Alcohol use as a potential moderator of risk factors for Alzheimer’s disease

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Alcohol use as a potential moderator of risk factors for Alzheimer's disease

Abstract
Several genetic and non-genetic factors have been shown to increase the risk for developing Alzheimer's disease (AD). Alcohol consumption has been examined as one factor that may increase risk for AD in heavy drinkers and decrease risk for light to moderate drinkers. Given the potential interaction between alcohol use history and other risk factors, the current study evaluated the moderating effect of alcohol consumption on specific risk factors for AD, including history of hypertension, hyperlipidemia, type 2 diabetes, and presence of ApoE-e4 allele. In this cross-sectional study, participants included 299 community-dwelling older adults, aged 65-88, with possible or probable AD, who were enrolled as research subjects or clinical patients at an aging and Alzheimer's disease clinic. History of diabetes was significantly skewed and kurtotic and removed from the final analysis. Results indicated that certain sociodemographic factors were positively predictive of lower age of AD onset. History of hyperlipidemia was significant for predicting lower age of onset of AD, but could reflect an age-related finding. Alcohol use was shown to moderate the relationship between history of hypertension and age of onset of AD, suggesting that low to moderate alcohol use may serve as a protective factor for individuals with a history of hypertension. Future directions and limitations of study findings are also discussed.

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ALCOHOL USE AS A POTENTIAL MODERATOR OF RISK FACTORS FOR
ALZHEIMER’S DISEASE

A DISSERTATION

SUBMITTED TO THE FACULTY

OF

SCHOOL OF PROFESSIONAL PSYCHOLOGY

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JULIJA STELMOKAS

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Abstract

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Alzheimer’s disease (AD) is a neurodegenerative disorder that involves the deterioration of cognitive and functional abilities, along with changes in behavior and personality. Although significant advances have been made over the years with respect to early detection of symptoms, there is still no agreed upon cause, and the number of individuals diagnosed continues to increase (Alzheimer’s Association, 2013). In order to better understand AD progression and improve patient care, a number of risk factors have been identified. Certain factors such as age, gender, education, dementia severity and apolipoprotein E (ApoE) genotype and have been identified as predictors of cognitive decline and incident dementia, however, these results have been inconsistent across studies (Teri, McCurry, Edland, Kukull, & Larson, 1995; Lobo et al., 2010; Suh, Ju, Yeon, & Shah, 2004).

Alcohol consumption has been examined as a protective factor and also as a risk factor for cognitive decline and incident AD. When reporting alcohol consumption levels, most studies have grouped individuals as abstainers, mild or moderate drinkers, or heavy drinkers. Findings from community- and cohort-based studies have identified a u-shaped or j-shaped curvilinear relationship between alcohol consumption levels and cognitive functioning (Mukamal, Kuller, Fitzpatrick Longstreth, Mittleman, & Siscovick, 2003; Ruitenberg et al., 2002), implying that light to moderate drinking patterns may reduce the likelihood of developing AD. Recent prospective studies have further supported this association, with a decreased risk of AD for low and moderate drinkers (Weyere et al., 2011).

In addition, the relationship between a history of heavy drinking and age of onset of AD has also been of recent interest. Theoretically, it can be assumed that risk factors for AD may affect its progression and also cause earlier onset. In a recent study by Harwood et al. (2010), heavy alcohol drinkers were found to have a reduced age of onset of AD by 4 years compared to
non-heavy drinkers. Thus, differences in history of alcohol use may be associated with either increased or lower age during which symptoms of AD first occur.

Despite a number of studies indicating a relationship of alcohol consumption to AD, results have been inconsistent across studies. For example, a handful of studies have reported no association between alcohol consumption and AD (Hebert et al., 1992; Broe et al., 1998; Graves et al., 1991). However, these inconsistencies may be reflected by differences in methodology, such as how alcohol use is measured or length of follow-up assessment, as well as other direct and indirect effects that increase a person’s risk for cognitive decline. In addition, covariates (e.g., smoking, type 2 diabetes, or other vascular factors) are often adjusted to account for differences in outcome, and some studies may have over-adjusted for covariates that play an important role in the relationship between alcohol use and AD (Lobo et al., 2010; Mukamal et al., 2003; Anstey, Mack, & Cherbuin, 2009). Therefore, it is worthwhile to investigate how specific variables might place an individual at higher risk for AD, and how past alcohol use may moderate this relationship.

**Review of the Literature**

To better understand the potential moderating effects of alcohol consumption, it is important to first identify key risk factors associated with AD. In the following pages, a review of risk factors for late-onset AD will be presented, which may be distinguished from early-onset AD that is diagnosed before the age of 65 or 60, depending on the study, and is associated with a strong family history and, in about 10% of cases, a specific autosomal dominant mutation (Wingo, Lah, Levey, & Cutler, 2012). In addition, the role of alcohol as a risk factor and as a protective factor will be discussed, and the potential for past alcohol use to moderate the relationship between AD risk factors and age of onset of AD will be addressed.
Risk factors for AD

To date, it is still unclear as to why some individuals develop late-onset AD and others do not. Fortunately, numerous studies have examined how various factors contribute to the etiology of AD and increase a person’s risk for developing the disease. A number of sociodemographic variables, such as increased age, female sex, and lower education have been associated with an increased risk of AD (Mortimer & Graves, 1993; Gao, Hendrie, Hall, & Hui, 1998; Musicco, 2009; Letenneur et al., 1999). However, these factors have been explained (Hebert, Scherr, McCann, Beckett, & Evans, 2001; Stern et al., 1994) as largely due to differences in life expectancy or “cognitive reserve.” Therefore, it is important to evaluate the contribution of specific risk factors for AD within the context of an age-related or neurogenerative process.

