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Extended Maternal and Paternal Hereditary Risk for Alzheimer's Disease Examined by Sex in a Sample of Community Dwelling Older Adults in Cache County, Utah

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EXTENDED MATERNAL AND PATERNAL HEREDITARY RISK FOR ALZHEIMER'S DISEASE EXAMINED BY SEX IN A SAMPLE OF COMMUNITY DWELLING OLDER ADULTS IN CACHE COUNTY, UTAH

by

Elizabeth K. Vernon

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ABSTRACT

Extended Maternal and Paternal Hereditary Risk for Alzheimer's Disease Examined by Sex in a Sample of Community Dwelling Older Adults in Cache County, Utah

by

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Utah State University, 2021

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More than 12.7 million Americans are expected to develop Alzheimer's Disease (AD) by 2050. Identified risk factors for AD include advanced age, female sex, family history, the presence the Ɛ4 allele of the apolipoprotein E (APOE) gene, and vascular risk factors and conditions. Differential effects by sex appear among some of these risk factors, however, sex differences have not been well-studied among others. This project examined sex differences in the association between family history of AD, direct maternal and paternal lineage of AD, parental longevity, and potential modifying effects of cardiovascular risk factors and conditions in the risk for AD in a single population. This project used extant data from the Cache County Study on Memory in Aging (CCSMA) of 5,092 older adults, enriched with data from Medicare claims and death certificates through the Utah Population Database. The results showed that having a first-degree relative with AD was associated with a 58% increase in AD in males, Odds Ratio *(OR)*= 1.58, *p*= .003, and a 66% increase in risk in females, *OR*= 1.66, *p*= <.001. In females, a direct maternal but not paternal lineage of AD was associated with a 56%

increased risk for AD, *OR*= 1.56, *p*=.005, whereas in males there was a trend, where having both direct maternal and paternal lineages of AD were associated with a 51.3% lower risk of AD, *OR*=0.487, *p* = .054. A history of maternal or paternal exceptional longevity was not associated with AD risk in females. In contrast, males who were APOE ε4 carriers and with a history of exceptional maternal longevity were at 3-fold greater risk of AD than those males with neither risk factor, *OR*= 3.15, *p*= .020. Interestingly, males had 11% reduced risk for AD with a history of both exceptional maternal and paternal longevity, *OR*= 0.894, *p*=.041. With respect to vascular factors and interactions with family history, females with a history of congestive heart failure (CHF) and direct paternal lineage of AD were at a 2-fold increased odds of AD, *OR*= 2.26, *p*= .013, compared to females with neither risk factor. Those with a history of CHF were at an 11-fold increased risk for AD, *OR*= 11.15, p=<.001. For males, there were no interactions between family history of AD and vascular risk factors and conditions. Amongst both females and males, several vascular factors or conditions were associated with increased risk of AD, for instance, cerebrovascular accident and CHF for both females and males, and hypertension and high cholesterol/triglycerides/atherosclerosis in males only. Notably, a history of myocardial infarction in females was associated with lower risk of AD. Overall, this study highlights the increased risk of AD among those with a positive family history of AD in first-degree relatives, and sex differences in maternal or paternal lineage, and vascular risk factors and conditions. Further research is needed to elucidate the mechanisms underlying the above associations to develop potential preventive interventions relevant to each sex.

(151 pages)

PUBLIC ABSTRACT

Extended Maternal and Paternal Hereditary Risk for Alzheimer's Disease Examined by Sex in a Sample of Community Dwelling Older Adults in Cache County, Utah

Elizabeth K. Vernon

More than 6 million Americans are living with Alzheimer's Disease (AD) and this number is expected to rise and surpass 12.7 million individuals by the year 2050. Currently there is no cure for the disease and prior research has focused on prevention by identifying risk factors. Known risk factors associated with AD include older age, female sex, genetics, family history of AD, genotype of the apolipoprotein E (APOE) gene, and vascular risk factors (e.g., cholesterol, hypertension) and conditions or events (e.g., CHF, stroke). The effects of many of the above risk factors have differed in men and women, but few studies have examined how family history of AD, direct maternal or paternal lineage of AD, parental longevity, and cardiovascular risk factors and conditions might influence risk for AD differently for men and women. This project analyzed existing data from a population-based longitudinal study, the Cache County Study on Memory in Aging (CCSMA), that included permanent residents of Cache County, Utah who were aged 65 years or older in 1995. The study's data were enriched through additional data obtained for extended family history and Medicare claims and death certificates that were made available through data linkage with the Utah Population Database. The original study ran from 1995-2007, but with the additional Medicare claims and death certificates, identification of AD related outcomes and risk factors were extended to 2019. The aim of

this current study was to examine whether the risk for AD differed between men and women with regards to family history of AD, maternal and paternal lineage of AD, longer-lived parents, and whether vascular health conditions affected these risks.

Results from this dissertation showed that having a first-degree relative (parents, siblings, or offspring) with AD increased the risk for AD in men by 58%, Odds Ratio *(OR)*= 1.58, *p*= .003, and women by 66%, *OR*= 1.66, *p*= <.001. Among women, direct maternal but not paternal lineage of AD was associated with a 56% increased risk for AD, *OR*= 1.56, *p*=.005, whereas in men, history of maternal or paternal lineage of AD (above age 87) did not affect their risk of developing AD. Having a longer-lived mother or longer-lived father was not associated with AD risk in women. However, men with a history of a longer-lived mother and who had an APOE Ɛ4 positive genotype had three times the risk of AD, *OR*= 3.15, *p*= .020. Men who had both a longer-lived mother and a longer-lived father compared to men without had an 11% reduction in risk for AD, *OR*= 0.89, *p*=.041. In relation to cardiovascular conditions and risk in women, those with a history of congestive heart failure (CHF) and a direct paternal lineage of AD had double the risk of AD compared to those without, though those women with no paternal lineage of AD were at an 11 times greater risk, *OR*= 11.15, *p*=<0.001. For men there were no associations between family history of AD and cardiovascular conditions. Among both men and women, several cardiovascular risk factors increased risk for AD. For instance, men and women with a history of stroke or CHF had an increased risk for AD. Men with a history of hypertension and high cholesterol/triglycerides/atherosclerosis were also at increased risk of developing AD. Notably, women with a history of myocardial infarction had a reduction in risk.

Although this study is observational in nature and thus does not prove a direct causal relationship between familial history and AD, it does support previous research that found having a first-degree relative with AD regardless of sex increased the risk for AD. The study also highlighted the importance of studying risk factors like family history, separately for men and women. Thus, women with a maternal history of AD were at greater risk than those with a paternal history of AD, but no such association was found in men. Men were at slightly reduced risk for AD when having both longer-lived parents and there were slight differences by sex in cardiovascular risk factors that predicted risk for AD. The different results obtained for men and women have clinical implications in monitoring for AD risk in older adults and suggest aggressive treatment for vascular risk factors and conditions amongst women in particular, with CHF and family history. Further research is needed to understand the underlying mechanisms with how these risks vary in males and females.

DEDICATION

To all those who have been affected by Alzheimer's disease and the dedicated researchers who continue to search for answers. To my wonderful family and friends who have supported me through this journey, I could not have completed this without you.

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CHAPTER I

INTRODUCTION

Approximately 6.2 million Americans are living with Alzheimer's Disease (AD) and this number is expected to rise to more than 12.7 million individuals by the year 2050 (Alzheimer's Association, 2021). Currently, there is no cure for the disease and one priority has been on prevention (Alzheimer's Association, 2021). Identified risk factors associated with sporadic, late-onset AD include advanced age (Guerreiro & Bras, 2015), female sex (Mielke et al., 2014), family history (Cannon-Albright et al., 2019), carrying the apolipoprotein Ɛ4 allele (APOE Ɛ4; Farrer et al., 1997), and vascular risk factors and conditions (Barnes & Yaffe, 2011). Among several of these risk factors, there appears to be differential effects in males and females.

Females account for two-thirds of cases of AD in the US (Alzheimer's Association, 2021). Differences in longevity have been used to explain the differing rates in males and females; however, some research suggests this does not fully explain the disparity (Mielke et al., 2014). The underlying mechanism associated with sex differences in AD risk remains unclear. One factor possibly contributing to this disparity includes the maternal/paternal transmission of the disease to the offspring (Mosconi et al., 2007; Mosconi et al., 2010).

A family history of AD is a risk factor for the disorder. Several studies have found that a positive family history is associated with a 4-10 times increased risk of developing AD (van Duijn et al., 1991; Fratiglioni et al., 1993). Having at least one first-degree relative with dementia increases the risk by approximately 4-fold; with each additional

affected first-degree relative, the risk further increases approximately 2-fold (van Duijn et al., 1991; Fratiglioni et al., 1993). A recent study reported that extended family history also was associated with risk of AD, and risk differed by sex of the affected parent (Cannon-Albright et al., 2019). Cannon-Albright and colleagues (2019) found that having a first-degree relative with AD increased the risk of AD, which exponentially increased with each additional first-degree relative affected. In addition, the authors found sex differences in the transmission of AD in second-degree relatives, with a greater increase in risk found in the maternal familial line (Cannon-Albright et al., 2019). Several other studies have also found varying risk associated with maternal and paternal transmission of AD, with a stronger association in the maternal transmission (Honea et al., 2012; Mosconi et al., 2007; Mosconi et al., 2010). Recent studies have found evidence of significant AD biomarkers in those with a maternal family history compared to those with a paternal family history or among those without a positive family history. The associations in biomarkers included an increased deposition of Pittsburgh B Compound (PiB) in the parietal, sensorimotor cortices, and precuneus of the brain (Honea et al., 2012) and reduced glucose metabolism in the medial-temporal lobe, parietotemporal region, posterior cingulate, and frontal cortices (Mosconi et al., 2007). In cerebrospinal fluid, reduced beta amyloid and increased tau/amyloid-beta ratio have been reported (Honea et al., 2012). However, a large study of 1,220 older adults, found an association with paternal but not maternal transmission of AD (Ehrenkrantz et al., 1999). It is unclear what factors underlie these discrepant results, although sex of the proband, health-related risk factors and genetic variables may contribute.

The apolipoprotein E (APOE) gene has been associated with risk for developing AD. Several studies have reported varying effects in males and females who carry the APOE Ɛ4 allele. Specifically, many have found a greater risk of AD in female APOE Ɛ4 allele carriers compared to male carriers of the allele (Bretsky et al., 1999; Farrer et al., 1997). However, males with two APOE Ɛ4 alleles also appear to be at greater risk of AD than those males carrying one or no APOE Ɛ4 allele (Payami et al., 1996). This sex difference may contribute to the differing rates of AD amongst males and females and may contribute to discrepant results in family history studies.

As noted above, greater longevity is associated with increased AD risk (Guerreiro & Bras, 2015). Sex differences also appear in longevity, with females living longer than males (Center of Disease Control [CDC], 2017), and thus, this factor may contribute to sex differences in AD rates and discrepant family history studies (Passarino et al., 2016). Exceptional longevity (generally defined as aging beyond age 85) however, is associated with lower risk of AD (Jorm & Jolley, 1998), delayed onset of cognitive decline (Andersen et al., 2012), as well as reduced morbidity (Andersen et al., 2012; Westendorp et al., 2009). Offspring of exceptionally long-lived parents have shown reduced cardiovascular health conditions (Westendorp et al., 2009) as well as reduced risk of developing AD (Lipton et al., 2010). Little research has examined how parental longevity relates to sex differences in AD risk or differences in maternal or paternal transmission.

As noted above, exceptional parental longevity is associated with reduced morbidity in offspring (Westendorp et al., 2009) and in particular, cardiovascular conditions (Westendorp et al., 2009). Cardiovascular risk factors and conditions, which have been associated with increased risk of developing AD, include hypertension,

hypercholesterolemia, low physical activity, diabetes mellitus, stroke, obesity, and metabolic syndrome (de Bruijn & Ikram, 2014). There are sex differences in the type or form of cardiovascular disease (CVD) as well. Females appear to have greater risk for developing CVD through microvascular disease, whereas males show greater risk with obstructive coronary disease (Bairey-Merz et al., 2006). In AD, significant microvascular changes have been observed in the brain and these changes have been associated with more severe AD symptomology (De la Torre, 2002). In addition, studies have found that compared to males, females are at greater risk for complications due to diabetes mellitus such as myocardial infarction, depression, and coronary heart disease (Kautzky-Willer et al., 2016). These conditions have also been associated with increased risk for AD (Barnes & Yaffe, 2011). Taken together, the unique cardiovascular profile in females may put them at higher risk for AD compared to males. However, few studies have investigated the type of coronary heart disease and risk for AD in either males or females.

The above literature discusses several modifiable and non-modifiable risk factors of AD. Interesting associations with AD are noted for familial history of AD in maternal vs. paternal lines, the role of exceptional longevity, the overall lower risk of cardiovascular morbidity with exceptional longevity and sex differences in cardiovascular disease risk. These studies have been conducted in various samples and together identify important risk factors for AD. However, sex differences in the role of family history, exceptional longevity and cardiovascular risk factors and conditions have not been well studied. This project examined the association between direct maternal and paternal lineage of AD and AD risk and examined sex differences in risk in a single population sample. Additionally, parental longevity and cardiovascular risk factors and

conditions were examined as potential modifiers of these relationships. This project used extant data from the Cache County Study on Memory in Aging (CCSMA), a longitudinal population-based study of antecedents of dementia and cognitive decline in a sample of 5,092 older adults. Linkage of the CCSMA with the Utah Population Database (UPBD) allowed for enrichment of the available data by extending data obtained from other sources to include extended family history information and through further linkage with Medicare claims data, additional health-related data (https://rge.utah.edu/).

CHAPTER II

REVIEW OF THE LITERATURE

Risk Factors for Alzheimer's Disease

It is estimated nearly 12.7 million individuals in the United States will be living with Alzheimer's Disease (AD) by the year 2050 (Alzheimer's Association, 2021). There is no cure for the disease, and efforts have focused on identifying risk factors for primary prevention (Alzheimer's Association, 2021). Several risk factors for AD have been identified and include mid-life hypertension, high cholesterol, diabetes mellitus, diet, and sleep disturbance (Barnes & Yaffe, 2011). The greatest risk factor appears to be advanced age, with those living longer exhibiting greater risk (Alzheimer's Association, 2021). Family history is also a strong predictor of AD, reflecting both genetic transmission as well as lifestyle traditions or psychosocial factors "handed down" across generations (Cannon-Albright et al., 2019). Sex differences have been reported in AD, with females exhibiting greater risk than males (Nebel et al., 2018). However, the underlying mechanisms contributing to this disparity (e.g., greater longevity in women, differences in hormonal changes in late life, and various lifetime psychosocial factors) remains unclear. This project examined select factors that may contribute to sex differences in AD risk.

Alzheimer's Disease in Females

AD is more prevalent among females where it accounts for approximately two-thirds of all cases in the US (Alzheimer's Association, 2021). Compared to males, females are also twice as likely to receive a diagnosis of dementia after age 60 (Nebel et

al., 2018). It is estimated that after the age of 45, the lifetime risk of developing AD in females is approximately 20%, compared to approximately 10% in males (Nebel et al., 2018).

Many studies have investigated sex differences in the risk for AD in advanced age. The Cache County Study on Memory in Aging (CCSMA) found modest differences in incidence rates of AD between males and females prior to age 78, after which the incidence of AD increased two-fold (with age) in females compared to males. Incidence rates for both males and females declined with age in the mid-to-late 90s and beyond (Miech et al., 2002). Similarly, Roberts and colleagues (2012) found conversion rates from Mild Cognitive Impairment (MCI) to AD did not significantly differ between males and females between the ages 70-79. After the age of 80, however, higher rates of conversion were found in females (Roberts et al., 2012). Beam and colleagues examined the incidence rate of AD in 16,926 females and males in The Swedish Twin study. They found the incidence rate to be greater in females after age 85 for AD and all-cause dementia (Beam et al., 2018). However, other studies have failed to report a sex difference in AD incidence. Hebert and colleagues (2001) examined incidence of AD in a population of 3,089 older adults, aged 65 and older, who were dementia free at baseline from the Established Populations for Epidemiologic Study of Elderly (EPESE) Project of East Boston. Six hundred forty-two individuals developed dementia over three years. The authors used life tables to estimate incidence for males and females for a hypothetical sample of 100,000 for each sex. They found that age-specific incidence of AD did not differ in males and females (Hebert et al., 2001). In addition, they found that the prevalence of AD did not differ by sex nor did mortality among those with AD. The

authors concluded that the excess number of females with AD was due to longevity rather than other sex-specific factors (Hebert et al., 2001). Similarly, a study examining 1,236 community dwelling adults aged 55 and older, from the Baltimore Longitudinal Study of Aging (BLSA), found no significant difference in AD incidence rates between males and females over a 13-year follow-up period (Hebert et al., 2001). However, there was a trend for females to have a 10% higher incidence of AD than males ($p=.065$) of similar age and educational attainment (Kawas et al., 2000). The studies above present mixed results in the incidence of AD for males and females, though differences in the ages of the samples and duration of follow-ups may contribute to discrepant findings.

Sex differences have also been observed in the prodromal stage of dementia, or MCI (Csukly et al., 2016). Several forms of MCI have been identified: amnestic MCI in which memory loss is predominant and non-amnestic MCI in which cognitive domains other than memory are impaired (e.g., visuospatial abilities) (Csukly et al.,2016). In at least one sample, males were found to have a higher prevalence rate of non-amnestic MCI (20%) compared to females (10.9%; Roberts et al, 2012). In addition, females appear to have greater MCI incidence rates in older ages than males (Roberts et al., 2012). Non-amnestic MCI has been associated with higher conversion rates to non-AD dementias, while amnestic MCI is considered a prodrome to AD (Petersen, 2004). Thus, some of the sex discrepancies in AD rates at later ages may be explained in part by greater prevalence of MCI in females at older ages, and possibly with males having greater non-amnestic MCI.

Recent research suggests that hormonal changes in females in mid-to-late life also may contribute to sex differences in AD risk (Mielke et al., 2014). Hormonal changes

that accompany menopause include reduced estrogen levels, which have implications for various physiological processes in the brain. For example, menopausal and perimenopausal females have reduced brain glucose metabolism, increased development of amyloid plaques, and reduced production of brain-derived neurotrophic factor (BDNF; a protein that is integral to synaptic development and plasticity) (Mosconi et al., 2010)). These changes have been postulated to contribute to the increased risk of AD amongst females (Mielke et al., 2014). In addition, structural changes such as reduced gray matter and white matter in areas of the brain associated with AD (e.g., the default mode network) also have been associated with menopause (Mosconi et al., 2010). Furthermore, hormone therapy, initiated near the onset of menopause is associated with a reduction in risk for AD in females (Zandi et al., 2002; Whitmer et al., 2010), though clinical trials have not borne conclusive results (Shumaker et al., 1998; Harman et al., 2005). While the specific mechanisms are unclear, the above research suggests physiological changes in relation to menopause in females that may also contribute to the sex differences in the rates of the disease.

Family History of Alzheimer's Disease, Maternal/Paternal Transmission, and Sex Differences in AD Risk

Several studies have found increased risk of developing AD in those individuals with a positive family history of the disease (van Duijin et al., 1991, Fratiglioni et al., 1993; Cannon-Albright et al., 2019). A positive parental history of AD has been associated with 4-10 times greater risk of developing AD or other dementias in the proband (van Duijn et al., 1991; Fratiglioni et al.,1993). In a re-analysis of seven case control studies by van Duijn and colleagues (1991), they found a 3.5-fold increased risk

of AD for those with at least one first-degree relative with all-cause dementia (van Duijn et al., 1991). In addition, they examined age of onset in relation to risk and found the relative risk *decreased* with increasing age of onset. Van Duijn and colleagues (1991) also found those with two or more first-degree relatives had more than seven times the risk of developing AD (RR=7.5; van Duijn et al., 1991) than those without a family history. Another study by Fratiglioni and colleagues (1993) examined the association between first-degree relatives with all-cause dementia and risk for developing AD in a case-control study. Ninety-eight cases and 216 controls were examined in a population-based study in Stockholm. The authors found that having at least one first-degree relative with all-cause dementia was associated with a 3.2-fold relative risk of developing AD compared to those without a first-degree relative with dementia (Fratiglioni et al., 1993). The above studies did not examine extended family history (e.g., second-or-higher degree relatives) or sex differences amongst the proband.

A recent study by Cannon-Albright and colleagues (2019) examined extended family history and sex differences associated with the risk of developing AD. They found in state-wide death certificates of older adults in Utah, family history of at least one first-degree relative doubled the relative risk of developing AD. The relative risk nearly doubled beyond that (RR=3.98) with having two first-degree relatives; having four first-degree relatives further increased the risk 14-fold (Cannon-Albright et al., 2019). Furthermore, the authors found sex differences among maternal/paternal lines. Having a first-degree *male* relative with AD was associated with a greater risk compared to having a first-degree female relative with AD (Cannon-Albright et al., 2019). However, the authors found evidence for increased *maternal* transmission of AD amongst second-

degree relatives (i.e., mother's brother; RR=1.58); paternal second-degree relative (i.e., father's brother; RR=0.95) was not significant. The maternal association was only found amongst analyses examining second-degree relatives and not those examining first- or third-degree relatives. Other studies have reported a stronger association with maternal transmission of risk for AD than paternal transmission *for both male and female* probands (Honea et al., 2012; Mosconi et al., 2007; Mosconi et al., 2010).

A recent study by Honea and colleagues (2012) examined biomarkers of AD in 403 individuals with vs. without a family history of AD in a cross-sectional analysis of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The participants were classified as having normal cognition, MCI, or AD. They found that a maternal family history of AD was associated with increased uptake of Pittsburgh B Compound (PiB; a biomarker reflecting beta amyloid deposition) in the parietal and sensorimotor cortices and the precuneus areas of the brain in all participants, regardless of cognitive status. (Note, the degree of PiB uptake did differ by cognitive status) (Honea et al., 2012). Additionally, those with a maternal family history of AD had reduced cerebrospinal fluid (CSF) amyloid-beta (Aβ) levels and increased tau/Aβ ratio, both known biomarkers of AD, compared to participants with a paternal family history only or no family history (Honea et al., 2012). Another study of cognitively normal older adults found that those with a maternal family history of AD showed reduced glucose metabolism in the medial-temporal lobe and parietotemporal, posterior cingulate, and frontal cortices compared to those with a paternal family history (Mosconi et al., 2007). In a follow-up to this study, the authors found that cognitively normal individuals at baseline with a maternal family history had progressive reductions in brain glucose

metabolism over a two-year period compared to those with a paternal or negative family history (Mosconi et al., 2010). These studies suggest greater AD pathology in those with a maternal family history of the disease. In contrast, however, Ehrenkrantz and colleagues (1999) found in a sample of 1,220 individuals, there was no evidence of maternal transmission of the disease but there was evidence of *paternal* transmission of AD. While this is a single study that does not support a maternal transmission, the study consisted of a large sample size and an extensive longitudinal follow-up period (up to 15 years) completed by the Mount Sinai Alzheimer's Disease Research Center.

In summary, several studies have reported the significance of a maternal family history of AD to be significant for AD risk, although at least one large study reports the importance of paternal family history. The above studies differed in sample size, geographic locations (lifestyle and cultural factors), determination of dementia diagnosis, and method of determining family history. Not examined was whether maternal/paternal transmission of AD varied by the sex of the proband or by genetic factors.

Sex Differences in Apolipoprotein Ɛ4 Allele Carriers in Risk for Alzheimer's Disease

Sex differences also appear in relation to the genetic risk associated with the apolipoprotein E (APOE) gene. Several studies have found a four-fold increased risk of developing AD amongst female APOE Ɛ4 carriers compared to female non- Ɛ4 carriers (Bretsky et al., 1999; Farrer et al., 1997; Payami et al., 1996). By contrast, male APOE Ɛ4 carriers reportedly exhibit little-to-no risk compared to male non- Ɛ4 carriers (Bretsky et al., 1999), though one study reported that males carrying *two* copies of the APOE Ɛ4 allele appeared to be at 5-fold greater risk compared to those without an APOE Ɛ4 allele

(Payami et al., 1996). A study by Corder and colleagues (2004) examined 5,000 autopsies of individuals between 25-96 years of age and found an interaction between age, sex, and APOE Ɛ4 status. They found that middle-aged female APOE Ɛ4 carriers had more brain regions affected by AD pathology than male APOE Ɛ4 carriers. In addition, they found, that among AD patients, female APOE Ɛ4-allele carriers (one or 2 copies) presented at autopsy with more amyloid plaques and neurofibrillary tangles compared to all non-carriers and male APOE Ɛ4 allele carriers in earlier Braak stages (a staging system of Alzheimer's neuropathology). However, the sex difference in amyloid plaques and tangles were not evident in later Braak stages (Corder et al., 2004). In addition, Fleisher and colleagues (2005), in a sample of cognitively normal adults, found greater loss of hippocampal volumes in female APOE Ɛ4 carriers compared to male APOE Ɛ4 carriers. Other differences in the brains between the sexes have been found in cortical thickness and volumes among cognitively normal adults, with a more pronounced loss in female APOE Ɛ4 carriers than in male Ɛ4 carriers (Liu et al., 2010). In summary, several studies suggest sex differences in AD risk by APOE genotype. However, not explored are whether familial transmission (maternal or paternal lines) further influence AD risk beyond the apparent sex-specific risk of APOE genotype. Additionally, overall family longevity has not been examined in prior studies.

Differences in Parental longevity and Risk for Alzheimer's Disease

As noted earlier, advanced age is the number one risk factor for AD (Guerreiro & Bras, 2015), though in extreme old age, risk appears to decline (Andersen et al., 2012; Miech et al., 2002). Studies report a 2-fold increase in risk for AD for both males and

females (or regardless of sex) for each year after the age of 65 (Jorm & Jolley, 1998). Longevity is related to both genetic and environmental factors (Passarino et al., 2016) and exceptional longevity (generally considered over age 86 is associated with reduced morbidity including reduced cognitive decline (Andersen et al., 2012). A study by Andersen and colleagues (2012) examined nonagenarians (87-99 years of age), centenarians (100-104 years of age), semicentenarians (105-109 years of age), and supercentenarians (110 and above years of age) and prevalence of at least one age related disease (cardiovascular disease, chronic obstructive pulmonary disease, dementia, diabetes mellitus, and stroke). The authors found delayed onset of at least one of the above age-related disease in those with exceptional longevity (aged 87 and older) compared to controls (those between 47-87 years of age without a family history of exceptional longevity) (Andersen et al., 2012). They also found significantly reduced hazard of morbidity in all advanced age groups compared with controls. The authors suggest the reduced hazards with extreme old age indicate compression of morbidity, meaning reduced risk of age-related diseases at the upper age ranges of the human life span (Andersen et al., 2012). In addition, with respect to cognitive functioning in this rare sample, older age was associated with a delay in the onset of cognitive difficulties (Andersen et al., 2012). Interestingly, males outperformed females on all cognitive tests at all ages (Andersen et al., 2012), which is not a pattern seen at younger ages (Sundermann et al., 2016). Similarly, Westendorp and colleagues (2009) examined risk of morbidity among familial nonagenarians (two siblings aged 90 and above), sporadic nonagenarians (one individual aged 90 and above), and the offspring of both groups. They found amongst nonagenarian siblings, there was a reduced risk of morbidity (41%)

compared to sporadic nonagenarians (Westendorp et al., 2009). The authors further examined comorbidity rates in the offspring of the familial and sporadic nonagenarians. They found that compared to offspring of sporadic nonagenarians, offspring of sibling nonagenarians had lower prevalence of myocardial infarction (2.4% vs. 4.1%), diabetes mellitus (4.4% vs. 7.6%), hypertension (23.0% vs. 27.5%) and use of cardiovascular medications (23.0% vs. 28.9%) (Westendorp et al., 2009). Lipton and colleagues (2010) examined exceptional parental longevity and risk of developing AD. They found in a sample of community-dwelling, non-demented older adults (at baseline) followed for 23-years, that those with a parent living longer than age 95 were at 43% reduced risk of developing AD compared to those whose parents died prior to age 95 (Lipton et al., 2010). Thus, it appears that parental exceptional longevity is inversely related to risk of AD.

