begins in later life (i.e., 60-70 years of age) and is generally distinguished by neuronal atrophy, synapse loss, and the buildup of beta-amyloid plaques and neurofibrillary tangles in medial temporal lobe limbic structures (Brion, 2006; Salmon & Bondi, 2009). Plaques and neurofibrillary tangles are the two principal traits found in the brain of individuals with AD. While the pattern in which AD pathology progresses is not fully known, evidence suggests that the earliest changes begin in the medial temporal lobe structures (e.g., hippocampus, entorhinal

cortex). As these structures are involved with episodic memory, deficits in this area are one of

the first, and most prominent, factors of AD. This can cause difficulty with tasks involving

delayed recall and semantic encoding. As the neuropathology of AD continues, the cortices of

the temporal, frontal and parietal lobes are affected, which can cause impairment in higher-order

cognitive abilities. These impairments usually include deficits in the areas of semantic memory,

involving loss of general knowledge and impairment in language abilities. Additionally,

cognitive domains of executive function, visual spatial ability, and naming are also frequently

impaired (Lichtenberg, Murman, & Mellow, 2003). The clinical course of AD is progressive and

generally worsens over time. While symptoms can vary from one individual to another, the

typical progression of AD can include increased memory loss, repeating statements or questions,

difficulty in recognizing familiar individuals, impulsive behavior, and wandering. Further,

individuals in the more severe stages of AD usually have trouble performing activities of daily

living (ADLs), such as bathing or getting dressed and may also experience weight loss as well as

an inability to communicate with those around them (Dubois et al., 2007; Rodgers, 2008).

Dementia with Lewy bodies (DLB) signifies between 10% and 15% of all cases (and

occurs in roughly 20% of all elderly patients with dementia) (Boot et al., 2013; Donaghy &

McKeith, 2014; Salmon & Bondi, 2009) and generally occurs when there is cell loss, a buildup

of Lewy bodies in brain stem nuclei, presence of Lewy bodies throughout the limbic system and

neocortex, and neuritic plaques neurofibrillary tangles (similar to the manner in which they are

seen in individuals with AD). Patients with vascular dementia (VaD) show an aggregate decline

in cognitive functioning that is thought to be due to vascular disease within the brain; and

therefore secondary to multiple or strategically placed infarctions, ischemic injury, or

hemorrhagic lesions (Salmon & Bondi, 2009). The incidence of VaD is greatly increased for

patients with cerebrovascular risk factors and is diagnosed only once evidence of cerebrovascular disease has been confirmed histopathologically. Lastly, frontotemporal dementia (FTD) is a progressive neurodegenerative syndrome, characterized by changes in personality as well as a decline in cognition and language abilities (Grossman, 2002; Salmon & Bondi, 2009; Warren, Rohrer, & Rossor, 2013). Overall, the clinical course of FTD is a gradual progression, with deterioration of the ability to function in activities of daily life as well as increasing disabilities in the social, cognitive, and neurological domains.

Further, there is emerging literature that investigates the consideration of mixed dementias. More specifically, recent research has suggested that dementia patients are likely to experience a mix of the subtypes detailed above rather than adhering to one strict diagnosis. As previously discussed, vascular risk factors and vascular disease are linked with increased risks of VaD and AD. Therefore, Helzner and colleagues (2009) examined the relationship between vascular factors and the course of AD among a multi-ethnic, community-based, sample. Their results indicated that higher levels of pre-diagnosis total cholesterol, LDL-C (low density lipoproteins), and diabetes were associated with quicker cognitive decline among those with AD. These results provide additional support with regard to the role of vascular risk factors in course of AD, reinforcing the view that dementia patients may experience a mix of the subtypes versus one distinct diagnosis. Therefore, diagnostic decisions may not always map on cleanly to the underlying neuropathology.

CHAPTER 2: ALCOHOL CONSUMPTION AND OLDER ADULTS

Alcohol Use –A Protective and Risk Factor

Several studies have identified moderate alcohol use as a protective factor among older adults, supporting the relationship between moderate alcohol intake and a reduction in all-cause mortality and mortality from coronary heart disease and cerebrovascular disease (Cawthon et al., 2007; Gronaek et al., 1995; Huang, Qiu, Winblad, & Fratiglioni, 2002; Hulse, Lautenschlager, Tait, & Almeida, 2005; Marmot & Brunner, 1991). Further, many studies have also examined the relationship between moderate alcohol consumption and cognitive functioning (Heuberger, 2009; Huang et al., 2002; Moussa et al., 2014; Mukamal et al., 2003). Huang, Qiu, Winblad, and Fratiglioni (2002) explored the association between moderate alcohol use and risk of incident dementia and Alzheimer's disease in the Kungsholmen Project, a longitudinal study of aging and dementia conducted in Stockholm, Sweden. A sample of 402, community-based dementia-free, individuals was followed for a six-year period. Their results indicated that moderate drinking (1–21 drinks per week for men, or 1–14 drinks per week for women), was significantly associated with a decreased incidence of dementia in general and Alzheimer's disease in particular, when compared to their non-drinking counterparts. Similarly, Mukamal et al. (2003) examined the prospective relationship between alcohol consumption and risk of dementia among older adults. They utilized the Cardiovascular Health Study (CHS) to identify 373 cases with incident dementia and 373 control cases that were matched on the criteria of age, clinic attendance, and date of death. Their results indicated that when compared with both abstention and heavy use, moderate alcohol consumption was associated with a lower risk of incident dementia among older adults.

In addition, there have also been several studies that have examined the relationship between moderate alcohol use and specific domains of cognitive functioning. For instance, Ganguli, Vander Bilt, Saxton, Shen, and Dodge (2005) examined the association between alcohol use and cognitive decline across six cognitive domains in 1,098 participants with a mean age of 74.4 years and an average follow-up of 7 years. Ganguli et al. (2005) found that, in general, mild-to-moderate drinking, when compared with abstaining, was associated with lesser average decline on the Mini-Mental State Examination (MMSE) and in the domains of trailmaking, learning, and naming. Further, in a large sample of older women (mean age of 74 years), Stampfer, Kang, Chen, Cherry, and Grodstein (2005) found that up to one drink per day decreased the risk of cognitive decline as measured by the Telephone Interview for Cognitive Status (TICS) and the MMSE. Additional research conducted by Ngandu et al. (2007) investigated the effects of moderate drinking in midlife with regard to cognitive functioning in later life. Their results indicated that those who abstained during midlife had worse performance on measures of memory, psychomotor speed, and executive function in later life. Similarly, in a sample of 6,033 middle-aged participants, Britton, Singh-Manoux, and Marmot (2004) found that those who consumed at least one drink per week had better cognitive function than those who abstained. Lastly, Stott et al. (2008) examined a community based sample of 5,804 individuals, with a mean age of 75 years, and found that low to moderate drinking was associated with slower decline across domains of global cognition, speed of information processing, and verbal memory. Although these studies document the link between moderate alcohol use and cognitive performance in later life, the use of a standard and reliable neuropsychology battery, adherence to the NIAAA guidelines for categorizing moderate drinking, and sufficient follow-up time would greatly increase the clinical utility and interpretation of this relationship.

Alcohol use among older adults can also be a health risk, most frequently associated with excessive use (Ferreira & Weems, 2008). Excessive alcohol use can lead to impairment in several domains, including but not limited to, impaired driving, interpersonal problems, financial problems, and health problems (Centers for Disease Control and Prevention, 2014). Due to age-related physiological changes, older adults are at unique risk for negative outcomes associated with excessive alcohol use (Heuberger, 2009; National Institute on Alcohol Abuse and Alcoholism, 1998; Sorocco & Ferrell, 2006). As individuals age, these changes can adversely affect an older adult's tolerance to alcohol (Heuberger, 2009). For example, older adults tend to experience higher concentrations of blood alcohol volume. As people age, the amount of water in the body decreases and the amount of fat generally increases. Alcohol is comprised of water-soluble molecules that distribute throughout the body. When older adults consume alcohol, they experience higher concentrations of blood alcohol volume because there is less water space for it to distribute into (Durfour, 1999). In addition, other factors such as existing diagnoses, number of comorbid conditions, and increased use of polypharmacy, puts them at greater risk of experiencing adverse reactions to alcohol consumption (Heuberger, 2009; Sorocco & Ferrell, 2006). Older adults also are more likely to experience age-related falls and cognitive dysfunction which makes them more susceptible to the effects of alcohol (Sorocco & Ferrell, 2006). Further, excessive alcohol consumption is likely to have a negative impact on cognitive function (Hulse et al., 2005). Results from cross-sectional studies investigating the effect of heavy and frequent alcohol consumption on the risk of dementia have consistently found an increased risk of dementia (Huang et al., 2002; Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004; Ruitenberg et al., 2002; Thomas & Rockwood, 2001; Truelsen, Thudium, & Gronbaek, 2002). For instance, Thomas and Rockwood (2001) conducted a cross-sectional analysis of the

Canadian Study of Health and Aging that included 2,764 (of the 10,268 national cohort) older adults. They found cognitive impairment and dementia was more likely to be found in subjects with either questionable or definite alcohol abuse than in older adults with no such history.

While moderate alcohol use among older adults has been associated with health benefits (Ferreira & Weems, 2008), there has been some difficulty when identifying the definition of "moderate" alcohol use. Although moderate alcohol use is generally considered in terms of quantity and frequency of consumption, levels of blood alcohol concentration (BAC), and negative consequences associated with use, this has been particularly difficult to categorize in older adults as a result of the physiological changes that accompany the aging process (i.e., decreased tolerance; (Heuberger, 2009). As a result, there are several ways to define moderate alcohol use for older adults. The National Institute on Alcohol Abuse and Alcoholism (NIAAA1998) define moderate use as up to two drinks per day for men and one drink per day for women. However, due to the age-related physiological changes, the NIAAA (1998) suggests that older adults consume no more than one drink per day, regardless of gender. However, the United States Departments of Agriculture and Health and Human Services 2010 Dietary Guidelines for Americans defines moderate drinking as no more than two drinks a day for men and one drink per day for women, without specific caveats for age (Agriculture. & Services., 2010). As the current guidelines present some ambiguity with regard to moderate drinking among older adults, results from the current study may provide evidence that would allow for more precise recommendations for the elder adult population.

