UNIVERSITY OF CALIFORNIA
RIVERSIDE

Using Developmental Trajectories of Cognitive Performance and Cardiovascular Risk Factors for the Early Prediction of Alzheimer's Disease and Vascular Dementia in Late Adulthood

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Psychology

by

Jennifer M. Koontz

December 2010

Dissertation Committee:
Dr. Chandra A. Reynolds, Chairperson
Dr. Mary Gauvain
Dr. John J. McArdle

The Dissertation of Jennifer M. Koontz is approved:

Committee Chairperson

University of California, Riverside

ABSTRACT OF THE DISSERTATION

Using Developmental Trajectories of Cognitive Performance and Cardiovascular Risk Factors for the Early Prediction of Alzheimer's Disease and Vascular Dementia in Late Adulthood

by

Jennifer M. Koontz

Doctor of Philosophy, Graduate Program in Psychology
University of California, Riverside, December 2010
Dr. Chandra A. Reynolds, Chairperson

The purpose of this thesis is to examine risk factors present before the diagnosis of dementia in the Aging, Demographics and Memory Study (ADAMS), a sample of 856 participants chosen from the Health and Retirement Study (HRS), a nationally representative sample of persons of retiring age and older, to take part in a clinical assessment for cognitive impairment and collection of other health information. A subset of 330 individuals from the ADAMS study diagnosed with either Alzheimer's disease (AD) or vascular dementia (VaD) was considered in the primary analyses. Risk factors examined were age, gender, years of education, APO-ε status, and empirical Bayes estimates of latent growth curve trajectory components of longitudinal episodic memory performance, mental status and cardiovascular risk to test whether it was possible to discriminate whether a participant would be later diagnosed with either Alzheimer's disease (AD) or vascular dementia (VaD). Data from the HRS from up to a decade before

diagnosis were used in logistic regression analyses to find the best fitting model of prediction into groups of either AD or VaD. Results showed that while age, gender, number of APO-ε4alleles, episodic memory and cardiovascular risk factors were predictive of later diagnosis of AD versus VaD subtypes, educational attainment and longitudinal mental status trajectories were not significant predictors. Each APO-ε4 allele more than doubled the odds of being classified into the AD group (OR =2.48). Higher levels of performance and maintenance of episodic memory ability across age decreased the odds of being classified in the AD group ($OR_{Intercept}$ = 0.92; OR_{Slope}= 0.79). Every unit of increased cardiovascular risk tended to decrease the odds of being classified into the AD group (OR = 0.77). An attempt was made to examine mixed dementia cases by a re-categorization of participants with vascular pathology into new groups of mixed cases versus a more 'pure' AD group but the percent of cases that were correctly classified decreased from 79.7% in the original analyses to 77.9% once re-organized, indicating more may need to be done to get at underlying risk and cognitive factors involved in mixed dementia.

TABLE OF CONTENTS

List of Tables

List of Figures

Using Developmental Trajectories of Cognitive Performance and Cardiovascular Risk Factors for the Early Prediction of Alzheimer's Disease and Vascular Dementia in Late Adulthood

INTRODUCTION

The present study seeks to obtain a window into the future of those who may one day develop one of the most devastating and rapidly growing illnesses that afflict our aging population of the United States today; a syndrome known as dementia. Many years of research, longitudinal studies and improvement of statistical analytic techniques have advanced the capability of using the knowledge we have at current to predict who will become demented in the future. Moreover, as was discussed at the latest task force meeting of the National Institutes of Health's National Institute on Aging and the Office of Medical Applications of Research in April, 2010, treatments to delay the onset of Alzheimer Disease are rather bleak at this time and prevention may be the better option right now (http://www.annals.org/content/153/3/176.full).

As is common to most studies of the prediction of future illness, the basic questions asked in the current study are: which behaviors can we observe that would tell us if a person would later develop dementia, how long before the diagnosis of dementia can these be identified, and can we use these to differentiate between the different types of dementia. Although it may be useful to examine what risk factors exist in those that are eventually diagnosed with dementia, subtypes of dementia may have markedly different etiologies (Langa et al., 2005); thus risk factors may be different across dementia subtypes. Studying more homogenous subtypes may help to eliminate some of the confusion in the literature. The current study examines the above questions with a

focus on the two most common dementia subtypes, Alzheimer's disease (AD) and vascular dementia (VaD). In addition to considering differential prediction of those with primary diagnoses of AD and VaD, we examine a re-categorization of AD individuals with evidence of vascular pathology to compare a more 'pure' AD group to those with mixed pathology

Literature Review

Development of Dementia in Human Life History

While the first third of the human lifespan is typically characterized by increases in most traits, such as height, weight, cognitive performance, and skill mastery, the last third of the human lifespan is typically looked at in terms of losses. This often leads to the conclusion that development does not occur in later life because of the commonly held conception of development as consisting of increases and beneficial changes (Baltes, 1997; Baltes et al, 1999). As a result, this has led to a relative neglect in looking at developmental processes in the latter half of the lifespan (Baltes, 1997; Baltes et al, 1999). Using the general concept of development as change, whether it is beneficial or not, changes that occur in late adulthood can be examined to find out what these processes are and what influences them. One of our most crucial functions, cognition, deteriorates in old age in many people and this trend is increasing at an alarming rate (Wilmoth et al., 2000). Cognition throughout the lifespan and especially in late adulthood has a complex epigenetic unfolding and is best understood in the context of natural selection.

Evolutionary psychology has altered the questions that are asked about cognition in late life. For example, adherents of the disease model may ask: Why does cognitive functioning decrease with age? On the other hand, evolutionary psychologists may ask: Why do humans retain cognitive functioning after their reproductive years have ended? Indeed, humans, according to the theory of natural selection, should not live beyond their reproductive years, just as it is with their nearest living relative, the chimpanzee, who dies shortly after reproductive years (Judge and Carey, 2000). Darwin (1859) first brought to light the idea that through natural selection, those who have produced the most offspring that live to reproductive maturity are more likely to pass along their genes, along with their qualities that gave them benefit over those who were less successful. In this way, gene frequencies in a population are slowly changed so that the species becomes better adjusted to their environment (Kimura, 1978). Parents produce offspring and successful parents become grandparents, and by ensuring that offspring live and reproduce, genetic benefits will be transmitted to future offspring. However, just as importantly, humans have passed along far more than just their genes from generation to generation. Human life history theorists remark at the correlation between brain size and long juvenile periods in primates, with human beings holding the largest brain size and longest juvenile period (Barrickman et al., 2008). It is believed by most human life history researchers that humans have large brains and long juvenile periods because we need this time to pass along cultural information in the form of tool making, hunting skills (which requires advanced cognition), and knowledge of edible and gatherable foods (Hawkes and Paine, 2006), What is more debated in the literature is whether an increased

lifespan with intact cognition evolved to allow grandparents to play a role in the transmission of cultural knowledge as well as parents, resulting in a special role for grandmothers in ensuring that their children and grandchildren live to a reproductive age (Hawkes and Paine, 2006). Although a difficult theory to test empirically, evidence has been provided for grandmothering as a potential force promoting late life intact cognition, i.e. the "grandmother hypothesis" (see Hamilton, 1966). Child mortality and grandmothering can be studied empirically because of differential X-chromosome relatedness between grandmothers and their grandchildren. In an analysis of historical records from multiple populations, Fox et al. (2009) showed that the likelihood of survival in boys was significantly higher when their maternal grandmother played a role in their caregiving (who are 25% X-chromosome related) than their paternal grandmother (who are 0% X-chromosome related) and that the involvement of a paternal grandmother tended to improve the likelihood of survival for girls (X-chromosome related 50%) more so than the boys (related 0%).

The need for cultural transmission of knowledge in early human evolution, which required a larger and larger cognitive capacity, together with the role that grandmothers may play raising their children's offspring, suggests that cognition should be preserved until late in life (Hawkes et al., 2000). In terms of natural selection, those grandmothers who have intact cognition and longer life-spans would be favored because their presence makes it more likely for their offspring to survive and these characteristics to be selected for (Hawkes et al., 2000). This reiterates the importance then of the earlier statement that the loss of cognition in later life, or more specifically the appearance of dementia

subtypes that are addressed in this paper, are likely to be the result of an important interplay between genetics and a long life-span filled with environmental interaction (Gatz, 2007). The fact that dementia seems to be more likely in those who, rather than having a genotype that negatively affects cognition, are actually *lacking* a certain genotype that *protects* from dementia (the more recently evolved Apolipoprotein-ε3 allele described later in detail) seems to support the premise of preserved late-life cognition as well (Finch and Sapolsky, 1999).

Even notwithstanding the evolutionary factors that may have led to intact cognition during post-reproductive years, the unprecedented increase in lifespan in the last century has led to the observation that the cumulative effects of environments and genes, as well as stochastic processes, impact late life health including cognitive health (e.g., Finch & Kirkwood, 2000). It is estimated that between 2 and 4.5 million people in the United States have dementia, a debilitating deterioration of cognition in late life (Bennett, 2007). The Aging, Demographics and Memory Study (ADAMS) study estimates that dementia prevalence in those over 71 years old is 13.9%, or 3.5 million people in the United States (Plassman et al., 2007). These facts are disturbing when considering the features of dementia and how it will impact the United States population; it is predicted that that rates of dementia will substantially increase as the number of retiring individuals increases assuming that the increase in the number of elderly persons will result in higher dementia rates (Plassman et al., 2007). Dementia is a syndrome that includes multiple cognitive deficits and disorientation (Pariel-Madjlessi et al., 2007). People with dementia may have difficulty in such cognitive areas as language, expressing

difficulties in both language production and comprehension, losses in short term memory and learning ability, and problems with executive and working memory dysfunctions. This may create a general atmosphere of disorientation in which the person may not know what day or year it is, where they are or how to get around in a once familiar city, or even recognize previously familiar people.

The dementia syndrome is typically divided into subtypes that consider in part the pattern of emerging deficits and the potential etiology. For example, those with Alzheimer's disease (AD) primarily express impaired learning and memory that emerges and worsens gradually leading to a general disorientation regarding current events such as the date and names of new acquaintances. AD may only later be confirmed by characteristic amyloid plaques (which is a buildup of protein fragments between neurons) and neurofibrillary tangles (which is the entanglement of certain proteins within the neuron) present in the brain at autopsy (Shen et al., 2001). Alternatively, vascular dementia (VaD) is characterized by different types of vascular insults (such as strokes) that affect blood flow to the brain, thus causing a dementia syndrome where individuals exhibit executive functioning deficits (such as problems with planning and organizing tasks) and disorientation that progresses in a stepwise fashion, i.e. an evident temporal relationship exists between cerebrovascular events and sudden declines in cognitive performance (Loeb and Meyer, 1996).

Dementia researchers and physicians recognize that it has been difficult to relate the clinical expression of dementia to the physiological and neuropathological underpinnings among the subtypes (Armstrong, 2006). Scientists have found

neuropathology in many (but not all) brains of people clinically diagnosed with dementia (Katzman et al., 1988), as well as pathology in the brains of those who didn't have clinical expression of dementia; thus it is difficult to relate brain pathology to the clinical pattern that may cause a once capable person to be unable to drive, cook, or even walk around the block. This frustrating lack of insight into the illness leaves scientists and researchers with one viable option: finding a way to predict dementia as early as is possible. The goals of the early prediction of later dementia and its subtypes are then two-fold: first, identifying modifiable risk factors, and second, identifying people at risk to receive treatment as early as possible. This study attempts to find early signs of cognitive change and cardiovascular risk that may distinguish between later dementia subtypes.