Although the genetic influence on AD has been widely investigated, a single gene mutation has not yet been identified that causes late-onset AD. Rather, several lines of research have highlighted key neuropathological changes that may contribute to late-onset AD, including amyloid-beta deposits, oxidative stress, and inflammatory response (Serretti, Olgiatic, & De Ronchi, 2007). Of these, the ApoE gene found on chromosome 19 has been associated with risk of AD (Rocchi, Pelegrini, Siciliano, & Murri, 2003; National Institute on Aging, 2011). The three most common genetic alleles are ApoE-ε2, ApoE-ε3, and ApoE-ε4. In particular, the ApoE-ε4 isoform has been identified as one of the strongest genetic risk factors for late-onset AD (Farrer et al., 1997). Although the exact function of the ApoE-ε4 allele has not been clearly established, strong evidence suggests that it may involve the clearance of amyloid beta protein, one of the main components of amyloid plaques that are a hallmark of AD (Kim, Basak, & Holtzman, 2009).
The ApoE-ε4 allele has been associated with differences in the progression and incidence of AD. For instance, it has been related to a lower age of onset in a dose-dependent manner, with a greater effect when both alleles are of this type (Goldstein et al., 2001; Sando et al., 2008). In addition, the allele has been shown to be associated with a faster rate of cognitive decline for individuals with AD (Craft et al., 1998), specifically AD and not other forms of dementia, such as vascular dementia (VaD) (Burlinson, Burns, Mann, Pickering-Brown, & Owen, 1998).

Strong evidence supports the ApoE-ε4 allele as a genetic risk factor for AD. However, development of late-onset AD is not necessarily dependent on the presence of this genetic variation, and many individuals who are carriers of the allele do not develop the disease, and vice versa. Interestingly, the association of the allele with development of AD appears strongest before the age of 70 (Blacker et al., 1997) and may particularly affect individuals between the ages of 60-70 years of age (Davidson et al., 2007). Again, although the presence of the allele may lower the age of onset for individuals who develop AD (Khachaturian, Corcoran, Mayer, Zandi, & Breitner, 2004), not all carriers develop the disease. Thus, other factors may contribute to the lifetime susceptibility of AD.

Reviews of AD risk factors (Flicker, 2010; Chen, Lin, & Chen, 2009; Qiu, De Ronchi, & Fratiglioni, 2007) have often separated genetic or non-modifiable factors from environmental or modifiable factors. Of the modifiable risk factors associated with AD, strong associations have been found for hypertension, obesity, type 2 diabetes, heart disease, body mass index, cerebrovascular disease, hypercholesterolemia, alcohol consumption, and cigarette smoking, as well as diet and nutrition. Although many of these risk factors (e.g., heart disease, hypertension) are frequently observed in older age and may contribute to the development of AD (Rosendorff, Beeri & Silverman, 2007), other common pathways (e.g., inflammation, oxidative stress) may
also provide a causal link. In particular, cerebrovascular pathology is one potential mechanism by which these factors may contribute to incident AD.

Factors associated with cerebrovascular disease have often been associated with AD. Although VaD may share several cerebrovascular pathologies to AD, AD patients can exhibit a significant amount of cerebrovascular pathology, with some studies (e.g., Tabet, Quinn, & Klugman, 2008) reporting up to 89% of cerebrovascular disease in patients with mild to moderate AD. Furthermore, these findings along with other common vascular risk factors (e.g., diabetes, hypertension, hyperlipidemia), may contribute to the pathogenesis of AD. In a review of vascular factors affecting the incidence of late-onset AD, cerebrovascular factors such as hypertension, type 2 diabetes, smoking, and hypercholesterolemia have been cited as possible underlying mechanisms for AD (De Toledo Ferraz Alves et al., 2010), and further supported by evidence that vascular variables may contribute to cerebral atrophy and cognitive decline (Meyer et al., 1999, Li et al., 2011).

The variables discussed thus far play a significant part in the incidence of late-onset AD. Barnes and Yaffe (2001) estimated that several risk factors, including type 2 diabetes, smoking, and hypertension may be contributing factors in almost half of individuals diagnosed with AD. Research has now focused on the identification of modifiable risk factors that may be amenable to treatment and prevention (Cummings, Vinters, Cole & Khachaturian, 1998; Patterson et al., 2008). A review by Daviglus et al. (2011) examined the effects of modifiable factors and AD risk. Despite significant methodological differences across studies, results suggest that type 2 diabetes, hyperlipidemia, and smoking increase an individual’s risk for developing AD, while other variables such as diet, exercise, and light to moderate alcohol use may serve a more protective role. Thus, further research is needed to better understand how certain factors interact
and increase one’s risk for developing AD. Of the variables reviewed thus far, a history of hyperlipidemia, hypertension, and type 2 diabetes appear to be the strongest modifiable risk factors for late-onset AD and hold promise for future risk reduction through appropriate intervention.

**Modifiable risk factors.** Dysfunction in cholesterol metabolism has long been associated with the progression of AD. An essential component of cell membranes, cholesterol is thought to contribute to healthy neuronal development and functioning. A number of reviews (Lukiw, Pappolla, Pelaez, & Bazan, 2005; Reiss, 2005; Mathew, Yoshida, Maekawa, & Kumar, 2011) have suggested that dysfunction in cholesterol’s intracellular distribution and homeostasis may contribute to the pathogenesis of AD. For instance, hypercholesterolemia in AD individuals may be due to dysfunction in the transportation and excretion of cholesterol from the brain due to changes in the lipoprotein carrier ApoE and the synthesis of 24(S)-hydroxycholesterol. Although the exact mechanism between cholesterol and AD pathology is unknown, several lines of research have suggested that cholesterol may influence amyloid beta peptide production, aggregation, and clearance (Stefani & Liguri, 2009).

Measurement of brain plasma cholesterol is particularly challenging given its high concentration of myelin and separation by the blood-brain barrier. As a result, much of the research surrounding the effects of hypercholesterolemia in AD has been derived from indirect evidence, including animal and cellular models of AD (Puglielli, Tanzi, & Kovacs, 2003). In one animal model, adult rats that were fed a cholesterol-rich diet for five months showed impaired memory performance as well as a number of AD-related histopathological changes, including cholinergic and acetylcholine dysfunction and an increased inflammatory response (Ullrich, Pirchl, & Humpel, 2010). Additional evidence linking AD to hypercholesterolemia comes from
studies investigating the use of statin medications. For instance, in cultured hippocampal neurons, statins have been shown to reduce the amount of cholesterol and inhibit formation of amyloid beta proteins (Simons, Keller, De Stropper, Beyreuther, Dotti, & Simons, 1998).