With respect to effects on health, results of numerous findings suggest a J- or U-shaped relationship between alcohol use and health outcomes, indicating that moderate alcohol intake may provide benefits with regard to health (Albert, 2003; Imhof et al., 2001; Lang et al., 2007;

Marmot & Brunner, 1991). Cardiovascular mortality is one example of this relationship, as greater levels of cardiovascular mortality can be found in both heavy drinkers as well as in non-drinkers when compared to those who drink in a moderate fashion. The relationship between these groups is complex as heavy drinkers have an increased risk of death compared to moderate users; but moderate users have a lower mortality rate than abstainers. One of the possible reasons that non-drinkers have higher risk than both abstainers and heavy drinkers, is that these groups are likely to include individuals with additional health comorbidities and abstainers can contain those who no longer drink due to negative health factors (i.e., 'sick quitters'; (Marmot & Brunner, 1991). Other studies have investigated whether or not the type of alcoholic beverage made a difference (i.e., wine, liquor, or beer); however, ultimately, it appears that type of drink did not influence the overall outcome of the relationship. While the mechanism underlying the protective effect of moderate alcohol consumption is not well understood, several possible mechanisms have been proposed explain the benefit.

CHAPTER 3: CLINICAL BIOMARKERS

C-reactive Protein (CRP)

C-reactive protein (CRP) is a plasma protein, which acts as a clinical biomarker of inflammation as its concentration quickly increases in response to tissue damage and inflammatory processes (Ansar & Ghosh, 2013). Therefore, CRP typically circulates in low concentrations in healthy individuals (Stewart, Mainous, & Gilbert, 2002). Due to CRP's sensitivity as a clinical indicator of inflammation, CRP levels are a valuable indicator of clinical disease course as well as response to treatment (Du Clos & Mold, 2004). There are very few pathologies, besides liver failure, and drugs that reduce CRP values (Hirschfield & Pepys, 2003). As previously stated, moderate alcohol consumption has been consistently linked with a decrease in cardiovascular disease mortality as well as its anti-inflammatory properties. Stewart, Mainous, and Gilbert (2002) examined the association between alcohol consumption and CRP on systemic inflammation and found that nondrinkers had the highest percentage of elevated CRP levels (31%) compared to 21% of low to moderate frequency drinkers, and 18% of high frequency drinkers; indicating that alcohol consumption is associated with lower CRP levels. Albert (2003) also found that lower CRP levels were associated with moderate alcohol consumption, when compared with abstention. Further, a study conducted by Volpato et al. (2004) found that individuals who drank between 1 and 7 drinks had the lowest levels of CRP when compared with those who abstained or consumed more than 7 drinks on a weekly basis. As heavy alcohol consumption contributes to oxidative stress and inflammation, the pro-oxidant effects of alcohol may be one mechanism by which increased cardiovascular risk among heavy users functions (Averina, Nilssen, Arkhipovsky, Kalinin, & Brox, 2006). Taken together, the results of these

studies provide support for a potential anti-inflammatory mechanism (CRP) through which

moderate alcohol consumption may operate.

Apolipoprotein E (ApoE)

Another component that may be a factor in the relationship between moderate alcohol use

and cognitive functioning is apolipoprotein E (ApoE). ApoE is a polymorphic protein with three

polymorphic alleles: e2, e3, and e4; and worldwide allelic frequencies of 8.4%, 77.9%, and

13.7%, respectively (C. Liu, Kanekiyo, Xu, & Bu, 2013). There are six possible combinations of

ApoE (e2/e2, e2/e3, e3/e3, e2/e4, e3/e4, and e4/e4), and the isoforms differ from one another by

a single amino acid. Further, e3 appears in the majority of individuals and is generally

associated with normal functioning, while e2 and e4 are less common and seem to be linked with

variable functional outcomes (Mahley & Huang, 1999). ApoE is a crucial regulator of plasma

liquid levels, facilitating lipid transport between tissues or cells and injury repair in the brain (C.

Liu et al., 2013; Mahley & Huang, 1999).

The relationship between ApoE and the development of AD has been well documented in

the literature. Research has shown that the ApoE alleles are one chief genetic risk factor of AD

associated risk. Moreover, the e3 allele is seen in the majority of individuals and is generally

correlated with typical functioning (Mahley & Huang, 1999). Further, it has been documented

that the presence of the e4 allele is the strongest genetic risk factor for developing AD, whereas

individuals with the e2 allele have been shown to have a decreased risk of AD development (C.

Liu et al., 2013; Mahley & Huang, 1999). The e4 allele has also been associated with an earlier

age of onset for AD. Blacker and colleagues (1997) examined the relationship between presence

of the e4 allele and age of onset of AD. They analyzed data from 310 families (679 individuals).

Their results supported the ApoE-4 allele as a risk factor for AD. Their results also indicated

that individuals who carried two copies of e4 had a significantly younger age of onset than those who had only one e4 allele or none at all. Additionally, Naj et al. (2014) analyzed data from over 9,000 respondents and found that each additional copy of the ApoE-4 allele reduced AD age of onset by 2.45 years.

Extant literature concerning the relationship between ApoE genotype and age-related cognitive decline presents a complex and unclear picture that does not yet appear to be well understood. Lui et al. (2010) reported that, in individuals older than 50 years of age, carriers of the ApoE-4 allele demonstrated worse performance on a measure of verbal learning than did those who are non-carriers of the ApoE-4 allele. Knopman, Mosley, Catellier, and Coker (2009) found that individuals with an ApoE-4 allele demonstrated decline in areas of verbal learning and processing speed. Moreover, Downer, Zanjani and Fardo (2014) found that, for non-ApoE-4 carriers, light and moderate consumption was associated with increased performance in learning and memory, while ApoE-4 carriers demonstrated greater decline in these areas. However, in a study cited above, Stampfer et al. (2005) conducted additional analyses as stratified by ApoE genotype. Their results did not find an interaction between either alcohol in-take or ApoE genotype nor global cognitive score and ApoE genotype. Similarly, Ngandu et al. (2007) also included analyses examining ApoE genotype with regard to alcohol use and cognitive functions. Their results also did not find any interactions between ApoE genotype, alcohol use, and cognitive performance among memory, psychomotor speed, or executive function. As this area of research continues to develop, we will gain a better understanding of the relationship between alcohol consumption, ApoE-4, and their combined effect on cognitive functioning.

CHAPTER 4: PROPOSED RESEARCH

The primary goals of this study were to: (1) examine the relationships of moderate alcohol use, with both cognitive aging and dementia risk, respectively in a demographically representative, longitudinal survey of Americans over the age of 65, and (2) examine one potential biological mechanism by which these putative relationships functions.

Cognitive Domains

It is hypothesized that (H1) participants who report consuming moderate alcohol (1-14 drinks per week) will demonstrate better cognitive performance than participants who report abstaining from alcohol use. (H2) Further, it is hypothesized that C-reactive protein will mediate the relationship between cognitive performance and moderate alcohol use, as characterized by a significant indirect relationship from moderate alcohol use to cognitive performance through CRP. It is also hypothesized (H3) that Apolipoprotein E (ApoE) will moderate the relationship between moderate alcohol use and CRP, and that the moderated CRP variable will mediate the relationship between moderate alcohol use and dementia risk. Building on Hypothesis 1, (H4) it is hypothesized that moderate alcohol use will relate to a slower rate of change in cognitive performance over time.

Dementia Diagnosis

It is hypothesized (H5) that moderate alcohol consumption will predict a lower rate of all-cause dementia at baseline and a slower increase in all-cause dementia over time. Further, (H6) it is hypothesized that C-reactive protein will mediate the relationship between dementia diagnosis and moderate alcohol use, as characterized by a significant indirect relationship from moderate alcohol use to diagnosis through CRP. (H7) It is further hypothesized that ApoE-4 carriage will moderate the relationship between moderate alcohol use and CRP, whereby

moderate drinkers who are ApoE-4 negative will have lower CRP than will those moderate

drinkers who are ApoE-4 positive.   Finally, (H8) it is also hypothesized that the moderated CRP

variable will mediate the relationship between moderate alcohol use and dementia risk.

CHAPTER FIVE: METHODOLOGY

Participants

The present utilized data collected through the Health and Retirement Study (HRS) as well as the Aging, Demographics, and Memory Study (ADAMS). The HRS is a longitudinal, cohort-style study on health, retirement, and aging conducted by the University of Michigan and supported by the National Institute of Aging. The first wave of data collection began in 1992 with adults over 50 years of age who were living in the United States. Data has been and continues to be collected biennially. Data is collected via interviews, surveys, and links to personal records. This methodology provides a wealth of information about each participant, including their physical health, mental health, disability status, employment status, and housing situation. Additional information on HRS survey design as well as data collection methods can be found in previously published reports (Hauser & Willis, 2004; Heeringa & Conner, 1995; Sonnega et al., 2014).