A preliminary body of research (Katzman et al., 1988; Kroger et al., 2008; Rea et al., 2005; Skoog et al., 1993) has associated certain established risk factors with dementia as a general category or 'all cause' dementia, however, there has been much greater difficulty in establishing whether or not there are any risk factors that belong exclusively to one subgroup versus the others. Multiple classifications or overlapping diagnoses may exist within one group, which means that there may be multiple causes or etiologies of the dementia syndrome (Aguero-Torres et al., 2006). One of the reasons that research has shown inconsistent results for the prediction of dementia and its subtypes is possibly due to a bias toward enrolling AD patients (versus other subtypes) into studies. A simple search in the database in the registry of clinical trials maintained by the National Institutes of Health (NIH) reveals 821 studies for the search term "Alzheimer's disease" while "vascular dementia" returns only 103 studies (http://clinicaltrials.gov/ct2/home).

Public attention has resulted in a large amount of research on AD, leaving the other dementia subtypes relatively neglected.

National and multinational studies of aging and dementia --with an emphasis on AD-- have used strict study criteria (which will be explained further) when it can be argued that no distinct line between dementia subtypes truly exist (Aguero-Torres et al., 2006; Bennett, 2007; Langa et al., 2004). Moreover, this may complicate the delineation of distinct and overlapping risk factors for each type, resulting in the confusing body of literature regarding risk factors of dementia and its subtypes, and thus a reduced ability to modify risk factors and prevent dementia. A better understanding of the patterns of risk in dementia subtypes, including 'mixed' subtypes, may help to clarify different etiologies and improve treatment goals (Langa et al., 2004).

If prediction were improved for VaD and mixed cases showing vascular histories, especially by identifying different behavioral profiles of lifestyle that increase cardiovascular risk, prevention may be possible by removing or modifying lifestyle risk factors, for example, increasing beneficial behaviors such as exercise. It has been hypothesized that VaD may even be more readily open to prevention and treatment than AD (Skoog et al., 1993). This may mean that prevention-focused programs would inform individuals that they were at risk for a late life cognitive illness such as dementia and would aim, for example, to increase physical activity and decrease poor dietary choices. Removal of risk factors such as high cholesterol diets and implementation of behavior and habit change such as daily exercise must start as early in the lifespan as possible,

decades before the onset of cognitive problems and subsequent dementia (e.g., see Gatz, Mortimer et al, 2006; Gatz, Prescott, & Pedersen, 2006).

It is necessary to find which risk factors are more predictive of VaD versus AD and after further clarifying these AD versus VaD risk factors, an attempt must be made to find risk factors of mixed dementia. Because both VaD and mixed dementia have underlying cardiovascular and cerebrovascular disease, it is not unreasonable to assume that their risk factors would be similar to each other. Moreover, as noted by Langa et al. (2004), it may be found that treating the underlying cardiovascular diseases of the mixed dementia group could be established as a first line treatment for the mixed subtype. It may be that those with mixed dementia can be combined with the VaD group to consider whether prediction is enhanced due to the underlying cardiovascular conditions involved in both VaD and mixed dementia and thereby leaving a 'purer' AD group. Therefore, this study examined the differences in the cognitive trajectories of people with AD, VaD, and mixed dementia to see if there were differences in the ability to discriminate between subtypes of dementia that a person may be at risk for later in life. Differences in the accumulation of cardiovascular risk over the course of decades and their relationship to later development of dementia are investigated and whether or not these potentially preventable risk factors may discriminate between subtypes of dementia.

Clinical Aspects and Classification of Dementia Subtypes

A. Vascular Dementia (VaD)

VaD is the second most common form of dementia and its prevalence lies between 1% and 4% in people over age 65 (Roman, 2002). In the previously mentioned nationally representative study (ADAMS), VaD was responsible for 17.4% of incident dementia cases when compared to 69.9% of incident dementia cases attributed to AD (Plassman et al., 2007). This is roughly in line with other studies which typically report between 10% and 28% percent of incident dementia cases being attributed to VaD and 40 to 77% percent being attributed to AD (Aguero-Torres et al., 2006; Akomolafe et al., 2008; Hayden et al., 2006; Hebert et al., 2000; Kivipelto et al., 2005; Rea et al., 2005; Rockwood et al., 2000). VaD has been described in many different ways according to the presence of different vascular pathologies such as strokes, “mini-strokes”, microvascular disease, narrowing in major brain arteries, and also by the location of these vascular insults in the brain such as whether they are cortical or subcortical (DeCarli, 2003; Baskys & Hou, 2007). Because of the varying types of pathology it is obvious that VaD itself is a heterogeneous group in terms of type of vascular injury but is still unified by the more general presence of vascular pathology.

There are many different criteria for the diagnosis of VaD which only speaks to the heterogeneity of the disorder. A comparison of four major VaD criteria was conducted by Wetterling et al. (1996) who examined criteria put forth by the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the International Classification of

Diseases, 10th revision (ICD-10), and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). In this study, after investigating 167 cases of probable dementia, Wetterling et al. (1996) found that the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosed 45 VaD cases, the ADDTC diagnosed 23 cases as ischemic VaD, the International Classification of Diseases, 10th revision (ICD-10) diagnosed 21 cases as VaD, the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria diagnosed only 12. In all, only 5 cases met all criteria for VaD in each classification system showing that there is room for improvement. This important review also shows the difficulty of diagnosing such a heterogeneous group (Wetterling et al., 1996).

The criteria listed above tend to emphasize AD-associated features and many of them require that a person with VaD have multiple cognitive deficits in addition to significant memory impairment; however, memory impairments/complaints are not typical for those with VaD (Ylikoski et al., 2007). It has been shown that executive function impairments are fairly common as a prominent deficit in people with VaD and that while these deficits in executive functioning generally progress in step-wise fashion where there are periods of major decline and then periods of stability, memory may decline only slightly and is otherwise rather stable (Lafosse et al., 1997; Mungas et al., 2005; Ylikoski et al., 2007). Stepwise decline in VaD is the most typical course, and declines or changes in executive functioning generally worsen and are often temporally

consistent with cerebrovascular incidents (Roman et al., 1993). For example, a person may experience transient ischemic attacks, which are sometimes referred to as 'mini-strokes' where the blood supply to part of the brain stops for a few minutes but quickly returns to normal. This would cause a person to become confused or disoriented or dizzy and weak, and there may be increasing cognitive impairment with each incident. These also often lead up to a stroke, where again a qualitative difference would be noticed in cognitive functioning compared to pre-stroke functioning (Loeb and Meyer, 1996). Another unique aspect of VaD is the presence of what are called focal neurological signs, such as a one sided gait disturbance or unilateral weakness; these would appear as a weakness or numbness and tingling in one arm or leg and may become worse and impair use of extremities with progression of VaD (Roman et al., 1993). The way that events such as stroke often precede each subsequent further decline in cognition (mostly executive functioning) is functionally different from the smooth and gradual progression of AD.

Consistent with the expected underlying cerebrovascular disease, risk factors for VaD are the same as those for cardiovascular disease. Obesity, poor diet, and high cholesterol leading to the lining the brain's arteries with plaques and high blood pressure may speed up this process in this established course of events ultimately leading to any or all of the following: clogged arteries, blood clots, or heart attacks (Yoshitake et al., 1995; Hassing et al., 2002). Advancing age and hypertension are the most common risk factors for both cardiovascular disease and stroke – suggesting that the underlying process may be the same or similar (DeCarli, 2003).

B. Alzheimer's Disease (AD)

Estimates of AD also vary widely, and in the ADAMS dataset it is estimated that the prevalence of AD in the US is 2.4 million individuals over the age of 71. In the population of those over 65 years old, the prevalence of AD is expected to increase annually from 35 million to 70 million by 2030 (Plassman et al., 2007). As noted above, in the ADAMS dataset VaD was responsible for 17.4% of incident dementia cases and AD was responsible for 69.9% of incident dementia cases (Plassman et al., 2007). In other studies 40 to 77% percent of incident dementia cases are diagnosed as AD (Aguero-Torres et al., 2006; Akomolafe et al., 2008; Hayden et al., 2006; Hebert et al., 2000; Kivipelto et al., 2005; Rea et al., 2005; Rockwood et al., 2000). People are diagnosed as having possible or probable AD according to behavioral criteria such as memory loss, trouble concentrating, and other cognitive impairments. In addition to these behavioral characteristics, neuropathological hallmarks (plaques and neurofibrillary tangles) of AD have been confirmed at autopsy. These are the characteristic plaques that are located between the neurons, comprised of fragments of protein called amyloid-beta (Aβ; Shen et al., 2001). Examinations of AD brains at autopsy have also shown neurofibrillary tangles, a condition within the neuron in which a protein called tau is tangled up inside the cell (Shen et al., 2001). This inhibits transport of neurotransmitters within the neuron. The behavioral (or clinical) expression of dementia plus the neuropathological signs on autopsy are both needed for a confirmed diagnosis of AD.

The most commonly used AD criteria are the National Institute of Neurological and Communicative Disorders and Stroke (now known as the National Institute of

Neurological Disorders and Stroke) /Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) or NINCDS/ADRDA criteria. These criteria assert that there must be a primary memory deficit, multiple cognitive deficits, and a gradual onset and progression. Diagnoses are divided into unlikely, possible, probable, and definite Alzheimer's disease based on inclusion of an increasing number of symptoms that increase the likelihood of AD up to and including neuropathologies confirmed at autopsy which would result in a definite AD diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and the International Classification of Diseases, 10th revision (ICD-10) are less commonly used for diagnosis, and contain slightly more vague criteria, but are similar to the widely accepted and used NINCDS/ADRDA criteria. Unlike VaD, whose criteria are still actively debated, there has been much more consensus around AD criteria (Loeb and Meyer, 1996).

C. Mixed Dementia

Less has been written on mixed dementia; however, this topic is becoming increasingly of interest in research because of the growing difficulties that strict classification criteria have created for drug development as well as studies identifying risk factors for dementia subtypes. Mixed dementia is primarily defined as having both the neuropathology associated with Alzheimer's disease, such as plaques and neurofibrillary tangles, and also the pathology associated with VaD such as infarctions and ischemic periventricular leukoencephalopathy (Langa et al, 2004). Some estimates of incident mixed dementia range from 5 to 31% though in many studies mixed dementia is

not reported or such cases are placed into a catch-all "other" category (Aguero-Torres et al., 2006 [5%], Rockwood et al., 2000 [20%], Rea et al., 2005[31%]).

Clinical diagnosis of mixed dementia is generally difficult as there is no mixed dementia category in the most popular diagnostic criteria mentioned above (NINDS-AIREN for VaD and NINCDS-ADRDA for AD) and when present in other criteria (ICD-10 and DSM-IV) they differ among one another (Langa et al., 2004). Most often a person will have behavioral symptoms that match criteria for both AD and VaD or sometimes they meet AD criteria and then cerebrovascular symptoms are discovered upon imaging results (Rockwood et al., 2000). Thus the pure AD and VaD may represent two poles on the ends of a spectrum with many people not fully meeting criteria in pure form for either illness.