Results from prospective studies investigating the effects of cholesterol in AD have been mixed. A large, case-control study (Green et al., 2006) suggested that past use of statin medication significantly lowered AD risk, even after controlling for several confounding variables such as ApoE genotype. However, results have been inconsistent across clinical trials (Shepardson, Shankar, & Selkoe, 2011) and may be influenced by a number of confounding variables (e.g., blood brain barrier permeability, statin type). In a review and meta-analysis of total serum cholesterol levels and risk of dementia (Anstey, Lipnicki & Low, 2008), high midlife total cholesterol level was associated with increased risk for AD. However, the generalizability of this study is limited, given that only a total of eight studies met inclusion criteria. Additional longitudinal studies investigating the age-dependent association of total cholesterol and incident AD have varied, with some reporting an increased risk of AD for those with midlife elevated total cholesterol (Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009) and others reporting a lack of association (Mielke et al., 2010). Results suggest that total cholesterol may vary across the lifespan, and therefore other genetic and/or environmental factors may contribute to the risk of developing AD.

Hypertension has also been investigated as a potential risk factor AD. With increased age, hypertension is quite common and often inadequately controlled (Lloyd-Jones, Evans, & Levy, 2005). Changes in blood pressure and history of hypertension have been linked to AD-related vascular pathology, including amyloid angiopathy, microvascular degeneration, blood-brain barrier dysfunction, and white matter lesions (Jellinger, 2002; Connelly, Prentice, &
Fowler, 2005). However, the relative mechanism and contribution of hypertension and related cerebrovascular disease to incident AD has not been firmly established.

Although hypertension has been associated with AD-related cerebropathology, studies investigating the effects of hypertension and incident AD have been inconsistent. A review and meta-analysis of prospective cohort studies investigating the association between hypertension and risk of AD (Power et al., 2011) found variability across studies, and overall history of hypertension was not related to increased risk for AD. However, results indicated a temporal relationship, such that people may be at risk for AD when there is a history of high blood pressure before the age of 65, and decreased risk when there is a history of late-life hypertension.

However, the temporal relationship between blood pressure fluctuations and development or progression of AD remains unknown. Some researchers (e.g., Kuyumcu et al., 2012) have suggested that low blood pressure may be the result of AD, and cerebral hypoperfusion may contribute to disease progression. On the other hand, a longitudinal study (Skoog et al., 1996) found that individuals with increased blood pressure at 70 years of age were at elevated risk for developing AD 10-15 years later. Notably, several fluctuations in blood pressure were measured across the study period and the relationship between low blood pressure and AD may be due to a cross-sectional analysis that may not be capturing the extent of blood pressure changes. Although blood pressure may fluctuate throughout the aging process, longitudinal studies suggest that a history of hypertension may nonetheless place an individual at risk for development of AD.

Type 2 diabetes has also been associated with AD. A complex metabolic disorder, type 2 diabetes can result in vascular changes in both peripheral (PNS) and central nervous systems (CNS). Some studies have suggested a potential underlying mechanism between type 2 diabetes and AD (Umegaki, 2010; Li & Holscher, 2007) due to a number of similarities between the two
diseases, including increased prevalence in older age and associated cognitive impairment. Although the effect of type 2 diabetes on the CNS has not been well defined, it may contribute to AD through chronic inflammation and dysfunction in key reparative processes in the brain (Taguchi, 2009). Type 2 diabetes is associated with hyperinsulinemia and insulin resistance, which along with impaired insulin signaling, may be associated with amyloid beta and tau metabolism and expression (Sims-Robinson, Kim, Rosko, & Feldman, 2010; Biessels & Kappelle, 2005). Thus, there may be a number of similar metabolic pathways that contribute to cognitive impairment in both type 2 diabetes and AD.

Individuals with type 2 diabetes have displayed a variety of cognitive impairments compared to individuals without the disorder. In a systematic review of prospective studies investigating the association between type 2 diabetes and cognitive functioning (Cukierman, Gerstein, & Williamson, 2005), individuals with type 2 diabetes were shown to have a greater rate of cognitive decline, particularly in the domain of perceptual speed. Differences in cognitive functioning have also been related to risk of AD, particularly for individuals with type 2 diabetes. Functional neuroimaging of individuals with and without type 2 diabetes has also suggested differences in cognitive functioning. Additionally, Hirao et al. (2011) found significantly decreased regional cerebral blood flow in more widespread regions for individuals with type 2 diabetes who also had a diagnosis of AD. Although no clear pattern of cognitive impairment has been indicated, results from these studies suggest that individuals with type 2 diabetes display differences in cognitive functioning that may also increase risk for developing AD.

Longitudinal studies investigating type 2 diabetes and increased risk of AD have provided mixed results. Some research has indicated that type 2 diabetes is not an independent
risk factor for AD (Akomolafe et al., 2006), and others have even suggested that it may slow progression of the disease (Musicco et al., 2009). However, results from a large, prospective study suggests that type 2 diabetes may increase the risk of AD (Cheng, Noble, Tang, Schupf, Mayeux, & Luchsinger, 2011). Furthermore, the relationship between type 2 diabetes and AD may be magnified when the ApoE-ε4 genotype is present (Peila, Rodriguez & Launer, 2002; Irie et al., 2008). Therefore, although certain risk factors such as type 2 diabetes may place an individual at increased risk for AD, additional attention should be paid towards other factors that may moderate this relationship.

**Alcohol as both a risk and a protective factor.** Alcohol use has also been indicated as a risk factor for the development of AD. In general, alcohol use is related to widespread changes in both PNS and CNS metabolism (Altura, Altura, Zhange & Zakhari, 1996), often exerting a depressant effect and decreasing overall glucose metabolism in the brain with immediate intoxication (Volkow et al., 2008). The effects of alcohol consumption share a number of commonalities with the development of AD, suggesting a possible underlying mechanism. Tyas (2001) highlighted that heavy or chronic drinking may be associated with brain atrophy and both may reduce cholinergic neurons. However, the effects of alcohol may be reversible, especially with increased abstinence (Bartels et al., 2006), which is not the case for AD.