The ADAMS is a supplement to the HRS. The primary goal of the ADAMS is to collect data that will allow researchers to estimate the prevalence, predictors, and outcomes of individuals diagnosed with dementia inside the U. S. elderly population. This information will aid in facilitating the understanding of the natural history of preclinical dementia as well as the ways in which dementia alters the health and social functioning of older adults. Further, data collected through the ADAMS allows for investigation of the relationship between the impact of dementia and cognitive impairment. The waves of data that will be utilized are from 2001, 2002, 2006, and 2008 and have documented data on 856, 252, 315, and 217 participants, respectively (Health and Retirement Study, 2013). Data used in these analyses incorporate both the direct data released from the HRS committee, and cleaned HRS data released by the RAND Center for

the Study of Aging (RAND HRS). Longitudinal data is available at 2-year intervals through

2012. The average inter-wave attrition rate is around 20%, the vast majority of which reflects

death or incapacity.

For analyses involving the use of biomarker data, the 2006 data will be utilized as

baseline for this thesis because this is the year in which CRP levels for participants are reported

and available.   Participants with missing CRP values, at either the 2006 or 2008 wave were

excluded (n=577). Of the remaining 279 participants in the sample, participants with CRP

values above 10µg/mL (n=29) were excluded as CRP values exceeding 10µg/mL indicate the

possibility of an acute phase response (Ridker, 2003). This CRP-related exclusion reduced the

sample, for biomarker analyses, to 250 participants.

Subsequently, for all analyses, heavy drinkers (i.e., those consuming more than 14 drinks

per week) were excluded from this study, and alcohol use was dichotomized as abstinent (0

drinks per week) and moderate (1-14 drinks per week). This method, supported by past research,

allowed us to better elucidate the mechanism by which moderate alcohol has a protective effect

by comparing moderate drinkers to non-drinkers (see *Figure 1*).

Measures

Demographic Variables. Data on the following demographic variables were collected through

either telephone or face-to-face interviews with participants.

Age/Gender/Race. The HRS includes data on age, identified gender, and race for

participants at each wave. Gender will be determined based on participants' reports. In the case

that reported gender differed from wave to wave, these instances were flagged and gender-

specific health questions were examined to determine participant gender. Race was established

by initially inquiring with participants as to whether or not they considered themselves to be

Hispanic of Latino. Following this, participants were then asked, which race they considered themselves to be (i.e., White, Black or African-American, American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, or something else). If participants selected more than one race, they were asked to specify which race they felt they identified with primarily. If race was missing and participants had identified with being Hispanic or Latino, their race was set to "White/Caucasian." Efforts were made during participant enrollment to oversample minority elders.

Education. The HRS data set also includes information pertaining to participants' level of education. Level of education was assessed by asking participants for the highest grade of school, or year of college, that they have completed. Participants who reported 12 or fewer years of school were asked about receiving a High School degree. Participants who reported 13 or more years of school were asked if they received a college degree, with the assumption being that they had completed high school, either by obtaining a high school diploma or their General Education Development (GED) certificate. If participants reported receiving a college degree, they were subsequently asked for the highest degree they have earned.

Alcohol Use. Alcohol use will be measured by the average number of reported drinks per week. In the HRS data set, alcohol use was determined by first asking participants, "Do you ever drink any alcoholic beverages, such as beer, wine, or liquor?" If participants answered "yes" to the initial question, they were then asked two follow-up questions in order to assess the frequency and intensity of their alcohol consumption. The first follow-up question requested that participants report the number of days per week, on average, that they consume an alcoholic beverage within the last three months. Participants who reported consuming at least one drink per week or greater, were then asked how many drinks they typically consume on days when

they do drink, with respect to the last three months. Average number of drinks per week will be computed by multiplying the number of drinks per day by the number of drinking days reported per week.

C-Reactive Protein. C-reactive protein (CRP) was gathered through an enzyme-linked immunosorbent assay (ELISA) using a dried blood spot (DBS) (Crimmins et al., 2013). ELISA is a test that utilizes antibodies in order to detect the presence and amount of a protein, typically designated by a color change once the antibody binds to the protein. The minimum CRP level required for detection is 0.035mg/L. CRP data for 2006 was collected using DBS assays, which were conducted at the University of Vermont, and small set done at Biosafe. CRP data for 2008 was also collected by DBS assays performed at the University of Vermont. Imprecision was measured as the coefficient of variation (i.e., ratio of standard deviation to the mean), and signifies the reliability and validity of the measurement method. The within-assay imprecision is 8.1%, and between-assay imprecision is 11.0% (Crimmins et al., 2013).

Apolipoprotein E. Apolipoprotein E (ApoE) genotype was determined via a buccal tissue sample for DNA testing. This sample was collected by a specially trained nurse during the in-person evaluation conducted in the participant's residence (Health and Retirement Study, 2013). Buccal sampling through mouth swabs has been shown to be a non-invasive technique that also generates high-quality genomic DNA for single nucleotide polymorphism genotyping (Yi, Wu, Luo, Zhou, & Wu, 2014).

Cognitive Variables. The instruments that comprise the neuropsychological assessment of the ADAMS represent several different domains of neurocognitive functioning that are critical in detecting and diagnosing cognitive and neurological disorders. For the purposes of this research

project, the utilized domains include (1) fluency, (2) executive function, (3) visuospatial, (4) memory, and (5) global cognition.

    Fluency Domain. The fluency domain is comprised of CERAD Animal Fluency, the Controlled Oral Word Association (COWA), and WAIS-III Digit Span. Animal Fluency assesses an individual's semantic fluency. For this test, subjects were asked to name as many animals as possible in a one-minute timeframe. The score is derived from the total number of animals that are named. As animal fluency is a part of the CERAD battery, this test also displays sound psychometric properties, with a high test-retest reliability ($r = 0.80$). Further, while inter-rater reliability is not available for this specific test, the inter-rater reliabilities for all subtests within the CERAD battery fall within the high range ($r = 0.92 - 1.0$) (Morris et al., 1989; Welsh-Bohmer & Mohs, 1997). The COWA test requires retrieval and oral production of spoken words beginning with a designated letter (C, F, and L). This test assesses an individual's ability to spontaneously produce words within a limited timeframe. Specifically, the examinee is asked to say as many words as possible that begin with the particular letter cited in sixty seconds. There are three trails administered, each utilizing a different letter (e.g., F, A, and S; C, F, and L). Further, not only has the COWA been indicated as a sensitive gage of brain dysfunction but the administration of verbal fluency tasks is also considered to be a crucial factor in the assessment of neuropsychological functioning (Ross et al., 2007). In terms of psychometric properties, the COWA has demonstrated high inter-rater reliability (all indices at or above $r = .9$) and modest test–retest reliability coefficients ($r = .6$) (Ross et al., 2007; Ross, Furr, Carter, & Weinberg, 2006). The Digit Span task is taken from the Wechsler Adult Intelligence Scales, Third Edition (WAIS-III). This test includes separate tasks of both forward and backward numerical repetition. For both the forward and backward tasks, the examiner reads a series of number

sequences to the examinee. The Digits Forward items require the subject to repeat the number

sequence in the same order as read aloud by the examiner. For Digits Backward, the subject

must repeat the number sequence in the reverse order as presented. The subject received scores

for Digits Forward, Digits Backward, and a combination of the two. The WAIS-III has

documented consistent reliability and validity, such that inter-rater reliability averaged in the

high .90's, and has shown high concurrent validity with the WAIS-R and WISC-III. Digit Span,

in particular, was shown to have a reliability score of .90 (calculated via Fisher's z

transformation) (Silva, 2008).

Executive Function Domain. The executive function domain includes the Reitan Trail

Making Test (TMT), Part B and the Symbol-Digit Modalities Test (SDMT). The TMT is

administered in two parts; A and B. For Part A, the subject is asked to draw lines connecting

consecutively numbered circles on a worksheet. Part B asks that the subject connect

consecutively numbered and lettered circles by alternating between the numbers and letters. The

test-retest reliability is moderate to high for Part A (r=.36 to .79) and Part B (r=.44 to .89). In

addition, inter-rater reliability has been found to be high for both Part A r=(.94) and Part B

(r=.90) and content validity has been shown to correlate moderately between Part A and B

(Reitan, 1958). The SDMT requires the subject to exchange a number for randomized

presentations of various geometric symbols. The subject is provided with a printed key, which

matches each of the Arabic numbers (1-9) with a specific symbol, so that each number is

represented by its own unique symbol. This test can be administered either via a written or oral

format. While the preferred method of testing is the written format, subjects who were unable to

execute this method (e.g., major motor impairment such as hemiparesis, Parkinsonism, etc.) were

administered the oral version of the test. However, the written and oral scores are not considered

to be equivalent. With regard to the psychometric properties of the SDMT, the test-retest

reliability is .80 for the written format and .76 for the oral format. Further, the SDMT has also

been shown to be sensitive to various types of neurological disorders (Sheridan et al., 2006).

     Visuospatial Domain. The visuospatial domain is comprised of the Benton Visual

Retention Test (BVRT) and the CERAD Constructional Praxis and CERAD Constructional

Praxis Delayed Recall tasks. This test required the subject to reproduce designs following a 10-

second exposure. The BVRT includes a total of ten different designs. The scoring of the BVRT

is calculated based on the types of errors that are made. These can include Omissions,

Distortions, Perseverations, Rotations, Misplacements, Size Errors, Total Left, and Total Right.

With regard to the psychometric properties of the BVRT, the test has adequate alternate form

reliability (ranging from .79 to .84 among the three forms). In addition, inter-rater reliability for

the BVRT is high, with reliabilities reaching from .90 to .97 for the Number Correct Score and

from .94 to .98 for the Number Error Score (Benton, 1998). With regard to the CERAD

Constructional Praxis and CERAD Constructional Praxis Delayed Recall tasks, the

constructional praxis task tests the ability of the subject to copy four geometric forms of

fluctuating difficulty (circle, overlapping rectangles, diamond and cube). Each figure is printed

on the top portion of a sheet of paper and subsequently presented to the subject, individually.