The above literature review highlights several non-modifiable (e.g., family history, APOE allele carrier status, parental longevity) risk factors that may in part underlie the sex differences in AD risk. A family history of AD is associated with increased risk of developing the disease and this association has been found in both immediate and extended family histories (Cannon-Albright et al., 2019), with differences depending on the sex of the affected relative (i.e., male first-degree relative increased the risk of developing AD in the proband compared to a female first-degree relative) and opposite effects amongst affected second-degree relatives (Cannon-Albright et al., 2019). While this study had strengths in the ability to examine extended family histories, a significant limitation was the reliance on death certificates for ascertainment of AD where dementia is often missed as a cause of death (Frecker et al., 1995; Raiford et al.,

1994). Many studies report greater risk of AD with maternal transmission (Honea et al., 2012; Mosconi et al., 2007; Mosconi et al., 2010, and an association with AD biomarkers in persons without dementia (Honea et al., 2012; Mosconi et al., 2007; Mosconi et al., 2010). However, at least one large study found greater risk of AD amongst probands with a *paternal* history (Ehrenkrantz et al., 1999). Sex differences are also found related to APOE genotype, with female APOE Ɛ4 carriers being at greater risk for AD than their non-Ɛ4 counterparts (Bretsky et al., 1999; Farrer et al., 1997; Payami et al., 1996). Amongst males, APOE Ɛ4 homozygotes are at greater risk for AD (Payami et al., 1996). While in general, advanced age is a risk factor for AD, exceptional longevity is inversely related to AD risk (Andersen et al., 2012). At least one study found exceptional longevity was associated with reduced risk of AD in offspring (Lipton et al., 2010). In the literature published to date, it is unclear how the above factors (family history, APOE genotype, and parental longevity) collectively or in interactions influence AD risk in males and females. Furthermore, it is unknown how these factors are associated with modifiable vascular risk factors for AD. In the section below, modifiable cardiovascular risk factors are discussed in relation to sex differences.

Modifiable Health-Related Cardiovascular Risk Factors for Alzheimer's Disease

A large number of observational studies have identified several modifiable risk factors for AD, including cardiovascular disease (CVD), diabetes mellitus, metabolic syndrome, and obesity (Barnes & Yaffe, 2011). In addition, hypertension, hypercholesterolemia, low physical activity, atrial fibrillation, stroke, and non-Mediterranean diets (the Mediterranean diet is high in vegetables, low in unsaturated

fatty acids) have also been associated with the development of AD pathology in the brain (de Bruijn & Ikram, 2014). In a meta-analysis, Barnes and Yaffe (2011) concluded that mid-life hypertension (OR=1.61), mid-life obesity (RR=1.6) and diabetes (RR=1.39) contributed to a significant portion of the cases of AD worldwide (Barnes & Yaffe, 2011). CVD interactions with APOE have also been reported in AD risk (Barnes & Yaffe, 2011). Further, a Swedish study of identical and fraternal twins found that non-stroke CVD was associated with a two-fold increased risk of developing AD in those individuals carrying the APOE Ɛ4 allele; noncarriers of the Ɛ4 allele were not at greater risk. The study also found that the twin with dementia was approximately two times more likely to have CVD than the twin without dementia (OR=1.86; Eriksson et al., 2010). Gottesman and colleagues (2017), found in a bi-racial sample of 15,744 black and white older adults, those with a history of midlife diabetes, prehypertension (systolic pressure = 120-139 mm Hg and diastolic pressure = 80-89 mm Hg), and hypertension (systolic pressure=140 and above and diastolic pressure=90 and above) were at a 39% increased risk of developing AD in later life. compared to those without these conditions. Diabetes was associated with a 77% increased risk of AD (Gottesman et al., 2017). Not well studied however, is whether the association between AD and CVD varies by sex, a potentially important question given the sex differences in the development of CVD (Kautzky-Willer et al., 2016). Females for example, appear to be at greater risk of developing CVD through microvascular disease (involvement of small vessels) whereas males appear at greater risk of CVD due to obstructive coronary heart disease (Bairey-Merz et al., 2006). Of note, microvascular changes in the brain have been associated with symptomatic AD and have been found patients with AD at autopsy (De la Torre, 2002).

By contrast, obstructive coronary heart disease has not been specifically studied as a risk factor for AD. The underlying differences in the cause of CVD between males and females may suggest that females are more susceptible to AD (through microvascular changes). Kautzky-Willer and colleagues (2016) also found that compared with males, females have greater risk for complications from diabetes, including myocardial infarction, depression and coronary heart disease, all of which have been identified as risk factors for AD (Barnes & Yaffe, 2011). Depending on the underlying cause of cardiovascular disease, sex may be an important consideration. Despite the large number of studies examining vascular risk factors and AD, few have examined sex differences in AD risk.

The above literature review summarizes a plethora of studies of risk factors for AD, particularly, family history, APOE genotype, advanced age, exceptional longevity, and modifiable cardiovascular factors. Some studies have examined sex differences, but few have attempted to study whether the above factors have similar associations in males and females or examined interaction amongst risk factors. The current project examines sex differences in the associations between extended familial maternal and paternal lineage of AD and interactions with parental longevity and cardiovascular risk factors and conditions within a single population. The Cache County Study on Memory in Aging (CCSMA) has conducted dementia surveillance in a sample of 5,092 older adults for up to 12 years. Linkage with demographic and health databases through the Utah Population Database (UPDB) allowed an enrichment of outcomes and risk factors including extended family history of AD and health data. The research questions/aims are:

1. Does extended (4-generations) family history of AD and risk for AD vary by the sex of the proband?
2. Does direct maternal or paternal lineage of AD differentially affect risk for AD and does this differ by sex of the proband?
3. Is parental (maternal and/or paternal) longevity associated with risk for developing AD and does this risk vary by sex of the proband?
4. As an exploratory aim, examine whether cardiovascular risk factors and conditions are associated with direct maternal or paternal lineage of AD and risk of AD in the proband, and examine if associations vary by sex.

CHAPTER III

METHOD

Study Design

This study is a secondary data analysis of an extant dataset from the Cache County Study on Memory in Aging (CCSMA), supplemented with linked datasets to the Utah Population Database (UPDB; Norton et al., 2016), including Medicare Claims data (Hanson, Smith, & Zimmer, 2015). CCSMA was a longitudinal study with data collection that began in 1995 and ended in 2007. It consisted of four triennial waves to examine antecedent risk factors of cognitive decline and dementia (Miech et al., 2002). All but one of the 5,092 participants of the CCSMA have been linked to the UPDB, a data repository that contains over seven million records, including the genealogical records of the founders of Utah and their descendants (Norton et al., 2016). The UPDB has been further linked to Utah birth and death certificates (Cannon-Albright et al., 2019) and includes primary and contributing causes of death. Via the UPDB, health data from Medicare Claims from approximately 1992 – 2012 are available for the majority of the CCSMA participants (Hanson et al., 2015; Norton et al., 2016). The Medicare claims data utilize the International Classification of Diseases (ICD) version 9 for the present study (Hanson et al., 2015). This study used data for those participants in CCSMA who have a deep genealogical history in the UPDB (two prior generations of information beyond the proband) and who have Medicare claims data. The study design and procedures of the CCSMA have been described previously (see Miech et al., 2002), and are briefly summarized below.

The Cache County Study

Five thousand six hundred and seventy-seven older adults met eligibility criteria for the CCSMA in 1995, which included being a permanent resident of Cache County, Utah and over the age of 64. Approximately 90% (5,092) enrolled. The study consisted of four triennial waves, which included a multi-stage dementia screening and assessment protocol. Baseline cognitive screening and risk factor interviews were conducted at the participant's place of residence. Cognition was assessed using the modified Mini-Mental Status Examination (3MS; 100-point measure; Teng & Chui, 1987) which was adapted for the study (Tschanz et al., 2002). A proxy interview was given to those participants who scored below 60 on the 3MS or could not complete the 3MS, scored below 15 (out of 20) on orientation questions, or were otherwise deemed unreliable (Breitner et al., 1999). The proxy interview included a rating of the subject's cognitive status using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm & Jacomb, 1989). Participants who scored below a cutoff of 87 on the 3MS or above a 3.27 on the IQCODE were sent to the second stage, a telephone interview, with a knowledgeable informant using the Dementia Questionnaire (DQ). Based on the interview, those subjects who were rated as significantly cognitively impaired or with dementia or who were members of a designated panel of participants to complete all stages of screening, were sent for clinical assessment (CA). The CA consisted of a registered nurse (RN) interview with a knowledgeable informant regarding the participant's history of cognitive symptoms, medical history, and current medications. The participant also received a physical examination, which consisted of anthropomorphic measurements, blood pressure and neurological exam, as well as neuropsychological assessment with a trained

psychometrist (Breitner et al., 1999). The results of the CA were reviewed at an initial diagnostic conference led by a study physician and a preliminary diagnosis of dementia was rendered using the Diagnostic Statistical Manual-III-Revised (DSM-III-R) criteria (American Psychiatric Association [APA], 1987). A diagnosis of AD was assigned if the subject met criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) and that of vascular dementia if the subject met criteria from the NINCDS-the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN; Román et al., 1993). Criteria for other dementias followed standard research diagnostic criteria at the time (Breitner et al., 1999). A follow-up CA (at approximately 18 months) was requested for those with a diagnosis of a dementia or its prodrome. Neuroimaging and laboratory studies were requested for those individuals with diagnoses of dementia or prodromal AD in order to rule out other causes of cognitive impairment (Breitner et al., 1999). An independent assessment was also conducted by a study physician. A final clinical diagnosis of dementia was determined at a consensus conference with a panel of clinical experts including a board-certified neurologist, geropsychiatrists, clinical neuropsychologists, and a cognitive neuroscientist. Presence of dementia was determined based on the participant's performance on the CA, DSM-III-R criteria, physician CA, and laboratory results and neuroimaging (Breitner et el., 1999). A classification of non-case was defined as those who received a "non-case" diagnosis based on the CA, or lacking a CA, were screen negative at prior stages of dementia screening. Age of onset for dementia was assigned as the age at which the participant consistently met DSM-III-R criteria for

dementia based on the chronological development of cognitive and functional impairment. All study procedures were approved by the Institutional Review Boards at Utah State University, Duke University, and the John Hopkins University. With the completion of all four waves, 942 cases of dementia were identified, 546 (58%) with AD. CCSMA data were supplemented with data from Medicare claims from 1992 to 2012, and death certificates from 1909 to 2019, for an additional 209 cases of AD. See section below on The Utah Population Database and Medicare Claims for detailed procedures.

CCSMA Derived Family History of Alzheimer's Disease and Vascular Factors

Family history of AD was assessed through a structured interview and administered at baseline and at subsequent waves. The interview ascertained information about the participants' biological parents and siblings and history of memory problems. An endorsement of memory problems for each family member was followed up with questions of the onset (sudden or gradual), course being progressive or static, and whether the problems resulted in limitations in activities of daily living. A final question asked if a physician diagnosed the cause of the memory issue. Each relative was classified as having suspected AD if a physician had diagnosed AD, or lacking a diagnosis, if the memory problems had worsened over time, and caused limitations with daily activities. If a first-degree relative died before age 50 and did not have dementia, that person's information was coded as missing. A study participant was classified as having a positive family history of AD if at least one first-degree relative was categorized as having suspected AD (Hayden et al., 2009). Maternal and paternal family histories were noted for each participant. Appendix A contains the family history questionnaire

with the specific questions used to derive family history of AD. The UPDB linkage with death certificates for extended genealogies supplemented family history information (see Utah Population Database). Overall family history of AD and maternal and paternal family histories were categorized using a combination of CCSMA self-report and supplemented with data from the UPDB (see The Utah Population Database).

Cardiovascular risk factors were obtained in the context of a medical and medication risk factor interview conducted at each wave of the CCSMA. History of stroke was ascertained by the question, “Has a doctor or nurse ever told you that you had a stroke?” Hypertension was ascertained through the question, “Have you been told by a doctor that you had hypertension or have you been treated for hypertension?” High cholesterol was asked with the question “Have you ever been told by a doctor you had high blood cholesterol/triglycerides or have you ever been treated for high blood cholesterol/trigylcerides?” Myocardial infarction was collected through the question “Have you ever had a heart attack, a myocardial infarction, or a coronary thrombosis?” Diabetes was ascertained through the question “Have you ever been told by a doctor you had diabetes or have you been treated for diabetes?” Coronary Artery Bypass surgery was ascertained through the question “Have you ever had a coronary bypass surgery?” Appendix B presents the medical history questionnaire with the specific questions associated with cardiovascular and related conditions. Additional risk factors and conditions were asked in subsequent stages or waves, for example congestive heart failure.

The Utah Population Database

All but one of the participants of the CCSMA has been linked to the UPDB (Norton et al., 2016). The UPDB is a computerized genealogy of founders of Utah and their descendants (Cannon-Albright, 2008; https://uofuhealth.utah.edu/huntsman/utah-population-database/). The database includes more than 11 million residents of Utah and their relatives, of which 3 million individuals have at least 3 generations of genealogy linked to the original Utah pioneers. Of the 3 million, 1.3 million have genealogy data from at least 12 of 14 immediate ancestors including both parents, all four grandparents, and at least six great-grandparents (Cannon-Albright et al., 2019). The genealogy data have also been linked with the Utah Death Certificates from 1904 to 2019 and include the primary cause of death using International Classification of Diseases (ICD)- 9th edition and ICD-10 codes (Cannon-Albright et al., 2019). Additionally, the UBPD has been linked to health care registries such as Utah Cancer Registry and Medicare Claims. Further information about the UPBD can be accessed at https://uofuhealth.utah.edu/huntsman/utah-population-database/data/.

Medicare Claims Database

Through the extensive linkage of the UPDB, there is access to Medicare claims data that were submitted with ICD-9 conditions from the Centers for Medicare and Medicaid services (CMS). Medicare offers health insurance for individuals aged 65 or older to all citizens or permanent residents of the US. Data for this project used Medicare claims that were available between 1992 to 2012. The ICD-9 billing codes were sought to supplement the CCSMA cognitive status for AD dementia (ICD-9 code 331.0) as well as

the following cardiovascular risk factors and conditions: hypertension (ICD-9 codes 401.1, 401.9), hyperlipidemia (272.39), diabetes mellitus (250, 205.12, 205.02), obesity (278, 278.01), myocardial infarction (410.01-410.91; 412), stroke (433.01, 433.11, 433.21, 433.31, 433.81, 434.01, 434.11, 435.8, 435.9), atrial fibrillation (427.31) and other arrythmias (427, 427.1, 427.2, 427.32, 427.41, 427.42, 427.69, 427.61, 472.81, 427.89), congestive heart failure (428), hypothyroidism (244.9), atherosclerosis (440.9, 440.8, 437, 440), and metabolic syndrome (277.7). In order to accept a claims diagnosis for AD, criteria by Nair and colleagues (2018) were followed. Specifically, having at least two claims of AD (331.0) at least 18 months apart (Nair et al., 2018). For vascular risk factors and conditions, a single claim for an ICD-9 code was accepted as presence of a condition. In order to be considered a risk factor, the cardiovascular condition had to predate the age of diagnosis of AD.

Extended Maternal and Paternal Family History

Family history was expanded upon by using the UPDB's linkage with the state's vital statistics database. For those with missing information on parental history regarding cognitive status, cause of death codes related to AD and related dementias (ICD-9 code 331.0) were used. Individuals with AD as a primary or contributing factor of death were coded as a positive family history of the disease. Second, third, and fourth generation family histories of AD were also ascertained in the same manner.

Exceptional Parental Longevity

Parental longevity was determined using the CCSMA family history interview and death certificate data as described above. The ages were classified for maternal and

paternal longevity, with the following cut points: those individuals who survived to age 87 and older were classified as “exceptional longevity”.

Other Variables

Age at study entry (Wave 1), sex, and years of formal education were ascertained through the CCSMA baseline interview. APOE genotype was available on 97% (4932) of the participants (Breitner et al., 1999). These variables were used as covariates in statistical models as described below.

Statistical Analyses

Inclusion criteria for the current analyses were outcomes of AD diagnosis or non-case (other forms of dementia and mild cognitive disorders such as MCI were excluded) and family history information sufficient to determine family history of AD and maternal and paternal longevity.

Descriptive statistics were used to characterize the sample with respect to demographic attributes for those with a diagnosis of AD compared to non-cases. Group differences were examined using Analysis of Variance (ANOVA) for continuous variables and chi-square or Fisher’s exact tests for categorical variables.

Overall, to examine the association of each risk factor and the outcome of AD, used binary logistic regression. Model building proceeded in which predictor variables were examined systematically. First, variables were entered into the model to examine main effects, followed by the inclusion of interaction terms. Those predictor variables that were considered theoretically necessary or significant in the model at the $p < .05$ were retained. For each of the models, covariates tested included: presence of an APOE Ɛ4

allele, age at baseline, and education. To explore a non-linear association between age and AD risk, a quadratic term for age (age^2) was also examined in each model. The models were compared using r-squared, ANOVA, Akaike's Information Criteria (AIC), and Bayesian Information Criteria (BIC) to determine the goodness of fit. The performance package in R (Lüdecke et al., 2021) was used to compare each model's overall quality and goodness of fit through r-squared, root mean squared error, interclass correlation, AIC, and BIC in one comparison table and provided a rank order list of the models. The final model retained for each research question included the predictor variables that met the criteria described above (statistical significance or theoretical importance) and those models that provided the best goodness of fit while being most parsimonious model given the above criteria. All statistical analyses were conducted in R Studio R-Version 4.0.4 (RStudio Team, 2021).

To address research question one, binary logistic regressions (separate models for sex) were used to examine extended family history of AD and risk for AD. Predictors included AD classification for first-degree relative (parents, siblings, and offspring), second degree relative, and third degree relative (each variable contained any ancestor within that degree that had a diagnosis of AD) associated with risk of AD in the proband. An interaction between APOE Ɛ4 status by family history of AD was also tested in the models.

To address research question two, binary logistic regression models (separate models for sex), using dichotomous direct maternal and paternal lineage of AD (see Appendix C for an illustration of maternal and paternal lineages), were used to examine their risk of AD in the proband. The following interactions in predicting AD outcome

were tested in the models: 1) direct maternal lineage by direct paternal lineage of AD 2) APOE Ɛ4 status by direct maternal lineage of AD; and 3) APOE Ɛ4 status by direct paternal lineage of AD.

To address research question three, binomial logistic regression models (separate models for sex), using separate dichotomous variables for maternal exceptional longevity and paternal exceptional longevity (or not), were used to examine whether each was associated with risk of developing AD. The following interactions in predicting AD outcome were also examined: 1) maternal exceptional longevity by APOE Ɛ4 status; 2) paternal exceptional longevity by APOE Ɛ4 status; and 3.) maternal exceptional longevity by paternal exceptional longevity.

The last research question concerned whether cardiovascular risk factors and conditions modified any associations between direct maternal/paternal lineage of AD and AD risk in the proband, and whether there were sex differences in these relationships. Vascular variables were classified as a risk factor if the age at first Medicare claim or age at first reported diagnosis of the condition in CCSMA predated the age of onset of AD. Metabolic syndrome was removed as a risk factor as individuals with a Medicare claim diagnosis (n=59) did not meet this criterion. Given the large number of health conditions, frequencies were examined, and a tetrachoric correlation matrix (Revelle, 2020; providing an inferred Pearson's *r* for binary variables) was used to determine if each binary cardiovascular risk factor was highly correlated (Revelle, 2020). To reduce issues with multicollinearity in the statistical models, those significantly correlated with one another, a tetrachoric *r* of at least .60 (Frost, 2020), and determined to have a biological link were collapsed into a single binary category. Thus, atrial fibrillation and other

dysrhythmias were collapsed as was cholesterol/triglycerides and atherosclerosis. To quantitatively examine the severity of multicollinearity among the cardiovascular variables, variance importance factor analysis provided an index measure of how much variance of the estimated regression coefficient was increased due to collinearity (Akinwande et al., 2015; cutoff was less than 5). None of the cardiovascular risk factors exceeded the cutoff of five in the variance importance factor analysis; thus, all were retained. The final cardiovascular variables included: CVA, diabetes (DM) mellitus, hypertension (HTN), congestive heart failure (CHF), triglycerides/cholesterol/atherosclerosis (chol/athero), atrial fibrillation and other dysrhythmias (afib/dysrhythmias), hypothyroidism, and myocardial infarction (MI). The cardiovascular variables that remained highly correlated ($r = 0.6$) were tested in separate models (e.g., afib/dysrthymias and hypothyroidism). Given the number of cardiovascular risk factors remaining, statistical methods were employed to enhance prediction accuracy and interpretation of the vascular variables through random forest and least absolute shrinkage and selection operator (lasso regression). Random forest is a machine learning technique that helps examine complex relationships between a set of predictor variables and the outcome variable (Breiman, 2001). Random forest utilizes a decision tree, but reduces the increased variance associated with having a single decision tree by using multiple decision trees to produce a more accurate prediction related to the outcome variable (Breiman, 2001). This is obtained by a process of bootstrapping samples of the original dataset, which are then used to build decision trees that are averaged to provide a prediction of the best fitting predictors for the outcome variable by providing a mean decrease in the Gini (Breiman, 2001). Lasso regression is also a method to help with

variable selection and regularization. It provides a value (Lambda) that produces the lowest possible mean squared error and those variables that survive a penalty, are retained to help with variable reduction (Tibshirani, 1996). Random Forest and Lasso regression are statistical methods that provided a systematic way of removing variables from the model (Breiman, 2001; Tibshirani, 1996). The lasso regression and random forest analyses were conducted in tandem; the predictor variables were then compared. The predictor variables that overlapped in both analyses were considered quantitatively as the most predictive outcome variables. Thus, for the final research question, the starting point was the final model in research question 2. This model (separate models for sex) was used as the base model. Vascular factors that were deemed to be highly predictive in the models were added. After the inclusion of each of the vascular factors into the base model, the following interactions were examined: 1) each vascular risk factor by direct maternal lineage of AD 2) each vascular risk factor by direct paternal lineage of AD and 3.) each vascular risk factor/condition by age at baseline.

CHAPTER IV

RESULTS

Demographics

There were 3677 individuals who met eligibility criteria. Excluded (from the 5092) were 1,071 individuals who were diagnosed with other forms of dementia or mild cognitive disorder (e.g., MCI), 134 individuals who had missing family history data, 209 individuals with missing maternal and paternal longevity data, and one individual who was not linked to the UPDB. The resulting sample consisted of 98.0% white individuals and 58.7% females. Mean (SD) age at baseline was 75.75, *SD*= 7.11. There were 825 individuals diagnosed with AD, 686 of whom had received a diagnosis from CCSMA, 126 from their death certificate, and 83 from Medicare claims. Compared to males, females were more likely to have AD (24.9% compared to 18.9% in males) and were more likely to have a high school/GED or less than high school education (57.5% compared to 44.7.% in males). Mean age of onset of AD for females was 82.62, *SD*= 6.57 and 81.61, *SD*= 6.96, for males. Table 1 presents the baseline characteristics for the overall sample by sex.

Family History and Risk of Alzheimer's Disease: Female Probands

Compared to non-case females, those who developed AD were more likely to have an APOE Ɛ4 allele (57% compared to 26.2) and a first-degree relative with AD (31.9% compared to 19.1%). Table 2 presents the risk factors by cognitive outcome.

Among females, having a first-degree relative with AD (vs. none) was associated with a 66% increase in the odds of developing AD, *Odds Ratio (OR)* = 1.66, *95%* Confidence Interval (CI) [1.31-2.10], $p = <.001$, when controlling for age at baseline,

Table 1

Overall Baseline Characteristics by Sex

Characteristic	Males (n = 1520)				Females (n = 2157)					
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Individual-Level Variables										
Alzheimer's Disease									18.47**	
Positive AD Diagnosis	287	18.9			538	24.9				
Non-Case	1233	81.1			1619	75.1				
Age at baseline			74.98	6.84			76.30	7.25		-5.63**
Education									57.59**	
High School or Less	680	44.7			1240	57.5				
Greater than High School	840	55.3			917	42.5				
APOE Ɛ4 Status									0.34	
APOE Ɛ4 Present	480	31.6			702	32.5				
APOE Ɛ4 Absent	1040	68.4			1455	67.5				
Family History Variables										
Direct Maternal Lineage of AD[a]									0.4	
Positive History	186	12.2			248	11.5				
Negative History	1334	87.8			1909	88.5				
Direct Paternal Lineage of AD[a]									1.33	
Positive History	94	6.2			113	5.2				
Negative History	1426	93.8			2044	94.8				
First-Degree Relative with AD[b]									0.4	
At Least One	329	21.6			487	22.6				
None	1191	78.4			1670	77.4				
Second-Degree Relative with AD[c]									0.09	
At Least One	285	18.8			414	19.2				
None	1235	81.2			1743	80.8				
Third-Degree Relative with AD[d]									2.58	
At Least One	947	62.3			1286	59.6				
None	573	37.7			871	40.4				
At Least One	947	62.3			1286	59.6				
Any Relative with AD Extending Back 4 Generations									0.56	
At Least One	1090	71.7			1521	70.5				
None	430	28.3			636	29.5				
Maternal Longevity									0.42	
Survival to age 87	489	32.2			717	33.2				
Survival to age 86 or below	1031	67.8			1440	66.8				
Paternal Longevity									0	
Survival to age 87	300	19.7			424	19.7				
Survival to age 86 or below	1220	80.3			1733	80.3				
Cardiovascular Variables										
Atrial Fibrillation									0	
Yes	50	3.3			70	3.2				
None	1470	96.7			2087	96.8				
Stroke									0.38	
Yes	142	9.3			216	10				
None	1378	90.7			1941	10				

Characteristic	Males (n = 1520)				Females (n = 2157)					
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Diabetes Mellitus									7.33*	
Yes	316	20.8			371	17.2				
None	1204	79.2			1786	82.8				
Hypertension									59.48**	
Yes	768	50.5			1366	63.3				
None	752	49.5			791	36.7				
Cholesterol/Triglycerides									3.4	
Yes	588	38.7			901	41.8				
None	932	61.3			1256	58.2				
Obesity									2.01	
Yes	—[e]	—[e]			12	0.6				
None	1517	99.8			2145	99.4				
Hypothyroidism									16.81**	
Yes	41	2.7			120	5.6				
None	1497	97.3			2037	94.9				
Myocardial infarction									73.37**	
Yes	344	22.6			258	12				
None	1176	77.4			1899	88				
Atherosclerosis									0.78	
Yes	33	2.2			51	2.4				
None	1487	97.8			2106	97.6				
Other Dysrhythmias									0.21	
Yes	69	4.5			90	4.2				
None	1451	95.5			2067	95.8				
Congestive Heart Failure									8.53*	
Yes	85	5.6			176	8.2				
None	1435	94.4			1981	91.8				

Note. N = 3677. AD = Alzheimer's disease; APOE = apolipoprotein; GED = General Educational Development.
[a] Direct Lineage is parents, grandparents and great grandparents extending back three generations.
[b] Parents, siblings, offspring
[c] Grandparents, grandchildren, half-siblings, aunts/uncles, nieces/nephews
[d] First cousins, great grandparents, great grandchildren, great aunts/uncles
[e] Subsample size was suppressed because it was under the Health Portability and Accountability Act's (HIPAA's) threshold for reporting data on this variable.
*p < .05. **p < .001.

age^2, education, and the presence of an APOE Ɛ4 allele. *P*-values for each predictor ranged from p =<.001 to .380 (see Table 3). Figure 1 presents a probability plot of risk of AD for females with compared to those without a first-degree relative with AD across various ages. Probability plots were produced in R (RStudio Team, 2021), and represent the division of the odds by one plus the odds. Binary logistic regression models for having a second-degree relative only, third-degree relative only, or any relative with AD were not significant. The interaction between the presence of an APOE Ɛ4 and each of the above family history variables was also not significant (each interaction p > .126).