Although alcohol can have deleterious effects on the brain, consumption in lower quantities may be beneficial. Past studies have identified a u-shaped or j-shape curve associated with alcohol use and development of AD (Mukamal et al., 2003), suggesting that light to moderate alcohol may reduce the risk of AD in older adults. In a review of the beneficial effects of alcohol use, Collins et al. (2009) indicated that low to moderate consumption of a variety of alcoholic beverages (e.g., wine, beer, spirits) might serve a neuroprotective role. For example,
recent studies have shown that low concentrations of alcohol may protect neurons against toxic damage from amyloid-beta and alpha-synuclein (Bate & Williams, 2011). Others have postulated that AD may be the result of a neuroinflammatory process (Akiyama et al., 2000) and moderate alcohol use may serve an anti-inflammatory role, deterring development of the disease (Imhof, Froehlich, Brenner, Boeing, Pepys, & Koenig, 2001).

Despite noteworthy neuropharmacological research, the association between the effects of alcohol and development of AD across epidemiologic studies has been inconclusive. In a review of the effects of alcohol consumption, cognitive functioning, and dementia, Panza et al. (2009) highlighted a number of studies that provided contrasting evidence regarding alcohol use as a protective factor for AD. This review also brought attention to the significant variability in study outcomes, with some studies identifying a link between alcohol use and AD, while others did not.

Several meta-analyses have explored the contrasting evidence regarding alcohol consumption and risk of AD. In general, these studies (e.g., Peters, Peters, Warner, Beckett, & Bulpitt, 2008) all found a relationship between low to moderate alcohol use and lower risk of cognitive decline. Neafsey and Collins (2011) conducted a large review and meta-analysis of studies investigating the relationship between moderate alcohol consumption and cognitive functioning. Two phases or “eras” of research were highlighted, including an initial period before 1997 that involved assessment of mainly young and middle aged adults and another period after 1997 that involved mental status examinations of mostly older adults. In the initial era, most studies found a relationship between a history of heavy drinking and cognitive impairment, but low or moderate alcohol use was not associated with performance on cognitive tasks. Approximately 80% of the studies reviewed took place in the second phase, and a meta-
analysis of these studies revealed that, compared to abstainers, moderate drinkers had a decreased risk of AD. Across studies, adjustment for several confounding variables such as age, education, sex, and smoking did not change these results, although adjustment for ApoE-ε4 allele resulted in a non-significant relationship. Therefore other factors may influence the relationship between moderate alcohol use and risk of AD.

Although meta-analyses have been helpful in examining the variability in results across studies of alcohol consumption and development of AD, a number of limitations remain. For example, comprehensive reviews and meta-analyses often report a significant amount of heterogeneity across studies, limiting generalizability of results. In both meta-analyses discussed (Neafsey et al., 2011; Peters et al., 2008) differences in study outcomes may have been influenced not only by methodological limitations, but also by genetic and non-genetic factors that may not have been considered. And, even when certain confounding variables are examined (e.g., ApoE-ε4 allele), there may not be enough evidence to support a relationship between alcohol use and risk of AD. Thus, further examination of risk factors is needed. Particular attention should be paid towards genetic and non-genetic factors that may interact with alcohol use and development of AD.

In sum, a variety of risk factors have been identified for AD. Many of these variables are purported to share common pathologic mechanisms (Martins et al., 2006) and interact with one another to influence the development of AD. For instance, factors such as type 2 diabetes, hyperlipidemia, and hypertension all affect the vascular system. Moreover, the presence of key sociodemographic differences (e.g., age, sex) interact with these risk factors (Jarvik, Wijsman, Kukull, Schellenberg, Yu, & Larson, 1995). However, despite a plethora of evidence relating
several risk factors to AD, the mechanism by which these factors interact and increase an individual’s risk for developing the disorder is still unknown.

Some evidence suggests that certain variables may moderate the relationship between other risk factors and AD. For example, the presence of the ApoE-ε4 allele has been shown to increase cognitive decline and dementia in the context of other vascular factors, including high blood pressure and type 2 diabetes (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Irie et al., 2008). When examined in the context of heavy alcohol consumption (i.e. greater than 2 drinks per day), ApoE-ε4 allele further increases the risk of AD at a lower age (Harwood et al., 2010). Although results from this study provided evidence that a history of heavy drinking may accelerate the disease process, there was no investigation of risk associated with low or moderate drinking. Therefore, additional research is needed to better understand how differences in alcohol consumption patterns serve as a potential moderator variable in the development of AD.

Alcohol consumption as a moderator variable. Although heavy drinking has often been associated with increased risk of AD, recent data suggests that low to moderate alcohol consumption may actually decrease risk. Given that a variety of genetic and non-genetic factors may interact with alcohol consumption (Sinforiani et al., 2011), it is possible that alcohol’s effects may interact with other risk factors to moderate the development of AD. Several studies have investigated how specific vascular factors relate to alcohol consumption patterns as well as risk of AD. Type 2 diabetes and hypertension have often been linked to alcohol consumption patterns. For example, a history of heavy drinking increases the risk for hypertension (Saremi et al., 2003), and a meta-analysis of randomized controlled trials reported that a reduction in alcohol use might reduce systolic and diastolic blood pressure (Xin et al., 2001). Moderate alcohol consumption also has been associated with a lowered risk of developing type 2 diabetes
It is therefore possible that alcohol consumption patterns may moderate the relationship between other risk factors such as hypertension and type 2 diabetes and risk for the development of AD.

Additional evidence that alcohol consumption may act as a moderating variable has arisen from studies adjusting for specific covariates. Although study variables are often controlled in order to account for differences in outcome, some (e.g., ApoE-ε4 allele, type 2 diabetes, other vascular factors) may interact with alcohol consumption as part of a causal relationship that influences the development of AD. A recent meta-analysis (Anstey et al., 2009) of prospective studies of alcohol use, cognitive decline, and dementia found that a history of light to moderate drinking was associated with a 25% reduced risk of incident AD. Notably, several studies adjusted for covariates, and in some cases, this adjustment increased the effect size.

