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Neuropsychiatric and Cardiovascular Risk Factors Along the Alzheimer's Disease Continuum

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Alexandrea Leigh Harmell is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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VITA

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ABSTRACT OF THE DISSERTATION

Neuropsychiatric and Cardiovascular Risk Factors Along the Alzheimer's Disease Continuum

by

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Rationale: Presently, there are over 5 million Americans living with Alzheimer's disease (AD); this number is projected to grow to over 7 million by 2025. In the absence of effective treatments, and difficulty reversing the neuropathological changes once they emerge, finding modifiable risk factors early in the course of the disorder is one of the most promising strategies to delay or prevent the progression of predementia [i.e., Mild Cognitive Impairment (MCI)] and dementia syndromes. Two factors that may be particularly important in influencing phenotype and rate of progression to MCI and AD are neuropsychiatric and cardiovascular symptoms.

Design: This study included 549 cognitively normal, MCI, and AD volunteers from the UC San Diego Alzheimer's Disease Research Center (ADRC). Participants were seen annually and underwent a one-hour neurological examination, comprehensive neuropsychological testing, ApoE genotyping, and assessments of cardiovascular symptoms, medication use and neuropsychiatric functioning. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals. Separate analogous models were conducted for individuals that converted to MCI and individuals that converted to AD and ApoE-e4 interaction terms were tested. Multilevel modeling analyses were performed separately for cognitively normal, MCI, and AD subgroups to identify any differential sensitivity among neuropsychological domains most sensitive to neuropsychiatric and vascular risk factors across time.

Results: There were 22 individuals that converted to MCI and 57 individuals that converted to AD during the course of the study. Apathy at baseline was found to significantly increase the risk of MCI after adjusting for age, sex, and education. Individuals endorsing agitation were more than two times as likely to convert to AD and individuals with at least mild depression were 2.5 times as likely to convert to AD. There were no significant interactions between neuropsychiatric symptoms and APoE-e4; cardiovascular risk factors did not predict change in cognitive status. Within-person increases in depressive symptoms were significantly related to decreases on memory and executive functioning among cognitively normal individuals; within-person increases in neuropsychiatric symptoms among AD patients were associated with worse attention, language, visuospatial skills, and processing speed. Moreover, AD patients with higher

levels of neuropsychiatric symptoms across time had worse executive functioning relative to AD patients with lower levels of neuropsychiatric symptoms.

Conclusions: Results suggest that apathy, and agitation and depression at baseline are associated with increased risk of future MCI and AD, respectively. As such, clinicians should monitor individuals presenting with both cognitive complaints and new neuropsychiatric symptoms closely, as these individuals may be at higher risk of developing MCI or AD. This study also found that higher reports of neuropsychiatric symptoms in cognitively normal and AD patients were associated with worse performance across time in specific cognitive domains. Additional studies are warranted that investigate whether treatments designed to improve neuropsychiatric symptoms result in subsequent improvements in specific areas of cognition.

CHAPTER 1: INTRODUCTION

AD is a chronic, neurodegenerative illness to which there is currently no effective treatment. Therefore, research focusing on modifiable risk factors early in the course of the disorder is of paramount importance.

The goal of the present study is to better understand the relationships among neuropsychiatric symptoms, vascular risk factors, and cognition. To accomplish this, this study sought to (1) elucidate the association between neuropsychiatric symptoms, individual vascular risk factors, and aggregate vascular risk factors and risk of conversion to MCI or clinically apparent AD; (2) investigate whether the ApoE-e4 genotype (presently the most consistently confirmed genetic risk factor for AD) modifies the association between significant neuropsychiatric and vascular risk factors and risk of conversion to MCI or AD; and (3) investigate the neuropsychological domains that are most sensitive to the effects of neuropsychiatric and vascular risk factors across time within the cognitively normal, MCI, and AD study groups.

Findings from this study may be used to help identify patients at higher risk of progressing to MCI or AD. In addition, establishment of an appropriate treatment for neuropsychiatric and/or cardiovascular symptoms may have the potential to reduce the risk for or delay the progression of MCI or AD.