Summary of Current Known Discriminative Risk Factors of Dementia

A. Neuropsychological Risk Factors

Evidence for the necessity of making the AD/VaD distinction is shown in the creation of the Vascular Dementia Assessment Scale (VADAS) developed in reaction to the Alzheimer's disease Assessment Scale Cognitive Subscale (ADAS-cog), the most widely used cognitive testing assessment for demented patients (Ylikoski et al., 2007). Because the primary cognitive deficits differ for VaD and AD, researchers and clinicians felt that another scale was needed to detect the sensitive differences in VaD that the popular ADAS-cog assessment was not capturing. Ylikoski (2007) found that the VADAS could discriminate between mild, moderate, and severe groups of VaD patients while the ADAS-cog could not. This was because of the unique trajectory of cognitive

impairments that VaD people show when compared to AD. Vascular cognitive impairment and white matter changes (which are visual signs of cerebrovascular events in the brain) shown in brain imaging have been specifically related to executive functions, attention and mental speed (Ylikoski et al., 2007). Indeed, the newly created VADAS-cog best discriminated between different white matter hyperintensity (as shown in brain imaging) and changes in the level of severity of white matter hyperintensities, and, therefore is suggested to be a more sensitive measure for vascular-related cognitive change (Ylikoski et al., 2007). Mungas et al. (2005) noted that those with VaD were less likely than those with AD to show memory declines and were more likely to show executive dysfunction as their primary cognitive deficit. Experimentally, many studies have identified these differences in their studies of neuropsychological function in dementia. Graham et al. (2004) found that tests that distinguished AD from VaD in their study were measures of executive functioning and episodic memory, where VaD individuals performed worse on the former and AD individuals performing worse on the latter. Lafosse et al. (1997) found that those with AD scored higher than those with VaD on the control oral word association test (executive function), AD individuals scored lower than VaD on delayed recall (memory), AD individuals were better than VaD individuals on the delayed cued recall intrusions (executive function), and AD individuals were worse than VaD individuals on the discriminability/ recognition (memory).

In summary, people who have VaD are more likely to experience problems with executive functioning and are less likely to show primary memory and learning deficits as are characteristic of people who are diagnosed with AD.

B. Genetic Risk Factors

There are numerous reports of gene candidate studies that identify risk variants for AD but not VaD and vice versa. Some examples of these include a study by Pandey et al. (2007) who found that a gene called presenilin 1 (PS1) may play a role in increasing the amount of plaque buildup in the brain has been found to be associated with early onset AD (such as before age 60 or early 60's) and also associated with other degenerative dementias, but not VaD. Kolsh et al. (2004) found that a gene called angiotension converting enzyme (ACE), which can constrict arteries and control water retention was associated with AD but not VaD. Also a gene called interleukin 1 receptor antagonist (IL1RN) plays a role in blocking immune and inflammatory response was associated with only AD, not VaD (Yucesoy et al., 2006). In the reverse, McCusker et al. (2001) found that a gene called tumor necrosis factor- α (TNF-α) which can both stimulate and inhibit growth in cells and also may affect inflammatory response was associated with risk for VaD but not AD. Although it is already known that these dementia subtypes are functionally and etiologically different, these findings suggest that they may have different genetic predispositions or protective factors. However, there are not many genes that have been extensively studied in VaD populations. Currently, there is only one gene that has been established as a substantial risk factor for AD, the apolipoprotein-E (APO-ε) gene (Corder et al, 1993; Strittmatter et al, 1993).

APO-ε is most commonly tested in demented populations but because of the problems of misclassification detailed in the introduction, the APO-ε research inconclusively illustrates whether or not the number of APO-ε4 alleles increases the odds

of having VaD. However, a large scale meta-analysis has determined APO-ε to be the most predictive genetic risk factor for AD (Farrer et al., 1997). It has also been found to be indicative of VaD in some studies but not all (Hebert et al., 2000). This leaves the possibility that in the proposed study, APO-ε may have some discriminative power between the subtypes of dementia and this will be examined.

C. Cardiovascular Risk Factors

Findings related to the cardiovascular risk factors of VaD and AD are inconclusive. A comprehensive meta-analysis of obesity as a risk factor for dementia showed that obesity constituted a high risk for AD and an even higher risk for VaD when divided by gender (Beydoun et al., 2008). Findings from the Swedish Twin Registry showed similar results where being overweight in midlife was related to an increased risk of both AD and VaD, but when adjustments were made for diabetes and vascular disease, the association with VaD dissipated supporting a role for diabetes and vascular disease etiologies in connection to VaD (Hassing et al., 2009). Using data from the Canadian Study of Health and Aging, Hebert et al. (2000) found that risk factors for VaD included having diabetes, taking aspirin (which may indicate that there is a concern for cardiovascular health), hypertension (women only) and heart disease (men only). Protective factors included engaging in exercise regularly in females only. Yoshitake et al (1995) found that prior stroke, systolic blood pressure and alcohol consumption were risk factors for VaD, while physical activity reduced the risk of AD. Hassing et al. (2002) found that Type 2 diabetes was selectively related to VaD and not AD in twins from the OCTO-Twin study, and Akolomafe et al. (2006) found that diabetes mellitus was only a

risk factor for AD in people who were already at low risk for AD. It has also been found in the Religious Orders Study that those with diabetes mellitus had a 65% increase in the risk of developing AD (Arvanitakis et al., 2004). Conflicting findings from these prior research studies will be further examined in this proposed study in the hopes of gaining a better understanding of the role of cardiovascular risk factors on dementia subtypes.

Research Questions

The aims of the present study are to find risk factors that may precede manifestation of dementia diagnosis and symptoms. The risk factors that will be examined include longitudinal performance on cognitive tests, cardiovascular risk factor trajectories, and the genetic risk due to carrying a certain form of the APO-ε gene (i.e., APO-ε4).

Hypotheses are as follows:

A. Early cognitive changes will be predictive of later dementia, and specific cognitive performance will discriminate between AD and VaD such that:

1. Lower episodic memory (immediate and delayed recall) will be predictive of classification as AD and the slope of decline in memory performance will be gradual.
2. Persons with VaD will have higher episodic memory which may decline slightly but remain relatively stable when compared to persons with AD.
3. Executive functioning may distinguish between dementia subtypes where those with AD will have higher performance than those with VaD.

B. Accumulation of cardiovascular risk factors will be predictive of later dementia, and more accumulated risk will predict classification into VaD versus AD groups.

C. APO-ε genotype may play a role in the discrimination of AD versus VaD classification.

These hypotheses will be examined using the Aging, Demographic, and Memory Study (ADAMS) and their data linked to the Health and Retirement Study described below.

METHOD

The current thesis includes participants and data from the Health and Retirement study (HRS) and the related Aging, Demographic, and Memory Study (ADAMS) study. The primary longitudinal predictors stem from the HRS study, which provides health and cognitive data as far back as 1992 for some participants, while the outcome data come from the ADAMS study, which was an intensive study of a subset of the HRS participants that have been evaluated for dementia. Therefore, the ADAMS subset is the main focus of this study and their longitudinal data is being drawn from the HRS. The HRS and ADAMS studies are described in turn.

The Health and Retirement Study

A. Participants

The Health and Retirement study (HRS) is designed as a nationally representative cohort-sequential study with over 30,000 participants since 1992. Participants provided information about their health, retirement and financial status, and other aging related aspects of their lives via phone or in-person interviews conducted every 2 years. If the

participants were over 80 years old then an attempt was made to interview the participant in person rather than by phone. The demographic characteristics of the HRS sample are described in detail in McArdle et al. (2007). Participants in the HRS had a mean age of 62.96 (SD=2.93) beginning in 1992, representing a uniquely representative sample of participants of retirement age in the United States (McArdle et al., 2007). The McArdle study of HRS cognitive variables (McArdle et al., 2007) used one person from every dyad (married couples) enrolled in the study. At the first cognitive testing they were 61.88 (SD=10.99) years old on average, had a mean of 12.37 (SD=3.27) years of education, 55.7% of them were female. Detailed information can be found on the HRS web site (http://hrsonline.isr.umich.edu).

B. Measures

Cardiovascular Variables

Cardiovascular risk factors available in the HRS were used to determine risk for AD versus VaD. Large-scale studies such as the Framingham Heart Study (Ho et al., 1993) have analyzed extensive longitudinal data to examine the relative risks for heart disease, stroke, and types of cancer, for example. In the interest of public health, findings have been applied to create a calculator of sorts where individuals enter information regarding their own disease risk, e.g., whether or not they smoke, are overweight, or have high blood pressure, etc. The calculator then applies the weights (i.e., risks) assigned to these variables to produce a prediction of the health event or illness occurring within, say, the next 10 years. For the current project we used the Your Disease Risk calculator for heart disease risk, which was originally created by the Harvard School of Public Health, which

collected prevalence estimates from many large studies such as the Framingham Heart Study, and numerous government institutions such as the CDC to compile and create relative risks that could be used in the equation (http://www.yourdiseaserisk.wustl.edu/english). While we do not have all of the items presented in their risk index, we used the relative risk estimates provided by the creators of the website to assign weights to our available variables and summed them at each time point from 1995 to 2002. There was little or no cardiovascular data for the ADAMS subset participants in the HRS data before 1995 and therefore the 1992, 1993, and 1994 waves were not included in cardiovascular analyses. Cardiovascular risk factor questions, their prevalence estimates from the Your Disease Risk site, (http://www.yourdiseaserisk.wustl.edu/english), and their assigned relative risks are shown in Table 1. Descriptive statistics of cardiovascular risk are shown in Table 2 for the ADAMS study subset of the HRS sample that were diagnosed with AD or VaD (N=330) who are the primary focus of this thesis.

Cognitive Variables

Cognitive variables in the HRS were collected via a phone survey called the Telephone Interview of Cognitive Status (TICS) (Brandt et al. 1988). The TICS was a mental status exam that was given over the phone at each data collection point and included the following items:

- Immediate Recall- ten words from a list and participants immediately recalled words from the list. Four different lists were used. The test was administered at all HRS time points.

- Delayed Recall- participants are asked to recall the previous ten words after a delay of five minutes. This data was collected at all HRS time points.
- Serial 7's- participants are asked to subtract 7 starting from 100 for five trials. This was given at all HRS time points.
- Backward Counting- participants were asked to start at 20 and count backwards for 10 consecutive numbers. This was administered at all HRS time points except 1992 and 1994.
- Dates- participants are asked the date, including the day, month, and year and the day of the week. This test is administered at all time points except 1992 and 1994.
- Names- participants must name common objects and the name of the current president and vice president.
- Vocabulary- participants were asked to define five words from the WAIS-R, two lists were used. This was given beginning in 1995 to each participant but was not repeated once the participant had already completed it.

The TICS scales have been used in many studies and validated in various populations such as the elderly (de Jager et al., 2003; Mangione et al., 1993), post-stroke samples (Barber and Stott, 2004; Desmond et al., 1994) and dementia samples (Järvenpää et al., 2000; Plassman et al., 1994; Welsh et al., 1993). McArdle et al. (2007) tested one-, two-, and three-factor models and identified three factors from the cognitive variables included in the TICS. The first factor was made up of the immediate recall and delayed recall items described above and was termed by McArdle et al. the episodic memory (EM) factor. The second factor was made up of what McArdle et al. called the mental status

variables (MS), which included serial 7's, backward counting, names, and dates. This MS factor has orientating questions such as naming political figures and asking the date, however it is also largely a test of executive functioning as it requires intact working memory to do the serial 7's and backwards counting but also to recall current events. The third factor was termed Vocabulary and included only vocabulary items. Only the episodic memory (EM) factor and mental status (MS) factor are examined in the present analyses as hypotheses were made regarding episodic memory and executive functioning, respectively. While the mental status factor is not the most ideal of executive functioning measures, due to the lack of available measures of executive functioning in the HRS study it is used as such. Descriptive data on cognitive variables in the HRS can be found in a review by McArdle et al. (2007). As has been shown in prior analyses by McArdle et al. (2010); the episodic memory factor intercept and slope were predictive of later all-cause dementia status; however it has not been examined for the dementia subtypes. Both the EM and MS intercept and slope, as predictors of group membership into either the AD or VaD group, are used in the present analyses.