Upon closer examination of studies that adjust for covariates, there was significant heterogeneity in terms of methodology and adjusted analyses. For example, some (e.g., Espeland et al., 2004) combined covariates for adjustment analyses, which may have overshadowed the impact of specific variables on alcohol consumption and AD. A prospective study by Deng et al. (2006) found significant differences at baseline between alcohol consumption and a number of confounding variables (e.g., blood pressure, stroke, smoking, age, gender). Although there was no follow-up data collected, baseline differences between drinking patterns and other risk factors may have affected the relationship between risk factors and the development of AD. Therefore, examination of the interaction between specific, individual covariates is necessary to address the possible moderating role of alcohol consumption.
Additional prospective studies of incident AD suggest that specific covariates may interact with various alcohol consumption patterns. Mukamal et al. (2003) found that mild-moderate drinking (i.e., 1-6 drinks per week) was related to a decreased risk of dementia overall, including AD. Sensitivity analyses indicated that, for moderate-heavy drinkers (i.e., 7-13 drinks per week), cholesterol and fibrinogen levels (a plasma glycoprotein associated with cerebrovascular disease and inflammation at high concentration) accounted for approximately 16% lower risk of dementia; presence of the ApoE-ε4 genotype appeared to moderate this association, especially for heavy drinkers (i.e., greater than 14 drinks per week). An additional prospective study further confirmed the relationship between ApoE-ε4 allele, alcohol consumption, and risk of AD (Luschinger, Tang, Siddiqui, Shea, & Mayeux, 2004), suggesting that the protective role of moderate alcohol use may be confined to individuals without the ApoE-ε4 genotype. Other possible covariates, including type 2 diabetes and hypertension, did not appear to modify the relationship between alcohol use and incident AD. However, the sample may have lacked sufficient numbers of heavy and moderate drinkers, which may have obscured this association.

Overall, a number of genetic and environmental risk factors may interact to influence the development of AD. Lower age of onset of the disease has been strongly related to genetic susceptibility (i.e., the presence of the ApoE-ε4 allele). However, other risk factors including a history of heavy drinking may also contribute to a lower age of onset (Rao et al., 1995).
Conclusion and Purpose of Current Study

In sum, there is a large body of evidence to suggest that the presence of the ApoE-ε4 allele, as well as history of hypertension, hyperlipidemia, and type 2 diabetes, increase an individual’s risk for developing AD. Although a history of heavy drinking is also known to be a risk factor, recent evidence suggests that alcohol at low or moderate doses may serve a protective function. Of the numerous studies that have investigated the association between alcohol consumption and onset of AD, studies overall have been limited by differences in methodology and differences in how alcohol consumption patterns and cognitive decline are assessed, as well as low sample sizes. In addition, much heterogeneity across studies may stem from the interaction of other risk factors that influence the development of AD. Often, these risk factors are adjusted for in analyses, however they may also have an important part in the development of AD. Low to moderate rates of alcohol consumption may serve as a protective factor by slowing age of onset of AD, while higher rates of consumption may increase risk. Few studies have specifically evaluated differences in alcohol consumption patterns in moderating the relationship between other risk factors and AD. Therefore, the purpose of the current study is to examine how past alcohol use interacts with other known risk factors (e.g., type 2 diabetes, ApoE-ε4 allele, hyperlipidemia, and hypertension) in the development and age of onset of AD.

Statement of the Hypotheses

**Hypothesis 1.** A positive past history of type 2 diabetes, hypertension, hyperlipidemia, and presence of ApoE-ε4 allele are expected to be positively associated with risk of AD. In particular, persons with a history of these risk factors are expected to have a significantly lower age of onset of AD compared to those without these risk factors.
Hypothesis 2. It is expected that history of alcohol use will moderate the relationships between individual risk factors and age of onset of AD, such that a history of type 2 diabetes, hypertension, hyperlipidemia, or presence of ApoE-ε4 allele will be more strongly related to a lower age of onset of AD when there is history of heavy alcohol use than when there is a history of low/moderate alcohol use.

Method

Participants and Setting

Participants were community-dwelling older adults already enrolled as either subjects in longitudinal study of aging or as patients at the Layton Aging and Alzheimer’s Disease Center at Oregon Health and Science University located in Portland, Oregon. Study data was collected from an existing database of participants’ visits. For a detailed description of the collection and storage of study data, see Morris et al. (2006) and Beekly et al. (2007). Data from participants were included in the present study if they met the following criteria: aged 65-88 with a diagnosis of possible AD or probable AD, and availability of the following information in the dataset: age of onset of AD, ApoE-ε4 allele type, history of type 2 diabetes, hypertension, and hyperlipidemia, smoking, and past alcohol use. From the database, a total of 307 individuals met inclusion criteria. A total of 173 females (56.4%) and 134 males (43.6%) composed this sample. Average participant age at baseline was 77.42 (SD = 6.55). The majority of participants identified as being Caucasian (95.7%), while 4% reported being African-American/Black and 0.3% reported being Asian. Most individuals (70%) reported completing 12 to 16 years of education, while 18.9% reported completing greater than 16 years and 11.1% reported completing less than 12 years of education.
Research Design and Procedure. The study was approved by OHSU and Pacific University’s institutional review boards prior to requesting data variables. Following approval, the following variables were requested:

Demographic information and covariates. Participant’s age (65-88 years of age), gender (coded as 0 = male, 1 = female), race (coded as 1 = Caucasian, 2 = Black/African American, 3 = Asian), and level of educational achievement were collected from the database. Past history of smoking (coded as 0 = negative history, 1 = positive history) and number of head injuries were collected as covariates.

Predictor and outcome variables. Presence of ApoE-ε4 allele, as well as history of type 2 diabetes, hypertension, and hyperlipidemia were collected as predictor variables. Age of onset of AD, when present, was collected as the outcome variable. Alcohol use history was collected from a visit summary in which the participant or collateral source (e.g., a caretaker) was asked to describe the participant’s past alcohol use. The Alcohol Use Disorders Identification Test (AUDIT-QF) is a measure that assesses quantity and frequency of alcohol use, and is comprised of the following questions: how often do you have a drink containing alcohol and how many drinks do you have on a typical day when you are drinking? The AUDIT-QF was used for the current study to categorize the patient’s self-report of alcohol use from clinic visits. Therefore, the initial data from the patient’s clinic visit describing alcohol use history was coded and transformed as a continuous variable based on this measure. Total scores range from 0-8, with heavy drinking classified by scores greater than 4 points (Aalto, Tuunanen, Silanaukee, & Seppa, 2006) and light/moderate drinking classified by scores ranging from 1-3 points. Non-drinkers had 0 points.
Results