CHAPTER 2: BACKGROUND & SIGNIFICANCE

2.1 Aging Trends and Alzheimer's disease Statistics

Due to advances in modern medicine, the United States is aging at an unprecedented rate. The average life expectancy in the U.S. is 78.8 years and the population of Americans aged 65 and older is projected to double during the next 25 years to around 72 million (Center for Disease Control and Prevention, 2013). As a result of this substantial increase in longevity, age-related disorders such as dementia are becoming increasingly prevalent, with the most common disorder being Alzheimer's disease (AD). AD is a debilitating, progressive neurodegenerative disorder that most often, but not invariably, begins with modest declines in episodic memory. The pathological hallmarks of the disorder are amyloid plaques and neurofibrillary tangles caused by aberrant tau protein and abnormally folded amyloid beta accumulation in the brain (Hashimoto, Rockenstein, Crews, & Masliah, 2003). Throughout much of the 20th century, the prevalence of AD was vastly underestimated, as "senile dementia" was viewed as a natural component of aging (Jeste & Palmer, 2003). However, now that AD is becoming widely recognized as a pathological, not inevitable process that comes along with aging, the disease statistics are staggering. According to the Alzheimer's Association, an American is diagnosed with AD every 66 seconds, which will increase to every 33 seconds in 2050. Moreover, currently one out of every nine Americans aged 65 and older and one out of every three Americans aged 85 and older has AD (Alzheimer's Association, 2016).

2.2 Public Health Impact of Alzheimer's disease

Financial Costs. Besides being one of the most prevalent chronic diseases, AD is also one of the most expensive to help manage. In 2016, the direct costs to the nation for caring for individuals with AD was over $236 billion, with just under half of these costs covered by Medicare. Given the alarming increase in the number of patients afflicted with AD each year, the economic burden associated with the disease is also projected to increase. In fact, in 2050, AD management is projected to rise to over $1 trillion (Alzheimer's Association, 2016). The direct costs of the disease include nursing home care, hospitalizations, physician visits, social services such as daycare, and medications, whereas indirect costs are associated with loss of productivity and premature death (Meek, McKeithan, & Schumock, 1998). Not only are these costs passed on to society, but also to the patient as well as the patient's family members, often resulting in bankruptcy and financial ruin.

Caregiver Burden. In addition to the financial stress associated with caring for a loved one with AD, there is also an immense amount of emotional distress. Although AD is largely thought of as a cognitive disorder, it is psychiatric manifestations in patients with AD that are among the strongest predictors of caregiver burden (Black & Almeida, 2004). One study found that some behavioral and psychological symptoms (delusions, hallucinations, agitation, disinhibition, irritability, and aberrant motor behavior) are associated with higher caregiver burden relative to others (depression, anxiety, and euphoria), irrespective of their severity or frequency (Matsumoto et al., 2007). However, care recipient depression has also had strong positive associations with caregiver burden and caregiver depression (Teri, 1997). These neuropsychiatric symptoms are so

distressing to caregivers, in fact, that they have been found to be a major precipitant for institutionalization (O'Donnell et al., 1992; Okura et al., 2011).

One of the main difficulties in AD is that although it initially impacts the patient's episodic memory, it gradually leads to complete mental and physical dependency, which can take a huge toll on caregiver's physical and emotional well-being. The chronic stress associated with caregiving has been linked to a host of negative physical health processes including higher allostatic load (Roepke et al., 2011), endothelial dysfunction (Mausbach et al., 2010), and increased stress hormones and inflammatory markers (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012; von Kanel et al., 2012), all of which can lead to heart disease. Spouses of patients with dementia have been shown to have a fourfold higher risk of depression relative to spouses of non-demented persons (Joling et al., 2010). Higher rates of anxiety have also been found in AD family caregivers, with female caregivers being especially vulnerable to developing anxiety (Mahoney, Regan, Katona, & Livingston, 2005). There is even some evidence to suggest that spousal caregivers of patients with dementia have six times the risk, themselves, of developing dementia after adjusting for theoretically relevant covariates such as age, sex, APoE genotype, and socioeconomic status (Norton et al., 2010). Thus, the disorder does not only have deleterious physical, emotional, and cognitive health consequences for the patient with AD, but also for the patient's family caregivers.

2.3 Lack of Effective Treatments

Pharmaceutical Trials. Although considerable efforts have been made to find an effective treatment for AD, pharmaceutical drug trials have shown limited therapeutic