The Aging, Demographic, and Memory Study (ADAMS)

The Aging, Demographic, and Memory Study (ADAMS) is a subset of participants drawn from the larger HRS study in 2002 and was created with the goal of identifying accurate dementia prevalence estimates and to investigate the economic impact and outcomes of dementia with a nationally representative sample (Langa et al., 2005). Population estimates require the use of relative weights used in McArdle et al., (2010) because of the oversampling of demented persons; however these weights have

not yet been applied in the present analyses described further below. Eight hundred and fifty six subjects over 70 years old from the HRS were chosen for an in-home assessment of dementia. Because the ADAMS subjects are a smaller group of participants that originally participated in the larger HRS study, they have data on health and cognition since the start of the HRS study in 1992 up until their work-up for dementia when they were selected in 2002. Therefore, this study examined risk factors that may predict a future diagnosis of dementia from up to ten years before it occurred. Thus, neuropsychological, genetic and cardiovascular data and risk factors are pulled from the earlier time points of the HRS, often before participants even showed signs of cognitive impairment. The average age of the ADAMS subset participants at each of their respective measurement points from the HRS dataset are shown in the Table 3.

A. Participants

The ADAMS sample is unique in nature since it has been designed to be a representative sample of the United States population. In addition, each dementia case has been very carefully reviewed by an expert panel of clinicians to ensure proper diagnosis and classification of dementia subtypes. Strict adherence to panel consensus has resulted in numerous categories of cognitive impairment with over 10 subtypes of dementia (Plassman et al., 2007), including the two most common subtypes, Alzheimer's disease (AD) and vascular dementia (VaD), which are examined in the present study. The details of the panel used for diagnosis of different levels of cognitive impairment are described in Plassman et al. (2007). ADAMS sample characteristics on selected variables for this study are shown in Table 4.

B. Dementia Diagnoses

Cognitively impaired subjects were identified in the HRS study using the TICS and were selected for a diagnostic evaluation which included a 3-4 hour in-home assessment by neuropsychology technicians (Langa et al. 2005). As described by Langa and colleagues (2005), the assessment included questions about cognitive symptoms, medical history, medications, family history, and measures of cognitive and functional impairment, depression, and neuropsychological testing. Diagnosis was made using all available information gathered from this assessment and a review of medical charts. ADAMS participants were either considered normal or given a diagnosis of cognitive impairment without dementia, of which there are several categories, or a diagnosis of dementia, of which there are also several categories. The current analyses focus on the two most common types of dementia only, AD and VaD. In some cases, subjects were also assigned a second and even third diagnosis. In the present analysis, primary diagnoses were used for the first set of analyses looking at predictors discriminating AD from VaD, and secondary diagnoses are included in the second set of analyses where any subjects with vascular pathology causing dementia secondary to a primary diagnosis of AD are moved to the VaD group to try to isolate a more 'pure' AD group.

C. APO-ε Status

The risk for AD or VaD may vary depending on genetic variation. Participants in the ADAMS study have been screened for their apolipoprotein-E (APO-ε) genotype, and this was used in analysis to consider differential genetic risk factors for AD versus VaD or mixed dementia. There are six possible APO-ε genotypes: two ε2 alleles, an ε2 and ε3

combination, an ε2 and ε4 combination, two ε3 alleles, an ε3 and ε4 combination, and two ε4 alleles. Thus a person may have zero ε4 alleles (ε2ε2 or ε3ε3), one ε4 allele (ε2ε4, ε3ε4), or two ε4 alleles (ε4ε4). It has been shown that with an increasing number of ε4 alleles, risk for AD increases (Corder et al., 1993; Strittmatter et al, 1993). Therefore, we have coded the APO-ε genotypes accordingly with a 0 for zero ε4 alleles, a 1 for any combination leading to one ε4 allele, and 2 for the ε4ε4 genotype. A breakdown of APO-ε status of the HRS/ADAMS participants is presented in Table 4. Note that there are no subjects who have the ε4ε4 genotype, which would be considered the highest dementia risk, in the group who is later diagnosed with VaD. This was an unexpected result in the data which must be interpreted cautiously and is addressed in the discussion.

Statistical Analyses

The present analyses used participants diagnosed with AD or VaD from the ADAMS substudy and their previous HRS data. In Analysis 1, latent growth curve models of the episodic memory, mental status factors and summed cardiovascular risk scores for each time point were fitted (McArdle & Nesselroade, 2003) using SAS Proc MIXED (SAS Institute, Inc., Raleigh, NC, USA) and the empirical Bayes estimates of intercept and slope were saved as predictors for the logistic regression models (see Table 4 for descriptive statistics of the empirical Bayes estimates of intercept and slope). In Analysis 2, logistic regression was then applied using SAS Proc LOGISITC (SAS Institute, Inc., Raleigh, NC, USA) to determine which of the hypothesized variables from the HRS data served as predictors of classification into AD or VaD groups.

Analysis 1: Growth Curve Modeling

Latent growth curve models (McArdle & Nessleroade, 2003) were used to examine trajectories of the cardiovascular risk variables which, as described previously, are the weighted summation of the 6 questions asked at each time point (see Table 1 and Table 2). This procedure resulted in one single score for each participant at each time point which was then examined in latent growth curve models (McArdle & Nessleroade, 2003). The latent growth curve model allows for an average cardiovascular risk of each of the participants over age to be estimated as well as how much the participants' cardiovascular risk scores change over the specified time of the model, which is centered at age 80. Therefore, the level (intercept) represents the participant's cardiovascular risk score at age 80, and change in the linear slope represents the participant's increase or decrease in risk index points over age, which is how many points are lost or gained over a decade. Three models were examined to investigate the shape of the slope, if any. The first model estimated only the intercept, or was a means only model. The next model estimated the intercept (or performance at age 80) and a linear slope. The third model estimated the intercept and investigated the possibility of what is called a dual change model or spline model. In this type of model, it is assumed that there is one rate of change (slope) before a certain age (such as the centered age, age 80 in these analyses) and that there is a different rate of change after age 80. This allows for a tipping point so that we could see whether the slope is non-linear (see McArdle & Wang, 2008). Using Maximum Likelihood Estimation, (MLE), model fits were generated and the misfit or deviance was then compared between models to find the best fitting model (i.e., the difference in -2 log

likelihood values). Based on the best-fitting model(s), empirical Bayes estimates of the growth parameters were then generated for all participants and saved. Once these empirical Bayes estimates were generated and saved they were added into the logistic regression analyses described further below.

The same model fitting procedures were applied to the cognitive variables, Episodic Memory (EM) and Mental Status (MS). Growth curve models were examined extensively by McArdle et al. (2007) and in the process empirical Bayes estimates of intercept and slope for both the EM and MS were generated for all ADAMS participants and saved. Unlike that for the CV risk growth models, the linear growth models for EM and MS were centered at age 60.

To summarize, the growth curve models generated empirical Bayes estimates for seven new variables for the ADAMS participants to add to the logistic regression analyses to increase the predictive accuracy of the model. These are the intercept from the means-only cardiovascular model (CV), the intercept and slope for the second cardiovascular index model (CV2), the intercept and slope for the EM factor (EM), and the intercept and slope for the MS factor (MS). Logistic regression analyses were then conducted.

Analysis 2: Logistic Regression

Logistic regression was used to model the discrimination between AD (coded as 1) and VaD (coded as 0) groups; specifically, logistic regression models the probability of group membership based on given covariates which are added to subsequent models. Eight models were compared to examine which predictors best discriminated between

AD and VaD years before diagnosis of the disease. The baseline model includes only the HRS demographic factors of age, gender, and years of education. Gender has been shown to be a risk factor for AD with more females than males being affected, likely due to increased longevity (e.g., Hebert et al, 2001), However, a gender effect for VaD is not clear; it has been suggested that females have more cardiovascular risk factors for dementia and the gender association with dementia may be more complicated than it appears (Azad et al. 2007).

The models and variable entry are shown in Table 5. The significance of each set of predictors entered was assessed by model fit comparisons of the deviance fit statistics, i.e. the -2 log likelihood values. The individual significance of predictors was assessed by the Wald Chi-square statistic. The models and their components are presented in Table 5.

Analysis 3: Reorganization of Dementia Groups

In the third set of analyses, the dementia subtype outcomes were changed to represent two new groups with differing cardiovascular–related diagnoses. All participants with a primary diagnosis of VaD were retained in one group. In addition all participants with a primary diagnosis of AD, but a *secondary* diagnosis of any vascular related dementia were included with the VaD patient group. This new group, denoted 'Mixed', thus contained all of those with a primary or secondary diagnosis of VaD or vascular related dementia. Those free of vascular pathology according to their first and second diagnosis were coded into a second group, denoted 'pure' AD patients.

The models and variable entry are in Table 5 and are identical to Analysis 2. Again, the significance of each set of predictors entered was assessed by model fit

comparisons of the deviance fit statistics, i.e. the -2 log likelihood values. Likewise, the individual significance of predictors was assessed by the Wald Chi-square statistic.

RESULTS

Analysis 1: Growth Curve Modeling

Results from latent growth curve model comparisons showed that the means-only model, which is estimating a fixed and random intercept, was the best fitting model of the three models compared (see Table 6). The linear model approached but did not reach significance when compared to the means-only model ($\chi 2=7.6$, $p<0.055$); given this, we examined both the means-only and linear model estimates in later logistic regression analyses, so termed CV and CV2. In the means-only model, participants had an average cardiovascular risk of 2.7 (SD=1.6) across age, which means that they had acquired at least one of the risk factors shown in Table 1 such as smoking, having diabetes, etc., while a participant who was healthy should not have any of the conditions presented among the cardiovascular risk variables. If a participant had every risk factor in its greatest form, their maximum risk score could have been 9 as some variables were assigned a relative risk of 2, while protective factors could have added up to -3 (see Table 1). Plots of individual cardiovascular risk trajectories are shown in Figure 1.

The linear model showed that participants had a mean CV risk of 2.6 at age 80 years (SD=1.6) and that they increased by 0.15 every decade (SD=0.6) (expected curve shown in Figure 2). Acquiring 0.2 of cardiovascular risk per decade would mean on average more than 40 years would pass before risk would increase by a full unit (e.g., acquiring hypertension, diabetes, etc.). However, there was variation about the average slope

estimate suggesting some individual variation in change in cardiovascular risk over age. The spline model was not significantly better than either the means-only or the linear model and was not used for the logistic regression analyses ($\chi 2 = 1.8$, $p = .8$). Based on the best-fitting model, empirical Bayes estimates of the growth parameters were then generated for all participants and saved. Descriptive statistics of the empirical Bayes estimates by dementia subtype are presented in Table 4. (Note that variances of the empirical Bayes estimates are 'shrunken' compared to the random effects variances; see Raudenbush & Bryk, 2002)

Empirical Bayes estimates of linear growth parameters were generated for episodic memory and mental status variables in similar fashion. Thus, each person has an estimated episodic memory factor score intercept (M=44.2, SD=12.3), the average participant's episodic memory score for age 60, and an episodic memory factor score slope (M=-8.0, SD=2.9), together indicating that the average participant in this study had an average episodic memory score of about 44 points at age 60 and lost 8 points on episodic memory per decade. Each participant had a mental status factor score intercept (M=104.9, SD=20.4) and a mental status factor score slope (-25.9, SD=7.5). The average participant of this study had an average mental status score of about 105 points at age 60 lost over 25 points on their mental status exam per decade. Descriptive statistics of the empirical Bayes estimates are presented by dementia subtype in Table 4.