Table 2

Predictor Variables by Alzheimer's disease or Non-Case Outcomes in Female Probands

	Non-Case (n = 1643)				Alzheimer's Disease (n = 551)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			75.14	6.84			79.63	7.32		-13.1**
Education									0.11	
High School or Less	942	57.3			321	58.3				
Greater than High School	701	42.7			230	41.7				
APOE Ɛ4 Status									119.83**	
APOE Ɛ4 Present	430	26.2			284	51.5				
APOE Ɛ4 Absent	1213	73.8			267	48.5				
First-Degree Relative with AD[a]									38.85**	
At Least One	313	19.1			176	31.9				
None	1330	80.9			375	68.1				
Second-Degree Relative with AD[b]										
At Least One	298	18.1			118	21.4				
None	1345	81.9			433	78.6				
Third-Degree Relative with AD[c]									0.11	
At Least One	960	58.4			327	59.3				
None	683	41.6			224	40.7				
Any Relative with AD Extending Back Four Generations									3.92*	
At Least One	1123	68.4			402	73				
None	520	31.6			149	27				

Note. N = 2194. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
[b] Grandparents, grandchildren, half-siblings, aunts/uncles, nieces/nephews
[c] First cousins, great grandparents, great grandchildren, great aunts/uncles
*p < .05. **p < .001.

Table 3

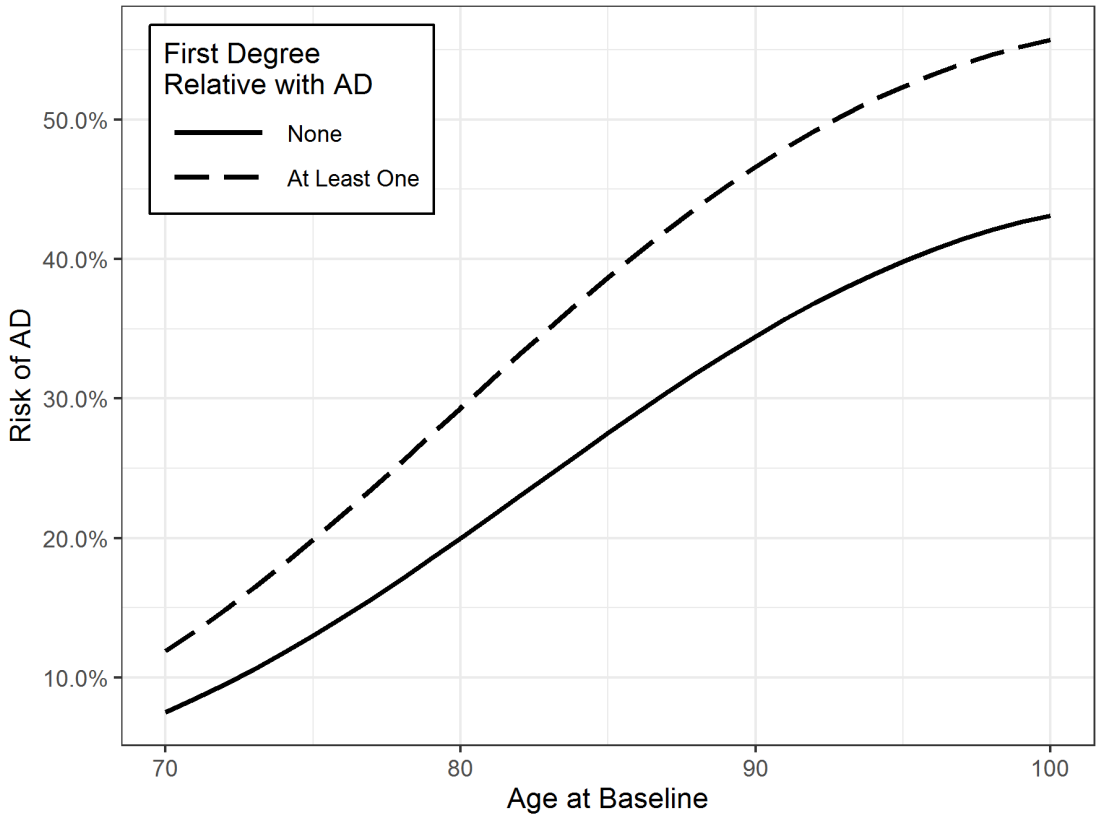
Females: Binary Logistic Regression With Extended Family History

Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	OR 95% *CI* Lower	OR 95% *CI* Upper
Intercept	-0.21	5.46	-3.83	1	<.001**	8.08^{-10}	1.65^{-14}	3.38^{-05}
Age, Years	0.40	0.14	2.87	1	.004*	1.48	1.14	1.95
Age^2, Years	-0.002	0.0008	-2.19	1	.029*	0.998	0.996	0.998
APOE Ɛ4 Status	1.26	0.11	11.40	1	<.001**	3.53	2.84	4.38
Education, High School Education or Less	0.10	0.11	0.88	1	.380	1.10	0.89	1.36
First-Degree Relative with AD[a]	0.51	0.12	4.22	1	<.001**	1.66	1.31	2.10

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
*$p < .05$. **$p < .001$.

Figure 1

Female Probands: First Degree Relative With Alzheimer's Disease



Note. This figure presents the probability of AD for females without the presence of an APOE Ɛ4 allele and with a high school/GED or less education by a first-degree relative with AD (vs. none) across various ages. First-degree relatives include parents, siblings, and offspring. AD= Alzheimer's Disease.

Family History and Risk of Alzheimer's Disease: Male Probands

Males with AD compared to non-cases, were more likely to have an APOE Ɛ4 allele (51.6% vs. 26.8%), a first-degree relative with AD (30.4% compared to 19.2%), a third degree relative with AD (66.8% vs. 60.2%), and at least one relative with AD extending back four generations (76.8% compared to 69.4). Table 4 presents the predictor variables for males by cognitive outcome.

Table 4

Predictor Variables by Alzheimer's Disease or Non-Case Outcomes in Male Probands

	Non-Case (n = 1252)				Alzheimer's Disease (n = 289)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			75.10	6.86			77.92	7.27		-7.9**
Education									1.76	
High School or Less	550	43.9			140	48.4				
Greater than High School	702	56.1			149	51.6				
APOE Ɛ4 Status									65.39*	
APOE Ɛ4 Present	336	26.8			149	51.6				
APOE Ɛ4 Absent	916	73.2			140	48.4				
First-Degree Relative with AD[a]									16.88**	
At Least One	241	19.2			88	30.4				
None	1011	80.8			201	69.6				
Second-Degree Relative with AD[b]									1.74	
At Least One	224	17.9			62	21.5				
None	1028	82.1			227	78.5				
Third-Degree Relative with AD[c]									3.99*	
At Least One	754	60.2			193	66.8				
None	498	39.8			96	33.2				
Any Relative with AD Extending Back Four Generations									5.88*	
At Least One	869	69.4			222	76.8				
None	383	30.6			67	23.2				

Note. N = 1541. AD = Alzheimer's Disease; APOE = Apolipoprotein; GED = General Educational Development.
[a] Parents, siblings, offspring
[b] Grandparents, grandchildren, half-siblings, aunts/uncles, nieces/nephews
[c] First cousins, great grandparents, great grandchildren, great aunts/uncles
*p < .05. **p < .001.

Among males, having a first-degree relative with AD (vs. none) was associated with a 58% increase in the odds of developing AD, *OR* = 1.58, *95%* CI [1.16-2.13], *p* = .003, when controlling for baseline age, education, and the presence of an APOE Ɛ4 allele. *P*-values for each predictor ranged from *p*=<.001 to .414 (see Table 5). Figure 2 presents a probability plot of risk of AD for males with a first-degree with AD compared to those without a first-degree relative with AD across various ages. Binary logistic regression models for having a second-degree relative only, third-degree relative only, or at least one relative with AD extending back four generations were not significant. The interaction between presence of an APOE Ɛ4 allele and each of the above family history variables was also not significant (each interaction $p > .230$)

Table 5

Males: Binary Logistic Regression With Extended Family History

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-8.55	0.80	-10.64	1	<.001**	0.0001	0.00004	0.0009
Age, Years	0.08	0.01	8.53	1	<.001**	1.09	1.07	1.11
APOE Ɛ4 Status	1.19	0.14	8.40	1	<.001**	3.30	2.50	4.36
Education, High School Education or Less	0.12	0.14	0.82	1	.414	1.12	0.85	1.48
First-Degree Relative with AD[a]	0.45	0.16	2.93	1	.003*	1.58	1.16	2.13

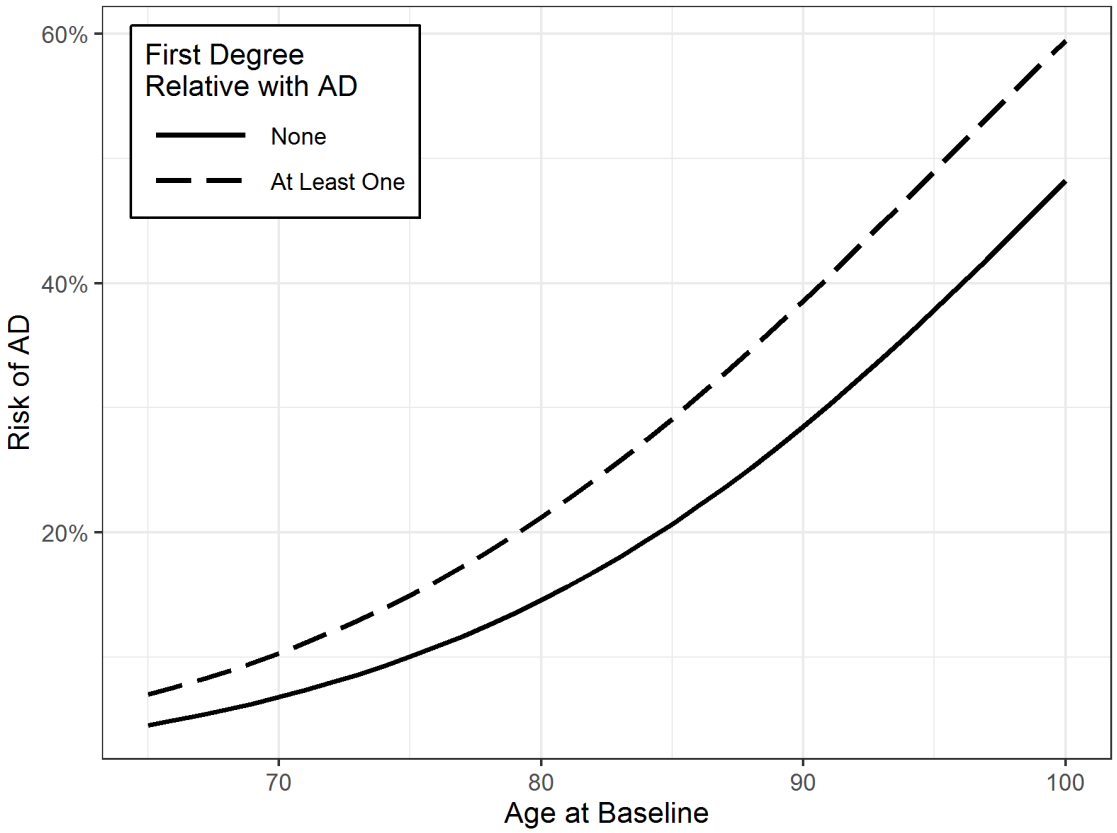
Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.

[a] Parents, siblings, offspring

*$p < .05$. **$p < .001$.

Figure 2

Male Probands: First Degree Relative With Alzheimer's Disease



Note. This figure presents the probability of AD for males without the presence of an APOE Ɛ4 allele and with a high school/GED or less education by a first-degree relative with AD (vs. none) across various ages. First-degree relatives include parents, siblings, and offspring. AD = Alzheimer's Disease.

Risk of Alzheimer's Disease for Direct Maternal and Paternal Lineage of Alzheimer's Disease Among Female Probands

Female probands with AD were more likely to be older, have an APOE Ɛ4 allele (51.7% compared to 26.1%) and a direct maternal lineage of AD (13.9% vs. 10.5%) compared to non-case females. Table 6 presents the predictor variables for direct maternal and paternal lineage of AD for female probands.

Table 6

Predictor Variables Including Maternal and Paternal Lineage of Alzheimer's Disease and Cognitive Outcomes in Female Probands

	Non-Case (n = 1707)				Alzheimer's Disease (n = 567)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			75.13	6.86			79.68	7.30		-13.47**
Education									0.18	
High School or Less	1304	57.3			330	58.2				
Greater than High School	920	42.7			237	41.8				
APOE Ɛ4 Status									125.48**	
APOE Ɛ4 Present	446	26.1			293	51.7				
APOE Ɛ4 Absent	1261	73.9			274	48.3				
Direct Maternal Lineage of AD[a]									4.69*	
Positive History	179	10.5			79	13.9				
Negative History	1528	89.5			488	86.1				
Direct Paternal Lineage of AD[a]									3.24	
Positive History	82	4.8			39	6.9				
Negative History	1625	95.2			528	93.1				

Note. N = 2274. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Direct Lineage is parents, grandparents and great grandparents extending back three generations.
*p < .05. **p < .001.

Compared to females with no family history of AD, direct maternal (but not paternal, p = .101) lineage of AD was associated with a 56% increase in the odds of developing AD, *OR* = 1.56, *95%* CI [1.14-2.13], p = .005, when controlling for age at baseline, age^2, education, and presence of the APOE Ɛ4 allele. Figure 3 presents a probability plot of risk of AD for females with a direct maternal lineage of AD across various ages. *P*-values for each predictor variable ranged from p =<.001to .427 (see Table 7). The interaction between the presence of an APOE Ɛ4 and the above direct lineage variables was non-significant as was the interaction between direct maternal and paternal lineage of AD (p values ranged from .133 to .757).

Table 7

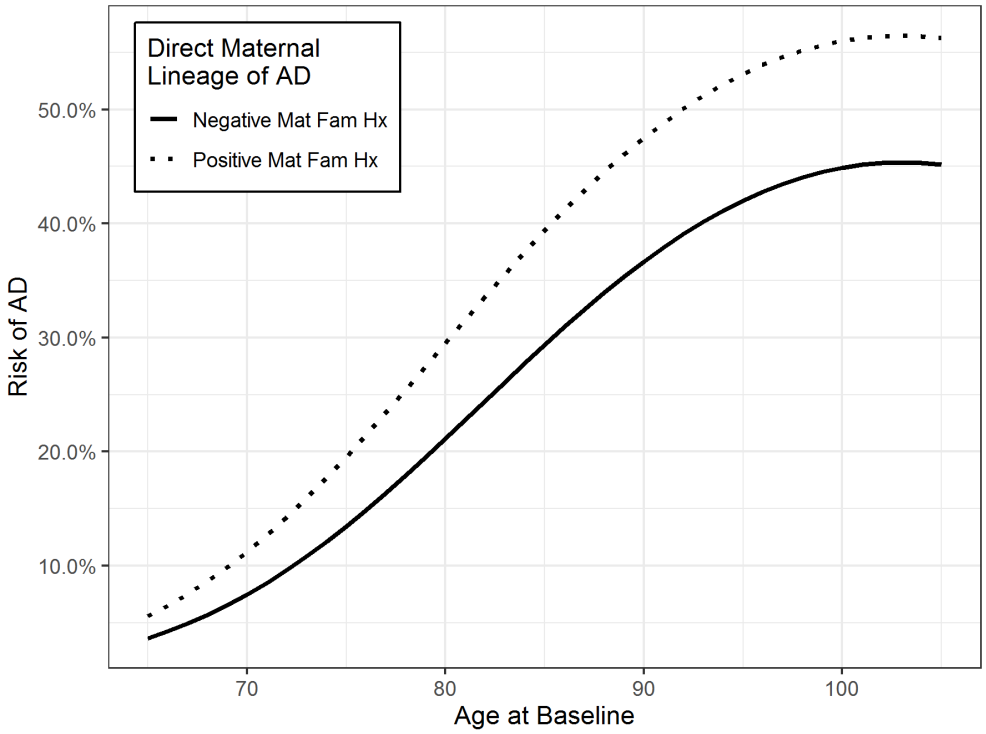
Females: Binary Logistic Regression With Direct Maternal and Paternal Lineage of Alzheimer's Disease

Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	OR 95% *CI* Lower	OR 95% *CI* Upper
Intercept	-22.91	5.38	-5.05	1	<.001**	<0.001	0.000	0.000
Direct Maternal Lineage of AD	0.45	0.22	2.43	1	.005*	1.56	1.14	2.13
Direct Paternal Lineage of AD	0.37	0.22	1.79	1	.101	1.44	0.92	2.22
APOE Ɛ4 Status	1.26	0.11	10.77	1	<.001**	3.53	2.86	4.39
Education, High School Education or Less	0.08	0.11	1.17	1	.427	1.09	0.88	1.34
Age, Years	0.44	0.14	4.11	1	.001*	1.55	1.19	2.03
Age^2, Years	-0.002	0.0009	-3.52	1	.012*	0.998	0.996	0.999

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
*p < .05. **p < .001.

Figure 3

Direct Maternal Lineage of Alzheimer's Disease in Females



Note. This figure presents the probability of AD for females without the presence of an APOE Ɛ4 allele and with a high school/GED or less education by a direct maternal lineage of AD (vs. none) across various ages. Direct Maternal Lineage of AD is presented in Appendix C. AD = Alzheimer's Disease.

Risk of Alzheimer's Disease for Direct Maternal and Paternal Lineage of Alzheimer's Disease Among Male Probands

Compared to male non-cases, males with AD were more likely to be older at baseline and have an APOE Ɛ4 Allele. Predictor variables for maternal and paternal direct lineage of AD for male probands is presented in Table 8.

Table 8

Predictor Variables Including Maternal and Paternal Lineage of Alzheimer's Disease and Cognitive Outcomes in Male Probands

	Non-Case (*n* = 1314)				Alzheimer's Disease (*n* = 299)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			75.10	6.85			77.94	7.31		-7.94**
Education										
High School or Less	796	44.4			143	47.8			1.47	
Greater than High School	995	55.6			156	52.2				
APOE Ɛ4 Status									71.79**	
APOE Ɛ4 Present	348	26.5			155	51.8				
APOE Ɛ4 Absent	966	73.5			144	48.2				
Direct Maternal Lineage of AD[a]									0.81	
Positive History	157	11.9			42	14				
Negative History	1157	88.1			257	86				
Direct Paternal Lineage of AD[a]									0.46	
Positive History	76	5.8			21	7				
Negative History	1238	94.2			278	93				

Note. *N* = 1613. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Direct Lineage is parents, grandparents and great grandparents extending back three generations.
*$p < .05$. **$p < .001$.

Among males, neither maternal, *OR*= 1.38, *p*= .19, nor paternal, *OR*= 1.69, *p*= .07, lineage of AD was associated with risk of AD in the proband. However, an interaction between maternal and paternal lineage was significant at a trend level *p* = .054 level, *OR*= 0.22, 95% CI [0.05-0.93], with males who had both a direct maternal and paternal lineage of AD having a 51.3% *reduced* odds of developing AD compared to

males with neither. This result was maintained with the following covariates: age at baseline, presence of an APOE Ɛ4 allele, and education. *P*-values for the covariates ranged from *p*= < .001 to .433 (see Table 9). Figure 4 presents a probability plot of the risk of AD for males from the model with the interaction between paternal and maternal lineage of AD. The interactions between the presence of an APOE Ɛ4 allele and each of the family history variables were not significant (each interaction *p*> .117).

Table 9

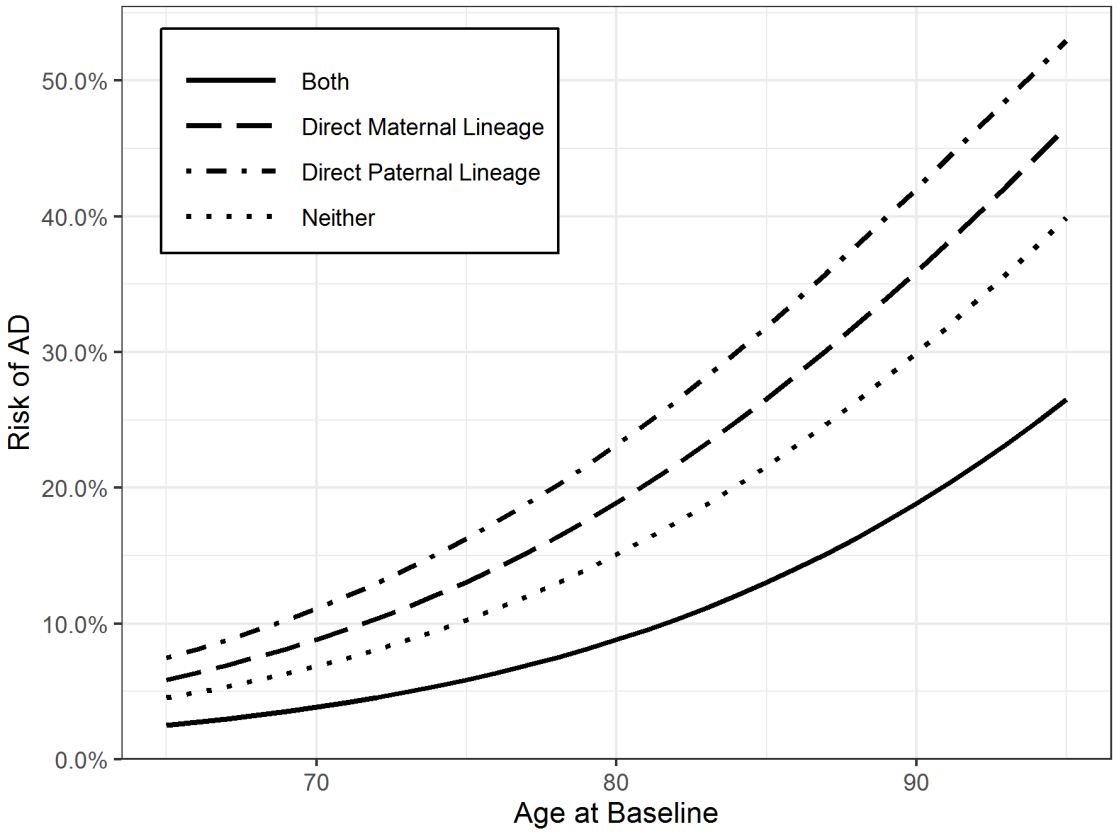
Males: Binary Logistic Regression With Direct Maternal and Paternal Lineage of Alzheimer's Disease

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-8.76	0.80	-10.96	1	<.001**	0.0001	0.000	0.000
Direct Maternal Lineage of AD	0.27	0.21	1.30	1	.193	1.31	0.86	1.96
Direct Paternal Lineage of AD	0.52	0.21	1.78	1	.074	1.69	0.93	2.98
APOE Ɛ4 Status	1.23	0.30	8.90	1	<.001**	3.48	2.65	4.59
Education, High School Education or Less	0.11	0.14	0.78	1	.433	1.11	0.85	1.47
Age, Years	0.09	0.14	8.94	1	<.001**	1.09	1.07	1.11
Direct Maternal Lineage of AD × Direct Paternal Lineage of AD	-1.41	0.73	-1.92	1	.054	0.22	0.05	0.93

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
*$p < .05$. **$p < .001$.

Figure 4

Direct Parental Lineage of Alzheimer's Disease in Males



Note. This figure presents the probability of AD for males without the presence of an APOE Ɛ4 allele and with a high school/GED or less education by a direct maternal and/or paternal lineage of AD (vs. none) across various ages. This model is not the most parsimonious, however, and includes a trend level interaction between maternal and paternal lineage of AD in male probands. AD = Alzheimer's Disease.

Parental Exceptional Longevity and Alzheimer's Disease Among Female Probands

Females with AD compared to female non-cases, were more likely be older (79.72 compared to 75.16) and have a first-degree relative with AD (32.5% vs. 19.3%), but did not differ by parental longevity. Table 10 presents the predictor variables for females with parental longevity for risk of AD.

Table 10

Predictor Variables for Parental Longevity and Cognitive Outcomes in Female Probands

	Non-Case (n = 1619)				Alzheimer's Disease (n = 538)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			75.16	6.85			79.72	7.36		-12.64**
Education									0.1	
High School or Less	1240	57.5			313	58.2				
Greater than High School	917	42.5			225	41.8				
APOE Ɛ4 Status									113.72	
APOE Ɛ4 Present	702	32.5			276	51.3				
APOE Ɛ4 Absent	1455	67.5			262	48.7				
Maternal Longevity									0.78	
Survival to age 87	717	33.2			170	31.6				
Survival to age 86 or below	1440	66.8			368	68.4				
Paternal Longevity									0.01	
Survival to age 87	317	19.6			107	19.9				
Survival to age 86 or below	1302	80.4			431	80.1				
First-Degree Relative with AD (Parents, Siblings, Offspring)									39.84**	
At Least One	312	19.3			175	32.5				
None	1307	80.7			363	67.5				
Parental Longevity									0.05	
Survival to age 87	739	54.4			242	45				
Survival to age 86 or below	880	45.6			296	55				

Note. N = 2157. AD = Alzheimer's Disease; APOE = Apolipoprotein.
*p < .05. **p < .001.

Neither exceptional maternal longevity, *OR*= 0.96, *95%* CI [0.76-1.20], *p*= .713, nor exceptional paternal longevity, *OR*=1.09, *95%* CI [0.83-1.42], *p*=.537, was associated with risk for AD in the proband, when controlling for age at baseline, education, and first-degree relative with AD. *P*-values for the predictor variables ranged from <.001 to .713 (see Table 11). The interaction between the presence of an APOE Ɛ4 allele and exceptional maternal longevity and the interaction between each parental longevity

variable were also not significant (each individual $p > .597$). However, the interaction between paternal exceptional longevity and APOE Ɛ4 was significant at trend level, with the presence of one or more APOE Ɛ4 alleles and having a longer-lived father being associated with 4.59 greater odds of developing AD, *OR*= 4.59, *p*=.063.

Table 11

Females: Binomial Logistic Regression With Maternal and Paternal Longevity and Risk of Alzheimer's Disease

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-9.14	0.62	-14.80	1	<.001**	<0.000	<0.001	<0.001
Maternal Longevity	-0.04	0.12	-0.36	1	.713	0.96	0.76	1.20
Paternal Longevity	0.08	0.14	0.62	1	.537	1.09	0.83	1.42
First-Degree Relative with AD[a]	0.53	0.12	4.40	1	<.001**	1.70	1.34	2.15
APOE Ɛ4 Status	1.24	0.12	11.13	1	<.001**	3.47	2.79	4.32
Education, High School Education or Less	0.09	0.11	0.79	1	.429	1.09	0.88	1.35
Age	0.10	0.01	12.58	1	<.001**	1.10	1.08	1.11

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
*$p < .05$. **$p < .001$.

Parental Exceptional Longevity and Alzheimer's Disease Among Male Probands

Males with AD (vs. non-case), were older, more likely to have an APOE Ɛ4 allele (59.1% compared to 31.6%) and have a first-degree relative with AD (30.7% compared to 19.5%). Table 12 presents the predictor variables for male probands with parental longevity and risk for AD.