success at treating the underlying neurodegenerative process. For example, in the decade of 2002-2012, 244 drugs for Alzheimer's disease were tested in clinical trials, of which only one received approval (Alzheimer's Association, 2016). Compounding the success of medication trials even further is the fact that patients with dementia may be more sensitive to adverse side effects in medications such as anticholinergic effects, nausea, orthostasis, sedation, and parkinsonism (Rabins et al., 2007). The most commonly prescribed medications for AD are acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and an approved N-methyl-D-aspartate antagonist (memantine) (Geldenhuys & Darvesh, 2015). Acetylcholinesterase inhibitors are licensed for mild-moderate AD, while NMDA antagonists have been marketed for moderate-severe AD. In some cases, both of these drug classes are prescribed, however the benefit of taking both medications concurrently remains controversial (Farrimond, Roberts, & McShane, 2012). Overall, these medications, whether used in isolation or in combination, have been shown to have very modest effects on symptoms compared to placebo over 6 months (e.g., 1-1.5 point improvements on the Mini-Mental Status Exam), and no clear effect on rate of disease progression (Lleo, Greenberg, & Growdon, 2006). Experimental efforts are also currently underway to clear amyloid plaques using β-secretase inhibitors, however past experimental trials have not been met with much success because the enzyme has many substrates and drugs to modulate this CNS enzyme must cross the blood-brain barrier (Mangialasche, Solomon, Winblad, Mecocci, & Kivipelto, 2010). One such example of these trials is a large scale three year, placebo controlled, randomized clinical study (called the "A4 study") being conducted to see if anti-amyloid treatment via the drug solanezumab, a humanized monoclonal antibody, may be able to

break down the accumulation of amyloid-beta in clinically normal older adults that showed evidence of amyloid accumulation on PET scans (Sperling et al., 2014). The results of this study have not yet been made public.

One leading theory for why clinical trials yield such disappointing results is because pharmacotherapy is administered too late in the disease process (Sperling et al., 2011). However, findings from the Alzheimer's Disease Neuroimaging Initiative (ADNI) suggest that patients with Mild Cognitive Impairment (MCI) treated with acetylcholinesterase inhibitors showed greater cognitive declines in scores and progressed sooner than patients who were not on these medications (Schneider, Insel, & Weiner, 2011). Unfortunately, despite the widespread use and marketing of dementia medications, no truly effective treatment has yet to be found. This lack of treatment successes in drugs and disease-modifying agents gives rise to the notion that we may still not truly understand the nature of neurodegeneration.

Psychosocial Interventions. Unlike other clinical populations such as traumatic brain injury or stroke, cognitive rehabilitation efforts in AD, particularly in the later stages, have been largely futile and can end up being frustrating for patients. The disease primarily affects episodic memory; therefore patients with AD are unable to cognitively encode new skills and information that is taught to them. Even rehabilitation programs capitalizing on procedural memory (which is often preserved in early AD patients) have reported that AD patients show a tendency to regress to baseline levels of performance (Farina et al., 2002) after some initial success in training of basic and instrumental activities of daily living (Tappen, 1994; Zanetti et al., 1997).

Considering the challenges in cognitive remediation and the unlikelihood of a persistent benefit, the large bulk of treatment in AD involves psychiatric management and/or specialized psychosocial treatments to help improve the patient's mood. Pleasurable activities such as art therapy (Chancellor, Duncan, & Chatterjee, 2014), music therapy and cooking interventions (Narme et al., 2014), and pet therapy (Majic, Gutzmann, Heinz, Lang, & Rapp, 2013) have shown some modest support in enhancing patient's mood and behavior but have not been subjected to large randomized controlled trials. To help treat neuropsychiatric factors in AD patients, non-pharmacological methods are a first-line treatment defense followed by medications if non-pharmacological approaches prove to be ineffective. A paper by Borisovskaya and colleagues (2014) reviews different treatment strategies for various neuropsychiatric symptoms. For example, in AD patients with depression, interventions such as behavioral activation, decreasing social isolation, psychotherapy, and exercise programs may be beneficial. If these interventions are not effective, low dose SSRIs may be prescribed (Borisovskaya, Pascualy, & Borson, 2014). In terms of agitation, using simple language and visual cues, avoiding overstimulating activities, and implementing predictable routines may help eliminate patient frustration. For hallucinations and delusions, a low dose of atypical antipsychotic medication can sometimes be prescribed to those patients who show clear benefits and minimal side effects (Borisovskaya et al., 2014). Acetylcholinesterase inhibitors, originally designed to treat cognitive decline in AD, have also been shown to be effective at treating some behavioral symptoms including apathy and agitation (Overshott, Byrne, & Burns, 2004).

Taken together, unfortunately, to date no intervention can stop or reverse the progression of AD, therefore risk assessment and trying to minimize the likelihood of an individual acquiring the disease should become a main priority for patients, caregivers, and researchers alike.