Analysis 2: Logistic Regression

Logistic regression analysis was used to examine the odds of a certain type of dementia occurring (AD, coded as 1, versus VaD, coded as 0) and included the following

predictors: age, gender, years of education, number of APO-ε4 alleles and the saved empirical Bayes estimates of intercept and slope for the episodic memory factor, mental status factor, and cardiovascular risk factor. The first model contained age, gender and years of education (see Table 5 and Table 6). Estimates from this baseline model showed that all of these variables discriminated significantly between the AD and VaD groups. Participants were more likely to be in the AD group if they were older, had fewer years of education, and were female.

Comparison of subsequent models showed that each subsequent model fit was significantly better than prior nested models until model 4, after which no variables added significantly to the discrimination of the AD and VaD groups. Model 4 included all demographics, APO-ε, the EM intercept and slope, and the CV intercept. Model 4 had a resulting deviance of 228.1 ($\Delta\chi 2$ (1) =3.9, $p < 0.049$ vs. model 3) and a pseudo-R^2 of .28. All estimates are shown in Table 7. Based on fit and parsimony, we chose model 4 as the best-fitting model compared to nested models that did not include the CV intercept. Moreover, we chose Model 4 over Model 7 which entered the CV2 intercept and slope estimates as it was most parsimonious. The odds ratio estimates from model 4 showed that people were 3.19 (CI=1.80-5.66) times more likely to be in the AD group for every ten year increase in age after 60. The addition of each APO-ε4 allele increased the chances of being in the AD group by 2.48 (CI=1.28-4.86), while those with higher episodic memory performance at age 60 (intercept) and less rapid decline across age (slope) were less likely to be in the AD group (OR=0.92, CI=0.88-0.97 and OR=0.79, CI=0.65-0.96). The odds of being classified as AD was reduced with every unit increase

of CV risk (OR=.77; CI=.59, 1.00). While comparison of the deviance statistic between Models 3 and 4 suggested that the CV intercept was a significant predictor ($\Delta\chi^2(1)=3.884$, $p < 0.049$), the confidence interval of the odds ratio estimates of the CV intercept included the value of 1.0 as the Wald $\chi 2$ value was slightly smaller (Wald $\chi 2$ = 3.814, p = .0508). Gender and education were not individually significant predictors in this model. Model 4 demonstrated the best correct classification percentage with the fewest predictors (assuming P = .5; see Table 7).

Analysis 3: Logistic Regression Mixed group versus 'Pure' AD

As described, the VaD versus AD groups were reorganized for the last set of analyses. Specifically, the initial AD versus VaD groupings were based on a primary diagnosis given by the ADAMS study consensus panel. Clinicians also gave some cases a secondary even tertiary diagnosis if comorbid conditions existed. Because of this, there were some cases where a subject may have a primary diagnosis of AD, but have a secondary diagnosis that states they have VaD in addition to AD, or that they have dementia related to vascular pathology. All participants with a primary diagnosis of VaD were retained in one group. In addition, all participants with a primary diagnosis of AD, but a *secondary* diagnosis of any vascular related dementia were included with the VaD patient group. This new group, denoted 'Mixed', thus contained all of those with a primary or secondary diagnosis of VaD or vascular-related dementia. Those free of vascular pathology according to their first and second diagnosis were coded into a second group, denoted 'Pure' AD. The results of the second set of analyses are presented in Table 8. Results showed very similar results to Analysis 2 in most cases, and again all

model comparisons were significant when compared to the previous nested model until Model 4. The fourth model again was the best fitting model, which used the CV means-only empirical Bayes intercept estimates as predictors. The intercept, years of education, and gender were not significant predictors of group membership. The odds ratio estimates from significant predictors in Model 4 are similar to Analysis 2, although significance was sometimes increased. For every ten years of increasing age, the increase in risk was 3.44 (CI=1.96-6.04) that a participant would later be diagnosed with 'pure 'AD versus mixed dementia. The addition of each APO-ε4 allele made it 2.01 (CI=1.10-3.66) times more likely that a participant would be classified as having 'pure' AD. However, those with higher episodic memory performance at age 60 (intercept) and less rapid decline across age (slope) were less likely to be classified into the 'pure' AD group (OR=0.92, CI=0.88-0.97 and OR=0.76, CI=0.63-0.91). The CV intercept estimate was more highly significant when entered as a predictor compared to Analysis 2: the odds of being classified as 'pure' AD was reduced with every unit increase of CV risk (OR=0.68; CI=0.53 - 0.88). No other predictor emerged as salient with the new outcome groupings than was observed for Analysis 2 above with the standard diagnostic categories. Again, Model 4 demonstrated the best correct classification percentage with the fewest predictors (assuming P = .5; see Table 8).

DISCUSSION

The goals of this study were: first, to examine whether early cognitive changes were predictive of later dementia, and whether specific cognitive performance would discriminate between AD and VaD; second, to test whether the accumulation of

cardiovascular risk factors was predictive of later dementia, whereby accumulated risk would predict classification into VaD group versus AD; and, third, to test whether APO-ε played a role in the discrimination of AD versus VaD. In addition, while mixed dementia was not a defined subtype in the ADAMS dataset, mixed dementia was examined in the current study by considering any dementia participant with vascular pathology in their first or second diagnosis as part of a 'mixed' category and retaining all those with AD and no vascular-related secondary diagnosis in a 'pure' AD group. While considering the accumulated cardiovascular risk may be useful in the discrimination of dementia subtypes, results showed that putting mixed AD cases together with VaD cases may not be useful.

Research Question 1

In the first research question, it was predicted that lower episodic memory (immediate and delayed recall) would be a predictor of a future diagnosis of AD and that the rate of decline would be greater than that of the VaD group. Impaired episodic memory (EM) is one of the hallmark clinical presentations of AD and many studies have shown that the decline of EM impairment is different than that of VaD which remains relatively more stable (Mungas et al., 2005). In this dataset, it has been shown that EM trajectories were predictive of all-cause dementia (McArdle et al., 2010). The current study aimed to examine whether the AD subtype was the driving force behind that finding. Consistent with this hypothesis, EM trajectories were a significant predictor in the logistic regression analyses for discriminating between those subsequently diagnosed with AD versus VaD dementia. Adding the empirical Bayes estimates of EM intercept

and slope to the model improved the fit significantly ($\Delta\chi2 = 76.7$, $p < .0001$) and both the intercept and slope coefficients were individually significant (Intercept Wald $\chi2 = 66.78$, $p < .0001$; Slope Wald $\chi2 = 42.26$, $p < .0001$). Those later diagnosed with AD had lower EM scores as much as a decade before their diagnosis and had exhibited more change (decline) than their VaD counterparts, consistent with other studies (Mungas et al., 2005). It was also hypothesized that those later diagnosed with VaD would have relatively stable episodic memory scores, and although they declined less compared to the AD group, they nonetheless evidenced a large decline in episodic memory across age.

Hypotheses about executive functioning, as measured by the mental status variables (MS), were that those with AD would have higher performance than those with VaD. In logistic regression analyses, MS appeared to offer no improvement to any of the models when added and was not a beneficial predictor for discriminating between the AD and VaD groups. While there may be many explanations for this, it is important to note that the TICS MS variable is not an ideal measure of executive functioning. Although the MS variable did have some components of working memory use, such as counting backward and subtracting from 100 by 7's, it included other cognitive domains such as the memory required to access names of common political figures and intact memory for current events. It is likely that a specific measure of executive functioning would have been able to discriminate between the groups and lead to more consistent results with the previous literature, which indicates that VaD patients exhibit greater frontal lobe impairment as demonstrated by performance on executive function tasks (Graham et al., 2004).

Research Question 2

The second research question hypothesized that the accumulation of cardiovascular risk factors (CV) would be predictive of later dementia subtypes, whereby a greater accumulated risk would predict classification into the VaD group versus the AD group. After evaluating latent growth curve models of the CV variable (c.f. McArdle & Nesselroade, 2003) it was found that a linear model was at trend significance over a means-only model. However, after testing estimates from both models in later logistic regression analyses, it was found that the best fitting logistic regression model, Model 4, was that which included the saved empirical Bayes estimates from the means-only model. Including these CV estimates in the model produced a just significant improvement in fit. Results showed that having a greater cardiovascular risk, as determined by the summation of risk factors chosen from the Your Disease Risk website (http://www.yourdiseaserisk.wustl.edu/english), was significantly predictive of a lower risk to be classified into the AD group (and thus a higher chance to be in the VaD group). Therefore, those who would be later diagnosed with VaD would are expected to have more risk factors for heart disease as early as 7 years prior to diagnosis, as compared to the AD group. These results may have clinical significance, considering that many of these risk factors are reversible. Future research would benefit from seeing if those who lower their cardiovascular risk save themselves the fate of (VaD) dementia. That is, if any of these participants had reversed their risk score from 1995 to 1996 or 1998, for example, would that have attenuated the events that were leading up to a diagnosis of VaD in 2002?

The VaD and AD groupings were reorganized in the last set of analyses. We recoded any AD dementia cases that included a secondary diagnosis of vascular dementia or vascular pathology into a 'Mixed' group which was made up of these participants plus VaD participants from the original grouping who already had a primary dementia diagnosis of VaD. Those free of vascular pathology according to both their first and second diagnosis were coded as 'pure' AD patients because they had dementia but were diagnostically free of vascular etiology. Results of logistic regression analyses showed very similar if not the same estimates compared to groupings made based on primary diagnoses. No other predictor emerged as salient with the new outcome groupings than was observed for the analyses with the standard diagnostic categories.

What can be learned from these findings is that while cardiovascular risk factors may have been predictive of which type of dementia a person may be diagnosed with, the current diagnostic process (or at least the one used by the ADAMS group) seems to be sufficient for examining early risk factors that can discriminate between subtypes of dementia. Indeed, while the CV intercept, perhaps not unexpectedly, proved to be a more significant predictor in logistic regression results under Analysis 3 versus Analysis 2, the percentage of correct classification was uniformly higher for Analysis 2 versus Analysis 3 (see Tables 7 and 8).

When the groups were re-coded, the VaD group (originally *n*=69) only gained 10 more people from the AD group (originally *n*=261), due to the very few participants who had a secondary diagnosis. Since so few people with mixed dementia were moved over to the mixed plus VaD group, power may have been an issue; however, it may have also

been beneficial to create a separate group of subjects in an official mixed category and compare them against both the VaD and AD groups. Future analyses should examine if improved prediction of dementia subtypes results by considering those who are exhibiting the ‘typical’ course of either AD or VaD versus those that are showing patterns indicative of both types of dementia.

Research Question 3

An early examination of the data showed a complete absence of any APO-ε ε4ε4 genotypes in the VaD group. There were fewer ε4 alleles in total in the VaD group. While APO-ε was a significant predictor of group membership in the logistic regression models, there is no way to be sure without further selection analyses whether this VaD group is experiencing a higher mortality rate due to cardiovascular problems. APO-ε genotyping was not collected until participants were selected for the ADAMS substudy in 2002. Thus it is even more likely that some factor of selection was working on the different APO-ε frequencies between the AD and VaD groups at the first ADAMS work-up. APO-ε genotype has been associated more strongly with AD, especially between ages 65 to about 75 or so, while VaD patients tend to be younger on average (Breitner and Welsh, 1995). Moreover, it has been more or less established in one of the largest meta-analyses to date (Farrer et al., 1997) that APO-ε is a risk factor for late onset AD. It has not been shown to be a stable predictor of VaD in current research as some studies find an association and some do not (Urakami et al., 1998; Kuller et al., 2005). Because of the likely selection effects, the results of APO-ε in the current analyses should be interpreted cautiously.