Data Cleaning

Before analyzing the data, each of the variable’s compliance with univariate and multivariate assumptions was examined using SPSS 18.0 (SPSS Inc., 2009). A total of 336 datasets from the initial database had the available demographic, predictor and outcome variables; however, 29 datasets had incomplete or limited alcohol use history and these were removed from analysis. The Mahalanobis distance test was conducted to assess for multivariate outliers. Using a conservative cut-off of $p < 0.001$, 8 outliers were detected and these datasets also were removed from the sample. This resulted in a final sample of 299 (see Table 1 for demographic information of excluded participants and Table 2 for the demographic information of the final sample). Upon inspection of the distribution of scores of the final sample, history of diabetes and number of head injuries were significantly skewed and kurtotic; therefore, these two variables were excluded from the final analysis. In all, the total number of datasets in which the patient had a history of diabetes was 22, and the total number of datasets in which the patient had a history of head injury was 47 (41 with at least 1 head injury and 6 with at least 2 head injuries).

Table 1

Demographic Characteristics of the Participants Excluded ($N = 37$)

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>n</th>
<th>Age (SD)</th>
<th>Sex</th>
<th>Race</th>
<th>Education (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient Information about Past Alcohol Use</td>
<td>29</td>
<td>75.71 (6.32)</td>
<td>10 Males</td>
<td>34 White</td>
<td>4 (&lt;12)</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td></td>
<td>19 Females</td>
<td>3 Black</td>
<td>10 (12-16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 Asian</td>
<td>5 (&gt;16)</td>
</tr>
<tr>
<td>Outliers</td>
<td>8</td>
<td>75.16 (6.77)</td>
<td>3 Males</td>
<td>5 White</td>
<td>1 (&lt;12)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td>5 Females</td>
<td>2 Black</td>
<td>5 (12-16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Asian</td>
<td>2 (&gt;16)</td>
</tr>
</tbody>
</table>
Table 2

_Demographic Characteristics of the Final Sample (N = 299)_

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Range</th>
<th>Median</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>299 (100)</td>
<td>23</td>
<td>77.60</td>
<td>77.43 (6.55)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131 (43.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>168 (56.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>290 (97.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American/Black</td>
<td>9 (3.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>33 (11.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-16</td>
<td>211 (70.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;16</td>
<td>55 (18.39)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Distribution of Variables and Descriptive Statistics_

Descriptive statistics, including the mean and standard deviation for age of onset of AD, as well as frequency of alcohol use and additional variables, are provided in Table 3.
Table 3

Means, Standard Deviation, Frequency, Skewness, and Kurtosis by Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Frequency (%)</th>
<th>Skewness (SE)</th>
<th>Kurtosis (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age AD*</td>
<td>78.408 (6.90)</td>
<td>-.157 (.141)</td>
<td>0.143 (0.141)</td>
<td>-1.19 (0.281)</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>125 (41.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>147 (49.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>27 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.292 (0.141)</td>
<td>-1.928 (0.281)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>128 (42.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>171 (57.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>1.426 (0.141)</td>
<td>0.034 (0.281)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (21.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>236 (78.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE4</td>
<td></td>
<td>0.155 (0.141)</td>
<td>-1.989 (0.281)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>138 (46.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>161 (53.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>-0.39 (0.141)</td>
<td>-1.86 (0.281)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>178 (59.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>121 (40.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Age AD = Age at AD diagnosis.

A hierarchical multiple regression analysis was performed; results are provided in Table 4. Demographic variables and covariates were added at step one. Together, the total effect was statistically significant and contributed to unique variance in the model ($\Delta R^2 = .922$, $p < 0.00$). However, when examined individually, only male sex ($\beta = 0.038$, and $p = 0.03$), age at baseline ($\beta = 0.963$ and $p < 0.00$), and years of education ($\beta = 0.963$ and $p < 0.011$) were significant positive predictors for age of onset of AD. Risk factors were added at step two. The total effect was statistically significant and contributed to an additional .07% of unique variance in the model ($\Delta R^2 = .007$, $p < 0.00$). Of the risk factors, alcohol use history ($\beta = 0.040$ and $p = 0.019$) and hyperlipidemia ($\beta = 0.068$ and $p < 0.00$) were significant positive predictors of age of onset of AD. However, other risk factors (i.e., hypertension, ApoE-ε4 allele) did not predict age of
onset of AD. Alcohol use history x risk factors was added at step three. Together, these interactions were statistically significant and accounted for an additional 0.03% of the variance in age of onset of AD (ΔR^2 = .003, p < 0.005). When each interaction was examined individually, hypertension and alcohol use history were statistically significant and positively predictive of age of onset of AD (β = 0.078 and p < 0.005). There were no additional statistically significant interactions.

In order to evaluate the interaction between history of hypertension and alcohol use, a simple slope analysis was used to plot age of onset of AD regressed onto hypertension at high (+1 SD) and low (-1SD) values of alcohol use history (see Figure 1). A statistically significant relationship was found between age of onset of AD and history of high alcohol use (β = 4.55, t = 4.16, p <0.00), whereas there was no statistically significant relationship between age of onset of AD and history of low alcohol use (β = 1.22, t = 1.12, p = 0.27).

Overall, results indicate that sex and age at baseline were significantly predictive of age of AD onset in the context of several risk factors for AD. Although level of education was positively predictive of AD onset, it was non-significant after additional risk factors were considered. Alcohol use history was also significantly predictive of age of AD onset when additional risk factors were included (step 2), but was not significant once the interaction between alcohol use and risk factors were considered (step 3). With regards to the first hypothesis, only history of hyperlipidemia was positively predictive of age of onset of AD. No other risk factors were associated with age of onset of AD. With regards to the second hypothesis, alcohol use history moderated the relationship between history of hypertension and age of AD onset. There were no additional significant moderating effects.
Table 4

Regression Analysis Predicting Age of AD Diagnosis from Alcohol Use, Hypertension, Hyperlipidemia, ApoE-ε4 allele, Smoking, and Demographic Variables