Table 12

Predictor Variables for Parental Longevity and Cognitive Outcomes in Male Probands

	Non-Case (n = 1233)				Alzheimer's Disease (n = 287)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			74.29	6.55			77.91	7.28		-7.73**
Education									1.77	
High School or Less	541	43.9			139	48.4				
Greater than High School	692	56.1			148	51.6				
APOE Ɛ4 Status									66.57**	
APOE Ɛ4 Present	480	31.6			149	51.9				
APOE Ɛ4 Absent	1040	68.4			138	48.1				
Maternal Longevity									1.21	
Survival to age 87	405	32.8			84	29.3				
Survival to age 86 or below	828	67.2			203	70.7				
Paternal Longevity									0.00	
Survival to age 87	243	19.7			57	19.9				
Survival to age 86 or below	990	80.3			230	80.1				
First-Degree Relative with AD (Parents, Siblings, Offspring)									16.31**	
At Least One	241	19.5			88	30.7				
None	992	80.5			199	69.3				
Parental Longevity									0.02	
Survival to age 87	562	45.6			129	44.9				
Non-Longer-Lived Parents	671	54.			158	55.1				

Note. N = 1975. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
*p < .05. **p < .001.

In male probands, there was a significant interaction between APOE Ɛ4 and exceptional maternal longevity (p = .020) and a significant interaction between maternal and paternal exceptional longevity (p = .041). With respect to the results of APOE Ɛ4 and maternal longevity, males who had a long-lived mother and at least one APOE Ɛ4 allele had triple the odds of AD, OR=3.15, p = .020, compared to males with neither attribute. Figure 5 presents the probability plot for males by exceptional maternal longevity and

APOE Ɛ4 allele status across various ages. These results were obtained controlling for age at baseline, education, any relative with AD, and paternal longevity. *P*-values for the predictor variables ranged from p= <.001 to .401 (see Table 13).

Table 13

Males: Binomial Logistic Regression With Maternal and Paternal Longevity and Risk of Alzheimer's Disease

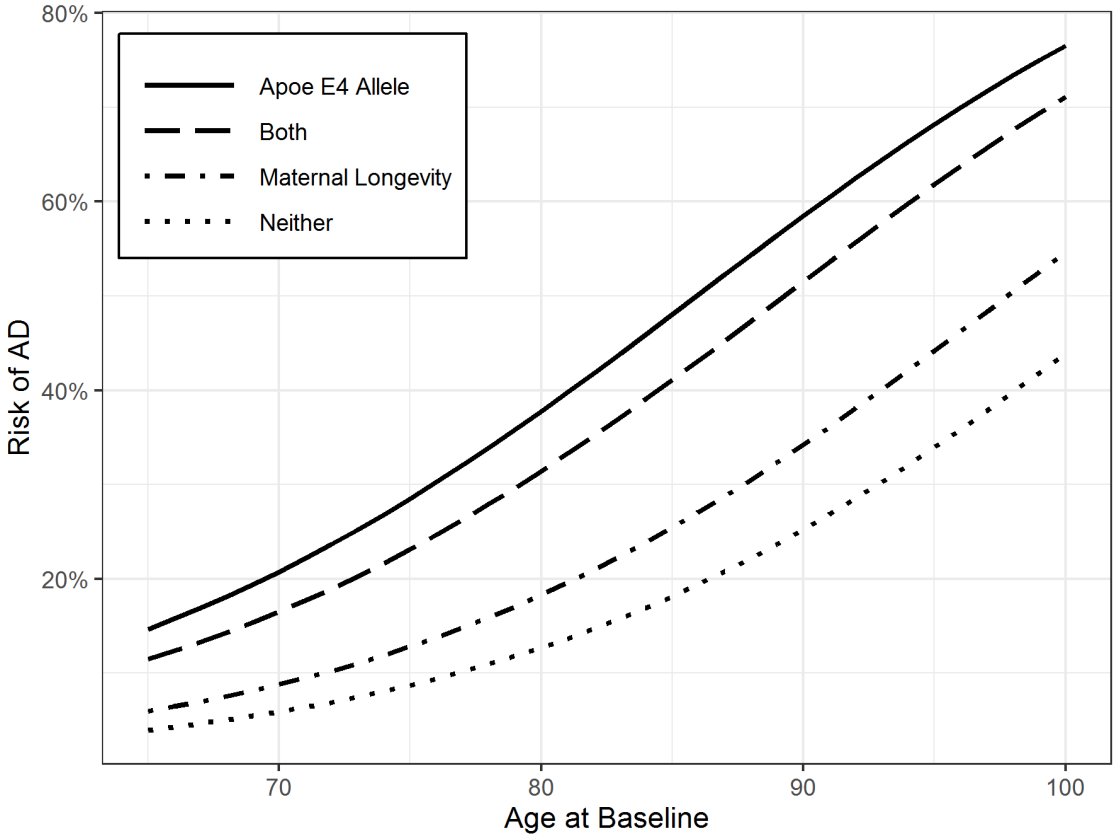
							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-8.66	0.83	-10.46	1	<.001**	<0.001	0.000	0.003
Maternal Longevity	0.43	0.21	2.03	1	.042*	1.54	1.01	2.33
Paternal Longevity	0.28	0.20	1.38	1	.171	1.32	0.88	1.97
First-Degree Relative with AD[a]	0.46	0.16	2.92	1	.004*	1.58	1.16	2.14
APOE Ɛ4 Status	1.43	0.17	8.28	1	<.001**	4.17	2.98	5.87
Education, High School Education or Less	0.12	0.14	0.84	1	.401	1.12	0.85	1.49
Age, Years	0.08	0.01	8.34	1	<.001**	1.09	1.07	1.11
Maternal Longevity × APOEƐ4 Status	-0.71	0.31	-2.33	1	.020*	0.49	0.27	0.89
Maternal Longevity × Paternal Longevity	-0.82	0.40	-2.04	1	.041*	0.44	0.19	0.95

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
*$p < .05$. **$p < .001$.

With respect to the interaction between maternal and paternal longevity and risk for AD, males with both a maternal and paternal history of exceptional longevity had an 11% *lower* odds of developing AD, *OR*= 0.89, *p*=.041. These results were obtained in a model controlling for baseline age, any relative with AD, education, and presence of an APOE Ɛ4 allele (*p* values ranged from <.001 to .401 for the covariates). See Table 13 for the fully adjusted model and parameter estimates. Figure 6 presents a probability plot of risk for AD for males by maternal and paternal longevity. The interaction between paternal longevity and APOE Ɛ4 allele status was non-significant (*p* = .284).

Figure 5

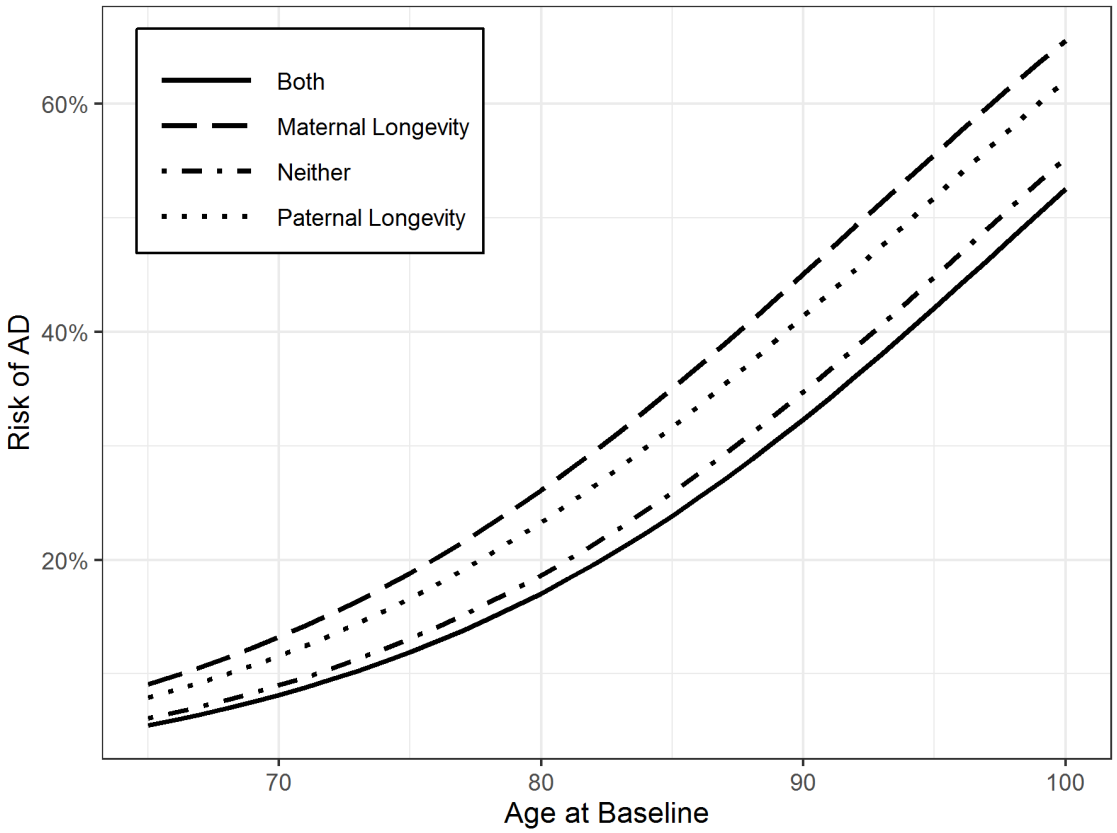
Maternal Longevity and APOE Status in Male Probands and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for males with a first-degree relative without AD and without paternal longevity and with a high school/GED or less education by maternal longevity and APOE Ɛ4 allele status across various ages. AD = Alzheimer's Disease; APOE = Apolipoprotein.

Figure 6

Maternal and Paternal Longevity in Male Probands and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for males with a first-degree relative without AD, paternal longevity, and the presence of an APOE Ɛ4 allele and with a high school/GED or less education by maternal longevity and paternal longevity across various ages. AD = Alzheimer's Disease.

Cardiovascular Risk Factors With Family History and Alzheimer's Disease

Tetrachoric correlation matrices were conducted to examine the associations between variables. Those variables that correlated above the r= 0.60 were collapsed with others based on the above criterion and their biological relationship (e.g., similar condition). Thus, atrial fibrillation and other dysrhythmias were collapsed, as was cholesterol/triglycerides and atherosclerosis. Afib/dysrhythmias remained highly correlated with hypothyroidism and CHF, but as they were less related biologically, were

tested separately in the model. Appendix D presents the output of the tetrachoric correlation matrices. Random forest analyses were conducted separately for each variable. In females, hypothyroidism, afib/dysrhythmias, CHF, HTN, and chol/athero resulted in the greatest decrease in the mean Gini (Gini importance is a metric of decreasing misclassification of the outcome variable, with smaller values indicating better classification accuracy; Menze et al., 2009; see Appendix D). In males, afib/dysrhythmias, hypothyroidism, CHF, MI, and HTN reduced the mean Gini (see Appendix D). Using the LASSO regression procedure with a cross-validated Lambda (Lambda value corresponding to the minimum mean-squared error; Tibshirani, 1996) found CHF, CVA, DM, obesity, hypothyroidism, and afib/dysrhythmias most predictive of the outcome variable for both females and males (see Appendix D). The random forest and Lasso regression outcomes were used in tandem to select the above-mentioned vascular variables for the binary logistic regression models for each sex.

Examination of Cardiovascular Risk Factors With Family History and Alzheimer's Disease Among Female Probands

Among females, those with AD (vs. non-case) were more likely to have a history of a CVA (15.7% vs. and 8%), obesity (2.6% compared to 0%), hypothyroidism (22.2% vs. 0%), afib/dysrhythmias (22.4% compared to 0%), CHF (15.7% vs. 2.8%), but less likely to have chol/athero (37.6% compared to 44.1%). Table 14 presents the predictor variables for the cardiovascular risk factors and family history of AD for female probands.

Table 14

Predictor Variables for Cardiovascular Risk Factors and Family History of Alzheimer's Disease and Cognitive Outcomes in Female Probands

	Non-Case (n = 1707)				Alzheimer's Disease (n = 567)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			76.19	7.33			79.68	7.30		-13.47**
Education									0.18	
High School or Less	974	57.3			330	58.2				
Greater than High School	733	42.9			237	41.8				
APOE Ɛ4 Status									125.48**	
APOE Ɛ4 Present	446	26.1			293	51.7				
APOE Ɛ4 Absent	1261	73.9			274	48.3				
Direct Maternal Lineage of AD[a]									4.69*	
Positive Maternal History	179	10.5			79	13.9				
Negative Maternal History	1528	89.5			488	79				
Direct Paternal Lineage of AD[a]									3.24	
Positive Paternal History	82	4.8			39	6.9				
Negative Paternal History	1625	95.2			528	93.1				
Stroke									27.66**	
Yes	136	8			89	15.7				
None	1571	92			478	84.3				
Diabetes Mellitus									2.47	
Yes	307	18			85	15				
None	1400	82			482	85				
Hypertension									2.24	
Yes	1055	61.8			371	65.4				
None	652	38.2			196	34.6				
Cholesterol/Triglycerides/ Atherosclerosis									7.07*	
Yes	752	44.1			213	37.6				
None	955	55.9			254	62.4				
Obesity									41.51**	
Yes	0	0			15	2.6				
None	1707	100			552	97.4				
Hypothyroidism									397.35**	
Yes	0	0			126	22.2				
None	1707	100			441	77.8				
Myocardial infarction									0.02	
Yes	211	12.4			68	12				
None	1496	87.6			499	88				

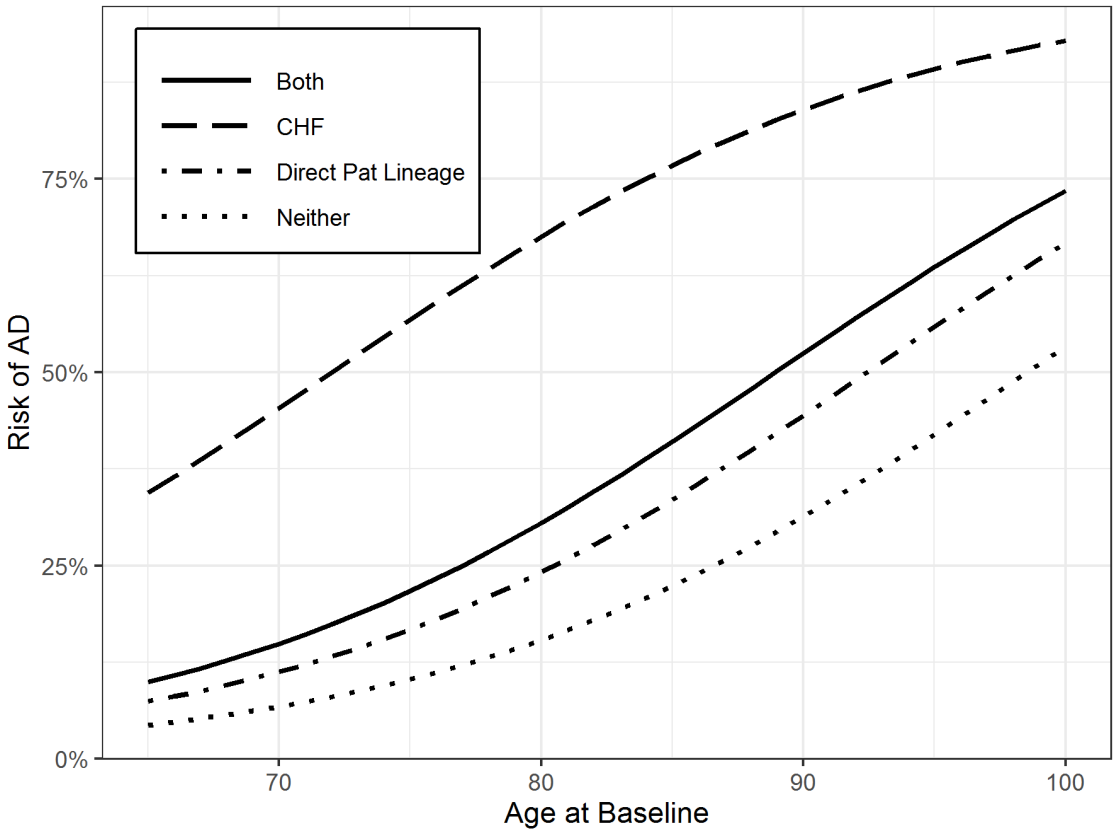
Characteristic	Non-Case (n = 1707)				Alzheimer's Disease (n = 567)					
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Atrial Fibrillation and Other Dysrhythmias									400.72*	
Yes	0	0			127	22.4				
None	1707	100			440	77.6				
Congestive Heart Failure									259.45**	
Yes	47	2.8			137	15.7				
None	1660	97.2			430	75.8				

Note. N = 2274. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Parents, siblings, offspring
*p < .05. **p < .001.

Among females, there was an interaction between CHF and paternal lineage of AD such that those with both attributes were at a 2-fold increase in the odds of developing AD, *OR*= 2.26, *p* =.013, compared to those females with neither attribute. See Figure 7 for a probability plot for females with a history of CHF and a direct paternal linage of AD.

Figure 7

Females With Direct Paternal Lineage of Alzheimer's Disease and Congestive Heart Failure With Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for female probands without the presence of an APOE Ɛ4 allele, MI, CVA, direct maternal lineage of AD, and with a high school/GED or less education by a history of CHF and direct paternal lineage of AD across various ages. AD = Alzheimer's Disease; CHF = Congestive Heart Failure; Pat = Paternal.

Among the other vascular variables examined, females with a history of MI had a 40% lower-odds of developing AD, *OR*=0.60, *95%* CI [.42-0.84], *p*= .004, than those without a history of MI (see Figure 8), while those with a history of a CVA were at a two-fold greater risk of developing AD, *OR*= 2.11, *9*5% CI [1.50-2.96], *p*= <.001 (see Figure 9). The above results were obtained in models controlling for age at baseline, presence of an APOE Ɛ4 allele, and education. *P*-values for the predictor variables ranged from *p*=<.001 to .564 (see Table 15). Note that a trend level-interaction existed between paternal lineage of AD and chol/athero such that those who had both attributes had a 2.69 greater odds of developing AD, *OR*= 2.69, *p*=.076. The interactions between the additional cardiovascular risk factors risk factors and family history variables were non-significant (each individual *p* >.192; refer to Appendix E; Table E.1).

Table 15

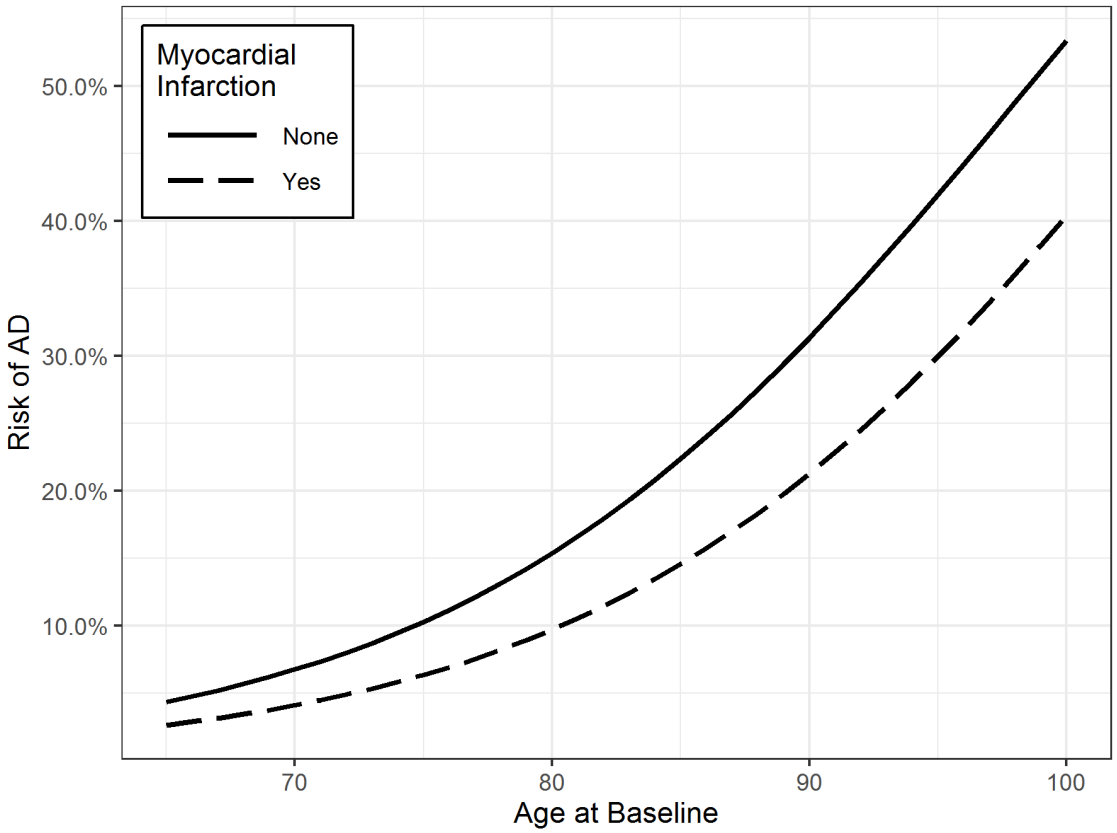
Female: Binary Logistic Regression With Cardiovascular Risk Factors and Family History of Alzheimer's Disease

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-9.27	0.64	-14.4	1	<.001**	<0.001	<0.001	<0.001
Congestive Heart Failure	2.44	0.20	11.97	1	<.001**	11.15	7.76	11.72
Myocardial Infarction	-0.51	0.18	-2.87	1	.004*	0.60	0.42	0.84
Cerebrovascular Accident	0.74	0.17	4.31	1	<.001**	2.11	1.50	2.96
Direct Maternal Lineage of AD	0.45	0.17	2.69	1	.007*	1.57	1.12	2.17
Direct Paternal Lineage of AD	0.53	0.23	2.26	1	.024*	1.69	1.06	2.67
APOE Ɛ4 Status	1.34	0.12	11.63	1	<.001**	3.85	3.07	4.84
Education, High School Education or Less	0.07	0.11	0.58	1	.564	1.07	0.85	1.33
Age, Years	0.09	0.01	11.89	1	<.001**	1.10	1.08	1.12
Direct Paternal Lineage of AD × Congestive Heart Failure	-2.10	0.83	-2.50	1	.013*	0.12	0.02	0.71

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
*$p < .05$. **$p < .001$.

Figure 8

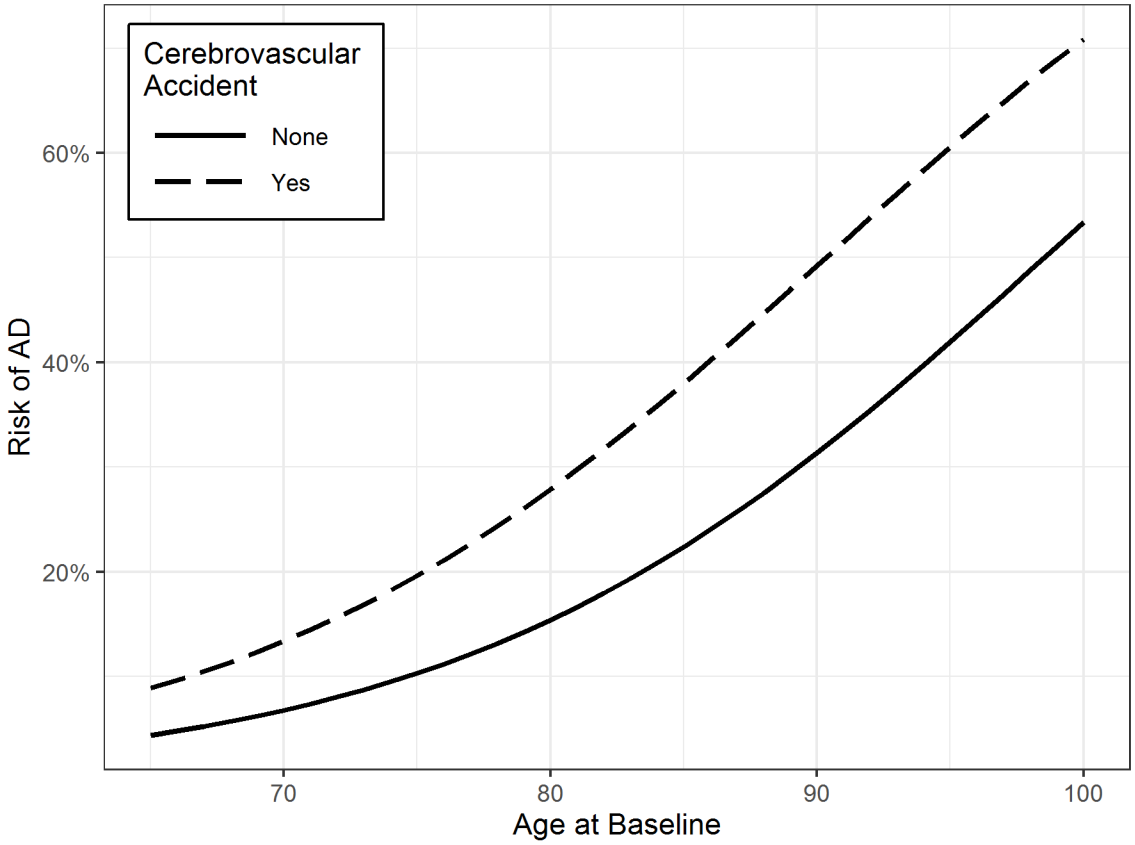
Myocardial Infarction in Females and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for females without the presence of an APOE Ɛ4 allele, CHF, CVA, and direct lineage of maternal and paternal of AD and with a high school/GED or less education by history of MI (vs. none). AD = Alzheimer's Disease.

Figure 9

Cerebrovascular Accident in Females and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for female probands with a history of CVA (vs. none) by risk for AD across various ages. This is for female probands without the presence of an APOE Ɛ4 allele, MI, CHF, and direct maternal and paternal lineage of AD with a high school education/GED/ or less. AD = Alzheimer's Disease.

Cardiovascular Risk Factors With Family History and Alzheimer's Disease Among Male Probands

Compared to males without AD, those with AD were more likely to have a history of HTN (57.9% compared to 48.9%), obesity (1% compared to 0%), hypothyroidism (14% compared to 0%), afib/dysthymias (31.4% compared to 0%), and CHF (20.7% compared to 0%). Table 16 presents the predictor variables for males with cardiovascular risk factors and a family history of AD.

Table 16

Predictor Variables for Cardiovascular Risk Factors and Family History of Alzheimer's Disease and Cognitive Outcomes in Male Probands

	Non-Case (n = 1314)				Alzheimer's Disease (n = 299)					
Characteristic	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Age at baseline			74.29	6.55			77.94	7.31		-7.94**
Education									1.47	
High School or Less	575	43.8			143	47.8				
Greater than High School	739	56.2			156	52.2				
APOE Ɛ4 Status									71.79**	
APOE Ɛ4 Present	348	26.5			155	51.8				
APOE Ɛ4 Absent	966	73.5			144	48.2				
Direct Maternal Lineage of AD[a]									0.81	
Positive Maternal History	157	11.9			42	14				
Negative Maternal History	1157	88.1			257	86				
Direct Paternal Lineage of AD[a]									0.46	
Positive Paternal History	76	5.8			21	7				
Negative Paternal History	1238	94.2			278	93				
Stroke									16.58**	
Yes	104	7.9			47	15.7				
None	1210	92.1			252	84.3				
Diabetes Mellitus									2.7	
Yes	262	19.9			73	24.4				
None	1052	80.1			226	75.6				
Hypertension									7.41*	
Yes	643	48.9			173	57.9				
None	671	51.1			126	42.1				
Cholesterol/ Triglycerides/ Atherosclerosis									5.71*	
Yes	501	38.1			137	45.8				
None	813	61.9			162	54.2				
Obesity									8.36*	
Yes	—[b]	—[b]			3	1				
None	1314	100			296	99				
Hypothyroidism									184.01**	
Yes	0	0			42	14				
None	1314	100			257	86				
Myocardial infarction									0.01	
Yes	298	22.7			69	23.1				
None	1016	77.3			230	76.9				
Atrial Fibrillation and Other									432.95**	

Characteristic	Non-Case (*n* = 1314)				Alzheimer's Disease (*n* = 299)					
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	X^2	*t*
Dysrhythmias										
Yes	0	0			94	31.4				
None	1314	100			205	68.6				
Congestive Heart Failure									162.53**	
Yes	26	2			62	20.7				
None	1288	98			237	79.3				

Note. *N* = 1613. AD = Alzheimer's Disease; APOE = Apolipoprotein.
[a] Direct Lineage is parents, grandparents and great grandparents extending back three generations
*$p < .05$. **$p < .001$.