The subject is then asked to copy the figure in the blank space. The delayed recall task was

administered after the Recognition Trial for the Word List Learning task and requires the subject

to draw the original four figures from memory. The scoring range for this test ranges from zero

to eleven (Fillenbaum, Burchett, Unverzagt, Rexroth, & Welsh-Bohmer, 2011). The

constructional praxis task has demonstrated high inter-rater reliability (0.92) and high test-retest

reliability (0.80) (Morris et al., 1989; Welsh-Bohmer & Mohs, 1997)

Memory Domain. The memory domain includes the CERAD Word List Delayed Recall and CERAD Word List Recognition tasks as well as WMS Logical Memory II and the Fuld Object Memory Evaluation (FOME). These tasks contain ten high imagery words that are visually presented for two seconds each. The individual reads each word aloud as it is presented and is subsequently tested on an immediate recall procedure. There are three trials with immediate recall and one trial of delayed recall. These are followed by one trial of a recognition task for ten target items, which appear among ten non-target items. Intrusions on the task are noted when a word is stated during recall that was not among the original words on the stimulus list. Lastly, if the subject was visually impaired or unable to read for any other reasons, the word list was read to the subject. In these cases, the individual was asked to repeat the words as they were read. The psychometric properties of the CERAD have been found to be both valid and reliable (Morris et al., 1989). More specifically, the Word List Learning Trials were shown to have high inter-rater reliability, with an intra-class correlation of $r = 1.0$. In addition, test-retest reliability for Word List Learning Trials, Word List Delayed Recall, and Word List Recognition have been found to be $r = 0.80$, $r = 0.56$, and $r = .53$, respectively (Morris et al., 1989; Welsh-Bohmer & Mohs, 1997). During the Wechsler Memory Scale (WMS) Logical Memory II (Delayed Recall) task, two brief stories were read to the subject. Following this, the subject was asked to recall as much of the story as they could. The delayed recall task asked subjects to again recall as much of the stories as possible and was administered following completion of the Symbol-Digit Modalities Test. The psychometric properties for the WMS Logical Memory I and II have been well validated. The four to six week test-retest reliability has been assessed at $r = 0.75$ for Logical Memory II. In addition, the Logical Memory subtest has demonstrated an inter-rater reliability of 0.99 (Franzen & Iverson, 2000). The FOME is centered around the recall of

ten common household objects, which are first identified by touch. The task utilized the modified 3-trial version and each recall trial was preceded by a distractor task which required word generation. Further, the subject was selectively reminded of items they were unable to recall. The FOME has demonstrated sound psychometric properties, with an alternate form reliability reported at .71, as well as test-retest reliability (r = .92), and high sensitivity and specificity for both total retrieval and delayed retrieval scores (Chung & W, 2009; Wall, Deshpande, MacNeill, & Lichtenberg, 1998)

Global Cognition Domain. The domain of global cognition was calculated as an aggregate of all measures from each domain.

Statistical Methods

Cognitive Domains.

To examine the effect of moderate alcohol use on the rate of change in cognitive performance over time, a series of slope-intercept models were run. For all slope-intercept models, control variables included number of years of education, medical burden (total number of medical diseases), and marital status. Following this, principal component analysis was conducted to ensure appropriate fit of the cognitive measures within each domain. All data was standardized and measures on which stronger performance yields higher scores (TMT, for instance) were inverted (Tabachnick & Fidell, 2013). Once the factor structure for the cognitive variables was established, the effect of moderate alcohol use on each domain of cognitive performance (memory, executive functioning, fluency, visuospatial, and global cognition) was assessed via structural equation modeling. More specifically, a path analysis utilizing a mediation analysis adapted from Baron and Kenny (1986) was used to determine the overall relationship between alcohol use, C-reactive protein, and cognitive performance. Control

24

variables included gender, age, education, race, and medical burden. Mediation of this relationship was identified based on a significant indirect relationship from alcohol to cognitive performance through CRP. As in multiple regression, moderation models using SEM paradigms model both the direct effect of a moderating variable, and the cross-product of the moderating variable with the variable hypothesized to be moderated. Thus, moderation of the relationship between alcohol use and CRP was examined by modeling the direct effect of ApoE carriage and the effect of the cross-product of ApoE carriage and moderate drinking on CRP. In such a paradigm, significant moderation is indicated by a significant pathway coefficient for the cross-product on the outcome variable, in this case, CRP. Data was prepared in SPSS and slope-intercept, as well as, structural equation model analyses were performed utilizing the *Mplus* software program (L. K. Muthen & Muthen, 2012).

Dementia Diagnosis.

The effect of moderate alcohol use on onset of dementia was determined using a logistic regression model. Both dementia onset and alcohol use were coded as binary variables. With regard to alcohol use, "Moderate Use" represents participants who reported consuming an average of 1-14 drinks per week; and "Abstained" represents participants who reported that they did not consume any alcoholic beverages during a typical week. Additional predictor variables used in the analysis include gender, age, race, and number of years of education.

Following this, a Kaplan-Meier survival analysis was performed to assess the effects of alcohol use (moderate versus abstaining) on the age of onset of dementia. The Kaplan-Meier method, also known as the product-limit estimate of the survival function, does not utilize a specified interval size, but instead calculates survival statistics each time an event is observed (Tabachnick & Fidell, 2013). One of the main characteristics that differentiates the Kaplan-

Meier survival analysis from other survival analyses is its ability to censor data. Censoring

occurs when there is incomplete survival time data for participants (i.e., dementia onset was not

noted during the span of the data collection; participants attritted from the sample). As the

sample for the current study included both participants who either did not receive a diagnosis or

attritted from the sample, a Kaplan-Meier survival analysis was performed in order to evaluate

the effect of alcohol use on the age of onset for dementia diagnosis (Collett, 1994; Tabachnick &

Fidell, 2013). Survival probabilities for dementia diagnosis among those who abstained from

alcohol use were compared with survival probabilities for dementia diagnosis among those who

consumed alcohol moderately. Group differences were tested via the log-rank test in SPSS.

Finally, the effect of moderate alcohol use on dementia onset was assessed via structural

equation modeling. More specifically, a path analysis utilizing a mediation analysis adapted

from Baron and Kenny (1986) was used to determine the overall relationship between alcohol

use, C-reactive protein, and dementia onset. Control variables included gender, age, education,

and medical burden. As the outcome variable for this analysis was categorical (those who

did/did not receive a dementia diagnosis), it was necessary to code this appropriately in the

Mplus syntax. When an outcome variable is categorical in Mplus, the estimator should be

changed to reflect weighted least squares with mean and variance adjustment (WLSMV) rather

than the standard maximum-likelihood (ML) estimator. WLSMV is a robust estimator which

does not assume normally distributed variables and provides the best option for modeling

categorical outcomes as it utilizes a diagonal weight matrix with robust standard errors and

mean- and variance-adjusted χ^2 test statistic (Brown, 2006; Hancock, 2006; B. O. Muthen &

Asparouhov, 2002; Yu, 2002). Mediation of the hypothesized relationship was identified based

on a significant indirect relationship from alcohol use to dementia onset through CRP. Further,

26

moderation of the relationship between alcohol use and CRP was identified by a significant

pathway from moderate alcohol use to CRP through ApoE. Data was prepared in SPSS and

structural equation model analyses were performed utilizing the *Mplus* software program (L. K.

Muthen & Muthen, 2012).

CHAPTER SIX: RESULTS

Cognitive Domains.

The full ADAMS sample (Waves A-D) consisted of 856 participants. As displayed in *Table 1*, the sample was predominantly female (58.6%), largely White/Caucasian (76.9%), and had a mean age of 81.56 years (*SD*=7.17), and a mean education of 10.03 years (*SD*=4.35). The sample reported a mean medical burden score of 7.08 (*SD*=3.67). Approximately 79% of participants included in this study reported being abstinent from alcohol. *Table 1* provides separate sample characteristics for non-drinkers (n=679) and moderate drinkers (n=139). As expected, moderate drinkers differed significantly on certain variables compared to non-drinkers.

Specifically, compared to non-drinkers, moderate drinkers were more likely to be Caucasian ($\chi^2_{(1, N=818)}$=16.01, *p*<0.001), male($\chi^2_{(1, N=818)}$=28.62, *p*<0.001), and partnered ($\chi^2_{(1, N=818)}$=15.07, *p*<0.001). In addition, compared to non-drinkers, moderate drinkers were more educated ($\chi^2_{(17, N=818)}$=74.36, *p*<0.001) and had less medical burden ($\chi^2_{(1, N=818)}$=37.55, *p*<0.05), overall. However, as certain variables (i.e., biomarker data) were not collected from all participants, it should be noted that not all analyses were able to utilize the full sample of ADAMS participants. Therefore, the structural equation models, which employed the use of both CRP and ApoE data, were subject to a smaller sample size. More specifically, of the 856 ADAMS participants, 250 participants had CRP and ApoE data, collected in either Wave C or Wave D. The available data from these two waves were merged, in order to optimize both sample size as well as statistical power.

To begin, we examined the hypothesis (H4) that moderate alcohol use would relate to a slower rate of change in cognitive performance over time, utilizing slope-intercept models for each cognitive measure. The final sample for the slope-intercept models included the full

ADAMS sample of 856 participants (demographics for these individuals can be found in *Table 1*). Overall, results of the slope-intercept models produced a similar pattern across cognitive domains (*Figure 2*). As a broad generalization, moderate alcohol use was significantly associated with increased baseline functioning ($p \leq .05$), but had no significant effect on rate of change over time. More specifically, individuals who engaged in using alcohol in a moderate manner displayed better performance at baseline across measures of cognition, but this effect was not associated with rate of change in performance over time suggesting that these differences at baseline persisted over eight years. The exceptions to this pattern were observed on Trails B (executive functioning domain; β (Slope) = -0.581, $p = 0.78$; β (Intercept) = -13.877, $p = 0.22$) and the Word List Recognition task (memory domain; β (Slope) = -0.025, $p = 0.49$; β (Intercept) = 0.265, $p = 0.23$). For both of these tasks, moderate alcohol use did not have a significant effect on either baseline functioning or rate of change over time. For all slope-intercept models, control variables include number of years of education, medical burden, and marital status. Fit indices for all models can be found in *Table 2*.