2.4 Importance of Identifying Early Risk Factors

It is hypothesized that neuropathic changes of AD can begin well before dementia onset becomes apparent (Sandberg, Stewart, Smialek, & Troncoso, 2001). Given the fact that the rate of AD is increasing rapidly and as aforementioned, there is no cure or effective treatment in the foreseeable future, when studying AD, an emphasis on early detection seems to be a logical target for research efforts. For this reason, there has been increased attention on Mild Cognitive Impairment (MCI), commonly believed to be the transitional state between normal aging and dementia. MCI is a broad term that is used to describe those individuals with slight impairment in cognitive function, but relatively intact performance in activities of daily functioning. MCI affects approximately 19% of individuals over the age of 65 (Lopez et al., 2007). There is variability in outcomes for patients with MCI with between 13.5-44% of individuals reverting back to normal or remaining stable (Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014) and more than half going on to later develop dementia within 5 years (Gauthier et al., 2006).

The annual rate of conversion from MCI to AD can range from 4-30%, with lower rates typically reported in community based studies and higher rates reported in selected clinical populations (Gainotti, Quaranta, Vita, & Marra, 2014). Being better able to discriminate between those individuals with a relatively benign form of MCI versus

those individuals who are at the highest risk to progress to dementia would strengthen future intervention efforts and would provide more accurate prognostic information. Additionally, in the absence of effective treatments, and difficulty reversing the neuropathological changes once they develop, finding modifiable risk factors early in the course of the disorder seems to be one of the most promising strategies to delay or prevent the progression of predementia and dementia syndromes. A number of factors may influence rate of progression to MCI and AD. Included among these factors may be neuropsychiatric and cardiovascular symptoms.

In terms of neuropsychiatric symptoms, the initial symptoms of Alzheimer's index case person Auguste D., seen by Dr. Alzheimer in 1901, were not memory deficits, but rather delusions that her husband was being unfaithful (Stelzmann, Norman Schnitzlein, & Reed Murtagh, 1995). Also notable is that pseudodementia, a now discontinued term used to describe cognitive impairment that looks like dementia in severely depressed individuals, was initially thought to be transient. However, current research suggests that moderate to severe depression may not only be related to cognitive impairment during the depressive episode, but in fact may be a strong predictor of developing actual dementia (Saez-Fonseca, Lee, & Walker, 2007). Given these findings highlighting the role that delusions and depression can play in individuals prior to clinically apparent AD, more research is needed to help elucidate whether or not various neuropsychiatric symptoms may predate and predispose older adults to develop AD.

Regarding cardiovascular risk factors, there is some evidence that there may be a link between atherosclerosis risk factors and the phenotypic expression of AD. For example, some neuropathologic studies suggest that the presence of vascular risk factors

may promote subclinical vascular brain injury, thereby lowering the amount of AD pathology needed to symptomatically unmask dementia (Chui, Zheng, Reed, Vinters, & Mack, 2012). This has been further evidenced in a study which showed that patients with AD and concomitant cerebrovascular disease had less AD pathology relative to AD patients without cerebrovascular disease, even though they had the same level of cognitive deficit (Nagy et al., 1997). In normal controls, hypertension has been associated with increased neurofibrillary tangles (Sparks et al., 1995) and white matter hyperintensities have been associated with brain volume loss (Barnes et al., 2013). Also, as noted in the widely cited "nun study," people with typical AD neuropathology may be less likely to manifest dementia in the absence of comorbid neurovascular pathology (Snowdon et al., 1997). Given the research that has already been conducted and the questions that still remain unanswered in the existing literature, the overarching goal of this study is to help identify the conditions that, if effectively managed, have the potential to reduce or delay the inception of MCI or AD. Identifying the factors associated with MCI or AD risk can help inform treatment and planning options not only for individuals, but also for family members and health care providers.

2.5 Literature Review: Investigation of Dementia Risk Factors

Neuropsychiatric Symptoms in MCI and AD. There is some emerging evidence that neuropsychiatric symptoms play a role in cognitive impairment. This finding is important as neuropsychiatric symptoms are thought to manifest very early on in patients with MCI and AD, with prevalence estimates between 35-85% and 50-90%, respectively (Apostolova & Cummings, 2008; Hwang,

Masterman, Ortiz, Fairbanks, & Cummings, 2004; Lyketsos et al., 2002; Mega, Cummings, Fiorello, & Gornbein, 1996; Sadak, Katon, Beck, Cochrane, & Borson, 2014). Depression, anxiety, and irritability have been found to be among the most reported symptoms in MCI, whereas apathy and depression have been found to be among the most persistent and frequently reported symptoms in patients with AD (Lyketsos et al., 2011; Monastero, Mangialasche, Camarda, Ercolani, & Camarda, 2009).