Unlike females, there were no interactions between vascular variables and parental family history. Individual vascular factors were associated with increased risk for AD. Specifically, males with CHF had 11 times greater odds of developing AD, *OR*=11.10, *95%* CI [7.31-20.42], *p*=<.001, those with a history of a CVA were 74% more likely to develop AD, *OR*= 1.74, *95%* CI [1.11-2.61], *p*=.013, those with a history of HTN (vs. none) 37% more likely to develop AD, *OR*= 1.37, *95%* CI [1.02-1.84], *p*=.035, and those with a history of high chol/athero were at 48% more likely to develop AD, *OR*= 1.48, *95%* CI [1.10-2.01], *p*=.011, compared to those lacking the risk factor. These results were obtained when controlling maternal family history, paternal family history, presence of an APOE Ɛ4 allele, age at baseline, and education. *P* values for the predictor variables ranged from *p*= <.001 to .660 (see Table 17). Figures 10-13 present the probability plots for each of the main effects above for male probands across various ages. While only main effects were significant for each of the vascular variables, there was a trend level interaction between CVA and direct maternal lineage of AD (p interaction = 0.069). Specifically, having a history of CVA and maternal lineage of AD was associated with a 34% reduced odds of AD, *OR*= 0.66 (see Appendix F for Table F.1 and Figure F.1). Appendix E; Table E.2 presents the other non-significant interactions between vascular variables and parental lineage of AD.

Table 17

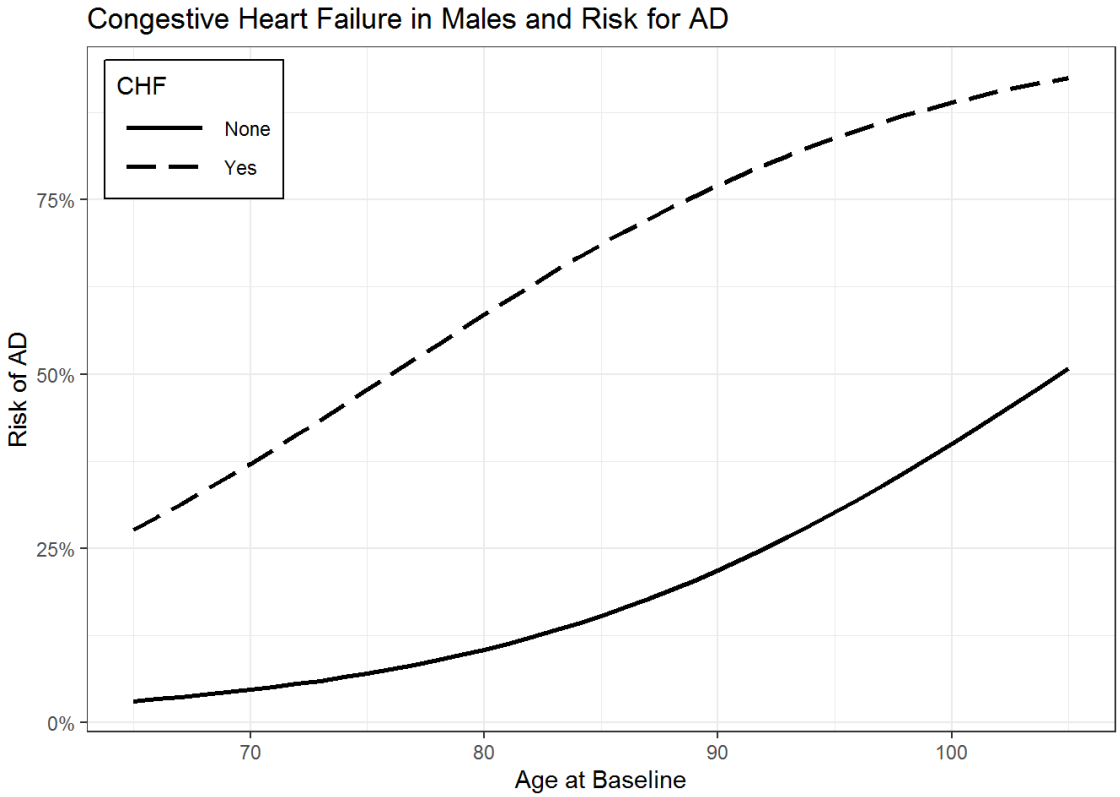
Male: Binary Logistic Regression With Cardiovascular Risk Factors and Family History of Alzheimer's Disease

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-9.64	0.90	-10.68	1	<.001**	<0.001	<0.001	<0.001
Congestive Heart Failure	2.38	0.26	9.08	1	<.001**	11.10	6.51	11.83
Cerebrovascular Accident	0.54	0.22	2.48	1	.013*	1.74	1.11	2.61
Hypertension	0.32	0.15	2.10	1	.035*	1.37	1.02	1.84
Cholesterol/Triglycerides/ Atherosclerosis	0.39	0.15	2.55	1	.011*	1.48	1.10	2.01
APOE Ɛ4 Status	1.28	0.15	8.59	1	<.001**	3.61	2.70	4.84
Direct Maternal Lineage of AD	0.15	0.21	0.69	1	.492	1.15	0.76	1.74
Direct Paternal Lineage of AD	0.29	0.28	1.03	1	.303	1.33	0.75	2.27
Education, High School Education or Less	0.06	0.15	0.44	1	.660	1.07	0.80	1.43
Age, Years	0.09	0.01	8.47	1	<.001**	1.10	1.08	1.12

Note. The final model retained had the best fit (AIC, BIC, and R-squared) while also being the most parsimonious. AD = Alzheimer's Disease; APOE = Apolipoprotein.
*$p < .05$. **$p < .001$.

Figure 10

Congestive Heart Failure in Males and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for males without the presence of an APOEƐ4 allele, CVA, HTN, chol/athero, and direct lineage of maternal and paternal of AD and with a high school/GED or less education by history of myocardial infarction (vs. none). AD = Alzheimer's Disease; CHF = Congestive Heart Failure.

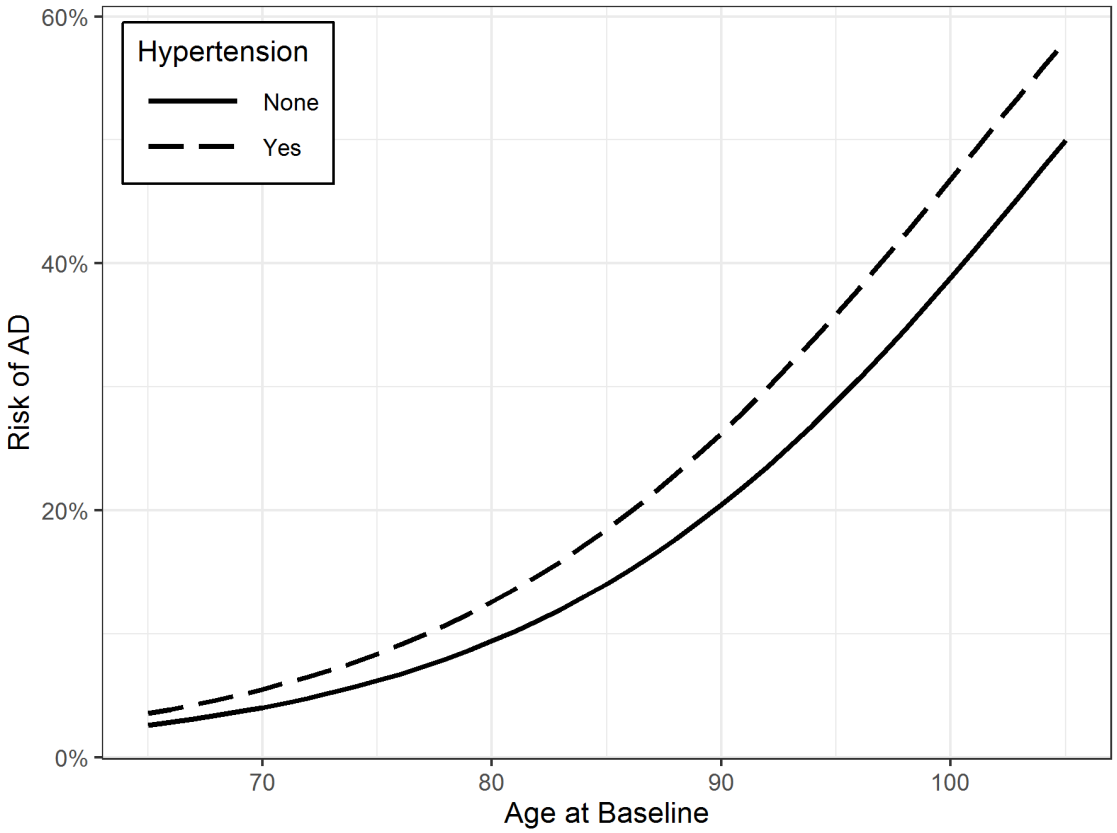
Figure 11

Males With a History of Cerebrovascular Accident and Risk for Alzheimer's Disease

Note. This figure presents the probability of AD for males without the presence of an APOEƐ4 allele, CHF, HTN, chol/athero, and direct lineage of maternal and paternal of AD and with a high school/GED or less education by history of myocardial infarction (vs. none). AD= Alzheimer's Disease.

Figure 12

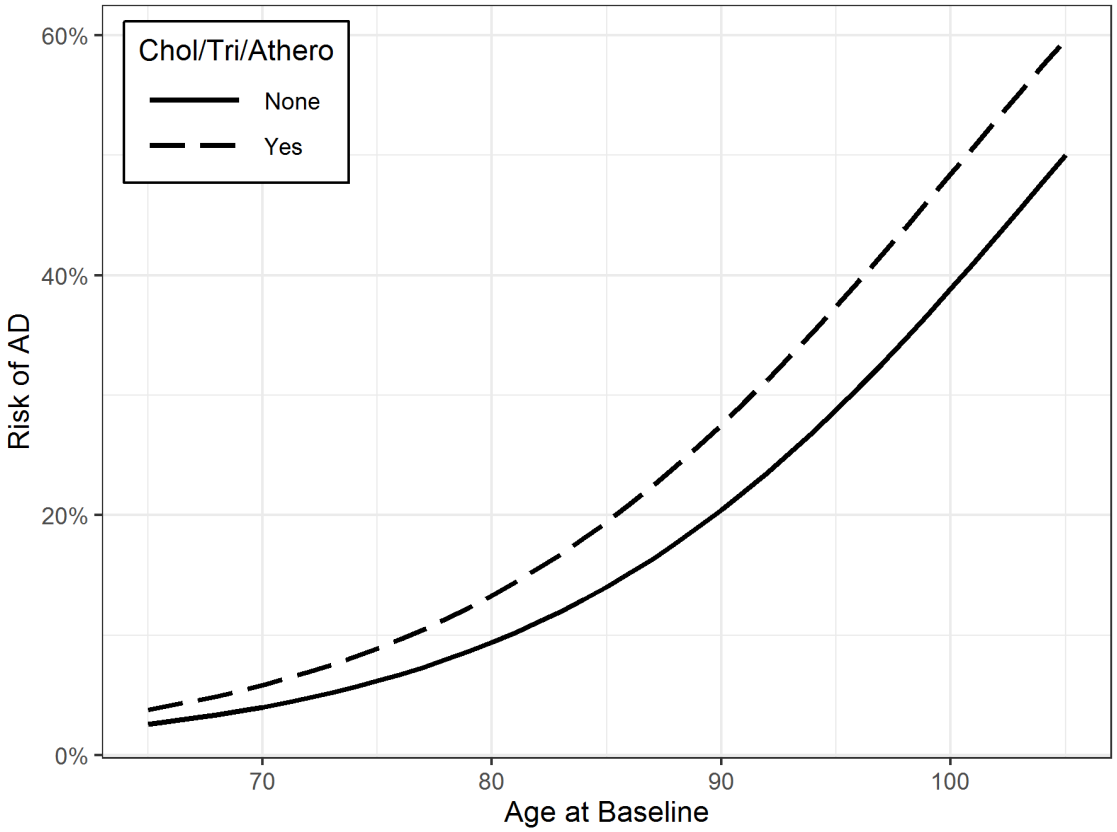
Hypertension in Males and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for males without the presence of an APOEƐ4 allele, CVA, CHF, chol/athero, and direct lineage of maternal and paternal of AD and with a high school/GED or less education by history of myocardial infarction (vs. none). AD = Alzheimer's Disease.

Figure 13

Males With a History of Cholesterol/Triglycerides/Atherosclerosis and Risk for Alzheimer's Disease



Note. This figure presents the probability of AD for males without the presence of an APOEƐ4 allele, CVA, CHF, HTN, and direct lineage of maternal and paternal of AD and with a high school/GED or less education by history of myocardial infarction (vs. none). AD= Alzheimer's Disease; Chol/Tri/Athero = Cholesterol/Triglycerides/Atherosclerosis.

Table 18 presents the overall findings for female and male probands in the current study.

Table 18

Overall Summary of the Findings for Females and Males

	Female	Male
First Degree Relative with AD	⇧ 66% (*p* = <.001; *OR*=1.66)	⇧ 58% (*p*=.003; *OR*=1.58)
Direct Maternal Lineage of AD	⇧ 56% (*p*= .005; *OR*= 1.58)	Not Significant
Direct Paternal Lineage of AD	Not Significant	Not Significant
Both Parental Lineage of AD	Not Significant	⇩ 51.3% (*p*=.054; *OR*=0.487)
Maternal Longevity	Not Significant	⇧ 54% (*p*=.041; *OR*= 1.54)
Paternal Longevity	Not Significant	⇧ 32% (*p*=.041; *OR*= 1.32)
Parental Longevity	Not Significant	⇧ 11% (*p* =.041; *OR*= 0.89)
Maternal Longevity and APOE Allele	Not Significant	⇧ 3.15-fold (*p*=.020; *OR*= 3.15)
CHF and Direct Paternal Lineage of AD	⇧ 2.26-fold (*p*=.013; *OR*=2.26)	Not Significant
Congestive Heart Failure	⇧ 11.15-fold (*p*=<.001; *OR*=11.15)	⇧ 11.10-fold (*p*=<.001; *OR*=11.10)
Myocardial Infarction	⇩ 40% (*p* =.004; *OR*=0.60)	Not Significant
Hypertension	Not Significant	⇧ 37% (*p*= .035; *OR*= 1.37)
Cholesterol/Triglycerides/Atherosclerosis	Not Significant	⇧ 48% (*p*= .011; *OR*= 1.48)
Cerebrovascular Accident	⇧ 2.11-fold (*p*= <.001; *OR*= 2.11)	⇧ 74% (*p*= .013; *OR*= 1.74)

Note. This was at a trend-level of significance. AD = Alzheimer's Disease. CHF = Congestive Heart Failure.

CHAPTER V

DISCUSSION

In this population-based sample of 3677 individuals, familial characteristics were associated with risk of AD, though some associations varied by sex. In both females and males, having a first-degree relative with AD was associated with a 66% (females) and 58% (males) increase in the odds of developing AD compared to individuals lacking a family history of AD. The risk of AD across the older age span varied by sex in that AD risk among females declined at extreme ages (e.g., age 106) whereas in males, the risk continued to increase well into the 100's. In females, a direct maternal lineage of AD was associated with a 56% increase in the odds of developing AD. Males having both a direct maternal and paternal lineage of AD were at a 51.3% reduced odds at a trend level significance compared to those with neither parental lineages. Variations by sex were also found in the association of exceptional maternal and paternal longevity in risk for AD, with females having no significant association with either parental exceptional longevity. However, at a trend-level, females with a longer-lived father who also had an APOE Ɛ4 allele had a 4.59-fold increase in the odds of developing AD compared to those females without. Males with an APOE Ɛ4 allele who also had a longer-lived mother had 3.15 times the odds of developing AD compared to males lacking each risk factor. In contrast, males with a longer-lived mother and longer-lived father had a 11% *reduced* odds of developing AD. Cardiovascular risk factors as main effects were found to be associated with risk of developing AD for both male and females, though differed slightly with regards to particular cardiovascular risk factors/conditions in the magnitude of increased odds. However, with respect to family history interactions with vascular

factors, females with a direct paternal lineage of AD and a history of congestive heart failure were at a 2.26-fold increased risk in the odds compared to those females without either risk factor. Vascular factors including, CVA and CHF were associated with higher odds of developing AD in both females and males, whereas a history of HTN and chol/athero were associated with increased risk of AD in males only.

Previous research has established an association between family history of all-cause dementia and risk for AD. Van Duijn and colleagues (1991) found in a re-analysis of 7 case control studies a 3.5-fold greater risk of developing AD when having a first-degree relative with all cause dementia, with greater risk associated with having two first-degree relatives with all cause dementia (7-fold). Fratiglioni and colleagues (1993) also found having a first-degree relative with all-cause is associated with a 3.2-fold increased risk for AD. Research has also found an association with having a first-degree relative with AD and increased risk in the proband. Cannon-Albright and colleagues (2019) found having one first-degree relative with AD doubled the risk of developing AD in the proband. The risk further doubled when having two first-degree relatives with AD and increased to 14 times greater when having four first-degree relatives. The current study is consistent with prior work, though the effects were several magnitudes lower in strength. Not examined in the current study were numbers of first-degree relatives affected.

Unlike prior work, however, the current study did not find an association between second-and-third degree family history of AD and risk of AD in either males or females. Cannon-Alright and colleagues (2019) used cause of death codes on death certificates for 270,818 individuals in the state of Utah to examine the association between the occurrence of AD in extended relatives and risk for AD in the proband. They found that

having a second-degree relative in addition to a first-degree relative with AD increased the risk two-fold and having an affected third-degree relative increased the risk of developing AD by 43%. Here, we found no associations of AD risk (either increased or decreased) for those with second-or third-degree relatives. The discrepant results are likely associated with differences in methodology, in that the current project relied primarily on self-report family history, supplemented death certificate AD diagnosis and Medicare claims diagnosis of AD in the proband, as well as variation in the samples (e.g., statewide vs. a single county).

Existing research has also found a link between maternal and paternal transmission of AD and risk for AD in the proband. In the Cannon-Albright study (2019), there was a link between maternal but not paternal family history of AD and increased risk of AD (56%) in the proband. Differences have also been reported in prior work with AD risk or AD related biomarkers for maternal and paternal family history of AD (Honea et al., 2012; Mosconi et al., 2007; Mosconi et al., 2010). In a cross-sectional study using the Alzheimer's Disease Neuroimaging Initiative (ADNI) data, Honea and colleagues found that regardless of the cognitive status of the individual, a maternal family history of AD was associated with increased uptake of Pittsburgh B Compound (PiB; a radiotracer marks the deposition of amyloid-beta (Aβ) in the brain, a common biomarker of AD) in the parietal and sensorimotor cortices and the precuneus (Honea et al., 2012). Mosconi and colleagues (2007) found in a cross-sectional study that having a *maternal* family history of AD was associated with reduced cerebrospinal fluid (CSF) Aβ and increased tau/Aβ ratios compared to those participants with a paternal family history or no family history of AD. The authors also found maternal family history of AD was linked to

reduced brain glucose metabolism in the medial-temporal lobe, parietotemporal lobe, posterior cingulate, and frontal cortices compared to those participants without a family history of the disorder (Mosconi et al., 2007). In a follow-up study, Mosconi and colleagues (2010) found that those individuals with a maternal family history of AD who were otherwise cognitively normal at baseline had progressive reductions in brain glucose metabolism over a two-year period when compared to those with a negative family history or a paternal family history of AD. In contrast to the above studies, Ehrenkrantz and colleagues (1999) found no evidence of maternal transmission of AD but did find evidence of paternal transmission. While the underlying mechanism associated with maternal and paternal history of AD and risk remains unclear, hypotheses have implicated the role of mitochondrial DNA (Mosconi et al., 2010). Mitochondrial DNA is typically passed down through the maternal lineage, though reports have found biparental transmission (Luo et al., 2018). Mitochondria are associated with cell metabolism and are cellular organelles that provide energy for cellular processes (Wallace, 2005). Certain mitochondrial genotypes may be associated with reductions in brain glucose metabolism or dysfunctional glucose utilization and thus serve as risk factors for AD (Castro et al., 2018). Indeed, brain glucose metabolism is reduced in AD (Mosconi et al., 2010) and dysfunction of mitochondrial chaperones (supportive structures that maintain homeostasis by shuttling, refolding, and coordinating the proteolytic system, thereby reducing the number of misfolded proteins) also occurs in AD (Castro et al., 2018). Alternatively, lifestyle factors (e.g., diet, exercise, etc.) could be a shared mechanism of familial transmission of AD as familial traditions are often passed down through the generations (Lourida et al., 2019). The current study supports a

relationship between direct maternal lineage and increased risk of AD in female probands. Notably, the current study found that in males, having both a paternal and maternal lineage of AD was associated with reduced risk. A potential explanation may include the effects of the competing risk of mortality with age for those with AD in both maternal and paternal lineages. Further research is needed to examine mechanisms of AD risk with parental lineages.

The current study found differential risk of AD across the extreme age spectrum for males and females. Prior work in the Cache County cohort reported a reduction in risk at extreme ages. Miech and colleagues (2002) reported that both incidence of dementia and AD exponentially increased until about ages 85 to 90, with decline in males at about age 93 and a decline at age 97 for females. This relationship was modified by the presence of an APOE Ɛ4 allele (Miech et al., 2002). We extended this work by adding an additional 9 years of surveillance for AD. Additionally, methodological differences are notable, in that the current work examined associations of AD obtained throughout the study, whereas the previous analyses relied only on newly diagnosed cases in the 2nd wave of the study. The relationship between longer-lived individuals and a reduction in AD risk may relate to compression of morbidity (lower risk of health conditions). Consistent with this notion is the finding in the current study that the decline in AD risk in late life was no longer evident when including cardiovascular risk factors in statistical models.

Longevity has been related to several social/environmental (e.g., diet and exercise) and genetic factors (Sebastiani et al., 2012). A prior study of 424 community-dwelling older adults found that individuals with at least one parent surviving past 95

years of age had a 43% reduction in risk of developing AD compared to those with parents living fewer years (Lipton et al., 2010). Andersen and colleagues (2012) found a delayed onset of at least one age related disease (cardiovascular disease, obstructive pulmonary disease, dementia, diabetes, and stroke) in those with exceptional longevity (aged 87 and older) compared to controls. Centenarians were observed to have a reduced risk for cancer (91%), hypertension (85%), and dementia (64%) (Andersen et al., 2012). Delay of onset of additional conditions and further reductions in the hazards were seen in supercentenarians (102-112), suggesting that increasing age was associated with greater reductions in morbidity (Andersen et al., 2012). Westendorp and colleagues (2009) examined risk of morbidity among familial nonagenarians (two siblings aged 90 and above), and sporadic nonagenarians (one individual aged 90 and above) and found reduced prevalence rates of MI, DM, HTN, and the use of cardiovascular medication. While reductions in morbidity have been found in longer-lived individuals, the presence of a genetic risk factor such as APOE may modify the associations between parental longevity and AD risk. The relationship between parental and offspring longevity is complex and likely reflects the influence of multiple factors including the environment, social/cultural practices, and genetics. Human twin studies have found that genetics explained 20-30% of the variance in those individuals who survived to age 85 and above (Herskind et al., 1996). Prior work has also shown extreme clustering of exceptional longevity within some rare families (Alpert et al., 1998; Perls et al., 2000). Sebastiani and colleagues (2012) found that 281 single nucleotide polymorphisms (SNPs; including those associated with APOE) discriminated between controls and cases of exceptional longevity with the greatest contribution of the SNPs being in those with older age

(median of 100). The authors note that exceptional longevity is unlikely to be associated with a single or a few genetic components, but rather genetic clusters (Sebastini et al., 2012). They also recognized that lifestyle and other environmental factors contribute to increased survival rates. The findings in the current study only found a relationship between maternal and paternal longevity and risk of AD in males. The Cache County cohort had greater longevity than the general population at the time (Breitner et al., 1999). Lack of variance or homogeneity in lifestyle and other genetic factors may have diminished the associations between longevity and reduced morbidity that were found in other samples. Further research is needed to elucidate this relationship.

Previous literature has reported on sex differences with regards to risk of AD and APOE Ɛ4 status in that, males with one APOE Ɛ4 allele exhibit little-to-no risk of AD compared to male non-carriers (Bretsky et al., 1999), and those with two APOE Ɛ4 alleles exhibit a 5-fold increase in risk (Payami et al., 1996). Among females, studies have found a four-fold increased risk of developing AD when carrying an APOE Ɛ4 allele regardless of having one or two Ɛ4 alleles. A prior study found, in a sample of 5,000 deceased and autopsied individuals between the ages 25-96, middle-aged females carrying the APOE Ɛ4 allele had more brain regions affected by AD pathology than male carriers of the APOE Ɛ4 allele (Corder et al., 2004). The current study found an interaction in males with parental longevity. Male APOE Ɛ4 carriers with a longer-lived mother showed a greater risk for AD. A trend was found in females with an APOE Ɛ4 allele and a longer-lived father being at greater risk for AD. These results may represent increased risk associated with greater longevity in the proband and an underlying genetic predisposition for AD.

Sex differences are also known to exist in cardiovascular conditions, some as a result of differences in gene expression from sex chromosomes (Garcia et al., 2016). Existing research has also found an association between cardiovascular risk factors and risk for AD (Barnes & Yaffe, 2011; Lennon et al., 2019). Prevalence and incidence rates of cardiovascular conditions differ between the sexes, with females being more likely to develop DM, strokes, and HTN after age 65 and males developing those conditions earlier in life (Mosca et al., 2011). Additionally, females have a greater mortality rate following strokes and coronary heart disease as well as increased morbidity at later ages (Bots et al., 2017). Research has also found variance in the clinical features of cardiovascular disease compared to males, with females expressing differences in the symptoms of cardiovascular diseases such as MI (Mosca et al., 2011). Additionally, estrogen has been found to be cardioprotective. Females after menopause are at greater risk for CVD, high low-density lipoprotein (LDL) cholesterol levels, hypertension, diabetes, and obesity (Rodgers et al., 2019). This suggests that sex-differences in cardiovascular risk factors may be influenced by changes in hormones. Additional research is needed to examine the underlying mechanisms associated with estrogen's role in cardiovascular conditions and risk for AD in women.

The current study found sex differences in the magnitude of effect for cardiovascular predictor variables and AD. Females had double the risk with having a history of a CVA, whereas males had a 74% increase in risk. Males and females had an 11-fold greater risk of AD with a history of CHF however, females had a two-fold increase in risk when having a paternal history of AD. Only males showed an increased

risk for AD with a history of HTN (37%), and for high cholesterol or atherosclerosis being at a 2.69 increased risk for AD at a trend level significance.

Prior work has examined the association between vascular risk factors and conditions and AD in the Cache County cohort (Hayden et al., 2006). Hayden and colleagues (2006) found that obesity doubled the risk for females in the hazards of developing AD, but not in males. They also found other cardiovascular risk factors were associated with risk for vascular dementia (VaD) and this association also differed by sex. The current study extends previous work by adding additional years of AD surveillance and supplementing data on cardiovascular risk factors from Medicare claims.