Prior to running the any of the structural equation models, a principal component analysis was conducted to ensure appropriate fit of the cognitive measures within each domain. This was necessary to confirm that the each measure was accurately placed within the appropriate cognitive domain. PCA serves to identify a set of dimensions that helps to explain the variance in a set of variables as well as to reduce a large set of correlated variables to fewer underlying orthogonal dimensions (Harlow, 2005). The factor loadings, as well as the eigenvalues, of the PCA are provided in *Table 3*, all of which indicate a strong fit within their respective cognitive domains.

Following this, the structural equation models were run to further examine the effect of

alcohol use on cognitive performance as mediated by CRP (H1, H2, H3). The subsample of ADAMS participants included in these structural equation models consisted of the 250 participants who had both CRP and ApoE data. As displayed in *Table 4*, the sample was predominantly female (53.2%), largely White/ Caucasian (79.2%), and had a mean age of 82.47 years (*SD*=5.45), and a mean education of 11.11 years (*SD*=4.14). The sample reported a mean medical burden score of 6.33 (*SD*=3.73). In addition, the mean CRP level was 2.77µg/mL (*SD*=2.34). Approximately 71% of participants included in this study reported being abstinent from alcohol. *Table 4* provides separate sample characteristics for non-drinkers (n=178) and moderate drinkers (n=69).

As expected, moderate drinkers differed significantly on certain variables compared to non-drinkers. Specifically, compared to non-drinkers, moderate drinkers were more likely to be Caucasian ($\chi^2_{(1, N=247)}$=6.85, *p*<0.01) , male ($\chi^2_{(1, N=247)}$=13.40, *p*<0.001), and partnered ($\chi^2_{(1, N=159)}$=4.75, *p*<0.05) .

Results of a structural model (*Figure 3*) examining hypotheses H1, H2, and H3 with regard to the fluency domain suggest that the hypothesized model fit the data well (RMSEA=0.032; Comparative Fit Index (CFI)=0.976; $\chi^2_{(df=26)}$=32.38, *p*=0.810). Although the model demonstrated adequate fit, not all of the pathways in the model were statistically significant. Contrary to the hypothesized model, moderate drinking was associated with neither lower levels of CRP (*β*=-0.275, *SE*=0.313, *p*=0.380) nor better performance on the measures of fluency (*β*=0.035, *SE*=0.681, *p*=0.959). Also contrary to the hypothesized model, higher CRP values were significantly associated with better performance on the measures of fluency (*β*=0.267, *SE*=0.128, *p*=0.037). The indirect pathway from alcohol to performance within the fluency domain through CRP was not statistically significant (*β*=-0.008, *SE*=0.011, *p*=0.456). In

addition, ApoE was neither a significant predictor of CRP values (β=-0.351, SE=0.331, p=0.289) nor a significant moderator (β=-0.392, SE=0.683, p=0.566) of the relationship between alcohol use and CRP.

Results for the second of these models examining the executive function domain suggest that the hypothesized model demonstrated a mediocre fit of the data (RMSEA=0.066; Comparative Fit Index (CFI)=0.856; $\chi^2_{(df=23)}$=47.97, p<0.01). Although the model demonstrated mediocre fit, the pathways in the model were not statistically significant. Moderate drinking was associated with neither lower levels of CRP (β=-0.275, SE=0.313, p=0.380) nor better performance on the latent variable measuring executive functioning (β=1.609, SE=1.749, p=0.357). Higher CRP values were also not associated with better performance in this cognitive domain (β=0.177, SE=0.355, p=0.617). Further, the indirect pathway from alcohol to performance within the executive function domain through CRP was not statistically significant (β=-0.002, SE=0.006, p=0.753). In addition, ApoE was neither a significant predictor of CRP values (β=-0.351, SE=0.331, p=0.289) nor a significant moderator (β=0.392, SE=0.683, p=0.566) of the relationship between alcohol use and CRP.

Results for the third model relating to the visuospatial domain suggest that the hypothesized model fit the data well (RMSEA=0.060; Comparative Fit Index (CFI)=0.926; $\chi^2_{(df=27)}$=50.870, p<0.01). Although the model demonstrated adequate fit, the pathways in the model were not statistically significant. Moderate drinking was associated with neither lower levels of CRP (β=-0.275, SE=0.313, p=0.380) nor better performance in this cognitive domain (β=0.086, SE=0.323, p=0.790). Higher CRP values were also not associated with better performance on the cognitive measures (β=0.089, SE=0.057, p=0.117). Further, the indirect pathway from alcohol to performance within the visuospatial domain through CRP was not

statistically significant (β=-0.006, *SE*=0.009, *p*=0.523). In addition, ApoE was neither a

significant predictor of CRP values (β=-0.351, *SE*=0.331, *p*=0.289) nor a significant moderator

(β=0.392, *SE*=0.683, *p*=0.566) of the relationship between alcohol use and CRP.

Results for the fourth and penultimate model relating to the memory domain suggest that

the hypothesized model demonstrated a mediocre fit of the data (RMSEA=0.067; Comparative

Fit Index (CFI)=0.892; $\chi^2_{(df=31)}$=65.513, *p*<0.001). Although the model demonstrated a mediocre

fit, the pathways in the model were not statistically significant. Moderate drinking was neither

associated with lower levels of CRP (β=-0.275, *SE*=0.313, *p*=0.380) nor better performance on

the cognitive measures within the memory domain (β=0.096, *SE*=1.261, *p*=0.939). Higher CRP

values were not associated with better performance on the cognitive measures (β=0.245,

SE=0.177, *p*=0.165). Further, the indirect pathway from alcohol to performance within the

memory domain through CRP was not statistically significant (β=-0.005, *SE*=0.008, *p*=0.539).

In addition, ApoE was neither a significant predictor of CRP values (β=-0.351, *SE*=0.331,

p=0.289) nor a significant moderator (β=0.392, *SE*=0.683, *p*=0.566) of the relationship between

alcohol use and CRP.

Results for last of these models examining global cognition suggests that the

hypothesized model fit the data adequately (RMSEA=0.084; Comparative Fit Index

(CFI)=0.848; $\chi^2_{(df=162)}$=343.127, *p*<0.001). Although the model demonstrated mediocre fit, the

pathways within the model were not statistically significant. Moderate drinking was neither

associated with lower levels of CRP (β=-0.367, *SE*=0.37, *p*=0.323) nor better performance on the

cognitive measures within the global domain (β=0.976, *SE*=1.592, *p*=0.540). Higher CRP values

were not associated with better performance on the cognitive measures (β=0.375, *SE*=0.301,

p=0.214). Further, the indirect pathway from alcohol to performance within the global domain

through CRP was not statistically significant (β=-0.138, *SE*=0.203, *p*=0.497). In addition, ApoE

was neither a significant predictor of CRP values (β=-0.337, *SE*=0.413, *p*=0.415) nor a

significant moderator (β=0.308, *SE*=0.777, *p*=0.692) of the relationship between alcohol use and

CRP.

Dementia Diagnosis.

The logistic regression and survival analysis (H5 & H6), were completed using the initial

ADAMS sample consisting of 856 participants (demographics for the sample are displayed in

Table 1). *Tables 5* and *6* provide separate sample characteristics for those in which a dementia

onset occurred (n=407) and did not occur (n=449) as well as non-drinkers (n=679) and moderate

drinkers (n=139). As expected, certain variables differed significantly between those who

received a dementia diagnosis and those who did not receive a diagnosis of dementia.

Results of the logistic regression predicting dementia diagnosis are displayed in *Table.7*.

Predictors that were used in the analysis include gender, age, education, race, and alcohol use

(abstained or moderate use). The overall model was significant (χ^2[5]=172.80, *p*<0.001; and

explained 25.4% (Nagelkerke R^2) of the variance and classified 69.7% of cases correctly.

Significant correlates of dementia diagnosis included gender (β=-0.50, Wald=9.39, *p*=0.002,

Exp(β)=1.65), age (β=0.12, Wald=92.66, *p*<0.001, *Exp(β)*=1.13), education (β=-0.06,

Wald=9.28, *p*=0.002, *Exp(β)*=0.94), and moderate alcohol use (β=-0.68, Wald=8.61, *p*=0.003,

Exp(β)=0.51). Race was not a significant predictor of dementia diagnosis (β=0.18, Wald=0.80,

p=0.373, *Exp(β)*=1.19).

Following this, a Kaplan-Meier survival analysis was performed to assess the effects of

alcohol use (moderate versus abstaining) on the age of onset of dementia. The Log Rank test

indicates that there is a significant difference in the survival rate between the two groups

(χ^2[1]=23.17, p<0.001). Further, the median survival time for moderate users (β = 97.00, SE=3.378, 95% CI 90.38 – 103.62) was about eight years longer than those who abstained from alcohol use users (β = 89.00, SE=0.545, 95% CI 87.931 – 90.069). Results of the survival analysis are presented in *Figure 4*.