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>ΔR^2</th>
<th>FΔ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.962</td>
<td>0.921</td>
<td>678.436</td>
<td>0.000</td>
</tr>
<tr>
<td>Race</td>
<td>0.017</td>
<td></td>
<td></td>
<td>0.304</td>
</tr>
<tr>
<td>Sex</td>
<td>0.038</td>
<td></td>
<td></td>
<td>0.030</td>
</tr>
<tr>
<td>Education</td>
<td>0.044</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.014</td>
<td></td>
<td></td>
<td>0.412</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td>0.007</td>
<td>6.646</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>0.963</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Race</td>
<td>0.013</td>
<td></td>
<td></td>
<td>0.412</td>
</tr>
<tr>
<td>Sex</td>
<td>0.037</td>
<td></td>
<td></td>
<td>0.032</td>
</tr>
<tr>
<td>Education</td>
<td>0.028</td>
<td></td>
<td></td>
<td>0.095</td>
</tr>
<tr>
<td>History Smoking</td>
<td>-0.003</td>
<td></td>
<td></td>
<td>0.866</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>0.040</td>
<td></td>
<td></td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.016</td>
<td></td>
<td></td>
<td>0.333</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.069</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>APOE4</td>
<td>-0.011</td>
<td></td>
<td></td>
<td>0.502</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td>0.003</td>
<td>4.367</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>0.959</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Race</td>
<td>0.014</td>
<td></td>
<td></td>
<td>0.375</td>
</tr>
<tr>
<td>Sex</td>
<td>0.040</td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>Education</td>
<td>0.028</td>
<td></td>
<td></td>
<td>0.088</td>
</tr>
<tr>
<td>History Smoking</td>
<td>-0.002</td>
<td></td>
<td></td>
<td>0.897</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>0.008</td>
<td></td>
<td></td>
<td>0.779</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.032</td>
<td></td>
<td></td>
<td>0.180</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.051</td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>APOE4</td>
<td>0.009</td>
<td></td>
<td></td>
<td>0.697</td>
</tr>
<tr>
<td>Alcohol x Hypertension</td>
<td>0.080</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Alcohol x Hyperlipidemia</td>
<td>0.032</td>
<td></td>
<td></td>
<td>0.217</td>
</tr>
<tr>
<td>Alcohol x APOE4</td>
<td>-0.035</td>
<td></td>
<td></td>
<td>0.195</td>
</tr>
</tbody>
</table>
Table 5 provides zero-order (bivariate) correlations between variables. Age at baseline was negatively correlated with education ($r = -0.150, p = .009$) and presence of ApoE-$\varepsilon 4$ allele ($r = -0.195, p = 0.001$), and positively correlated with age of onset of AD ($r = 0.956, p = 0.000$) and hypertension ($r = 0.193, p = 0.001$). Male sex was negatively correlated with history of smoking ($r = -0.261, p < 0.000$) and alcohol use history ($r = -0.164, p = 0.004$). Years of education was negatively correlated with male sex ($r = -0.210, p < 0.000$) and positively correlated with alcohol use history ($r = 0.206, p <0.000$). History of smoking was positively correlated with alcohol use history ($r= 0.262, p < 0.000$). Age of onset of AD was positively correlated with history of hypertension ($r = 0.219, p < 0.000$) and negatively correlated with presence of ApoE-$\varepsilon 4$ allele ($r = -0.204, p < 0.000$).

Table 5
Intercorrelations Between Variables

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Education</th>
<th>Smoking</th>
<th>Age AD</th>
<th>Alcohol Use</th>
<th>HN</th>
<th>HL</th>
<th>APOE4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.065</td>
<td>-0.042</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>-0.150**</td>
<td>-0.089</td>
<td>-0.210**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.015</td>
<td>-0.014</td>
<td>-0.261**</td>
<td>0.032</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age AD</td>
<td>0.956**</td>
<td>0.170</td>
<td>0.090</td>
<td>-0.109</td>
<td>-0.015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALC</td>
<td>-0.132</td>
<td>-0.009</td>
<td>-0.164**</td>
<td>0.206**</td>
<td>0.262**</td>
<td>-0.088</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.193**</td>
<td>0.045</td>
<td>0.069</td>
<td>-0.027</td>
<td>0.080</td>
<td>0.219**</td>
<td>0.043</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-0.059</td>
<td>0.005</td>
<td>-0.023</td>
<td>0.116</td>
<td>0.075</td>
<td>0.014</td>
<td>0.056</td>
<td>0.100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE4</td>
<td>-0.195**</td>
<td>-0.124</td>
<td>-0.088</td>
<td>0.037</td>
<td>-0.002</td>
<td>-0.204**</td>
<td>-0.015</td>
<td>-0.42</td>
<td>0.065</td>
<td></td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed). Age = Age at baseline, Age AD = Age of AD Onset, ALC = Alcohol Use, HN = Hypertension, HL = Hyperlipidemia, APOE4 = ApoE-$\varepsilon 4$ allele.
Figure 1. Simple slope for history of hypertension in the prediction of age of AD diagnosis at low (-1 SD) and high (+1 SD) values of alcohol use. The values for history of hypertension and alcohol use are centered to have a mean of zero.
Discussion

The purpose of this dissertation was to assess whether alcohol use history moderates the relationship between certain risk factors (i.e., hypertension, hyperlipidemia, ApoE-ε4 allele) and age of onset of AD. Inconsistent with the first hypothesis, the only risk factor that was predictive of age of onset of AD was hyperlipidemia. Furthermore, the results of the current study partially support the second hypothesis and suggest that alcohol use may moderate the relationship between history of hypertension and age of AD onset. Alcohol use history did not appear to moderate the relationship between other risk factors.