The possible association between depression, specifically, and future MCI or dementia risk has become an increasingly popular area of interest (Gabryelewicz et al., 2007; Modrego & Ferrández, 2004). For example, a meta-analysis of 20 studies reported that having depression doubles the risk of subsequent AD (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Additionally, a large-scale longitudinal study found that even low levels of depressive symptoms measured at baseline were associated with an increased risk of MCI during 6 years of follow-up (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006). Furthermore, depression in MCI has been associated with neuropathological changes in the brain including reduced cortical thickness in the entorhinal cortex and accelerated atrophy in the anterior cingulate cortex (Zahodne, Gongvatana, Cohen, Ott, & Tremont, 2013).

Of note, however, data is very limited as to whether or not other neuropsychiatric symptoms besides depression may predate or be linked with dementia. Of the few studies that have investigated this putative association, some have reported that symptoms of apathy and psychosis may increase the vulnerability of older adults to go on and later develop dementia (Kohler et al., 2013; Richard et al., 2012). Interestingly, there have

been conflicting reports of whether or not patients diagnosed with schizophrenia are at an increased risk for AD with some literature suggesting a much higher risk (Prohovnik, Dwork, Kaufman, & Willson, 1993) and other literature suggesting equal or even less risk than the general population (Jellinger & Gabriel, 1999). Non-psychotic symptoms such as agitation, apathy, irritability, anxiety, and depression have been found to predict incident MCI (Geda et al., 2014) and another, more recent study, found that increases in euphoria, eating disorders, aberrant motor behavior, as well as worsened sleep quality, predicted more rapid decline in cognitive functioning in patients already diagnosed with MCI (Pocnet et al., 2015). Anxiety in individuals at baseline has also been associated with faster decline and progression to MCI and AD (Wadsworth et al., 2012).

A possible contributing mechanism linking NPS to cognitive impairment was discussed in an article by Geda and colleagues (2013) (Geda et al., 2013). Included among their differing theories is the etiological pathway theory, which argues that NPS may reflect an underlying pathology on the brain, such as activation of the neuroendocrine system (Sapolsky, 2000), which in turn, could lead to the development of AD pathology. In terms of depression and dementia, Byers and Yaffe (2011) reviewed several biological mechanisms that the two disorders have in common including alterations in glucocorticoid steroid levels and hippocampal atrophy, increased deposition of amyloid-β plaques, inflammatory changes, and deficits in nerve growth factors (Byers & Yaffe, 2011). Functional findings have provided further insight into the brain changes associated with affective symptoms including more frontal, parietal, and temporal white matter atrophy (regions affected by AD) and decreased connectivity in the fronto-parietal control network (Munro et al., 2015). Furthermore, there could be indirect mechanisms

such as low activity and exercise that may contribute to the relationship between affective symptoms (e.g., depression) and cognitive decline.

It is of great importance that more research continues to focus on studying NPS in patients with MCI and dementia, as these symptoms have been associated with reduced quality of life, more rapid cognitive decline, institutionalization, and increased caregiver burden (Kalapatapu & Neugroschl, 2009). However, one major limitation of current research is that with the exception of some of the aforementioned studies, most extant research focuses on neuropsychiatric symptoms that are already present in patients with dementia. Therefore, it remains unknown whether NPS represent risk factors for dementia, coincide with dementia onset, or immediately follow dementia. Exploring whether neuropsychiatric symptoms may be present in prodromal phases, prior to dementia onset, is a worthy goal as interventions targeting neuropsychiatric symptoms have the potential to delay MCI or AD.

Vascular Risk Factors in MCI and AD. There is some evidence that vascular risk factors such as hypertension, diabetes, smoking, and high cholesterol are harbingers of cognitive decline, particularly among older adults. However, the role of vascular risk factors in relation to neurodegenerative processes remains poorly understood, despite the high rate of co-occurrence. Moreover, of the studies that do look at the relationship between vascular risk factors and neurodegenerative disorders, many focus on individual vascular risk factors of dementia rather than looking at the impact that multiple vascular risk factors can have when present simultaneously.

For example, systemic hypertension, often associated with advancing age, is garnering increased attention as a possible contributor to age-related cognitive decline.

However, the association between hypertension and cognition has been fairly inconsistent. In a recent review article, it was reported that among eight studies that operationally defined hypertension as a categorical variable (present/absent), four found an association with accelerated cognitive decline and four found no such association (Blom, Emmelot-Vonk, & Koek, 2013). Moreover, while two meta-analyses from 2011 that combined midlife and late-life hypertension found no association between hypertension and AD risk (Guan et al., 2011; Power et al., 2011), a recent systematic review found strong evidence in favor of hypertension and increased risk of dementia (Deckers et al., 2015). The possible biological mechanisms linking hypertension to AD are poorly understood, but hypertension that is either already present by midlife or long-standing appears to be related to cerebral vascular changes including white matter lesions (Vuorinen et al., 2011), which in turn may increase the risk of conversion to AD (Tokuchi et al., 2014). High blood pressure has also been reported to have pathophysiologic effects on the brain such as impaired cerebral autoregulation, cerebral microbleeds, unrecognized lacunar infarcts, and amyloid-angiopathy and cerebral atrophy, the latter two being particularly relevant to AD (Manolio, Olson, & Longstreth, 2003).