Following the logistic regression and survival analysis, a structural equation model was run to examine the hypothesis (H6, H7, H8) evaluating the effect of alcohol use on dementia diagnosis as mediated by CRP. As with prior analyses incorporating CRP, this analysis included the subsample of 250 participants used to test H1-H3, above. Demographics for these participants can be found in *Table 4*. Results for this analysis suggest that the hypothesized model demonstrated a mediocre fit of the data (RMSEA=0.036; Comparative Fit Index (CFI)=0.882; $\chi^2_{(df=9)}$=10.849, p=0.286). Although the model demonstrated a mediocre fit, the pathways in the model were not statistically significant. Moderate drinking was neither associated with lower levels of CRP (β=-0.296, SE=0.410, p=0.471) nor dementia diagnosis (β=0.251, SE=0.285, p=0.378). Higher CRP values were not associated with increased risk of dementia diagnosis (β=-0.073, SE=0.057, p=0.203). Further, the indirect pathway from alcohol to dementia diagnosis through CRP was not statistically significant (β=-0.022, SE=0.033, p=0.517). In addition, ApoE was neither a significant predictor of CRP values (β=-0.371, SE=0.436, p=0.396) nor a significant moderator (β=0.264, SE=0.985, p=0.789) of the relationship between alcohol use and CRP.

CHAPTER SEVEN: DISCUSSION

Cognitive Domains.

Primary findings from this study partially support initial hypotheses. Moderate alcohol use was broadly associated with better performance across cognitive measures at baseline, and these differences persisted over time with no significant differences in the rate of change in cognition. As hypothesized, number of years of education, medical burden, and marital status significantly predicted cognitive performance. More complex hypotheses, including CRP as a moderated mediator of the relationship between moderate drinking and cognitive functioning, however, were not supported.

Overall, results of the slope-intercept models produced a similar pattern across cognitive domains. In general, the slope-intercept models indicated that moderate alcohol use was significantly associated with better baseline performance, but did not have a significant effect on the rate of change over time in performance. Although moderate use did not have a significant effect on rate of change over time, the baseline effect of better performance associated with moderate use persisted throughout the observed period time. This indicates that there is a difference between the groups in cognitive performance over time. Further, it is likely that the divergence of cognitive functioning between these groups takes place at an earlier age than that captured by the available data.

The current findings support existing literature regarding the relationship between moderate alcohol use and cognitive functioning. More specifically, this study supports the association between moderate alcohol use and better cognitive functioning (Albert, 2003; Imhof et al., 2001; Lang et al., 2007). The current study also offers auxiliary evidence that expands upon the findings of past studies, particularly with regard to length of follow-up time and

comprehensiveness of the testing battery. Specifically, although Stott et al. (2008) found an association between moderate alcohol consumption and decrease in cognitive decline, they had a limited follow-up period of 3.2 years. Several previous studies utilized screening measures (i.e., MMSE, TICS) as assessments of cognitive functioning (Ganguli et al., 2005; Stampfer et al., 2005; Stott et al., 2008). The current study employed a neuropsychological battery, which encompassed several different cognitive domains by use of psychometrically valid and reliable instruments. With regard to classification of alcohol use, Ngandu et al. (2007) categorized those who drank less than once per month as 'infrequent' and those who drank more than once per month as 'frequent', which could cause ambiguity when interpreting results, particularly with respect to the amount that constitutes moderate drinking. As the current study followed the NIAAA Guidelines for moderate drinking, this facilitates interpretation of findings within the context of the broader healthcare literature.

Past research has also found that CRP typically circulates in low concentrations in healthy individuals (Stewart et al., 2002). When investigating CRP levels among a sample of abstainers, moderate drinkers, and high frequency drinkers, Stewart, Mainous, and Gilbert (2002) found that nondrinkers had the highest percentage of individuals with elevated CRP levels (31%) when compared to 21% of low to moderate frequency drinkers, and 18% of high frequency drinkers; indicating that alcohol consumption is associated with a decreased CRP levels. Further, Volpato et al. (2004) found that older adults who drank between 1 and 7 drinks had the lowest levels of CRP when compared with other participants who either abstained or consumed more than 7 drinks on a weekly basis.

The results of this study also contradict past findings, particularly those related to CRP and cognition.   Many studies have documented the link between lower CRP values and better

cognitive performance. However, when examining the fluency domain, this study found the opposite; that higher CRP values were associated with improved cognitive performance. More recent work examining the role of CRP in the very old (75 years and older) has examined the premise that elevated CRP levels, within this age group, may act as a protective factor surrounding cognitive decline. Lima and colleagues (2014) utilized a longitudinal sample of the Medical Research Council Cognitive Function and Ageing Study (CFAS) to investigate the relationship between CRP and cognitive performance over a 4-year period (266 participants, mean age 77 years). They found that increased levels of CRP were associated with a decreased risk of decline in cognitive performance; however, this relationship was only seen in those without an ApoE-4 allele. Further, Silverman et al. (2009) found that among a cognitively healthy sample of older adults, aged 75 years or older (mean age 85 years), elevated CRP values were positively associated with better performance on memory measures, for those without an ApoE-4 allele. However, Silverman and colleagues (2009) also found that elevated CRP values were modestly associated with comparably worse performance on measures of executive functioning. As the sample in the current study included older adults between the ages of 73.83 and 99.67 years of age, with a mean age of 82.47, it is possible that age played a factor in the relationship between CRP values and cognitive performance. Conflicting results of past studies regarding CRP and cognition suggest a complex relationship, and it is possible that the results of the current study may serve as an additional piece of evidence that higher CRP values within the older-old age group serve as a buffer with regard to cognitive abilities in later life. Future research may aim to further investigate the relationship between elevated CRP levels and cognitive functioning among individuals within the very old age group.

The findings of this portion of the current study extend our knowledge of the relationship

between alcohol use and cognitive performance in later life. As the population of older adults continues to grow, alcohol use among the elder population will likely increase in prevalence as well. Findings from this study may also serve to build upon existing empirical literature and provide additional support for a protective factor with regard to cognitive aging. In addition, results may also be utilized to provide supplementary empirically supported data with regard to the drinking guidelines for moderate use among older adults. However, based on the current state of the literature, it would be premature to correlate the findings of this study with an increased benefit for cognitive rehabilitation and/or maintenance.

Dementia Diagnosis.

The primary conclusion, when examining the effect of moderate alcohol use on dementia diagnosis, is that moderate users of alcohol develop dementia at lower rates, and later in life, than do abstinent older adults. This finding supported *a priori* hypotheses. The final logistic regression model, with control variables, explained 25.4% of the variance and classified 69.7% of cases correctly. Results that dementia risk was also significantly predicted by gender, age, education, and race are consistent with past findings (Huang et al., 2002; Hulse et al., 2005). In this sample, the median survival time for those who reported using alcohol moderately was about eight years longer than those who reported abstaining from alcohol use. As with analyses predicting cognitive domain performance, hypotheses identifying CRP as a moderated mediator of the relationship between moderate drinking and dementia risk were not supported. This model may have been more sensitive to the complex hypothesized effects had the subsample used for this portion of the analysis been larger. Other possible causes of poor fit include variable relationships between CRP and other variables throughout later life, mentioned above (Lima et al., 2014; Silverman et al., 2009).

Conclusions

     Taken together, results suggest that older adults who consume alcohol in moderate levels (1-14 drinks/week) have better global cognition than those who abstain from use, which also translates to lower dementia risk with later dementia onset. However, results do not support a mediating role of CRP in the relationship between moderate alcohol use and cognitive outcomes. The current findings build upon previous literature that has linked moderate alcohol with positive health outcomes in older age, including better cognitive performance and decreased risk of dementia (Albert, 2003; Huang et al., 2002; Hulse et al., 2005; Imhof et al., 2001; Lang et al., 2007; Marmot & Brunner, 1991).   The current study builds on these findings by utilizing a larger, more representative sample, with a longer follow-up time, which may provide additional insight as to the timing of the benefits associated with moderate use and positive health outcomes.

Directions for Future Research

     The current study hypothesized CRP as a potential biological mechanism by which the relationship between moderate alcohol use and cognitive functioning operates. However, results did not support for this hypothesis. Therefore, future research may aim to investigate additional biological mechanisms that could elucidate the relationship between moderate alcohol use and cognitive functioning in later life. As moderate alcohol consumption typically involves a social component, one potential moderating variable of interest may involve the level of social interaction experienced by older adults. Additionally, future research may also assess the likelihood by which moderate drinkers tend to also moderate additional lifestyle behaviors (i.e., diet, exercise, drug use, etc.) and the effect that this may have on subsequent cognitive performance. Future research may also look to further examine the relationship between

elevated CRP levels and cognitive functioning among individuals within the very old age group, as this appears to be a complex relationship that may be mediated by age.

In addition, as the current study found that moderate alcohol use was significantly associated with better baseline performance on cognitive measures, future studies may aim to investigate the effects of a change in pattern of consumption in later life (i.e., moderate consumer in midlife to abstainer in late life). Lastly, prospective studies may also examine a wider-ranging age group, in order to better assess the age at which the divergence of cognitive functioning between moderate users and abstainers may take place.

One of the limitations of this study includes the use of subjective data rather than objective data. While this method obtaining alcohol use data is subject to measurement error, it is standard in alcohol research as collecting objective measures of alcohol use, such as blood alcohol levels, can be difficult due to both time and cost considerations. In addition, self-report was used in order to calculate medical burden scores, in that participants either confirmed or denied the presence of physical disease(s). While there have been weaknesses associated with self-report measures, this is a common method in obtaining data among population-cased samples. A second limitation of the current study is the limited size of the sample. As a result, this also limited the statistical power that is needed for complex analyses, such as structural equation modeling. Further, the use of a moderated mediator tends to also require a significant amount of statistical power, and may have been underpowered due to the sample size limitation.