Strengths

The ADAMS sample represents a rare opportunity to extrapolate findings to the general population. There is a decade of previous cognitive data prior to the diagnosis of dementia, up to 7 years prior of cardiovascular data, and an extensive diagnostic work-up of dementia using an expert panel and consensus procedures. We applied state-of-the art

growth modeling methods (McArdle & Nesselroade, 2003) to examine the predictive impact of episodic memory, mental status, and cardiovascular risk trajectories on the AD and VaD subtypes, in addition to other established risk factors. While this study did not apply the ADAMS study population weights, when used statistical values would provide estimates that are representative of the US population.

Limitations

Most notably, the largest concern with the present study is the issue of selection. While a decade of data had been collected previously in the HRS, only those who were alive and who agreed were selected for the ADAMS substudy. Analyses by the ADAMS study group have shown those participants who were alive and chosen for participation in ADAMS versus those who were not were more likely to be male and have a previous diagnosis of stroke or cancer (Heeringa et al., 2009).

Limitations with the measures used in the study may have also weakened the results of the study. The cardiovascular risk assigned to participants applied the risk index from the Your Disease Risk website (http://www.yourdiseaserisk.wustl.edu/english). This website had considerably more risk factors included to accurately assess a person's risk of heart disease within the next ten years than were available to the current study. Among the variables that were most notably missing in the current study were established dietary factors known to either increase or reduce heart disease risk. Also, information on length of time smoking cigarettes was absent. While the body mass index (BMI) could have been calculated from the HRS dataset, risk for heart disease was increased at certain BMI

levels for ages that were younger than anyone in the current dataset and thus could not contribute to these analyses.

The mental status (MS) factor was also a significant weakness in this study. While the hypotheses postulated differential executive functioning in these participants, the MS variable was heterogeneous. It included some components that would be considered working memory, an aspect of executive functioning, but also tapped into other aspects of cognitive functioning that were not. Considering that the MS variable did not add to predictions for discrimination between the two groups in any set of analyses, it is obvious that the MS measure was not helpful.

Future Implications

This study represented an attempt to examine the critical next step in dementia research by attempting to address potentially modifiable lifestyle factors that put some individuals at risk of one type of dementia versus another. The driving force behind this is to identify people who are at risk for a potentially modifiable illness (vascular dementia) which may have considerably more treatment options than an illness for which little progress in treatment has been made (Alzheimer's disease). The preservation of late life cognition is an important human aspect from an evolutionary perspective (Judge and Carey, 2000; van Shaik et al., 2008; Wilmoth et al., 2000), and most certainly at an individual and societal level. Unfortunately, very little progress has been made in treating dementia. An emerging focus on lifespan development has led to an increase in the examination of early and mid-life factors in that may modify life course risk of dementia (e.g., Gatz, 2007; Gatz, Mortimer et al, 2006; Gatz, Prescott, & Pedersen, 2006). Indeed,

a recent NIH task force (National Institute on Aging and the Office of Medical Applications of Research, April, 2010; http://www.annals.org/content/153/3/176.full) put forth statements implying that the most promising action to take for dementia is prevention. The current study has produced results that have, in part, affirmed this position.

The next step in future analyses is to further examine the group of mixed dementia subjects. The attempt at modifying disease classification to improve predictive accuracy did not reveal useful information regarding those with mixed dementia. While all subjects in the study had a primary diagnosis of either AD or VaD, very few of these same subjects had a secondary diagnosis. There is very little information on the prediction of later mixed dementia, but it is believed that most of AD and VaD cases are indeed represented by mixed underlying pathologies (Langa et al., 2005). In addition to addressing the issue of mixed dementia, selection issues must also be further addressed. It is possible in future analyses to examine a third risk outcome besides AD or VaD, which would be death, to examine what characteristics can be attributed to those who were essentially selected out of the study and compare them to the identified participants with AD versus VaD. This may help explain some of the current findings that were counter to what was expected, such as the surprising absence of APO-ε4ε4 genotype in the VaD group. While selection is a common problem in aging research, this dataset as a whole may have some potential to unravel some of the mysteries accorded to the development of dementia in future analyses.

REFERENCES

Aguero-Torres, H., Kivipelto, M. & von Strauss, E. (2006). Rethinking the dementia diagnoses in a population-based study: What is Alzheimer's disease and what is vascular dementia? A study from the Kungsholmen project. *Cognitive Disorders*, 22(3), 244-249.

Akomolafe, A., Beiser, A., Meigs, J.B., Au, R., Green, R.C., Farrer, L.A., Wolf, P.A. & Seshadri, S. (2006). Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. *Archives of Neurology*, 63(11), 1551-1555.

Armstrong, R.A. (2006). Plaques and tangles and the pathogenesis of Alzheimer's disease. *Folia Neuropathologica*, 44(1), 1-11.

Arvanitakis, Z., Wilson, R.S., Bienias, J.L., Evans, D.A. & Bennett, D.A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology*, 61(5), 661-666.

Azad, N.A., Bugami, M.A. & Loy-English, I. (2007). Gender differences in dementia risk factors. *Gender Medicine*, 4(2), 120-129.

Baltes, P. B. (1997). On the incomplete architecture of human ontogeny: Selection, optimization, and compensation as foundation of developmental theory. *American Psychologist*, 52, 366-380.

Baltes, P B., Staudinger, U.M., & Lindenberger, U. (1999). Lifespan psychology: Theory and application to intellectual functioning. *Annual Review of Psychology*, 50(1), 471-507.

Barber, M. & Stott, D.J. (2004). Validity of the Telephone Interview for Cognitive Status (TICS) in post-stroke subjects. *International Journal of Geriatric Psychiatry*, 19, 75–79.

Barrickman, N.L., Bastian, M.L., Ishler, K & van Shaik, C.P. (2008). Life history costs and benefits of encephalization: A comparative test using data from long-term studies of primates in the wild. *Journal of Human Evolution*, 54(5), 568-590.

Baskys, A. & Hou, A.C. (2007). Vascular dementia: Pharmacological treatment approaches and perspectives. *Clinical Interventions in Aging*, 2(3), 327-335.

Bennett, D A. (2007). Editorial Comment on 'Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study' by Plassman et al. *Neuroepidemiology*, 29(1-2), 133-135.

Beydoun, M.A., Beydoun, H.A. & Wang, Y. (2008). Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obesity Reviews*, 9(3), 204 – 218.

Brandt, J., Spencer, M. & Folstein, M. (1988). The Telephone Interview for Cognitive Status. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*, 1, 111–117.

Breitner, J.C.S., & Welsh, K.A. (1995). Genes and recent developments in the epidemiology of Alzheimer's disease and related dementia. *Epidemiologic Reviews*, 17(1), 39-47.

Chen, P., Ratcliff, G., Belle, S.H., et al. (2000). Cognitive tests which best discriminate between presymptomatic AD and those who remain non-demented. *Neurology*, 55, 1847-1853.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L. and Pericak-Vance, M.A. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, 261, 921–923.

Darwin, C. (1859). *On the Origin of Species by Means of Natural Selection*. Penguin: New York.

Daviglus, M.L., Bell, C.C., Berrettini, W., Bowen, P.E., Connolly Jr., E.S., Cox, N.J., Dunbar-Jacob, J.M. Granieri, E.C., Hunt, G., McGarry, K., Patel, D., Potosky, A.L., Sanders-Bush, E., Silberberg, D. & Trevisan, M. (2010). National Institutes of Health state-of-the-science conference statement: Preventing Alzheimer disease and cognitive decline. Annals of *Internal Medicine*, 153(3), 176-181.

DeCarli, C. (2003). The role of cerebrovascular disease in dementia. *The Neurologist*, 9(3), 123-136.

de Jager, C.A., Budge, M.M. & Clarke, R. (2003). Utility of TICS-M for the assessment of cognitive function in older adults. *International Journal of Geriatric Psychiatry*, 18, 318–324.

DeKosky, S. (2003). Early intervention is key to successful management of Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 17, S99-S104.

Desmond, D.W. (1994). The Telephone Interview for Cognitive Status (TICS): reliability and validity in a stroke sample. *International Journal of Geriatric Psychiatry*, 9(10), 803-807.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R.H., Pericak-Vance, M.A., Risch, N., & van Duijn, C.M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. *JAMA*, 278, 1349-1356.

Finch, C. E., & Kirkwood, T.B.L. (2000). *Chance, development, and aging*. New York: Oxford University Press.

Finch, C.E. & Sapolsky, R.M. (1999). The evolution of Alzheimer disease, the reproductive schedule, and APO-ε isoforms. *Neurobiology of Aging*, 20(4), 407-428.

Fox, M., Sear, R., Beise, J., Ragsdale, G., Volan, E. & Knapp, L.A. (2010). Grandma plays favourites: X-chromosome relatedness and sex-specific childhood mortality. *Proceedings of the Royal Society: Biological Sciences*, 277(1681), 567-573.

Gatz, M. (2007). Genetics, dementia, and the elderly. *Current directions in Psychological Science*, 16(3), 123-127.

Gatz, M, Mortimer, J.A., Fratiglioni, L., Johansson, B., Berg, S., Reynolds, C.A., & Pedersen, N.L. (2006). Potentially modifiable risk factors for dementia in identical twins. *Alzheimer's & Dementia*, 2(2), 110-117.

Gatz, M., Prescott, C.A.1, & Pedersen, N.L. (2006). Lifestyle Risk and Delaying Factors. *Alzheimer Disease and Associated Disorders*, 20(supplement 2), S84-S88.

Graham, N.L., Emery, T. & Hodges, J.R. (2004). Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, 75, 61–71.

Hamilton, W. D. (1966). The moulding of senescence by natural selection. *Journal of Theoretical Biology*, 12(1), 12-45.

Hassing, L.B., Johansson, B., Nilsson, S.E., Berg, S., Pedersen, N.L., Gatz, M. & McClearn, G. (2002). Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: A population-based study of the oldest old. *International Psychogeriatrics*, 14(3), 239-248.

Hassing, L.B., Dahl, A.K., Thorvaldsson, V., Berg, S., Gatz, M., Pedersen, N.L. & Johansson, B. (2009). Overweight in midlife and risk of dementia: A 40-year follow-up study. International *Journal of Obesity*, 33, 893–898.

Hawkes K, & Paine R, Eds. (2006). *The Evolution of Human Life History*. Santa Fe, New Mexico: School of American Research Press.

Hawkes, K., O'Connell, J.F., Blurton Jones, N.G., Alverz, H & Charnov, E.L. (2000). In L. Cronk, N.A. Chagnon, and W. Irons. *Adaptation and human behavior: an anthropological perspective.* Walter de Gruyter: Hawthorne.

Hayden, K M., Zandi, P.P., Lyketsos, C.G., Khachaturian, A.S., Bastian, L.A., Charoonruk, G., Tschanz, J.T., Norton, M.C., Pieper, C.F., Munger, R.G., Breitner, J.C.S. & Welsh-Bohmer, K.A. (2006). Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Disease and Associated Disorders*, 20(2), 93-100.

Hebert, L.E., Scherr, P.A., McCann, J.J., et al. (2001). Is the risk of developing Alzheimer's disease greater for women than for men? *American Journal of Epidemiology*, 153(2), 132-6.