A number of sociodemographic variables, including age, sex, and education, were positively predictive of age of onset of AD. Specifically, being male and having a lower education were predictive of a lower age of onset. However, when additional risk factors and alcohol use history were considered, only age at baseline and sex remained predictive of age of AD onset. This study strengthens current research and suggests that men may develop AD earlier than women, even after adjusting for several risk factors. However, it is important to note that several studies have only found higher incidence rates in females who were older than 90 years of age (Jorm & Jolley, 1998; Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001) and that any gender-related risk factors may be attributed to differences in life expectancy (Hebert et al., 2001). In addition, the finding that age at baseline visit was positively correlated with age of AD onset may reflect a methodological limitation. In this study, the reported age of onset may have also been collected during the first clinic visit when diagnosis was made at that time, which was then confounded with age at baseline. Research has consistently shown the opposite finding; in fact, age has been shown to be the single greatest predictor of the development of AD (Alzheimer’s Association, 2013).
The relationship between risk factors and age of onset of AD were mixed and generally did not support the first hypothesis. Initial correlations indicated that history of hypertension was positively correlated with age of AD onset and that presence of ApoE-ε4 allele was negatively correlated with age of AD onset. The negative correlation between the ApoE-ε4 and age of AD onset is also consistent with previous research, which suggests that the presence of this risk factor may correlate with a lower age of onset of AD. However, when considering additional demographic and risk factors, the presence of the ApoE-ε4 was not predictive of age of onset of AD. Interestingly, only history of hyperlipidemia was positively predictive of age of onset of Alzheimer’s disease. This paradoxical finding may be due to a number of factors, including the possible differential impact of hyperlipidemia in early versus late-life. A number of studies have found that individuals with hyperlipidemia in midlife may have increased risk for AD (Solomon et al., 2009; Anstey et al., 2008). However, our results strengthen previous findings from Meilke et al. (2005), who found that individuals with high total cholesterol levels at age 70 had a lower risk of developing AD in later life; these findings were also explained in terms of differences in frailty, such that individuals who survived the negative health consequences associated with hyperlipidemia in mid-life were less likely to develop dementia later. Additional evidence of hyperlipidemia history for providing a survival, rather than a protective, effect comes from West et al. (2008), who found that cholesterol levels were positively associated with memory performance in non-demented, very elderly individuals. These findings suggest that very elderly individuals may perform better on cognitive testing not necessarily because of a history of high cholesterol, but rather, that these individuals were able to survive and overcome the negative health consequences associated with high cholesterol. Furthermore, elderly individuals with a
history of high cholesterol who also perform better on memory tests than their elderly counterparts, may be less frail and are better able to recover from chronic health conditions.

Although alcohol use history was not significantly correlated with age of AD onset in itself, results suggest that alcohol use is positively predictive of age of onset of AD in the context of additional demographic and risk factors. These results suggest that alcohol use, by itself, may not impact the development of AD but rather may interact with additional factors that influence the disease process. Consistent with hypothesis two, alcohol use appeared to moderate the relationship between history of hypertension and age of AD onset, such that when there is a history of higher levels of alcohol use, the relationship between age of AD onset and history of hypertension is stronger than when there is a history of low alcohol use.

Overall, these results suggest that alcohol use may serve both as a protective and a risk factor for individuals with history of hypertension. This appears to be the first study to date that has shown a moderating effect of alcohol use on age of onset of AD for individuals with a history of hypertension. These results are not surprising given that alcohol usage has been shown to have a linear relationship with hypertension, such that a reduction in alcohol use may decrease blood pressure (Xin et al., 2011). However, the mechanism by which hypertension may impact the development of AD and, by extension, how alcohol usage may further moderate this relationship, is unknown. Several studies have suggested that hypertension may impact a number of cerebrovascular changes that underlie the AD process, including changes in blood vessel walls and breakdown of the blood-brain barrier (e.g., Jellinger, 2002). Recently, an animal study by Carnevale et al. (2012) demonstrated that, through oxidative stress induction, chronic hypertension leads to activation of the receptor for advanced glycation endproducts (RAGE), which resulted in $\beta$-amyloid deposition and cognitive decline similar to AD pathology. It is
hypothesized that higher alcohol use in the current study may have increased the effects of hypertension as a risk factor for AD and that lower alcohol use may reduce these effects, possibly through moderating differential effects of oxidative stress.

The current study has several limitations. First, this study was cross-sectional in nature, and therefore causal interpretations about the results cannot be made. The method by which risk factors were assessed also presented a number of limitations. In particular, history of risk factors were assessed by self-report or from caretaker, and direct assessment was not available. Also, the absence of certain risk factors, such as alcohol use, cannot be certain based on retrospective report, and the presence of low alcohol use for at least some datasets in the current study may reflect limits to accurate data collection in this area rather than actual low use by some patients. Additionally, all of the risk factors in this study were analyzed for mere presence or absence for each participant. Therefore, differences in onset/time since diagnosis and severity of specific risk factors were unavailable, and results should be interpreted within this context. As a whole, the sample was predominantly White and well-educated, which further limits the generalizability of findings. In addition, the type of alcohol consumed (e.g., beer, spirits, wine) was not considered, and some research suggests that wine may be more beneficial than other types of alcohol (Luchinsger et al., 2004).

History of medication, used for treating several of these risk factors was not taken into account and could significantly impact the results from the study. For example, a number of individuals with history of hypercholesterolemia may have also been taking statin medications, which could impact the development of AD. Specifically, there is some evidence to suggest that lipid-lowering medications may serve a protective role (Rodriguez, Dodge, Birzescu, Stoehr, &
Ganguli, 2002; Zamrini, McGwin, & Roseman, 2004), although other studies have found a lack of association or inconclusive results due to methodological differences (Li et al., 2004).

It is also important to mention that, even though hypertension and age-related increases in blood pressure are common in older age (e.g., Franklin et al., 1997), there is general fluctuation and variability in blood pressure (e.g., Skoog et al. 1996). Recently, a study by Alperovitch et al. (2013) found that blood pressure variability, rather than hypertension in and of itself, increased an individual’s risk for incident AD. Therefore, future studies may consider evaluating whether a history of low to moderate alcohol use may function to stabilize blood pressure variability and protect against the development of AD.

Overall, the current study has a number of strengths, including a large sample size and good sensitivity of AD diagnosis (see Beach, Monsell, Phillips, & Kukull, 2013 for more information), this study also focused on age of onset to investigate increased risk for development of AD, which can be a better indiector than other methods such as brief cognitive assessment (Clark et al., 1999). Future studies should continue to assess the impact of modifiable factors that could delay the onset of AD, as this has the potential to significantly impact prevalence rates and economic burden (Brookemeyer, Gray, & Kawas, 1998). Furthermore, given that several risk factors for AD are chronic, future research should focus on participatory medicine, such as how patient engagement in treatment of chronic diseases may impact the development of AD.
References