APPENDIX A: TABLES

Table 1*: Sample Characteristics for all ADAMS Participants.*

Variable	Total (n=856) M(SD)	Non-Drinkers (0 Drinks/Wk) (n=679) M(SD)	Moderate Drinkers (1-14 Drinks/Wk) (n=139) M(SD)
Age†	81.56(7.17)	82.03(7.12)	79.77(7.29)
Education (yrs)***	10.03(4.35)	9.53(4.30)	12.17(4.09)
Medical Burden*	7.08(3.673)	7.31(3.81)	5.98(2.96)
		Percentage of Sample	
Gender***			
Male	41.40	36.70	61.20
Female	58.60	63.10	38.80
Partnered***	38.90	35.60	53.20
Race***			
Caucasian	76.90	74.20	89.90
Other	23.10	25.80	10.10

*** *p≤0.001*

* *p≤0.05*

† n = 834

Table 2: *Fit Indices and Results for Slope-Intercept Models of moderate alcohol use on cognitive performance over time.*

	RMSEA	CFI	χ2	β (Slope)	β (Intercept)
Executive Function Domain					
Trails B	0.027	0.988	14.179	-0.581	-13.877
Symbol Digit Modalities	0.036	0.993	18.576	-0.034	3.108**
Fluency					
Animal Fluency	0.000	1.000	9.853	0.004	2.390***
COWA	0.049	0.984	28.213**	-0.243	3.441***
Digit Span	0.021	0.997	14.515	-0.093	1.344***
Visuospatial					
BVRT	0.000	1.000	8.555	0.010	0.422*
Constructional Praxis	0.018	0.997	13.107	-0.021	0.474**
Delayed Constructional Praxis	0.000	1.000	7.267	-0.051	0.783*
Memory					
WMS II	0.008	0.999	11.517	0.042	2.178**
FOME	0.000	1.000	9.323	-0.027	2.418**
Delayed Word List	0.000	1.000	7.292	-0.017	0.566*
Word List Recognition	0.000	1.000	7.852	-0.025	0.265

*** *p≤0.001*

***p≤0.01*

* *p≤0.05*

Table 3: *Exploratory Factor Analysis for Cognitive Domains*

Variable	Factor Loading	Eigenvalues
Executive Function Domain		1.639
Trails B	0.751	
Symbol Digit Modalities	0.759	
Fluency Domain		1.003
Animal Fluency	0.510	
COWA	0.776	
Digit Span	0.729	
Visuospatial Domain		1.074
BVRT	0.672	
Constructional Praxis	0.866	
Delayed Constructional Praxis	0.655	
Memory Domain		7.083
WMSII	0.810	
FOME	0.741	
Delayed Word List	0.677	
Word List Recognition	0.745	

Table 4: *Sample Characteristics for Participants with CRP & ApoE Data*

Variable	Total (n=250) M(SD)	Non-Drinkers (0 Drinks/Wk) (n=178) M(SD)	Moderate Drinkers (1-14 Drinks/Wk) (n=69) M(SD)
Age	82.47(5.45)	82.88(5.69)	81.59(4.64)
Education (years)***	11.11(4.14)	10.47(4.34)	12.65(3.09)
Medical Burden†	6.33(3.73)	6.51(3.91)	6.02(3.36)
CRP	2.77(2.34)	2.80(2.40)	2.53(2.06)
	Percentage of Sample		
Gender***			
Male	46.80	39.30	65.20
Female	53.20	60.70	34.80
Partnered*	50.30	44.50	63.30
Race**			
Caucasian	79.20	74.70	89.90
Other	20.80	25.30	10.10

*** $p \leq 0.001$

**$p \leq 0.01$

* $p \leq 0.05$

† n = 161

Table 5: *Dementia Sample Characteristics for Logistic Regression and Survival Analyses by Onset*

Variable	Total (n=856) M(SD)	Onset Occurred (n=407) M(SD)	No Onset (n=449) M(SD)
Age***	81.56(7.17)	84.54(7.04)	78.95(6.21)
Education (years)***	10.03(4.35)	9.32(4.44)	10.68(4.17)
		Percentage of Sample	
Gender***			
Male	41.40	32.20	49.70
Female	58.60	67.80	50.30
Race**			
Caucasian	76.90	73.00	80.40
Other	23.10	27.00	19.60
Alcohol Use***			
Abstained	83.00	90.40	76.40
Moderate Use	17.00	9.60	23.60

*** $p \leq 0.001$

**$p \leq 0.01$

* $p \leq 0.05$

Table 6: *Dementia Sample Characteristics for Logistic Regression and Survival Analyses by Alcohol Use*

Variable	Total (n=856)	Non-Drinkers (0 Drinks/Wk) (n=679)	Moderate Drinkers (1-14 Drinks/Wk) (n=139)
	M(SD)	M(SD)	M(SD)
Age***	81.56(7.17)	82.03(7.12)	79.77(7.29)
Education (years)***	10.03(4.35)	9.53(4.30)	12.17(4.09)
		Percentage of Sample	
Gender***			
Male	41.40	36.70	61.20
Female	58.60	63.30	38.80
Race***			
Caucasian	76.90	74.20	89.90
Other	23.10	25.80	10.10
Dementia Diagnosis***			
No Onset	52.50	48.70	73.40
Onset Occurred	47.50	51.30	26.60

*** $p \leq 0.001$

**$p \leq 0.01$

* $p \leq 0.05$

Table 7: *Results of Logistic Regression Predicting Dementia Onset (n=818)*

	β	*SE*	*Wald*	*Exp(β)*
Gender	-0.50	0.16	9.39**	0.61
Age	0.12	0.01	92.66***	1.13
Education (years)	-0.06	0.02	9.28**	0.94
Race	0.18	0.20	0.80	1.19
Alcohol Use	-0.68	0.23	8.61**	0.51