There has also been a growing literature highlighting the role of insulin resistance or insulin deficiency, as evidenced in diabetes, and AD. The relationship between diabetes and AD has been largely borne out of epidemiological work. Diabetes and AD share many commonalities and both diseases are on the rise, especially among older adults living in developed countries. These two diseases share so much overlap, in fact, that the term “type 3 diabetes” has been coined to reflect how similar the two diseases are

in some of their molecular and biochemical features (de la Monte & Wands, 2008). Type 2 diabetes and AD share biological underpinnings including insulin resistance, impaired glucose metabolism, beta-amyloid formation, and oxidative stress (Mushtaq, Khan, & Kamal, 2014). Moreover, the medial temporal lobe, which is specifically implicated in early AD, contains insulin receptors (Schulingkamp, Pagano, Hung, & Raffa, 2000) and insulin dysregulation, in particular, has been shown to change cellular processing and transport of beta amyloid (Craft & Watson, 2004). Despite these findings, results of studies that link diabetes and AD remain equivocal. One meta-analysis of six prospective studies reported that patients with diabetes were at a 47% increased risk of dementia (Lu, Lin, & Kuo, 2009). Another study further reported a 1.5 to 2.5 fold increase in dementia risk for adults with Type Two diabetes relative to the general population (Strachan, Reynolds, Marioni, & Price, 2011). In contrast, other studies have found no association between diabetes and increased dementia risk (Curb et al., 1999; Euser et al., 2010).

Smoking has been associated with a whole host of negative consequences including coronary artery disease, stroke, and lung cancer. In addition, a recent meta-analysis of 37 studies reported that current smokers, when compared with never smokers, showed an increase risk of all-cause dementia with a 34% increased risk for every 20 cigarettes smoked per day. The specific risk ratio reported for AD was 1.40 (95% confidence interval 1.13-1.73) (Zhong, Wang, Zhang, Guo, & Zhao, 2015). Barnes and Yaffe (2011) further reported that smoking accounts for 574,000 (11%) of AD cases in the US and 4.7 million (14%) cases worldwide (Barnes & Yaffe, 2011). Yet, some older review papers found that having ever smoked is associated with a decreased risk of AD, perhaps due to a possible neuroprotective effect of nicotine and nicotinic drugs (Lee,

1994; Newhouse, Potter, & Levin, 1997; Van Duijn et al., 1994). It is possible that survival bias may at least partially be to blame for these latter findings (Almeida, Hulse, Lawrence, & Flicker, 2002). Another possibility is that nicotine may have a positive effect on cognition, but the most common delivery method, smoking, has adverse pulmonary and cardiovascular effects, which could lead to a negative net effect. Inconsistencies surrounding the role of smoking on cognition continue to abound, and more research in this area may provide much needed clarification.

Similarly to the other vascular risk factors, a positive relationship between high cholesterol and AD has been reported by some (Kivipelto et al., 2001), but not all studies (Kalmijn et al., 2000; Tan et al., 2003). In a review paper focusing on cholesterol in relation to AD, Sjogren and colleagues (2006) outlined several articles that provided strong support that reduction in cholesterol (whether via the use of statins or non-statin cholesterol lowering drugs) can lead to a reduction in amyloid-beta (Sjogren, Mielke, Gustafson, Zandi, & Skoog, 2006). Oddly enough, however, other studies have found the exact opposite results and reported cases where *higher* cholesterol levels were associated with a reduced risk for AD (Mielke et al., 2005; Reitz, Tang, Luchsinger, & Mayeux, 2004). Additional studies in this area are clearly warranted to help clarify the direction and strength of the relationship between cholesterol and AD risk. The brain has the highest concentration of cholesterol relative to any other organ in the body, with approximately 25% of the total cholesterol in the body being present in the brain (Mathew, Yoshida, Maekawa, & Kumar, 2011). Cholesterol has been shown to be a necessary component of myelin, neuronal membranes, and glial membranes and to assist in cerebral structure as well as function (Muldoon, Flory, & Ryan, 2001). Therefore,

despite the lack of consensus outlining the exact role that cholesterol may play in AD, it likely plays some pivotal role in brain function.