Cardiovascular risk factors such as HTN, hypercholesteremia, and DM have been associated with risk for AD (e.g., Lennon et al., 2019), particularly with onsets in mid-life (Barnes & Yaffe, 2011). Honig and colleagues (2003) found a history of stroke was associated with a 60% increase in the hazards for AD. Cholesterol has also been found to be associated with AD and the APOE Ɛ4 allele (Sjögren & Blennow, 2005). Lennon and colleagues (2019) in a systematic review found that systolic hypertension was associated with a 25% increased risk. Additionally, a meta-analysis by Barnes and Yaffe (2011) found that conditions occurring in mid-life (i.e., hypertension, obesity, and DM) contributed to a significant portion of cases of AD. CHF in the current study, was among the greatest risk factor for AD. CHF has been associated with cognitive decline independently of AD and the structures affected by CHF significantly overlap with those found to be affected by AD (e.g., hippocampus, precuneus, orbitofrontal cortex, etc.; Alosco & Hayes, 2015; Mueller et al., 2020). Thus, CHF may represent a vulnerability

factor (e.g., hypoxia and reduced cerebral blood flow to the inferior mesial temporal lobe structures) rather than a condition that drives AD pathology.

The current study did not examine the use of pharmacological interventions for treatment of CHF and the other cardiovascular conditions. Treatments for CHF include diuretics, antihypertensives, and beta-blockers (American Heart Association [AHA], 2015). One common medication for the treatment of CHF is angiotensin-converting enzyme (ACE) inhibitors (AHA, 2015), which previous literature has found to be associated with reduced risk for AD (Soto et al., 2013). Similarly, within the Cache County sample previous research has found a 30% and 31% reduced risk associated with thiazide and potassium-sparing diuretics, respectively (Chuang et al., 2014). Conversely, the use of medications such as beta-blockers has been associated with an increased risk of dementia in older adults (Fares, 2012). Zandi and colleauges (2005) examined the use of statins, and risk within the Cache County population and found that statin use at baseline was not significantly associated with risk for dementia or AD nor was it associated with progression to AD. Previous research suggests that various medications used to treat CHF and other cardiac conditions may have varying effects on the overall risk of AD related to the cardiac condition. Future research is needed to examine how various types of pharmacological interventions for the cardiac conditions may modify their associations with AD. The current study was also limited in its ability to examine the underlying cause of CHF as well as various classes of CHF, which are associated with differences in functional abilities and outcomes (AHA, 2015). There may be a specific underlying etiology or specific classes of CHF that elevate the risk for AD and further research is warranted.

In general, the risk for cardiovascular conditions increases with age and is associated greater risk of mortality (Virani et al., 2020). Future research is needed to examine the competing risk of mortality versus AD and its association with cardiovascular risk factors/conditions. Cardiovascular conditions are also associated with reduced longevity (Virani et al., 2020), and thus those with parental family history of cardiovascular conditions may have greater cardiovascular load and shorter survival time. The current findings with cardiovascular risk factors/conditions and reduced risk and the limited associations with family history may be related to the competing risk of mortality and the survival time of the proband.

Significant overlap also exists between vascular dementia (VaD) and AD, which increases with advanced age (Strub, 2003). Both disorders are associated with the presence of cardiovascular conditions (Strub, 2003), though condition differ in their pathophysiological mechanisms. The current study was restricted in examining AD and did not examine the association with VaD. The presence of both VaD and AD, may have different associations with cardiovascular risk factors and conditions. Future research should examine the relationship between cardiovascular risk factors/conditions and family history with risk of VaD in the proband.

A trend-level association was found in the current study in males with a history of CVA and a direct maternal lineage of AD being at 34% reduced risk for AD. This finding was unexpected and warrants replication in other samples.

Study Strengths and Limitations

The current study had a number of strengths. The base Cache County Study was a large community-based sample with 90% enrollment of the base population. Thus, generalizability to other community-dwelling individuals is likely greater than studies relying on samples from other settings, such as clinical sites or medical centers. The follow-up extending up to 12 years is an additional strength. Furthermore, the rich dataset was supplemented up to an additional seven years through the addition of Medicare Claims and death certificate data via linkage with the UPDB. This linkage provided greater surveillance of both AD (additional 209 cases of AD) and cardiovascular risk factors and condition beyond the end of data collection. Additionally, UPDB linkage was critical in providing data on extensive familial genealogy extending back four generations. Nonetheless, data from Medicare claims and death certificates are limited. Death certificates have been known to underestimate the prevalence of AD, as the certifying physician may be unaware of an AD condition (Frecker et al.,1995; Raiford et al., 1994). Alternatively, certifying physicians may assume an AD diagnosis for a different form of dementia. For example, disorders that mimic the clinical symptoms of AD such as limbic-predominant age-related TDP-43 encephalopathy (LATE) (Robinson et al., 2020) and argyrophilic grain disease (Tolnay & Clavaguera, 2004). Medicare claims data, which are used for billing purposes, are not a direct substitute for clinical diagnoses (American Medical Association [AMA], 2014). To reduce misclassification for AD from claims data, the current study required the occurrence of a minimum of two ICD-9 AD claims within 18 months. This criterion is highly correlated with autopsy confirmed diagnoses of AD (Nair et al., 2018). For cardiovascular risk factors and

conditions, the age of onset inferred from Medicare claims data may post-date the actual onsets as individuals are eligible for Medicare at age 65 (AMA, 2014). Many of the chronic health conditions such as hypertension and hypothyroidism occur frequently in mid-life (Fryar et al., 2017), and thus some conditions were not considered risk factors if the inferred age of onset postdated the onset of AD. Despite the limitations with Medicare claims and death certificates they were used to augment Cache County Study data and the majority of the AD designations and risk factors were obtained from the Cache County Study directly, mitigating these concerns. While the Cache County cohort may be broadly generalizable as community-dwelling individuals, participants were primarily white, of Northern European descent, and relatively highly educated. Thus, study results may not generalize to other populations with greater ethnic and cultural diversity. Lastly, the rich Cache County Study dataset with linkage to genealogical, state, and federal health data allowed for the examination of sex differences, family history of AD, familial exceptional longevity, and vascular factors as risk factors for AD within a single sample.

Implications and Future Directions

There are several implications from the current study. This study highlights the importance of ascertaining first-degree relative information about AD for both males and females. It may also be beneficial clinically when working with patients to provide sex-specific interventions/counseling related to modifiable cardiovascular risk factors. Heightened surveillance and treatment for males at risk for CHF, CVA, HTN, and chol/tri/athero are warranted as a primary prevention strategy. Similarly, females at risk

for CHF and CVA would also benefit from surveillance and primary prevention to reduce future risk of AD. This includes changes in diet, improving sleep, increasing physical activity, managing menopausal changes, and use of pharmacological interventions such as ACE inhibitors, which has been associated with reducing risk for AD (Ju et al., 2013; Soto et al., 2013; Tang et al.,1996; Tschanz et al., 2013; Yaffe et al., 2014) and improving cardiovascular health (Shay et al., 2015). This study also supports the notion of managing cardiovascular health as an area of lowering risk for AD and suggests the benefit of providing sex-specific intervention strategies. Additionally, monitoring both males and females for specific cardiovascular conditions when a positive first-degree family history of AD, may also be an effective prevention strategy.

There was limited association between direct maternal and paternal lineage of AD and cardiovascular risk factors. Future research should continue to assess these risk factors and modifying relationships with risk for AD. Not examined in this study was family history of vascular risk factors or conditions. A family history of stroke and MI has been found to be more predictive of risk for the condition in females compared to males (Patel et al., 2007; Touzé & Rothwell, 2007). Specifically, females who had experienced a stroke were 15% more likely to have a first-degree relative with a history of a stroke than males who had a stroke, and females with a paternal family history of a stroke were at a 25% increased risk for a stroke compared to males with a similar family history (Touzé & Rothwell, 2007). A study by Patel and colleagues (2007), found an association with family history of MI and greater risk in females compared to males. These studies suggest sex differences may exist in family history of vascular factors. Future research on sex differences in AD and vascular factors is warranted. Research

examining family history of AD and vascular factors together may potentially identify high risk individuals for both conditions and a group for whom strategies in primary prevention may be particularly beneficial. Overall, this study highlights the importance of future research in exploring and clarifying the nature of sex differences in risk factors for AD.

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Appendices

Appendix A: Family History Interview

SECTION H: FAMILY HISTORY

H1.This section is a brief family history. Please tell me the names of your brothers and sisters starting with oldest and continuing to the youngest. Please include yourself in the list. Do not include siblings that are adopted, step, half brothers or sisters.

RECORD FIRST AND LAST NAME OF EACH SIBLING THEN ASK QUESTIONS ACROSS COLUMNS. FOR R. ONLY RECORD NAME IN BIRTH ORDER.

|_|_| Birth order of R

	FIRST NAME	LAST NAME	SEX		Is (NAME) living?		What is (NAME"S) approximate age or age at time of death?	Did (NAME) ever have a heart attack, stroke, or other cardio vascular problem?			Did (NAME) ever have memory problems?		
			M	F	Y	N		Y	N	DK	Y	N	DK
1.			1	2	1	2	_|_|_	1	2	8	1	2	8
2.			1	2	1	2	_|_|_	1	2	8	1	2	8
3.			1	2	1	2	_|_|_	1	2	8	1	2	8
4.			1	2	1	2	_|_|_	1	2	8	1	2	8
5.			1	2	1	2	_|_|_	1	2	8	1	2	8
6.			1	2	1	2	_|_|_	1	2	8	1	2	8
7.			1	2	1	2	_|_|_	1	2	8	1	2	8
8.			1	2	1	2	_|_|_	1	2	8	1	2	8
9.			1	2	1	2	_|_|_	1	2	8	1	2	8
10.			1	2	1	2	_|_|_	1	2	8	1	2	8
11.			1	2	1	2	_|_|_	1	2	8	1	2	8
12.			1	2	1	2	_|_|_	1	2	8	1	2	8
13.			1	2	1	2	_|_|_	1	2	8	1	2	8
14.			1	2	1	2	_|_|_	1	2	8	1	2	8
15.			1	2	1	2	_|_|_	1	2	8	1	2	8
16.			1	2	1	2	_|_|_	1	2	8	1	2	8

H2. Now, I'd like to ask you the same information about your biological parents starting with your father.

ADOPTED NO INFO (GO TO INTERVIEWER CHECKPOINT) 1

	FIRST NAME	LAST NAME	SEX		Is (NAME) living?		What is (NAME"S) approximate age or age at time of death?	Did (NAME) ever have a heart attack, stroke, or other cardio vascular problem?			Did (NAME) ever have memory problems?		
			M	F	Y	N		Y	N	DK	Y	N	DK
30.			1	2	1	2	⌊⌋⌊⌋	1	2	8	1	2	8
31.			1	2	1	2	⌊⌋⌊⌋	1	2	8	1	2	8

INTERVIEWER CHECKPOINT: DID ANY SIBLINGS OR PARENTS HAVE MEMORY PROBLEMS?

YES (CONTINUE) 1
NO (GO TO H4) 2

H3. Now I'd like to ask you a few questions about those relatives who experienced memory problems.

RECORD NAME FROM H OR H2 WITH MEMORY PROBLEMS.

A. NAME:_____ RELATIONSHIP ..... ☐☐

1. How old was (NAME) when (he/she) started having memory problems? AGE ..... ⌊⌋⌊⌋

2. Did the memory problems begin suddenly or slowly?
SUDDENLY 1
SLOWLY 2
DK 8

3. Did the memory problems get worse over time?
YES 1
NO 2
DK 8

4. (Did/do) the memory problems cause limitations with daily activities?
YES (RECORD) 1
NO (GO TO 5) 2
DK (GO TO 5) 8

SPECIFY TYPES OF LIMITATION

RECORD: _____
_____
_____

5. Did a doctor ever give a diagnosis for the cause of the memory trouble?
YES (RECORD) 1
NO (GO TO INT. CHECKPOINT) 2
RF (GO TO INT. CHECKPOINT) 7
DK (GO TO INT. CHECKPOINT) 8

SPECIFY THE DIAGNOSIS

RECORD: _____
_____
_____

☐☐☐
MEM

INTERVIEWER CHECKPOINT: IF DECEASED CONTINUE IF LIVING GO TO NEXT CHECKPOINT

6. IF DECEASED: What was the cause of death?

   RECORD:_____

7. Was an autopsy performed?

   YES 1
   NO 2
   DK 8

INTERVIEWER CHECKPOINT: ARE THERE OTHER RELATIVES LISTED WITH NEW MEMORY PROBLEMS?

   YES 1
   NO (GO TO H4) 2

RECORD NEXT NAME FROM H1OR H2 WITH MEMORY PROBLEMS.

B. NAME:_____ RELATIONSHIP ..... ☐☐

1. How old was (NAME) when (he/she) started having memory problems?

   AGE ..... ☐☐☐

2. Did the memory problems begin suddenly or slowly?

   SUDDENLY 1
   SLOWLY 2
   DK 8

3. Did the memory problems get worse over time?

   YES 1
   NO 2
   DK 8

4. (Did/do) the memory problems cause limitations with daily activities?

   YES (RECORD) 1
   NO (GO TO 5) 2
   RF (GO TO 5) 7
   DK (GO TO 5) 8

   SPECIFY TYPES OF LIMITATION

   RECORD:_____
   _____
   _____

5. Did a doctor ever give a diagnosis for the cause of the memory trouble?

   YES (RECORD) 1
   NO (GO TO INT. CHECKPOINT) 2
   RF (GO TO INT. CHECKPOINT) 7
   DK (GO TO5 INT. CHECKPOINT) 8

   SPECIFY THE DIAGNOSIS

   RECORD:_____
   _____
   _____

☐☐☐
MEM

INTERVIEWER CHECKPOINT: IF DECEASED CONTINUE IF LIVING GO TO NEXT CHECKPOINT

6. IF DECEASED: What was the cause of death?

   RECORD:_____

7. Was an autopsy performed?

   YES 1
   NO 2
   DK 8

INTERVIEWER CHECKPOINT: ARE THERE OTHER RELATIVES LISTED WITH NEW MEMORY PROBLEMS?	YES ..... 1 NO (GO TO H4) 2

RECORD NAME FROM H1 OR H2 WITH MEMORY PROBLEMS.

C. NAME:_____ RELATIONSHIP ..... ☐☐

1. How old was (NAME) when (he/she) started having memory problems? AGE ..... ☐☐☐

2. Did the memory problems begin suddenly or slowly?
   SUDDENLY 1
   SLOWLY 2
   DK 8

3. Did the memory problems get worse over time?
   YES 1
   NO 2
   RF 7
   DK 8

4. (Did/do) the memory problems cause limitations with daily activities?
   YES (RECORD) 1
   NO (GO TO 5) 2
   RF (GO TO 5) 7
   DK (GO TO 5) 8

   SPECIFY TYPES OF LIMITATION

   RECORD: _____
   _____
   _____

5. Did a doctor ever give a diagnosis for the cause of the memory trouble?
   YES (RECORD) 1
   NO (GO TO INT. CHECKPOINT) 2
   RF (GO TO INT. CHECKPOINT) 7
   DK (GO TO INT. CHECKPOINT) 8

   SPECIFY THE DIAGNOSIS

   RECORD: _____
   _____
   _____

☐☐☐
MEM

INTERVIEWER CHECKPOINT: IF DECEASED CONTINUE IF LIVING GO TO NEXT. CHECKPOINT.

6. IF DECEASED: What was the cause of death?

   RECORD: _____

7. Was an autopsy performed?
   YES 1
   NO 2
   DK 8

INTERVIEWER CHECKPOINT: ARE THERE OTHER RELATIVES LISTED WITH MEMORY PROBLEMS?	YES (GO TO FAMILY HIS. SUPP.) ..... 1 NO (CONTINUE) 2

H4. Now I am going to read you a list of problems people sometimes have. For those relatives we've been talking about, your full brothers and sisters and your biological parents, please tell me if <u>any</u> of them have been told by a doctor that they had:

	YES	NO	DK

A.	Alzheimer's disease?	1	2	8
B.	Parkinson's disease?	1	2	8
C.	Down's Syndrome?	1	2	8
D.	Senile dementia?	1	2	8
E.	"Hardening of the arteries?"	1	2	8
F.	Mini-strokes of TIA's?	1	2	8
G.	"Arteriosclerosis of the brain"?	1	2	8
H.	Any other neurological conditions?	1	2	8

SPECIFY: _____ ☐☐☐ MEM

SPECIFY: _____ ☐☐☐ MEM

H5. Now, I'd like to do the buccal swab, to take a few cells from the inside of your cheek.

2 SWAB SAMPLE 1
1 SWAB SAMPLE 2
RF 7

1. PREPARE 4 LABELS
2. PUT ON GLOVES.
3. OPEN SWAB.
4. INSERT SWAB IN R'S RIGHT CHEEK FOR 30 SECONDS.
5. ATTACH RIGHT LABEL TO BRUSH.
6. PLACE SECOND LABEL ON PACKET.
7. TAKE LEFT SAMPLE AND REPEAT.
8. TAKE OFF GLOVES
9. PLACE SAMPLE IN COOLER.

Appendix B: Medical History Questionnaire

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1mhxdt FP1:MEDHX:Date	Medical History: DATE MEDICAL HISTORY WAS GATHERED.		
			Date
fp1pd FP1:MEDHX:Parkinson's disease	Item: D5 Medical History: In the past year or so, has a doctor or nurse ever told (NAME) that (he/she) has Parkinson's disease?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1ldopa FP1:MEDHX:L-DOPA or Sinemet	Item: D6 Medical History: In the past year or so, has (NAME) taken L-DOPA or Sinemet?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva FP1:MEDHX:Stroke ever	Item: D7 Medical History: In the past 12-18 months, has a doctor or nurse told (NAME) that (s/he) had a stroke?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva# FP1:MEDHX:Stroke number	Item: D8 Medical History: How many strokes has (NAME) had?		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1cva1a FP1:MEDHX:Stroke #1 date MONTH	Item: D9 Medical History: When did the (last) stroke take place? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1cva1b FP1:MEDHX:Stroke #1 YEAR	Item: D9 Medical History: When did the (last) stroke take place? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1cva1c FP1:MEDHX:Stroke #1 weaker side	Item: D9a Medical History: Did one side of (NAME's) body, or one arm or leg, become weaker than the other?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva1d FP1:MEDHX:Stroke #1 speaking ability	Item: D9b Medical History: Did (NAME) lose the ability to speak or understand what was said to (him/her) for a day or more?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva1e FP1:MEDHX:Stroke #1 hospital/MD	Item: D9c Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw Doctor
		2	Went to Hospital
		0	No Doctor or Hospital (Originally coded as 3)
		7	Refused
		8	Don't Know
		9	Missing
fp1cva1f FP1:MEDHX:Stroke #1 hospital/MD RECORD	Item: D9c RECORD Medical History: Did (NAME) see a doctor or go to a hospital? RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1cva2a FP1:MEDHX:Stroke #2 date MONTH	Item: D10 Medical History: When was the stroke before the last one? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1cva2b FP1:MEDHX:Stroke #2 YEAR	Item: D10 Medical History: When was the stroke before the last one? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1cva2c FP1:MEDHX:Stroke #2 weaker side	Item: D10a Medical History: Did one side of (NAME's) body, or one arm or leg, become weaker than the other?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva2d FP1:MEDHX:Stroke #2 speaking ability	Item: D10b Medical History: Did (NAME) ever lose the ability to speak or understand what was said to (him/her) for a day or more?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva2e FP1:MEDHX:Stroke #2 hospital/MD	Item: D10c Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw Doctor
		2	Went to Hospital
		0	No Doctor or Hospital (Originally coded as 3)
		7	Refused
		8	Don't Know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1cva2f FP1:MEDHX:Stroke #2 hospital/MD RECORD	Item: D10c RECORD Medical History: Did (NAME) see a doctor or go to a hospital? RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text
fp1cva3a FP1:MEDHX:Stroke #3 date MONTH	Item: Stroke Supplement: STSUPP 1 Medical History: When did the (last) stroke take place? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1cva3b FP1:MEDHX:Stroke #3 YEAR	Item: Stroke Supplement: STSUPP 1 Medical History: When did the (last) stroke take place? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1cva3c FP1:MEDHX:Stroke #3 weaker side	Item: Stroke Supplement: STSUPP 1a Medical History: Did one side of (NAME'S) body, or one arm or leg, become weaker than the other?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva3d FP1:MEDHX:Stroke #3 which side weaker	Item: Stroke Supplement: STSUPP 1b Medical History: Which side?		
		1	Right
		2	Left
		7	Refused
		8	Don't know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1cva3e FP1:MEDHX:Stroke #3 speaking ability	Item: Stroke Supplement: STSUPP 1c Medical History: Did (NAME) lose the ability to speak or understand what was said to (him/her) for a day or more?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cva3f FP1:MEDHX:Stroke #3 hospital/MD	Item: Stroke Supplement: STSUPP 1d Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw Doctor
		2	Went to Hospital
		0	No Doctor or Hospital (Originally coded as 3)
		7	Refused
		8	Don't Know
		9	Missing
fp1cva3g FP1:MEDHX:Stroke #3 hospital/MD RECORD	Item: Stroke Supplement: STSUPP 1d RECORD Medical History: Did (NAME) see a doctor or go to a hospital? RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text
fp1tia1 FP1:MEDHX:TIA or funny spell	Item: D11 Medical History: In the past 12-18 months, has (NAME) had any TIA's, mini-stroke's, or funny spells suggestive of a stroke?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1tia# FP1:MEDHX:TIA number	Item: D11a Medical History: How many of these episodes has (NAME) had in this period of time?		
			Range of values
		97	Refused
		98	Don't know
		99	Missing

CCMS Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name:** ***FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1tia2 FP1:MEDHX:TIA date MONTH	Item: D11b Medical History: When was the (first) TIA? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1tia3 FP1:MEDHX:TIA date YEAR	Item: D11b Medical History: When was the (first) TIA? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1tia4 FP1:MEDHX:TIA hospital/MD	Item: D11c Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw doctor
		2	Went to hospital
		3	No doctor or hospital
		7	Refused
		8	Don't Know
		9	Missing
fp1tia5 FP1:MEDHX:TIA hospital/MD RECORD	Item: D11c RECORD Medical History: Did (NAME) see a doctor or go to a hospital? RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text
fp1tia6 FP1:MEDHX:TIA description	Item: D11c DESCRIBE Medical History: DESCRIBE EACH TIA (I.E., HEMIPARESIS, SPEECH/LANGUAGE OR DISORDER, CONFUSION, LENGTH OF TIA, ETC.)		
			Text
fp1hd FP1:MEDHX:Head injury ever	Item: D13 Medical History: In the past 12-18 months, has (NAME) had a head injury so severe that (s/he) lost consciousness, lost (his/her) memory for a period of time, or had to see a doctor?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1hd# FP1:MEDHX:Head injury number	Item: D14 Medical History: How many times has this happened?		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1hd1a FP1:MEDHX:Head injury date MONTH	Item: D15 Medical History: Now I want you to think about (NAME'S) (last) head injury. When did this happen? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1hd1b FP1:MEDHX:Head injury date YEAR	Item: D15 Medical History: Now I want you to think about (NAME'S) (last) head injury. When did this happen? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1hd1c FP1:MEDHX:Head injury #1 description	Item: D15a Medical History: Could you please describe each injury?		
			Text
fp1hd1d FP1:MEDHX:Head injury #1 hospital/MD	Item: D15b Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw doctor
		2	Went to hospital
		3	No doctor or hospital
		7	Refused
		8	Don't Know
		9	Missing
fp1hd1e FP1:MEDHX:Head injury #1 hospital/MD RECORD	Item: D15b RECORD Medical History: Did (NAME) see a doctor or go to a hospital? IF SO, RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1hd1f FP1:MEDHX:Head injury #1 consciousness	Item: D15c Medical History: Did (NAME) lose consciousness?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1hd1g FP1:MEDHX:Head injury #1 time unconscious	Item: D15d Medical History: If so, how long was (NAME) unconscious?		
		1	<5 Minutes
		2	5-29 Minutes
		3	30-59 Minutes
		4	1-24 Hrs
		5	>1 Day
		7	Refused
		8	Don't Know
		9	Missing
fp1hd1h FP1:MEDHX:Head injury #1 amnesia	Item: D15e Medical History: Sometimes, after a head injury, people experience amnesia or loss of memory. Did (NAME) have a period of amnesia after the injury?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1hd1i FP1:MEDHX:Head injury #1 amnesia length	Item: D15f Medical History: How long did (NAME) have this memory loss?		
		1	1-24 Hours
		2	2-6 Days
		3	>1 Week
		7	Refused
		8	Don't Know
		9	Missing

CCMS Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1hd1j FP1:MEDHX:Head injury #1 penetration to brain	Item: D15g Medical History: At the time of this injury was there any penetration of the skull to the brain (e.g. such as from shrapnel, a bullet wound, or other object)?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1hd2a FP1:MEDHX:Head injury #2 date MONTH	Item: D16 Medical History: Now I want you to think the previous head injury. When did this happen? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1hd2b FP1:MEDHX:Head injury #2 date YEAR	Item: D16 Medical History: Now I want you to think about the previous head injury. When did this happen? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1hd2c FP1:MEDHX:Head injury #2 description	Item: D16a Medical History: Could you please describe the injury to me?		
			Text
fp1hd2d FP1:MEDHX:Head injury #2 hospital/MD	Item: D16b Medical History: Did (NAME) see a doctor or go to a hospital?		
		1	Saw Doctor
		2	Went to Hospital
		0	No Doctor or Hospital (Originally coded as 3)
		7	Refused
		8	Don't Know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1hd2e FP1:MEDHX:Head injury #2 hospital/MD RECORD	Item: D16b RECORD Medical History: Did (NAME) see a doctor or go to a hospital? RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL		
			Text
fp1hd2f FP1:MEDHX:Head injury #2 consciousness	Item: D16c Medical History: Did (NAME) lose consciousness?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1hd2g FP1:MEDHX:Head injury #2 time unconscious	Item: D16d Medical History: How long was (NAME) unconscious?		
		1	<5 Minutes
		2	5-29 Minutes
		3	30-59 Minutes
		4	1-24 Hrs
		5	>1 Day
		7	Refused
		8	Don't Know
		9	Missing
fp1hd2h FP1:MEDHX:Head injury #2 amnesia	Item: D16e Medical History: Sometimes, after a head injury, people experience amnesia or loss of memory. Did (NAME) have a period of amnesia after the injury?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name:** ***FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1hd2i FP1:MEDHX:Head injury #2 amnesia length	Item: D16f Medical History: How long did (NAME) have this memory loss?		
		1	1-24 Hours
		2	2-6 Days
		3	>1 Week
		7	Refused
		8	Don't Know
		9	Missing
fp1hd2j FP1:MEDHX:Head injury #2 penetration to brain	Item: D16g Medical History: At the time of this injury was there any penetration of the skull to the brain? (e.g. such as from shrapnel, a bullet wound, or other object)?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1brn FP1:MEDHX:Brain injury	Item: D17 Medical History: In the last 12-18 months, has (NAME) had brain surgery or any other kind of brain injury?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1brn1 FP1:MEDHX:Brain injury SPECIFY	Item: D17 SPECIFY Medical History: In the last 12-18 months, has (NAME) had brain surgery or any other kind of brain injury? SEPCIFY AND DESCRIBE RECOVERY, RESIDUALS, ETC.		
			Text
fp1epsy FP1:MEDHX:Epileptic seizures	Item: D18 Medical History: In the past 12-18 months, has (NAME) had any epileptic seizures or fits?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name:** ***FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1epsy1 FP1:MEDHX:Epileptic seizures date MONTH	Item: D18a Medical History: When did this happen? MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1epsy2 FP1:MEDHX:Epileptic seizures date YEAR	Item: D18a Medical History: When did this happen? YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1epsy3 FP1:MEDHX:Epileptic seizures medication	Item: D18b Medical History: Did (s/he) take medication for this?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cv1 FP1:MEDHX:Chest pain	Item: D36 Medical History: This next group of questions is about cardiovascular or heart problems. In the past 12-18 months, has (NAME) had a severe pain across the front of (his/her) chest lasting for half an hour or more?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cv2 FP1:MEDHX:Angina	Item: D37 Medical History: Has (NAME) been told (s/he) had angina in the past 12-18 months?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing

CCMS

Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1cv3 FP1:MEDHX:SOB	Item: D38 Medical History: Has (NAME) sometimes been troubled by shortness of breath when walking up a slight hill or when hurrying on level ground since our last visit?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1htn FP1:MEDHX:HTN	Item: D39 Medical History: Has (NAME) had a new diagnosis of high blood pressure or hypertension in the past 12-18 months?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1htn1 FP1:MEDHX:HTN date MONTH	Item: D39a Medical History: Date MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1htn2 FP1:MEDHX:HTN date YEAR	Item: D39a Medical History: Date YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1htn3 FP1:MEDHX:HTN now	Item: D39b Medical History: Does (NAME) have high blood pressure now or is (s/he) under current treatment for high blood pressure?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1htn4 FP1:MEDHX:HTN MD	Item: D39c Medical History: Who is the doctor who is treating (his/her) high blood pressure?		
			Text

CCMS

Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1chol FP1:MEDHX:Cholesterol	Item: D40 Medical History: Has (NAME) had a new diagnosis of high blood cholesterol or triglycerides (lipids) in the past 12-18 months?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1chol1 FP1:MEDHX:Cholesterol date MONTH	Item: D40a Medical History: Date MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1chol2 FP1:MEDHX:Cholesterol date YEAR	Item: D40a Medical History: Date YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1chol3 FP1:MEDHX:Cholesterol now	Item: D40b Medical History: Does (NAME) have high cholesterol or blood lipids now or is (s/he) currently under treatment for this condition?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1chol4 FP1:MEDHX:Cholesterol MD	Item: D40c Medical History: Who is the doctor who is treating (him/her) for high cholesterol?		
			Text
fp1chol5 FP1:MEDHX:Cholesterol treatment	Item: D40d Medical History: Describe treatment, results. Comments.		
			Text

CCMS Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name:** *FP1_MEDHX*

SPSS Variable/Label	Description	Coding	
fp1cabg FP1:MEDHX:CABG	Item: D41 Medical History: In the past 12-18 months, has (NAME) had coronary bypass surgery?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1cabg1 FP1:MEDHX:CABG date MONTH	Item: D41a Medical History: Date MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1cabg2 FP1:MEDHX:CABG date YEAR	Item: D41a Medical History: Date YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1cabg3 FP1:MEDHX:CABG who performed	Item: D41b Medical History: Who performed the (last) bypass surgery?		
			Text
fp1mi FP1:MEDHX:MI	Item: D42 Medical History: In the past 12-18 months, has (NAME) had a heart attack, a myocardial infarction, or a coronary thrombosis?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1mi# FP1:MEDHX:MI number	Item: D42a Medical History: How many heart attacks has (NAME) had?		
			Range of values
		97	Refused
		98	Don't know
		99	Missing

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Cache County Memory Study Code Book

Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name: *FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1mi1 FP1:MEDHX:MI date MONTH	Item: D42b Medical History: Date MONTH		
			Range of values
		97	Refused
		98	Don't know
		99	Missing
fp1mi2 FP1:MEDHX:MI date YEAR	Item: D42b Medical History: Date YEAR		
			Range of values
		997	Refused
		998	Don't know
		999	Missing
fp1mi3 FP1:MEDHX:MI description	Item: D42c Medical History: Describe each heart attack, recovery, treatment, complications, and residual problems. Comments.		
			Text
fp1mi4 FP1:MEDHX:MI MD	Item: D42d Medical History: Who was the (last) doctor who treated (NAME) for a heart attack?		
			Text
fp1dm FP1:MEDHX:Diabetes	Item: D43 Medical History: In the past 12-18 months since our last visit has (NAME) had an onset of diabetes, high blood sugar or sugar in (his/her) urine?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing
fp1dm1 FP1:MEDHX:Diabetes MD Dx	Item: D43a Medical History: Did a doctor diagnose this condition?		
		0	No (Originally coded as 2)
		1	Yes
		7	Refused
		8	Don't Know
		9	Missing

CCMS

Cache County Memory Study Code Book

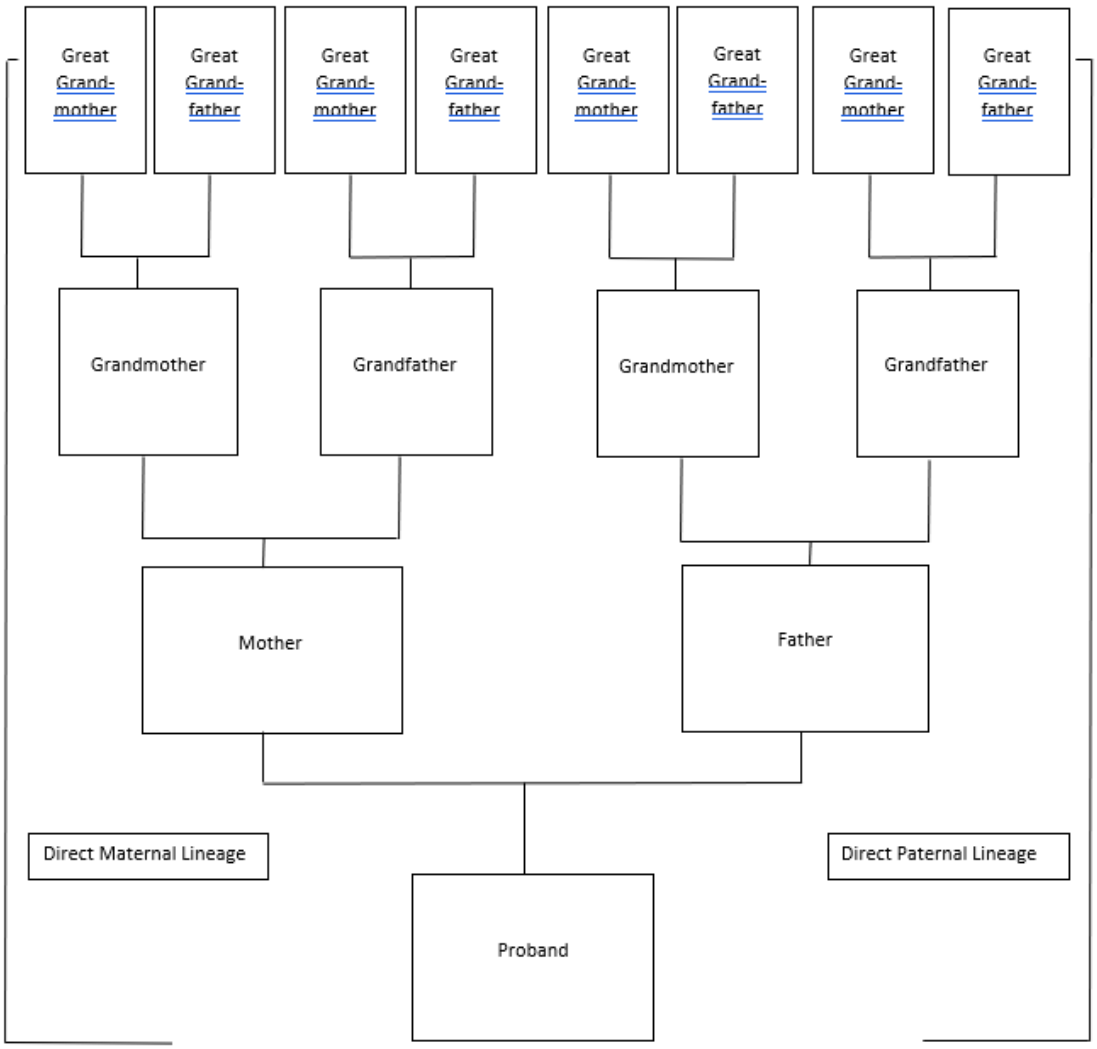
Prevalence Follow Up Clinical Assessment Medical History **SPSS Dataset Name:** ***FP1_MEDHX***

SPSS Variable/Label	Description	Coding	
fp1dm2 FP1:MEDHX:Diabetes treatment	Item: D44 Medical History: What sort of treatment was prescribed for (NAME's) diabetes?		
		1	Diet only
		2	Oral treatment (pills)
		3	Insulin
		0	None (Originally coded as 4)
		7	Refused
		8	Don't Know
		9	Missing
fp1dm3 FP1:MEDHX:Diabetes describe treatment	Item: D44 Medical History: What sort of treatment was prescribed for (NAME's) diabetes? DESCRIBE		
			Text

Appendix C: Direct Maternal and Paternal Lineage Diagram

Figure C.1

Direct Maternal and Paternal Lineage Diagram



Appendix D: Tetrachoric Correlation Matrix, Random Forest Analyses, and Lasso Regression Output

Table D.1

Tetrachoric Correlation Matrix

	CHF	CVA	DM	MI	CHOL	HTN	AFIB	ATHERO	OBESE	HYPO	DYSRHY
CHF	1.00	0.23	0.22	0.28	0.04	0.22	0.61	0.44	0.47	0.40	0.54
CVA	0.23	1.00	0.20	0.21	0.10	0.26	0.25	0.30	0.19	0.20	0.25
DM	0.22	0.20	1.00	0.24	0.16	0.34	0.13	0.17	0.36	0.10	0.16
MI	0.28	0.21	0.24	1.00	0.29	0.17	0.17	0.08	0.21	0.06	0.19
CHOL	0.04	0.10	0.16	0.29	1.00	0.28	0.09	0.19	0.19	0.18	0.17
HTN	0.22	0.26	0.34	0.17	0.28	1.00	0.28	0.34	0.41	0.23	0.33
AFIB	0.61	0.25	0.13	0.17	0.09	0.28	1.00	0.59	0.33	0.68	0.83
ATHERO	0.44	0.30	0.17	0.08	0.19	0.34	0.59	1.00	0.44	0.61	0.66
OBESE	0.47	0.19	0.36	0.21	0.19	0.41	0.33	0.44	1.00	0.50	0.50
HYPO	0.40	0.20	0.10	0.06	0.18	0.23	0.68	0.61	0.50	1.00	0.71
DYSRHY	0.54	0.25	0.16	0.19	0.17	0.33	0.83	0.66	0.50	0.71	1.00

Table D.2

Tetrachoric Correlation Matrix With Combined Atrial Fibrillation and Dysthymias

	CHF	CVA	DM	MI	CHOL	HTN	ATHERO	OBESE	HYPO	RHYTHMIAS
CHF	1.00	0.27	0.17	0.27	0.02	0.25	0.50	0.55	0.49	0.66
CVA	0.27	1.00	0.13	0.20	0.08	0.23	0.35	0.12	0.26	0.33
DM	0.17	0.13	1.00	0.24	0.15	0.32	0.18	0.35	0.11	0.17
MI	0.27	0.20	0.24	1.00	0.25	0.15	0.08	0.24	0.07	0.23
CHOL	0.02	0.08	0.15	0.25	1.00	0.26	0.19	0.23	0.18	0.14
HTN	0.25	0.23	0.32	0.15	0.26	1.00	0.34	0.51	0.23	0.33
ATHERO	0.50	0.35	0.18	0.08	0.19	0.34	1.00	0.51	0.59	0.65
OBESE	0.55	0.12	0.35	0.24	0.23	0.51	0.51	1.00	0.59	0.62
HYPO	0.49	0.26	0.11	0.07	0.18	0.23	0.59	0.59	1.00	0.69
RHYTHMIAS	0.66	0.33	0.17	0.23	0.14	0.33	0.65	0.62	0.69	1.00

Table D.3

Tetrachoric Correlation Matrix With Collapsed Cholesterol/Atherosclerosis and Atrial Fibrillation and Other Dysrhythmias

	CHF	**CVA**	**DM**	**MI**	**CHOL/ATHERO**	**HTN**	**OBESE**	**HYPO**	**RHYTHMIAS**
CHF	1.00	0.27	0.17	0.26	-0.02	0.28	0.53	0.52	0.67
CVA	0.27	1.00	0.16	0.26	0.11	0.26	0.16	0.27	0.31
DM	0.17	0.16	1.00	0.31	0.15	0.33	0.31	0.12	0.13
MI	0.26	0.26	0.31	1.00	0.17	0.22	0.27	0.13	0.16
CHOL/ATHERO	-0.02	0.11	0.15	0.17	1.00	0.22	0.22	0.14	0.07
HTN	0.28	0.26	0.33	0.22	0.22	1.00	0.47	0.15	0.32
OBESE	0.53	0.16	0.31	0.27	0.22	0.47	1.00	0.59	0.59
HYPO	0.52	0.27	0.12	0.13	0.14	0.15	0.59	1.00	0.71
RHYTHMIAS	0.67	0.31	0.13	0.16	0.07	0.32	0.59	0.71	1.00

Table D.4

Variance Inflation Factors Analysis for Research Question 4

Variable	Variance Inflation Factors
Sex	1.05
Age	1.19
Education	1.03
Ethnicity	1.01
APOE Ɛ4 Allele	1.07
Direct Maternal Lineage	1.03
Direct Paternal Linage	1.03
CHF	1.03
CVA	1.02
DM	1.04
MI	1.06
HTN	1.08
Obesity	1.00
Cholesterol/Atherosclerosis	1.12
Hypothyroidism	1.00
Atrial Fibrillation and Other Dysrhythmias	1.00

Note. The cutoff for variance inflation is 5.

Table D.5

Female: Random Forest Analysis Output for Research Question 4

Variable	Mean Decrease in Gini
Age at Baseline	127.68
Education	9.63
Ethnicity	1.83
APOE Ɛ4 Status	37.47
Direct Maternal Lineage	7.84
Direct Paternal Lineage	7.20
Congestive Heart Failure	50.19
Cerebrovascular Accident	9.16
Diabetes Mellitus	8.34
Myocardial Infarction	7.16
Hypertension	10.79
Obesity	5.87
Cholesterol/Atherosclerosis	10.12
Hypothyroidism	101.75
Atrial Fibrillation and Other Dysrhythmias	96.69

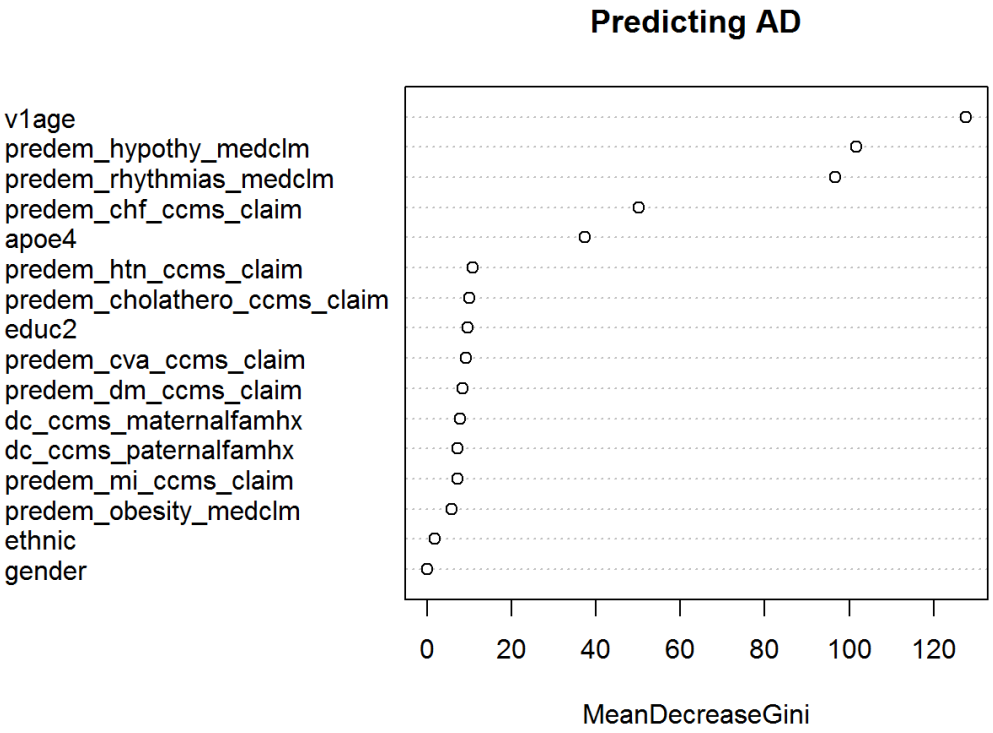
Table D.6

Male: Random Forest Analysis Output for Research Question 4

Variable	Mean Decrease in Gini
Age at Baseline	74.44
Education	7.86
Ethnicity	0.94
APOE Ɛ4 Status	18.79
Direct Maternal Lineage	4.90
Direct Paternal Lineage	3.86
Congestive Heart Failure	29.17
Cerebrovascular Accident	4.92
Diabetes Mellitus	5.37
Myocardial Infarction	6.85
Hypertension	6.77
Obesity	0.60
Cholesterol/Atherosclerosis	6.29
Hypothyroidism	34.51
Atrial Fibrillation and Other Dysrhythmias	96.83

Figure D.1

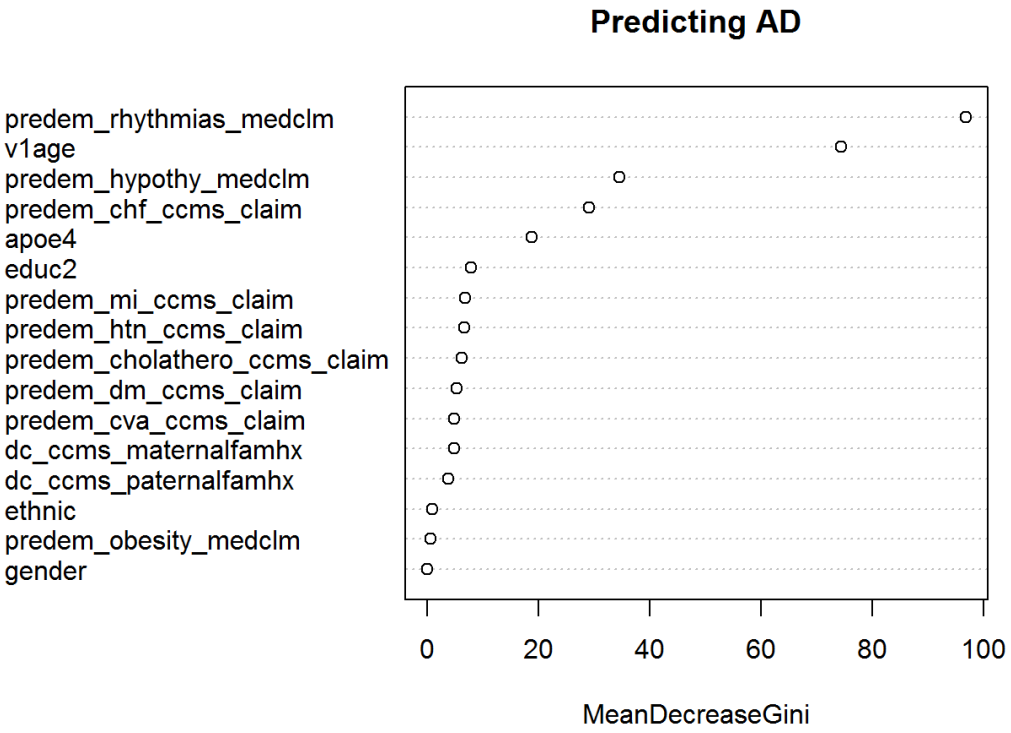
Female: Random Forest Plot for Importance of Variable for Model Prediction



Note. Gender/sex is not predictive as this is a stratified model and males were removed. v1age = Age at baseline; predem_hypothy_medclm = hypothyroidism;predem_rhythmias_medclm = Atrial fibrillation and other dysrhythmias; predem_chf_ccms_claim = congestive heart failure; apoe4= APOE Ɛ4 status; predem_htn_ccms_claim = hypertension; educ2 = education; predem_cva_ccms_claim = cerebrovascular accident; predem_dm_ccms_claim = diabetes mellitus; dc_ccms_maternalfamhx = Direct Maternal Lineage of AD; dc_ccms_paternalfamhx = direct paternal lineage of AD; predem_mi_ccms_claim = myocardial infarction; predem_obesity_medclm = obesity; ethnic = ethnicity; gender = sex.

Figure D.2

Male: Random Forest Plot for Importance of Variable for Model Prediction



Note. Gender/sex is not predictive as this is a stratified model and females were removed. v1age = Age at baseline; predem_hypothy_medclm = hypothyroidism; predem_rhythmias_medclm = Atrial fibrillation and other dysrhythmias; predem_chf_ccms_claim = congestive heart failure; apoe4 = APOE Ɛ4 status; predem_htn_ccms_claim = hypertension; educ2 = education; predem_cva_ccms_claim = cerebrovascular accident; predem_dm_ccms_claim = diabetes mellitus; dc_ccms_maternalfamhx = Direct Maternal Lineage of AD; dc_ccms_paternalfamhx = direct paternal lineage of AD; predem_mi_ccms_claim = myocardial infarction; predem_obesity_medclm = obesity; ethnic = ethnicity; gender = sex.

Table D.7

LASSO Regression Analysis With Lambda Set at 0.09 for Research Question 4

Variable	LASSO Coefficient
Intercept	-4.78
Sex	—
Age at Baseline	0.01
Education	—
APOE Ɛ4 Status	0.00
Direct Maternal Lineage of AD	—
Direct Paternal Lineage of AD	—
Congestive Heart Failure	0.26
Cerebrovascular Accident	—
Diabetes Mellitus	—
Myocardial Infarction	—
Hypertension	—
Obesity	—
Cholesterol/Atherosclerosis	—
Hypothyroidism	1.04
Atrial Fibrillation and Other Dysrhythmias	1.57

Table D.8

LASSO Regression Analysis With Cross-Validation Lambda

Variable	LASSO Coefficient
Intercept	20.92
Sex	-0.09
Age at Baseline	-0.09
Education	—
APOE Ɛ4 Status	-1.14
Direct Maternal Lineage of AD	-0.04
Direct Paternal Lineage of AD	-0.11
Congestive Heart Failure	-1.45
Cerebrovascular Accident	-0.21
Diabetes Mellitus	0.02
Myocardial Infarction	0.47
Hypertension	—
Obesity	-0.94
Cholesterol/Atherosclerosis	—
Hypothyroidism	-4.10
Atrial Fibrillation and Other Dysrhythmias	-4.42

Appendix E: Male and Female Binary Logistic Regression Nonsignificant Interactions

Table E.1

Female: Binary Logistic Regression Cardiovascular Risk Factors by Direct Maternal and Paternal Lineage of Alzheimer's Disease

Parameter	β	*SE*	Wald	*df*	Sig.	Exp(β)
Congestive Heart Failure × DMLAD	0.54	0.71	0.76	1	.445	1.72
Cerebrovascular Accident × DMLAD	0.51	0.48	1.05	1	.300	1.66
Cerebrovascular Accident × DPLAD	-0.69	0.73	-0.95	1	.344	0.50
Diabetes Mellitus × DMLAD	-0.50	0.48	-1.05	1	.295	0.60
Diabetes Mellitus × DPLAD	-0.17	0.55	-0.31	1	.760	0.84
Myocardial Infarction × DMLAD	-0.15	0.50	-0.31	1	.760	0.86
Myocardial Infarction × DPLAD	-0.59	0.87	-0.70	1	.500	0.55
Hypertension × DMLAD	0.20	0.33	0.33	1	.552	1.22
Hypertension × DPLAD	0.22	0.45	0.45	1	.635	1.24
Cholesterol/Triglycerides/Atherosclerosis × DMLAD	-0.42	0.32	-1.30	1	.192	-0.42
Cholesterol/Triglycerides/Atherosclerosis × DPLAD	0.79	0.45	1.77	1	.076	2.21
Hypothyroidism × DMLAD	-0.52	871.4	-0.0006	1	.999	0.59
Hypothyroidism × DPLAD	-0.14	1427.0	-0.0001	1	.999	0.87
Obesity × DMLAD	0.26	821.1	0.0003	1	.997	1.29
Obesity × DPLAD	NA	NA	NA	—	NA	NA
Atrial Fibrillation and Other Dysrhythmias × DMLAD	-0.38	906.4	-0.0004	1	.999	0.68
Atrial Fibrillation and Other Dysrhythmias × DPLAD	-0.22	1209	-0.0002	1	.999	0.81

Note. Each cardiovascular risk factor by direct maternal and paternal lineage of AD is from a different binary logistic regression. AD = Alzheimer's Disease; DMLAD = Direct Maternal Lineage of AD; DPLAD = Direct Paternal Lineage of AD.
*$p < .05$. **$p < .001$.

Table E.2

Male: Binary Logistic Regression Cardiovascular Risk Factors by Direct Maternal and Paternal Lineage of Alzheimer's Disease

Parameter	β	*SE*	Wald	*df*	Sig.	Exp(β)
Congestive Heart Failure × DMLAD	-0.22	0.91	-0.25	1	.805	0.80
Congestive Heart Failure × DPLAD	1.13	1.22	0.93	1	.353	3.11
Cerebrovascular Accident × DMLAD	-1.38	0.76	-1.82	1	.069	0.48
Cerebrovascular Accident × DPLAD	0.12	0.98	0.12	1	.901	0.12
Diabetes Mellitus × DMLAD	0.10	0.46	0.21	1	.833	1.10
Diabetes Mellitus × DPLAD	-0.50	0.68	-0.73	1	.463	0.61
Myocardial Infarction × DMLAD	0.39	0.47	0.83	1	.404	1.48
Myocardial Infarction × DPLAD	0.56	0.69	0.82	1	.413	1.76
Hypertension × DMLAD	-0.15	0.42	-0.35	1	.725	0.86
Hypertension × DPLAD	0.78	0.60	1.30	1	.193	2.19
Cholesterol/Triglycerides/Atherosclerosis × DMLAD	0.05	0.40	0.14	1	.884	1.25
Cholesterol/Triglycerides/Atherosclerosis × DPLAD	0.23	0.54	0.42	1	.671	1.30
Hypothyroidism × DMLAD	-0.19	983.34	-0.0002	1	.999	0.83
Hyperthyroidism × DPLAD	-0.23	1617.26	-0.0001	1	.999	1.27
Obesity × DMLAD	NA	NA	NA	—	NA	NA
Obesity × DPLAD	0.16	655.67	0.0003	1	.999	1.18
Atrial Fibrillation and Other Dysrhythmias × DMLAD	-0.11	1020.51	-0.0001	1	.999	0.89
Atrial Fibrillation and Other Dysrhythmias × DPLAD	-0.31	1955.38	-0.0002	1	.999	1.37

Note. Each cardiovascular risk factor by direct maternal and paternal lineage of AD is from a different binary logistic regression. AD = Alzheimer's Disease; DMLAD = Direct Maternal Lineage of AD; DPLAD = Direct Paternal Lineage of AD.
*$p < .05$. **$p < .001$.