Hebert, L.E., Scherr, P.A., Bienias, J.L., & Evans, D.A. (2003). Alzheimer's disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology*, 60, 1119-1122.

Heeringa, S.G., Fisher, G.G., Hurd, M., Langa, K.M., Ofstedal, M.B., Plassman, B.L., Rodgers, W.L. & Weir, D.R. (2009). Aging, Demographics, and Memory Study (ADAMS): Sample design, weighting and analysis for ADAMS. Unpublished Report.

Ho, K.K., Anderson, K.M., Kannel, W.B., Grossman, W. & Levy, D. (1993). Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*, 88, 107-115.

Järvenpää, T. (2000). Characteristics of two telephone screens for cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, 13(3), 149-155.

Judge, D.S. & Carey, J.R. (2000). Postreproductive life predicted by primate patterns. *Journal of Gerontology: Biological Sciences*, 55A(4), B201–B209.

Katzman, R., Terry, R. DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X. & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology*, 23, 138-144.

Kimura, M. (1978). Change of gene frequencies by natural selection under population number regulation. *Proceeds of the National Academy of Sciences*, 75(4), 1934-1937.

Kivipelto, M. Ngandy, T., Fratiglioni, L. et al. (2005). Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology*, 62(10), 1556-1560.

Kölsch, H., Jessen, F., Freymann, N., Kreis, M., Hentschel, F., Maler, W. & Heun, R. (2005). ACE I/D polymorphism is a risk factor of Alzheimer's disease but not of vascular dementia. *Neuroscience Letters*, 377(1), 37-39.

Kroger, E., Andel, R., Lindsay, J., Benounissa, Z., Verreault, R. & Laurin, D. (2008). Is complexity of work associated with risk of dementia? The Canadian Study of Health and Aging. *American Journal of Epidemiology*, 167(7), 820-830.

Lafosse, J.M., Reed, B.R., Mungas, D., Sterling, S.B., Wahbeh, H. & Jagust, W.J. (1997). Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology*, 11, 514–22.

Langa, K M., Foster, N.L. & Larson, E.B. (2004). Mixed dementia emerging concepts and therapeutic implications. *JAMA*, 292(23), 2901-2908.

Langa K.M., Plassman, B.L., Wallace, R.B., Herzog, A.R., Heeringa, S.G., Ofstedal, M.B., Burke, J.R., Fisher, G.G., Fultz, N.H. & Hurd, M.D. (2005). The Aging, Demographics, and Memory Study: study design and methods. *Neuroepidemiology*. 25, 181–191.

Loeb, C. & Meyer, J.S. (1996). Vascular dementia: Still a debatable entity? Journal of the *Neurological Sciences*, 143(1-2), 31-40.

McArdle, J.J., Koontz, J., Plassman, B. & Langa, K.M. (2010). Mixed Effects Modeling of the Early Prediction of Dementia using ADAMS and HRS Longitudinal Data. In preparation.

McArdle, J.J., Fisher, G.G. & Kadlec, K.M. (2007). Latent variable analyses of age trends of cognition in the Health and Retirement Study, 1992-2004. *Psychology and Aging*, 22(3), 525-545.

McArdle, J. J., & Nesselroade, J. R. (2003). Growth curve analysis in contemporary psycho- logical research. In J. Schinka & W. Velicer (Eds.), *Comprehensive handbook of psychology, Volume II: Research methods in psychology*. New York: Pergamon Press.

McCusker, S.M., Curran, M.D., Dynan, K.B., McCullough, C.D., Urquhart, D.D., Middleton, D., Patterson, C.C., McIlroy, S.P. & Passmore, A.P. (2001). Association between polymorphism in regulatory region of gene encoding tumour necrosis factor α and risk of Alzheimer's disease and vascular dementia: a case-control study. *The Lancet*, 357(9254), 436-439.

Mungas, D. Harvey, D., Reed, B.R., Jagust, W.J., DeCarli, C., Beckett, L., Mack, W.J., Kramer, J.H., Weiner, M.W., Schuff, N. & Chui, H.C. (2005). Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*, 65(4), 565-571.

National Institutes of Health. (2010 September 16). Clinical Trials.gov: A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/home

Pandey, P., Pradhan, S. & Mittal, B. (2007). Presenilin gene predisposes to late-onset degenerative but not vascular dementia: A comparative study of PS1 and APO-ε genes in a north Indian cohort. *Dementia and Geriatric Cognitive Disorders*, 24, 151-161.

Pariel-Madjlessi, S., Opéron, C., Péquignot, R., Konrat, C., Léonardelli, S. & Belmin, J. (2007). Dementia syndromes in the elderly: diagnostic procedures. *La Presse Medicale*, 36(10 pt2), 1442-1452.

Plassman BL, Newman T, Welsh K & Breitner J. (1994). Properties of the telephone interview for cognitive status. Application in epidemiological and longitudinal studies. *Neuropsychiatry, Neuropsychology & Behavioral Neurology*, 7, 235–241.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Ofstedal, M.B., Burke, J.R., Hurd, M.D., Potter, G.G., Rodgers, W.L., Steffens, D.C., Willis, R.J. & Wallace, R.B. (2007). Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*, 29, 125–132.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical linear models: Applications and data-analysis methods*. Newbury Park, CA: Sage.

Rea, T.D., Breitner, J.C., Psaty, B.M., Fitzpatrick, A.L., Lopez, O.L., Newman, A.B., Hazzard, H.R., Zandi, P.P., Burke, G.L., Lyketsos, C.G., Bernick, C. & Kuller, L.H. (2005). Statin use and the risk of incident dementia: The Cardiovascular Health Study. *Archives of Neurology*, 62(7), 1047-1051.

Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C & McDowell I. (2000). Prevalence and outcomes of vascular cognitive impairment.Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology*, 54, 447-51.

Román, G C., Erkinjutti, T., Wallin, A., Pantoni, L. & Chui, H.C. (2002). Subcortical ischaemic vascular dementia. *Lancet Neurology*, 1(7), 426-436.

Román, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H, Amaducci, L., Orgogozo, J-M., Brun, A., Hofman, A., Moody, D.M, O'Brien, M.D., Yamaguchi, T., Grafman, J., Drayer, B.P, Bennett, D.A., Fisher, M., Ogata, J., Kokmen, E. Bermejo, F., Wolf, P.A, Gorelick, P.B., Bick, K.L., Pajeau, A.K., Bell, M.A., DeCarli, C., Culebras, A., Korczyn, A.D., Bogousslavsky, J., Hartmann, A. & Scheinberg, P. (1993). Vascular dementia- Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology*, 43(250).

Shen, Y., Luea, L-F., Yanga, L-B., Rohera, A., Kuoa, Y-M., Strohmeyera, R., Gouxb, W.J., Leec, V., Johnsond, G.V.W., Webstere, S.D., Cooperf, N.R., Bradtf, B. & Rogers, J. (2001). Complement activation by neurofibrillary tangles in Alzheimer's disease. *Neuroscience Letters*, 305(3), 165-168.

Skoog, I., Nilsson, L., Palmertz, B. Andreasson, L-A. & Svanborg, A. (1993). A population-based study of dementia in 85-year-olds. *New England Journal of Medicine*, 328, 153–158.

Strittmatter, W.J., Saunders, A.M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G.S. and Roses, A.D. (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, 90, 1977–1981.

Wetterling, T., Kanitz, R.D. & Borgis, K.J. (1996). Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). *Stroke*, 27, 30–36.

Wilmoth, J.R., Deegan, L.J., Lundstrom, H. & Horiuchi, S. (2000). Increase of maximum life-span in Sweden, 1861-1999. *Science*, 289(5488), 2366 – 2368.

Ylikoskia, R., Jokinena, H., Andersena, P., Salonenc, O., Madureirad, S., Ferrod, J., Barkhofe, F., van der Flierf, W., Schmidtg, R., Fazekasg, F., Scheltensf, P., Waldemarh, G., Salvadorii, E., Pantonii, L., Inzitarii, D., & Erkinjunttia, T. on behalf of the LADIS Study Group. (2007). Comparison of the Alzheimer's Disease Assessment Scale Cognitive Subscale and the Vascular Dementia Assessment Scale in Differentiating Elderly Individuals with Different Degrees of White Matter Changes. The LADIS Study. *Dementia and Geriatric Cognitive Disorders*, 24(2), 73-81.

Yoshitake, T., Kiyohara, Y., Kato, I., Ohmura, T., Iwamoto, H., Nakayama, K., Ohmori, S., Nomiyama, K., Kawano, H & Ueda, K.. (1995). Incidence and risk factors of vascular dementia and Alzheimer’s disease in a defined elderly Japanese population: the Hisayama Study. *Neurology*, 45, 1161–1168.

Yucesoy, B., Peila, R., White, L.R., Wu, K.M., Johnson, V.J., Kashon, M.L., Luster, M.I. & Launer, L.J. (2006). Association of interleukin-1 gene polymorphisms with dementia in a community-based sample: The Honolulu-Asia Aging Study. *Neurobiology of Aging*, 27(2), 211-217.

Table 1. Cardiovascular items from HRS and assigned weights by the Harvard Heart Disease Risk Index.

ITEM	Prevalence (US Population)	Relative Risk
	Gender	
Male	--	+2
Female	--	--
	Hypertension	
Male	29.8%	+2
Female	27.5%	+2
	Diabetes	
Male	9.3%	+2
Female	8.1%	+2
	Cigarettes per Day	
<15	9%	+1
15-25	10%	+2
>25	5%	+3
	Alcoholic Beverages	
<1/day	89%	--
1/day	9%	-1
2/day	1%	-1
≥3/day	1%	-1
	Physical Activity ≥3 Hours/Week	
Male	18.9%	-2
Female	19.4%	-2

Table 2. Means and standard deviations for cardiovascular risk at each time point by dementia subtype.

Time Point	AD	N	Mean(SD)	VaD	N	Mean(SD)
1995		261	0.8 (1.2)		69	2.3 (2.3)
1996		261	2.7 (2.3)		69	3.9 (1.9)
1998		261	2.3 (1.8)		69	3.4 (2.1)
2000		261	4.3 (1.2)		69	5.2 (1.9)
2002		261	2.6 (1.7)		69	3.6 (1.9)

Table 3. HRS measurement points, sample sizes and average ages of the ADAMS sample.

Time of HRS Measurement	N	Mean (Standard Deviation)
1992	124	62.96 (2.93)
1993	552	75.15 (4.72)
1994	122	64.90 (2.95)
1995	543	77.05 (4.72)
1996	128	67.02 (2.95)
1998	826	75.06 (6.19)
2000	836	77.03 (6.29)
2002	842	79.18 (6.30)

Table 4. ADAMS Participant Characteristics on HRS Variables: AD and VaD subtypes.

Variables	AD (1) N=261	VAD (0) N=69
Age	82.56 (7.02)	79.50 (6.96)
Years Ed (-12)	-2.85 (4.42)	-2.07 (4.09)
Male	68 (26.05%)	33 (47.83%)
Female	193 (73.95%)	36 (52.17%)
ApoE alleles 0	159 (62.11)	51 (77.27)
ApoE alleles 1	82 (32.03)	15 (22.73)
ApoE alleles 2	15 (5.86)	0 (0.00)
EM Mean at Age 60 (Intercept)	43.49 (12.00)	46.84 (12.86)
EM Change per Decade (Slope)	-8.09 (2.87)	-7.78 (3.21)
MS Mean at Age 60 (Intercept)	105.81 (20.20)	101.63 (20.95)
MS Change per Decade (Slope)	-26.46 (7.15)	-23.59 (8.25)
CV Mean at Age 80 (Intercept)	2.49 (1.35)	3.38 (1.69)
CV2 Mean at Age 80 (Intercept)	2.43 (1.32)	3.33 (1.64)
CV2 Change per Decade (Slope)	0.18 (0.22)	0.06 (0.29)

Note: Years Ed=years of education, centered at 12; EM= Episodic Memory; MS= Mental Status; CV= Cardiovascular Summed Score

Table 5. Models compared in logistic regression analyses.