One plausible reason for the discrepancy in findings looking at individual risk factors and dementia risk may be that they only provide limited information, as they fail to take into account the presence of combined vascular risk factors. In recognition of the multifactorial, heterogenous nature of AD, there has been a recent shift in research focus towards acknowledging that aggregate vascular risk factors, in combination, may be particularly useful markers of cognitive decline. One groundbreaking longitudinal cohort study that has paved the path for this new area of focus is the Framingham Heart Study (D'Agostino & Kannel, 1989). The overarching goal of the Framingham Heart study was to establish the major risk factors associated with CVD. Since its inception, it has expanded its research breadth and combined individual risk factors into a multivariate function to assess the probability of developing a CVD event over the span of a specific time period (e.g., 10 years). Recent studies have adopted this multivariate method and are using the Framingham Stroke Risk Profile (FSRP) as a way to assess dementia risk (Bangen et al., 2010; Rondina et al., 2014; Unverzagt et al., 2011), using an equation put forth by Anderson and colleagues that includes information on age, gender, systolic blood pressure, ratio of total cholesterol to HDL, diabetes, and cigarette smoking (Anderson, Odell, Wilson, & Kannel, 1991). Notably, however, one major limitation of using the FSRP to assess dementia risk is that it incorporates age into its equation, which presents an independent confound, as age is one of the most robust risk factors for dementia.

2.5.1 Specific Aim 1

Aim 1: Elucidate the association between NPS (including but not limited to depression) and individual vascular risk factors, aggregate vascular risk factors, and risk of conversion to MCI or clinically apparent AD.

Rationale: With regards to NPS and dementia risk, the vast majority of studies focus on either the prevalence of NPS in patients that already have MCI or AD or on depression, in isolation, and risk for dementia. Therefore, this study seeks to address this gap in the literature by exploring the prevalence of NPS across the entire cognitive spectrum (cognitively normal, MCI, AD) and expanding the definition of NPS to include but not be limited to depression. Other NPS's that will be explored include delusions, hallucinations, agitation, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. It is important to help clarify the temporal sequence of NPS because besides being a consequence of AD, NPS could also be a risk factor.

Moreover, despite the fact that several studies have found a significant association between individual vascular risk factors and dementia onset, a large number of studies have found no such association. This gives rise to discrepant conclusions regarding vascular contributions to Alzheimer's disease risk. There is also a lack of studies looking at the precise role that aggregate risk factors, in combination, may have on future cognitive decline.

Hypothesis 1.1. Patients with more neuropsychiatric symptoms will have an increased risk of conversion in diagnostic status to MCI and AD.

Hypothesis 1.2. Individual vascular risk factors such as hypertension, high cholesterol, diabetes, and smoking will be associated with increased risk of conversion to MCI and AD. Moreover, individuals with multiple vascular risk factors will have an even stronger association with dementia risk.

2.6. Studies of Apolipoprotein E4 allele (APoE-e4)

APoE-e4 and Its Relationship to Cognition. The APoE gene exists as three different allele types, e2, e3, and e4. Among these, e4 occurs in roughly 15% of the general population, with this frequency increasing to over 45% in patients with AD (Roses, 1995). Moreover, there appears to be a dose dependent relationship for this gene, with some researchers going as far as suggesting that being a homozygous e4 carrier may, in and of itself, be sufficient to cause AD by age 80 (Corder et al., 1993). Since the discovery of the APoE-e4 genotype as an established genetic risk factor for AD (Henderson et al., 1995), there has been increased interest in studying the gene's unique role in cognitive functioning. As such, studies have revealed that e4 carriers with AD exhibit poorer memory performance and faster cognitive decline, particularly in the early stages of AD (Cosentino et al., 2008). Poorer memory performance has also been detected in e4 carriers with MCI (Farlow et al., 2004). In cognitively normal patients, those individuals that reported subjective memory complaints in conjunction with e4 carriage had two times the rate of cognitive decline over 3 and 6 year follow-up intervals

than patients without both of these factors (Dik et al., 2001). A meta-analysis of 38 studies found significant APoE-e4 group differences in global cognitive functioning, episodic memory, and executive functioning with lower scores found in e4 carriers (Small, Rosnick, Fratiglioni, & Backman, 2004).