Appendix F: Male: Binary Logistic Regression Trend Level Interaction for Cerebrovascular Accident and Direct Maternal Lineage of Alzheimer's Disease

Table F.1

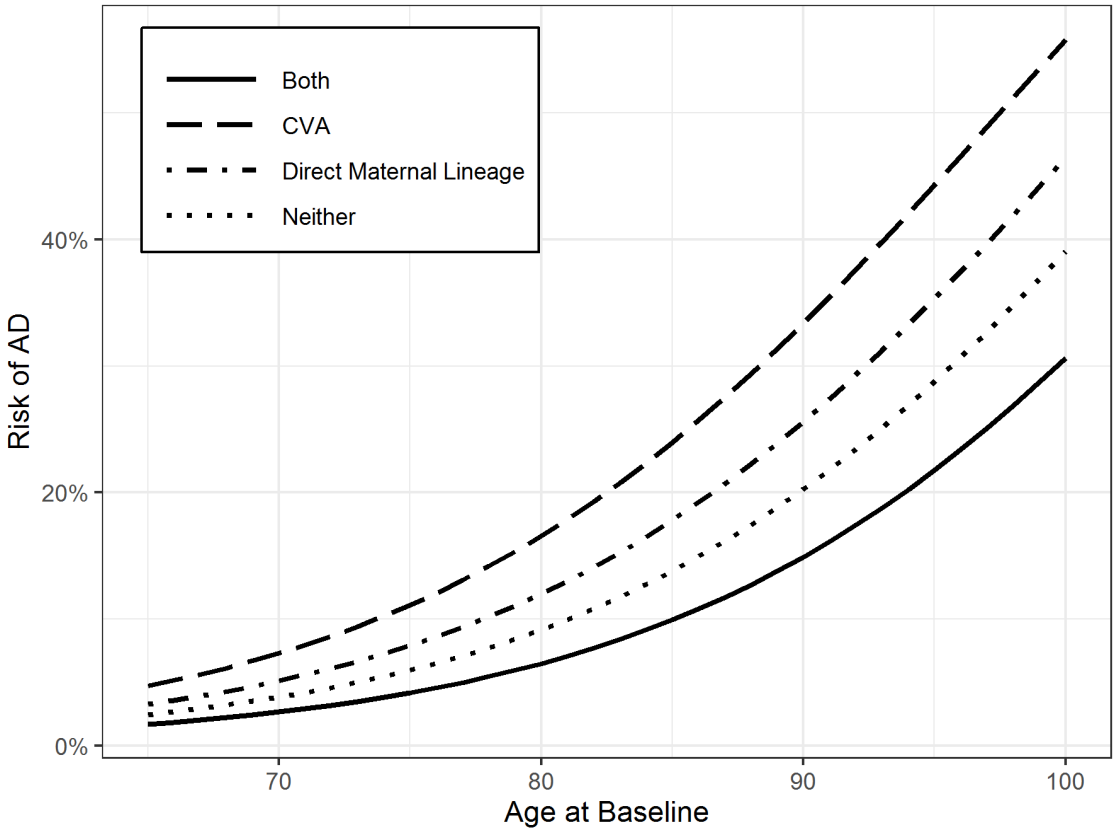
Male: Binary Logistic Regression for Cerebrovascular Accident and Maternal Family Lineage of Alzheimer's Disease

							OR 95% *CI*	
Parameter	*b*	*SE*	Wald	*df*	Sig.	*OR*	Lower	Upper
Intercept	-9.77	0.91	-10.76	1	<0.001**	<0.001	<0.001	<0.001
Congestive Heart Failure	2.37	0.26	9.04	1	<0.001**	11.71	6.47	11.82
Cerebrovascular Accident	0.69	0.23	3.02		0.002*	1.99	1.26	3.09
Hypertension	0.30	0.15	2.07	1	0.04*	1.36	1.02	1.83
Cholesterol/Triglycerides/ Atherosclerosis	0.41	0.15	2.63		0.001*	1.50	1.11	2.04
APOE Ɛ4 Status	1.28	0.15	8.57	1	<0.001**	3.60	2.69	4.84
Direct Maternal Lineage of AD	0.28	0.22	1.30	1	0.19	1.33	0.86	2.03
Direct Paternal Lineage of AD	0.30	0.28	1.09	1	0.28	1.35	0.77	2.30
Education	0.07	0.15	0.45	1	0.65	1.07	0.80	1.43
Age	0.09	0.01	8.56	1	<0.001**	1.10	1.07	1.12
Direct Maternal Lineage of AD × Cerebrovascular Accident	-1.38	0.52	-1.82	1	0.07	0.25	0.48	1.01

Note. AD = Alzheimer's Disease.
*$p < .05$. **$p < .001$.

Figure F.1

Males With History of Cerebrovascular Accident and Direct Maternal Lineage and Risk for Alzheimer's Disease



Note. This figure presents a probability plot male probands with a direct maternal lineage of AD by history of a cerebrovascular accident (CVA) across various ages for male probands without the presence of an APOE Ɛ4 allele, without a history of hypertension or cholesterol/triglycerides/atherosclerosis or congestive heart failure and with a high school/GED/or less education. This model was not retained as it was not the most parsimonious and did not have the lowest AIC, BIC, and R-squared compared to the model presented in cardiovascular risk factors with family history and Alzheimer's disease among male probands section. AD = Alzheimer's Disease.

CURRICULUM VITAE

Elizabeth K. Vernon, M.S.

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Education

Doctor of Philosophy in Psychology (APA Accredited; Graduation expected June 2021)
Utah State University – Logan, Utah
Dissertation: *Extended Maternal and Paternal Hereditary Risk for Alzheimer's Disease Examined by Sex in a Sample of Community Dwelling Older Adults in Cache County, UT*
Dissertation Chair: JoAnn Tschanz, Ph.D.
Expected Defense: May 2021

Master of Science in Psychology (APA Accredited; November 2018)
Utah State University – Logan, Utah
Thesis Chair: JoAnn Tschanz, Ph.D.
Master's Thesis: *Insomnia and Use of Sleep Medications in Predicting Risk of Alzheimer's Disease in the Cache County Study*

Bachelor of Arts in Psychology (August 2011)
Indiana University – Bloomington, Indiana

Clinical Experience

Neuropsychology Track Intern (APA Accredited; July 2020 – Present)
Missouri Health Sciences Psychology Consortium
Department of Health Psychology, Columbia, MO

Major Rotations

Opioid Use Disorder (March 202-June 2021)
Supervisor: Bonny Thacker, PsyD

- Observe inpatient and outpatient individual and group psychotherapy sessions.
- Observe structured health and intake evaluations for an inpatient facility.

Adult Neuropsychology (November 2020-February 2021)
*Supervisors***:** Eric Hart, PsyD., ABPP-CN
Laura Schopp, Ph.D., ABPP-CN

- Administer, score, and interpret flexible neuropsychological test batteries (currently via telehealth) for adults with stroke, neurodegenerative disorders, traumatic brain injury, movement disorders, developmental disabilities, stroke, complex psychiatric conditions, and other neurological conditions.
- Conduct 3-4 semi-structured clinical interviews and comprehensive neuropsychological reports per week.

Rusk Rehabilitation Rotation (July 2020-October 2020)
Supervisor: Renee Stucky, Ph.D., ABPP-Rehabilitation Psychology

- Administered brief neuropsychological and cognitive screeners, provided feedback to the interdisciplinary team, families, and patients, provided patient support, consulted with interdisciplinary team members, provided psychoeducation, assisted with discharge planning and case management, and conducted brief psychotherapy with acute medically complex individuals with new onset spinal cord injuries, stroke, traumatic brain injury, amputations, or other medical conditions.
- Reviewed medical charts as consultant to medical providers in developing and implementing treatment plans; attended weekly didactics with PM&R residents.

Minor Rotations

Neurosurgery Clinic (March 2021-June 2021
Supervisor: Kimberley Kimchi, Ph.D.

- Conduct brief psychological evaluations and provide brief intervention and psychoeducational services.
- Administer pre-and-post operative neuropsychological screeners for neurosurgical patients.

Neurology Clinic (November 2020-June 2021)
Supervisor: Andrew Kiselica, Ph.D.

- Conduct brief neurocognitive screeners to triage older adults for a full neuropsychological evaluation; assist providers with developing and implementing treatment plans.
- Administer flexible neuropsychological test batteries for older adults with various neurodegenerative or other neurological disorders.
- Conduct 1-2 semi-structured interviews and comprehensive integrated neuropsychological reports in an outpatient setting per week.

Bariatric Surgery Clinic (July 2020-October 2020)
Supervisor: Kimberley Kimchi, Ph.D.

- Conducted comprehensive pre-surgical bariatric psychological evaluations via telehealth and completed comprehensive psychodiagnostic reports.

Graduate Clinical Experience

Graduate Practicum Student (August 2019 – March 2020)
University of Utah Physical Medicine and Rehabilitation, Salt Lake City, UT
Supervisors: Jeremy Davis, PsyD., ABPP-CN
Summer Rolin, PsyD.

- Administered flexible neuropsychological test batteries, assisted in conducting structured clinical interviews, provided comprehensive feedback of assessment results, and completed comprehensive neuropsychological reports in a physical

medicine and rehabilitation setting for adults with traumatic brain injury, acquired brain injury, neurodegenerative disorders, or other neurological conditions.
- Participated in weekly didactic training with the neuropsychology team and attended monthly didactics with PMR residents.

Graduate Assistant (January 2019 – March 2020)
Neuropsychology Center of Utah, Clinton, UT
Supervisor: Adam Schwebach, Ph.D.
- Conducted neuropsychological intake interviews, administered, and interpreted flexible neuropsychological test batteries for adults, adolescents and children with learning disabilities, neurodevelopmental disorders, neurocognitive disorders, and psychiatric concerns.
- Provided comprehensive feedback to patients and completed comprehensive integrated neuropsychological reports.

Graduate Student Therapist (August 2018 – May 2019)
Brigham City Cardiac Wellness, Brigham City, UT
Supervisor: Scott DeBerard, Ph.D.
- Provided treatment services to adults with recent cardiac events in a cardiac rehabilitation setting using CBT, CBT-I, Mindfulness, Behavioral Activation, psychoeducation (Stress Management Training) and Motivational Interviewing.
- Reviewed medical charts to assist medical staff in developing and implementing treatment plans, conducted biopsychosocial in-service for the cardiac hospital staff, and taught stress management skills to general hospital staff.

Graduate Student Therapist (August 2017 – May 2019)
Utah State University Student Health Center, Logan, UT
Supervisor: Scott DeBerard, Ph.D.
- Conducted structured intake interviews and provided focused, brief-interventions in a primary care setting using CBT, ACT, Behavioral Activation, and Motivational Interviewing
- Consulted with primary care providers for the integration of care and participated in weekly case consultation with my practicum team, conducted case presentations and psychoeducational presentations.

Graduate Assistant (August 2018 – January 2019)
Neurobehavioral Center of Growth, Bountiful, UT
Supervisor: Jennifer Cardinal, Ph.D.
- Observed intake and feedback sessions, wrote comprehensive integrated neuropsychological reports, administered flexible neuropsychological test batteries for children, adolescents, and adults with learning disabilities, intellectual disabilities, neurodevelopmental disorders, and psychiatric conditions.

Graduate Student Therapist (August 2016 – October 2017)
Integrative Practicum with Adults, Adolescents, and Children, Psychology Community Clinic, Utah State University, Logan, UT
Supervisors: Susan L. Crowley, Ph.D., ABPP
Sara Boghosian, Ph.D.
Marietta Veeder, Ph.D.

- Provided treatment for children, adolescents, and adults with anxiety disorders, depressive disorders, adjustment disorder, sleep disorders, and chronic pain using CBT, ACT, Behavioral Activation, and Motivational Interviewing.
- Completed neuropsychological assessments for children with learning disabilities and completed comprehensive assessment reports.
- Participated in weekly classes of assessment and the practice of clinical and counseling psychology with child, adolescent, and adult populations

Previous Clinical Training

Psychometrist (May 2013-June 2015)
Knight Alzheimer Disease Research Center, Washington University in St. Louis School of Medicine, St. Louis, MO
Supervisor: Jason Hassenstab, Ph.D.

- Administered and scored a standard research test battery to older adults and middle-aged adults with family history of dementia.
- Attended at weekly case-staffings to determine dementia diagnoses and weekly neurology grand rounds and presented at grand rounds on distracted driving and older adults

Peer-Reviewed Publications

Vernon, E. K., Cooley, B., Rozum, W., Rattinger, G.B., Behrens, S., Mayti, J., Fauth, E., Lyketsos, C.G., & Tschanz, J.T. (2019). Caregiver-care recipient relationship closeness is associated with neuropsychiatric symptoms in dementia. *The American Journal of Geriatric Psychiatry, 27*(4), 349-359. https://doi.org/10.1016/j.jagp.2018.11.010.

Rozum, W., Cooley, B., **Vernon, E.K.,** Mayti, J., & Tschanz, J.T. (2019). Neuropsychiatric symptoms in severe dementia: association with specific cognitive domains: the cache county dementia progression study. *International Journal of Geriatric Psychiatry, 34*(7), 901-903. https://doi.org/10.1002/gps.5112.

Rattinger, G.B., Sanders, C., **Vernon, E.K.,** Schwartz, S., Behrens, S., Lyketsos, C.G., & Tschanz, J.T. (2018). Neuropsychiatric symptoms in dementia patients and longitudinal costs of informal care in the cache county population. *Alzheimer's & Dementia, 5*,81-88. https://doi.org/10.1016/j.trci.2019.01.002.

Mayti, J., Tschanz, J.T., Rattinger, G.B., Sanders, C., **Vernon, E.K.,** Corcoran, C, Kauwe, J.S.K, & Buhusi, M. (2017). Sex differences in risk for Alzheimer's disease related to neurotrophin gene polymorphisms: the Cache County Memory

Study. *Journal of Gerontology: Series A, 72*(12), 1607-1613. https://doi.org/10.1093/gerona/glx092.

Roe, C.M., Babulal, G.M., Head, D.M., Holtz-Stout, S., **Vernon, E.K.,** Ghoshal, N., Garland, B., Barco, P.P., Williams, M.N., Johnson, A., Fierberg, R., Fague, S., Xiong, C., Mormino E., Grant, E.A., Holtzman, D.M, Benzinger, T.L., Fagan, A.M., Ott, B.R., Carr, D.B., & Morris, J.C. (2016). Preclinical Alzheimer disease and longitudinal driving decline. *Alzheimer's & Dementia, 3*(1), 74-82. https://doi.org/10.1016/j.trci.2016.11.006.

Babulal, G.M., Addison, A., Ghoshal, N., Holtz-Stout, S., **Vernon, E.K.,** Sellan, M., & Roe, C.M. (2016). Development and interval testing of a naturalistic driving methodology to evaluate driving behavior. *F1000Research, 5*, 1716.doi: 10.12688/f1000research.9150.2.

Babulal, G.M., Ghoshal, N., Head, D.M., **Vernon, E.K.,** Holtzman, D.M., Benzinger, T.L., Fagan, A.M., Roe, C.M., & Morris, J.C. (2016). Mood changes in cognitively normal older adults linked to Alzheimer's disease biomarker levels. *The American Journal of Geriatric Psychiatry*,*24*(11), 1095-1104. https://doi.org/10.1016/j.jagp.2016.04.004.

Roe, C.M., Barco, P.P., Head, D.M., Ghoshal, N., Selsor, N., Babulal, G.M., Fierberg, R., **Vernon, E.K.,** Shulman, N., Johnson, A., Fague, S., Xiong, C., Grant, E.A., Campbell, A., Ott, B.R., Holtzman, D.M., Benzinger, T.L., Fagan, A.M., Carr, D.B., & Morris, J.C. (2016). Amyloid imaging, cerebrospinal fluid biomarkers predict driving performance among cognitively normal individuals. *Alzheimer Dis Associated Disorders*, *31*(1), 69. doi: 10.1097/WAD.0000000000000154.

Vernon, E.K., Babulal, G.M., Head, D., Carr, D., Ghoshal, N., Barco, P., Morris, J.C. & Roe, C.M. (2015). Older adults, ages 65 and older, use potentially distracting electronic devices while driving. *Journal of the American Geriatric Society*, *63*(6), 1251. doi: 10.1111/jgs.13499.

Papers in Preparation

Vernon, E.K., Rattinger, G.B., DeBerard, M.S., Schwartz, S., Kugler, J., & Tschanz, J.T. (in preparation). Sex differences in the association between pharmacological agents to treat insomnia and risk of Alzheimer's disease.

Published Encyclopedia Entries

Vernon, E.K. & Tschanz, J.T. (2018). Dopamine. In Kreutzer, J.S., Deluca, J., & Caplan. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_1762.

Vernon, E.K., & Tschanz, J.T. (2018). Amphetamine. In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_1755.

Vernon, E.K. & Tschanz, J.T. (2018). Amyloid plaques. In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_490.

Tschanz, J.T. & **Vernon, E.K**. (2018). Anticholinesterase inhibitors. In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_1770.

Tschanz, J.T. & **Vernon, E.K.** (2018). Neurofibrillary tangles. In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_492.

Tschanz, J.T. & **Vernon, E.K**. (2018). D-Amphetamine. In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_1645.

Tschanz, J.T. & **Vernon, E.K.** (2018). In Kreutzer, J.S., DeLuca, J., & Caplan, B. (eds) Acetylcholine. *Encyclopedia of Clinical Neuropsychology*. Springer, Cham. https://doi.org/10.1007/978-3-319-57111-9_1622.

Oral and Poster Presentations

Vernon, E.K., Rattinger, G.B., DeBerard, M.S., Kugler, J., & Tschanz, J.T. (July 2019). Sex Differences in the Association between Sleep Medications and Risk of Alzheimer's Disease: The Cache County Study (USA). Poster Presentation at the Alzheimer's Association International Conference, Los Angeles, CA

Hammond, A.G., **Vernon, E.K.,** Kauzor, K.E., Tschanz, J.T. (July 2019). Baseline Cognitive Status and Conversion to Alzheimer's Disease Based on Gender: The Cache County Memory Study. Poster Presentation at the Alzheimer's Association International Conference, Los Angeles, CA

Tschanz, J.T., **Vernon, E.K.,** Kauzor, K.E., Hammond, A.G., Corcoran, C., Cannon-Albright, L., Teerlink, C., & Kauwe, J.S. (July 2019). Risk of Alzheimer's Disease and Related Dementias varies by Maternal, Paternal, and Sibling Family History & Sex: The Cache County Study. Poster Presentation at the Alzheimer's Association International Conference, Los Angeles, CA

Vernon, E.K., Behrens, S., Rattinger, G.B., Schwartz, S., & Tschanz, J.T. (July 2018). Use of Sleep Medications is Associated with Poorer Cognition in Older Male Adults: The Cache County Study (USA). Poster Presentation at the Alzheimer's Association International Conference, Chicago, IL

Mayti, J., West, N., Rattinger, G.B., **Vernon, E.K.**, Buhusi, M., & Tschanz, J.T. (July 2018). Reproductive Window and Moderating Factors Associated with Risk for Alzheimer's Disease: The Cache County Study. Poster presentation at the Alzheimer's Association International Conference, Chicago, IL

Vernon, E.K., Cooley, B., Rozum, W., Rattinger, G.B., Behrens, S., Fauth, B., & Tschanz, J.T. (July 2017). Caregiver-Care Recipient Relationships are Associated with Neuropsychiatric Symptoms in Dementia. Poster presentation at International Association of Gerontology and Geriatrics, San Francisco, CA

Rozum, W., Cooley, B., **Vernon, E.K.,** Richens, A., Mayti, J., & Tschanz, J.T. (April 2017). Specific Cognitive/Behavioral Domains Predict Neuropsychiatric Symptoms in Severe Dementia. Poster presentation at Rocky Mountain Psychological Association, Salt Lake City, UT

DeBerard, M.S., Rattinger, G., Marley, M., Cooley, B., Sanders, C., Behrens, S., **Vernon, E.K.**, & Tschanz, J.T. (March 2017). Self-Rated Health Predicts Mortality in Older Adults Regardless of Cognitive Status. Poster Presentation at Society of Behavioral Medicine, San Diego, CA

Vernon, E.K., Behrens, S. B., Mayti, J., & Tschanz, J.T. (January 2016). Sleep Disturbances and Their Association with Cognitive Status in a Population Based Sample of Older Adults: The Cache County Memory Study. Poster presentation at the International Neuropsychology Society, New Orleans, LA

Mayti, J., Rattinger, G.B., Sanders, C., **Vernon, E.K.**, Corcoran, C., Kauwe, J.K., Buhusi, M., & Tschanz, J.T. (November 2016). Sex Differences in Neurotrophin Genes and Risk for Alzheimer's Disease. Poster presentation at Gerontological Society of America, New Orleans, LA

Tschanz, J.T., Rattinger, G.B., Marley, M., Cooley, B., Sanders, C., Behrens, S., **Vernon, E.K.,** & DeBerard, M.S. (November 2016). Self-Rated Health Predicts Mortality in Older Adults Regardless of Cognitive Status. Poster presentation at the Gerontological Society of America, New Orleans, LA

Babulal, G.M., **Vernon, E.K.,** Ghoshal, N., Head, D.M., Carr, D.B., Barco, P., Morris, J.C., & Roe, C.M. (November 2015). Stress and Driving Errors in Older Adults with and without Preclinical Alzheimer's Disease. Poster Presentation at the Gerontological Society of America, Orlando, FL

Vernon, E.K., Babulal, G.M., Head, D., Wallendorf, M., Carr, D.B, Ghoshal, N., Barco, P.P., Morris, J.C., & Roe, C.M. Adults 65 and Older Use Potentially Distracting Electronic Devices while Driving. Poster presentation at the Alzheimer's Association International Conference, Washington, D.C.

Babulal, G.M., **Vernon, E.K.,** Ghoshal, N., Head, D.M., Barco, P.P., Carr, D.B., Morris, J.C., & Roe, C.M. (July 2015). Poster Presentation at the Alzheimer's Association International Conference, Washington, D.C.

Roe, C.M., Barco, P.P., Head, D.M., Ghoshal, N., Selsor, N., Babulal, G.M., Fierberg, R., **Vernon, E.K.,** Shulman, N., Johnson, A., Fague, S., Xiong, C., Grant, E.A., Campbell, A., Holtzman, D.M., Benzinger, T., Fagan, A.M., Carr, D.B., Morris,

J.C. (July 2015). Amyloid Imaging and Cerebrospinal Fluid Biomarkers Predict Driving Performance in Preclinical Alzheimer's Disease. Poster presentation at the Alzheimer's International Conference, Washington, D.C.

Ruvolo, D., Chasse, R., **Vernon, E.K.,** Maue-Dreyfus, D., Grant, E., Morris, J.C., & Hassenstab, J. (July 2013). Attenuation of Practice Effects is a Potential Marker of Pre-Clinical Alzheimer's Disease. Poster Presentation at the Alzheimer's Association International Conference, Boston, MA

Vernon, E.K., Sweet, L., McCaffery, J., Phelan, S., McDermott, K., Cohen, R.A., Wing, R.R., & Hassenstab, J. (April 2013). Neural Response to High-Calorie Food Words in Obesity and Successful Weight Loss Maintenance. Poster Presentation at the Cognitive Neuroscience Society Conference, San Francisco, CA

Research Press Releases/Press Articles

Interviewee (February 2020)

- Sleep Medication in Older Adults. ALZ magazine.

Presenter (July 2019)

- Sleep Drugs, Sex Differences in the Association between Sleep Medication and Risk of Alzheimer's Disease: The Cache County Study, Alzheimer's Association International Conference, Los Angeles, CA

Interviewee (July 2019)

- Utah State doctoral student featured in Alzheimer's Association International Conference, Logan, UT
- A Complicated Connection between Sleep and Alzheimer's risk. Wtop. https://wtop.com/health-fitness/2019/07/a-complicated-connection-between-sleep-and-alzheimers-risk/
- Sleep Medication Linked to Dementia. AARP. https://www.aarp.org/health/dementia/info-2019/dementia-sleep-medication.html
- Sleep Medications Tied to Slightly Higher Risk For Alzheimer's Disease in Women. Healio. https://www.healio.com/primary-care/womens-health/news/online/%7B57024686-718d-4dab-9c13-acb01a650a47%7D/sleep-medications-tied-to-slightly-higher-risk-for-alzheimers-disease-in-women
- Utah State University Student Featured in Alzheimer's Association International Conference. https://kutv.com/news/local/utah-state-doctoral-student-featured-in-alzheimers-association-international-conference
- Sleep Medication and Dementia. The Gilmer Mirror. www.gilmermirror.com/view/full_story/27661613/article-Sleep-Medications-and-Dementia?instance=home_news_bullets
- Use of Sleep Meds May Elevate Dementia, Alzheimer's Risk. MIMS. https://specialty.mims.com/topic/use-of-sleep-meds-may-elevate-dementia--alzheimer-s-risk?topic-grouper=news

- AAIC Roundup: Alzheimer's, Seizures, Sleep Medications, the LGBT Community and More. https://www.biospace.com/article/aaic-roundup-alzheimer-s-seizures-sleep-medication-the-lgbt-community-and-more/

Research Experience

Graduate Research Assistant (August 2015 – Present)
Alzheimer's Disease and Cognitive Disorders Lab, Utah State University, Logan, UT.
Supervisor: JoAnn Tschanz, Ph.D.
Completed literature reviews, collaborated with colleagues on manuscripts, conducted analyses, mentored undergraduate research assistants, and created tables and figures.

Graduate Research Assistant (March 2020-May 2020)
Cache County Family Study, Utah State University, Logan, UT.
Supervisor: JoAnn Tschanz, Ph.D.
Researched neuropsychological batteries and tests to be administered via telehealth.

Graduate Research Assistant (August 2017-August 2018)
Cache County Family Study, Utah State University, Logan, UT.
Supervisor: JoAnn Tschanz, Ph.D.
Created a database in RedCap, assisted in completing IRB protocol, supported the study running, collected field interview data, and entered data.

Psychometrician and Research Assistant (May 2012-June 2015)
Knight Alzheimer Disease Research Center, Washington University in St. Louis School of Medicine, St. Louis, MO.
Supervisor: Dr. Jason Hassenstab, Ph.D.
Administered neuropsychological batteries to older adults with and without cognitive impairment, analyzed collected data, maintained data integrity, and recorded behavioral observations.

Research Assistant and Research Coordinator (May 2013- June 2015)
Roe Lab: R01 Grant-Factors Impacting Driving in Older Adults, Washington University in St. Louis School of Medicine, St. Louis, MO.
Supervisor: Dr. Catherine Roe,
Conducted navigational assessments, analyzed, and maintained data, insured compliance with IRB protocol, collaborated on manuscripts, and worked with an integrated disciplinary team.

Research Coordinator (May 2014-June 2015)
Dominantly Inherited Frontotemporal Dementia Study, Washington University in St. Louis School of Medicine, St. Louis, MO.
Supervisor: Nupur Ghoshal, M.D., Ph.D.
Maintained protocol compliance, assisted in grant renewal process, coordinated, and helped organize the research study.

Research Assistant (May 2014-June 2015)
Driving Simulator Lab, Washington University in St. Louis School of Medicine, St. Louis, MO.
Supervisor: David Carr, M.D.
Assisted in grant writing, running participants, conducted data analyses, maintained data compliance, and assisted in manuscript writing.

Undergraduate Research Assistant (June 2011-August 2011)
Perception and Action Lab, Indiana University, Bloomington, IN
Supervisors: Geoffery Bingham, Ph.D. and Winona Snapp-Childs, Ph.D.
Administered experiments, assisted in data analyses, and conducted experiments with bimanual rhythmic coordination

Teaching Experience

Guest Lecturer

Abnormal Psychology (Summer 2016, Fall 2016, Summer 2017)
Research Methods (Fall 2015)

Graduate Teaching Assistant

Intellectual Assessment (Spring 2017)
Health Psychology (Spring 2017)
Introductory Psychology (Fall 2015-Spring 2016)
Scientific Thinking and Research Methods (Fall 2015-Spring 2016)

Awards and Honors

Utah State University – Gloria Foster George Scholarship (2017 – 2018)
Utah State University – Annual Kranz Travel Research Award (2015 – Current)

Professional Memberships and Organizations

2019 to Current American Psychological Association Student Affiliate
APA Division memberships
Division 12 Student Membership
Division 40 Student Membership

Professional Services

Ad hoc reviewer for The American Journal of Geriatrics Society.