*** $p \leq 0.001$

**$p \leq 0.01$

* $p \leq 0.05$

APPENDIX B: FIGURES
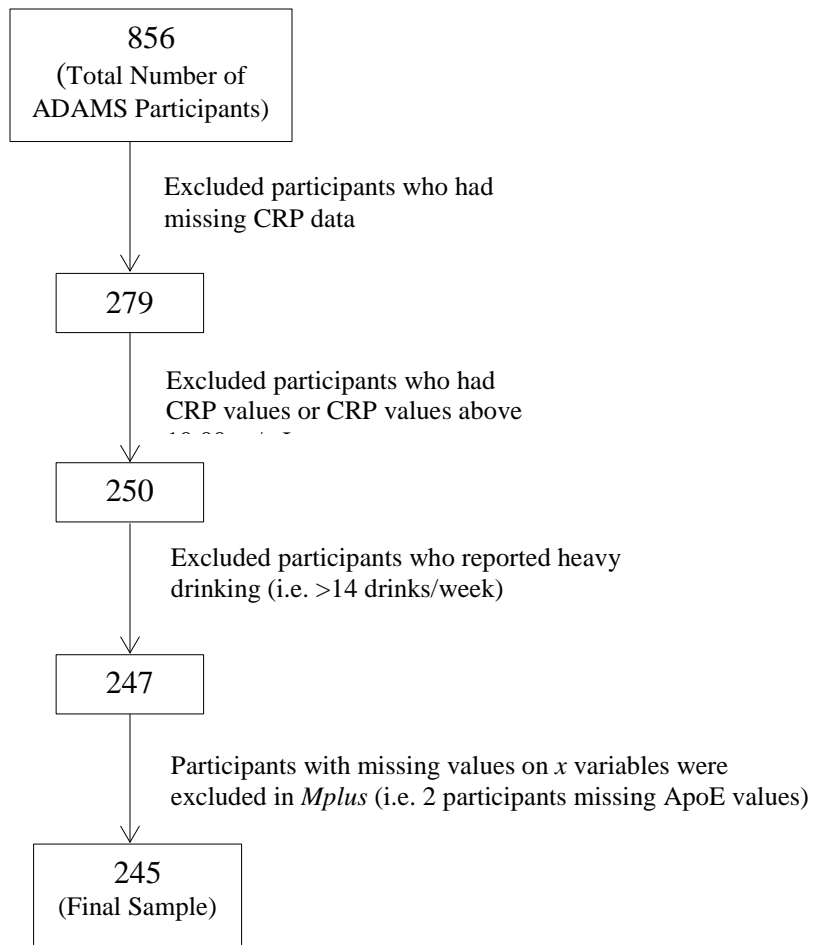
Figure 1: *Sample selection for participants with ApoE & CRP data.*
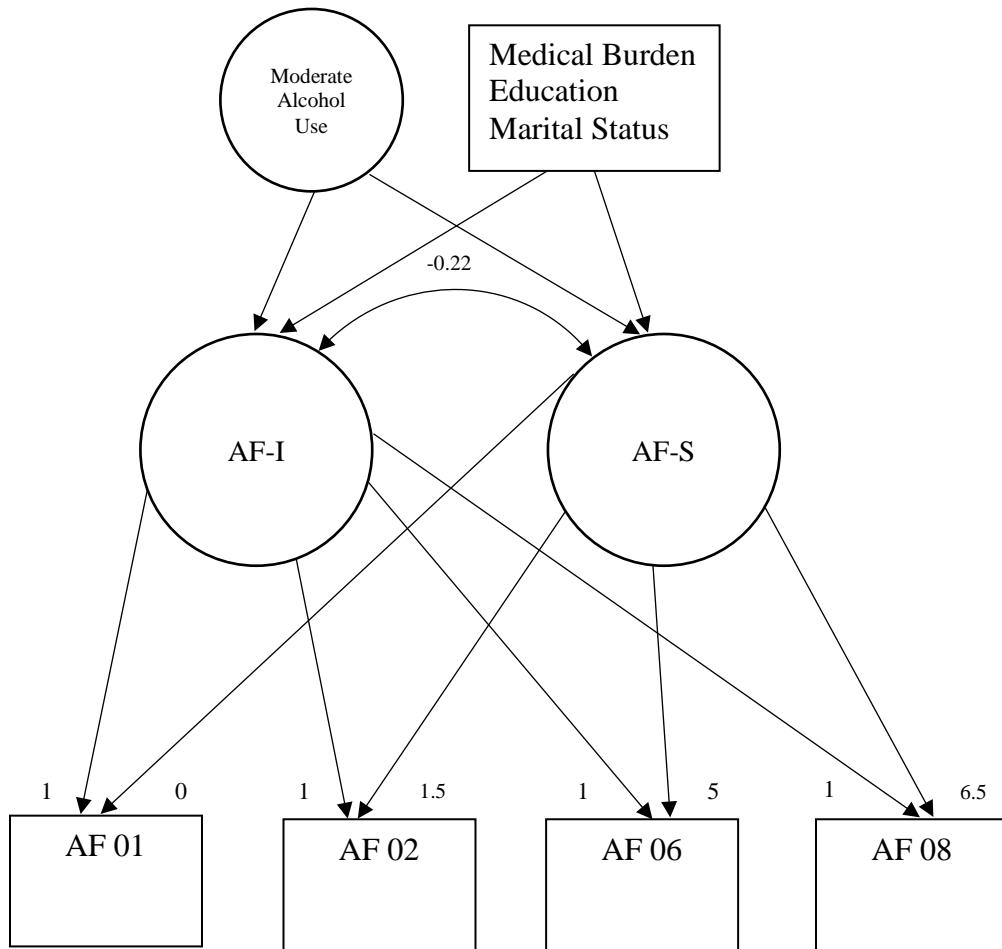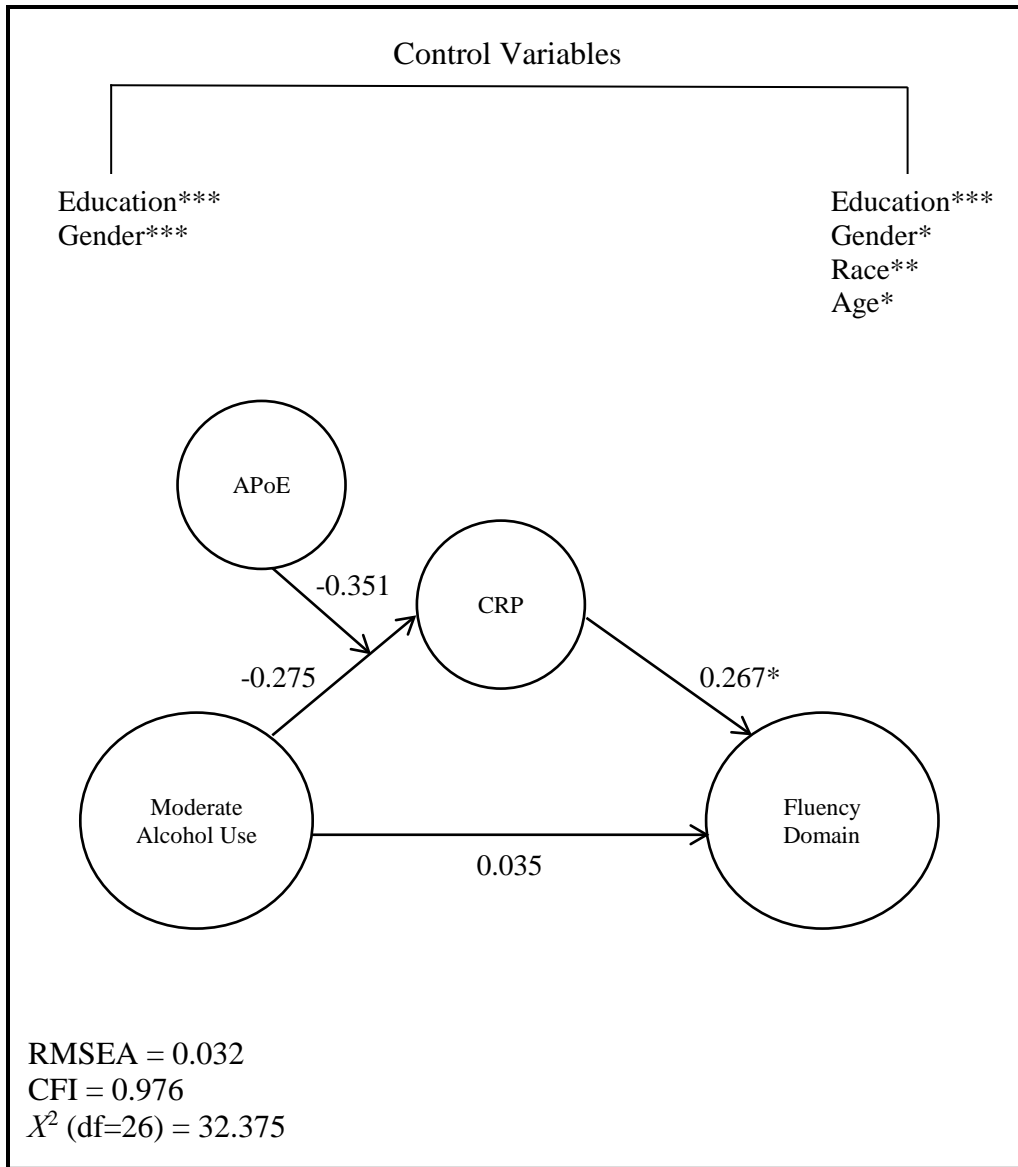
Figure 2: *Slope-Intercept Model for Animal Fluency (AF)*.

Figure 3: *Structural model depicting the relationship between moderate alcohol use, C-reactive protein, and the fluency domain.*

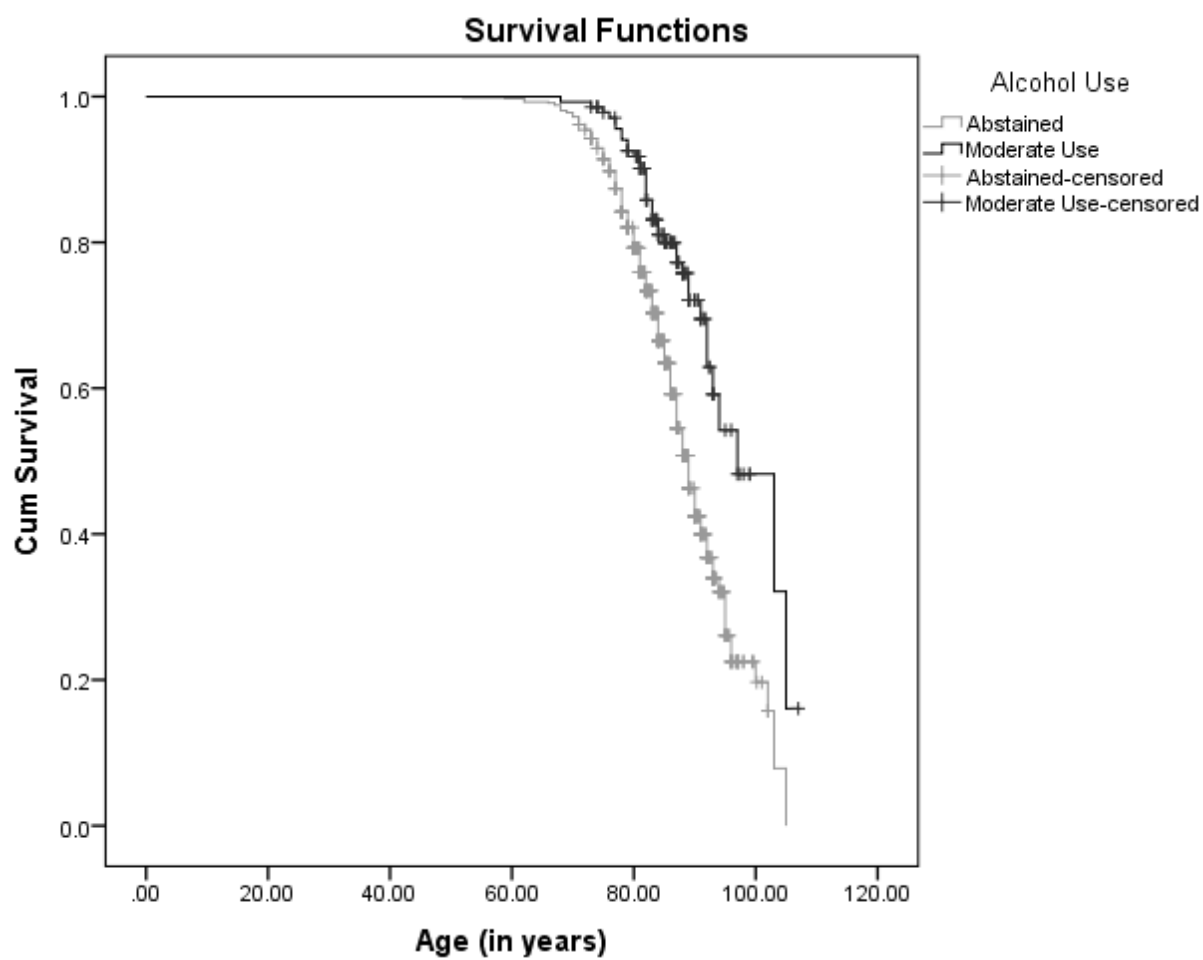*p≤0.05; **p≤0.01; ***p≤0.001; CRP=C-reactive protein; ApoE=Apolipoprotein-E

Figure 4: *Survival Analysis for Dementia Onset according to Alcohol Use.*

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