Model	Variables
1	Age, Gender, Years Ed
2	Age, Gender, Years Ed, APO-ε
3	Age, Gender, Years Ed, APO-ε, EM intercept & slope
4	Age, Gender, Years Ed, APO-ε, EM intercept & slope, CV intercept only
5	Age, Gender, Years Ed, APO-ε, EM intercept & slope, MS intercept & slope
6	Age, Gender, Years Ed, APO-ε, EM intercept & slope, MS intercept & slope, CV intercept
7	Age, Gender, Years Ed, APO-ε, EM intercept & slope, CV intercept & slope
8	Age, Gender, Years Ed, APO-ε, EM intercept & slope, MS intercept & slope, CV intercept & slope.

Note: Age = age in 2002; Years Ed=years of education; EM= Episodic Memory; MS= Mental Status; CV= Cardiovascular Risk Index Score

Table 6. Model fits for cardiovascular index latent growth models.

Model	-2log likelihood	# of parameters	χ^2	*p*-value
M1: Means Only	2564.5	2	--	--
M2: Linear	2556.9	5	7.6	.055
M3: Dual Rate of Change	2555.1	9	1.8	.772

Table 7. Logistic regression results for VaD (0) versus AD (1).

	1. Baseline	2. Baseline+ APO-□	3. Baseline+ APO-□+ EM	4. Baseline+ APO-□+ EM+CV	5. Baseline+ APO-□+ EM+MS	6. Baseline+ APO-□+ EM+MS +CV	7. Baseline+ APO-□+ EM+ CV2	8. Baseline+ APO-□+ EM+MS +CV2
				Estimates (Wald χ^2)				
Intercept	-0.69 (1.59)	**-1.94 (7.26)**	-0.45 (0.24)	0.44 (0.17)	-1.03 (0.69)	-0.12 (0.01)	1.12 (0.88)	0.58 (0.15)
Age in 2002	**0.71 (10.54)**	**1.06 (15.25)**	**1.18 (16.69)**	**1.16 (15.63)**	**1.20 (13.26)**	**1.21 (12.96)**	**1.17 (15.51)**	**1.21 (12.86)**
Gender	**0.94 (10.56)**	**1.13 (12.05)**	**1.03 (9.29)**	0.72 (3.76)	**0.96 (7.60)**	0.64 (0.38)	0.66 (3.16)	0.60 (2.40)
Years Ed	-0.06 (0.03)	-0.07 (2.89)	-0.03 (0.43)	-0.04 (0.99)	-0.03 (0.31)	-0.04 (0.66)	-0.04 (0.61)	-0.03 (0.43)
APOE Status		**1.15 (12.04)**	**1.01 (8.79)**	**0.91 (7.19)**	**1.01 (8.74)**	**0.91 (7.07)**	**0.91 (7.02)**	**0.90 (6.93)**
EM Intercept			**-0.08 (10.35)**	**-0.08 (9.71)**	**-0.07 (7.55)**	**-0.07 (6.65)**	**-0.08 (10.30)**	**-0.08 (7.18)**
EM Slope			**-0.25 (6.82)**	**-0.24 (5.81)**	**-0.22 (4.55)**	-0.20 (3.66)	**-0.26 (6.49)**	**-0.23 (4.19)**
MS Intercept					0.001 (0.01)	-0.001 (0.01)		-0.001 (0.01)
MS Slope					**-0.02 (0.46)**	-0.02 (0.60)		-0.02 (0.49)
CV Intercept				**-0.26 (3.81)**		**-0.26 (3.89)**	**-0.44 (4.34)**	**-0.44 (4.21)**
CV Slope							-1.23 (1.11)	-1.17 (0.99)
				Goodness of Fit				
-2ll	312.773	243.059	232.028	228.144	231.454	227.498	226.824	226.286
df	4	5	7	8	9	10	9	11
χ^2	--	**69.714**	**11.031**	**3.884**	**0.574**	**3.956**	**5.204**	**5.168**
Model		M1-M2	M2-M3	M3-M4	M3-M5	M5-M6	M3-M7	M5-M8
% Class	78.8	79	79.4	79.7	78.6	78.6	79.4	79.7

Note: EM= Episodic Memory Intercept and Slope; MS= Mental Status Intercept and Slope; CV= Cardiovascular Index Means Only Models; CV2= Cardiovascular Index Intercept and Slope Models; Significant estimates are in bold; -2ll = -2 log likelihood (i.e., deviance); Age is centered at 60 years; Years Ed=Years of Education, centered at 12; Gender is effects coded as -0.5=male and 0.5=female; % Class= Percent of cases correctly classified at the probability level of .50.

Table 8. Logistic regression results for Mixed (0) versus 'pure' AD (1).

	1. Baseline	2. Baseline+ APO-□	3. Baseline+ APO-□+ EM	4. Baseline+ APO-□+ EM+CV	5. Baseline+ APO-□+ EM+MS	6. Baseline+ APO-□+ EM+MS +CV	7. Baseline+ APO-□+ EM+ CV2	8. Baseline+ APO-□+ EM+MS +CV2
				Estimate (Wald χ^2)				
Intercept	**-1.12 (4.38)**	**-2.30 (10.90)**	-0.94 (1.14)	0.32 (0.10)	-1.75 (2.10)	-0.47 (0.13)	0.92 (0.61)	0.11 (0.01)
Age in 2002	**0.80 (14.23)**	**1.13 (18.76)**	**1.24 (19.67)**	**1.23 (18.41)**	**1.15 (13.54)**	**1.19 (13.56)**	**1.21 (17.71)**	**1.15 (12.92)**
Gender	**0.94 (11.21)**	**1.09 (12.22)**	**0.97 (9.02)**	0.52 (2.10)	**0.91 (7.41)**	0.45 (1.50)	0.48 (1.78)	0.42 (1.27)
Education	**-0.07 (4.77)**	**-0.08 (4.23)**	-0.04 (1.13)	-0.07 (2.57)	-0.06 (1.55)	-0.08 (2.70)	-0.06 (1.98)	-0.07 (2.25)
APOE Status		**0.94 (10.13)**	**0.82 (7.19)**	**0.70 (5.17)**	**0.82 (7.41)**	**0.70 (5.18)**	**0.69 (5.01)**	**0.69 (5.05)**
EM Intercept			**-0.09 (12.59)**	**-0.08 (11.68)**	**-0.08 (10.39)**	**-0.08 (9.13)**	**-0.09 (12.22)**	**-0.09 (9.61)**
EM Slope			**-0.30 (10.17)**	**-0.28 (8.37)**	**-0.27 (7.36)**	**-0.25 (5.81)**	**-0.30 (8.99)**	**-0.27 (6.28)**
MS Intercept					0.01 (0.64)	-0.01 (0.32)		0.01 (0.37)
MS Slope					-0.01 (0.11)	-0.01 (0.24)		-0.01 (0.19)
CV Intercept				**-0.39 (8.50)**		**-0.38 (8.31)**	**-0.52 (6.32)**	**-0.51 (6.02)**
CV Slope							-0.91 (0.66)	-0.84 (0.55)
				Goodness of Fit				
-2ll	331.633	265.471	251.505	242.566	250.360	241.65	241.877	240.971
df	4	5	7	8	9	10	9	11
$\Delta\chi^2$	--	**66.162**	**13.97**	**8.939**	**1.145**	**8.71**	**9.628**	**9.389**
R-Square	0.1369	0.2138	0.2762	0.3145	0.2812	0.3184	0.3174	0.3212
Model	--	M1-M2	M2-M3	M3-M4	M3-M5	M5-M6	M3-M7	M5-M8
% Class	74.8	75.4	76.5	77.9	76.2	76.5	77.9	77.2

Note: EM= Episodic Memory Intercept and Slope; MS= Mental Status Intercept and Slope; CV= Cardiovascular Index Means Only Models; CV2= Cardiovascular Index Intercept and Slope Models; Significant estimates are in bold; -2ll = -2 log likelihood (i.e., deviance); Age is centered at 60 years; Years Ed=Years of Education, centered at 12; Gender is effects coded as -0.5=male and 0.5=female; % Class= Percent of cases correctly classified at the probability level of .50.

Figure 1. Observed trajectories of repeated cardiovascular index variables over Age for ADAMS participants with AD or VaD dementia (N=330).

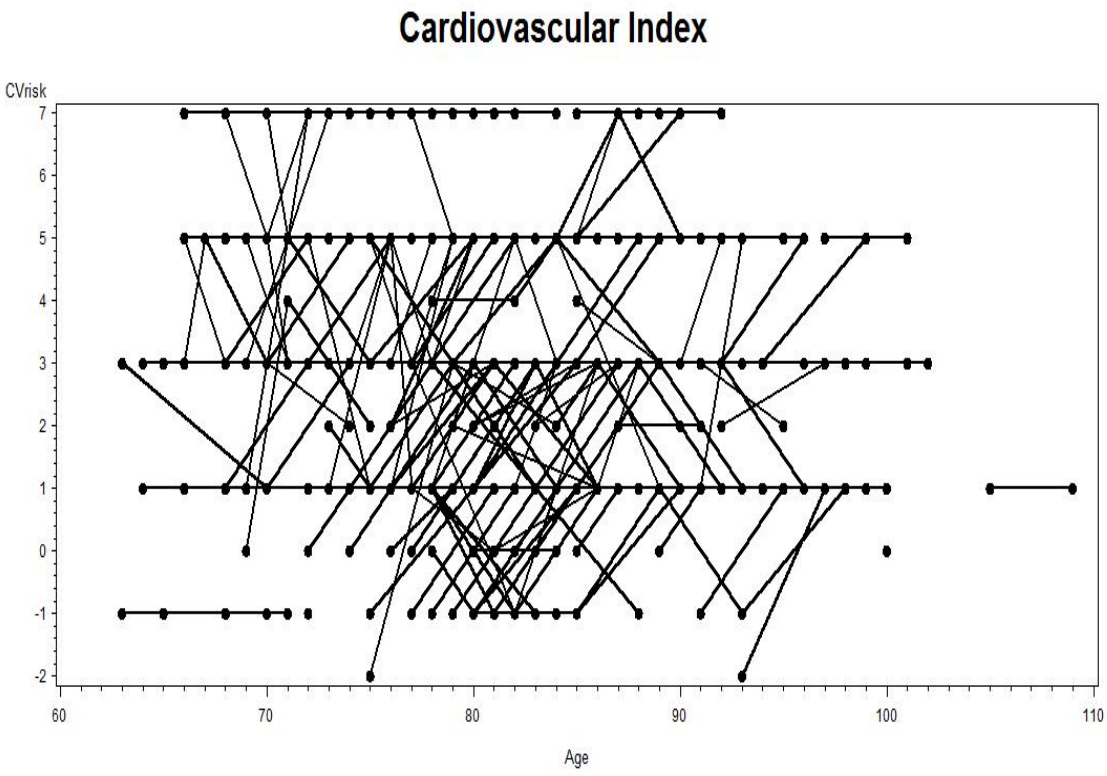

Figure 2. Cardiovascular latent growth models, linear and spline.