APoE-e4 and Neuropsychiatric Symptoms. The role of the APoE genotype and neuropsychiatric syndromes has yet to be clearly delineated. It is possible that a synergistic interaction may occur between neuropsychiatric symptoms and APoE-e4, thereby increasing the susceptibility for individuals to go on and develop MCI or AD. This theory was supported by a longitudinal study of 840 cognitively normal elderly subjects in which the hazard ratio of developing MCI in patients with depression was 2.0, but increased to 5.0 in patients with both depression and APoE-e4 carrier status (Geda et al., 2006). Geriatric depression, APoE-e4, and the interaction between the two have also been associated with an imbalanced hippocampal functional connectivity network (Shu et al., 2014). Moreover, other findings among AD patients have found that the APoE-e4 genotype may be over-represented in patients with depression (Delano-Wood et al., 2008), with one group finding a three-fold increase in depression and psychosis among AD patients with the APoE-e4 allele compared to patients without the allele (Ramachandran et al., 1996). In direct contrast, however, other studies have suggested that the APoE-e4 allele may in fact be protective against depression (Ballard, Massey, Lamb, & Morris, 1997), or have no association with depression at all (Borroni et al., 2006; Hollingworth et al., 2006).

Although far less studied, some researchers have explored the association between other neuropsychiatric symptoms and APoE-e4. A cross-sectional study found

that the APoE-e4 allele may modulate anxiety in AD (D'Onofrio et al., 2011), however one longitudinal study did not find this association (Pritchard et al., 2007). Within patients with AD, apathy has also been associated with APoE-e4 status in some studies (Monastero et al., 2006). However, another study found that the APoE-e4 genotype did not modify apathy, but instead modified the association between the presence of delusions and agitation/ aggression in patients with AD (van der Flier et al., 2007). A review paper on the topic discussed some of the mechanisms linking neuropsychiatric symptoms with the APoE-e4 genotype. Among some of the theories proposed is that the APoE-e4 allele is associated with poorer neuronal reparative capacity, which may be implicated in cognitive decline and NPS, such as depression (Panza et al., 2011). Data on this topic is limited, though, as researchers primarily look at the association between NPS and APoE-e4 in patients who already have probable AD. Therefore, it is unknown whether the interaction between NPS and APoE-e4 precedes the diagnosis of AD, thereby increasing one's risk of AD or succeeds the diagnosis of AD, as a result of the manifestation of the disease. NPS are thought to increase as the disease progresses, however it is possible for some NPS to be detectable prior to AD diagnosis and these NPS, combined with the presence of the APoE-e4 gene, may predispose a person to be at greater risk of AD.

APoE-e4 and CVD Risk Factors. There are a paucity of studies looking at the relationship between APoE-e4 and vascular risk factors. This may be because one of the predominant theories surrounding APoE is that the gene binds to amyloid-beta peptides resulting in differential amyloid-beta aggregation and clearance in the brain (Liu,

Kanekiyo, Xu, & Bu, 2013). Importantly, however, APoE-e4 has also been associated with damage to vascular systems in the brain, which could directly or indirectly influence AD pathogenesis (Liu et al., 2013). Given this speculative relationship between APoE-e4 and vasculature, what remains largely unanswered is whether APoE-e4 may modify the association between vascular risk factors and cognition; there is some evidence emerging to suggest that this may be the case. For example, one recent study found that heavy alcohol consumption, hypertension, diabetes, and current smoking and the APoE-e4 allele interact to negatively affect white matter integrity, with multiple risk factors being more detrimental to white matter among APoE-e4 carriers compared to non-carriers (Wang et al., 2015). Another study showed that individuals that had both diabetes and APoE-e4 allele had the highest incidence of dementia compared to individuals with only one or both of these factors (Irie et al., 2008).

In 563 non-demented adults, researchers found that the presence of APoE-e4 and hypertension was associated with steeper cognitive decline across 7 different cognitive domains over a 21-year period (de Frias, Schaie, & Willis, 2014). Furthermore, another recent study found that APoE-e4 carriers had impairments in cerebrovascular risk factors such as carotid artery intima-media thickness (IMT) and cerebrovascular reactivity (breath-holding index), which was hypothesized to influence progression towards dementia in patients with MCI (Viticchi et al., 2014). Smoking status has also been found to interact with APoE-e4 carrier status, with a smoker +APoE-e4 carrier group showing lower glucose metabolism and poorer performance on a cognitive test relative to individuals that had one or none of these two factors (Durazzo, Mattsson, & Weiner, 2016). Despite some of these promising findings, there are still a relative lack of studies

exploring the relationship between APoE-e4, vascular risk, and cognitive impairment. Therefore, more research is needed in this area to help identify whether the APoE-e4 genotype and vascular risk factors may act in concert to increase risk of cognitive decline.

2.6.1 Specific Aim 2

Aim 2: To investigate whether APoE-e4 modifies the association between neuropsychiatric and vascular symptoms and leads to an increased risk of conversion to MCI and AD (above and beyond the effects of APoE-e4 in isolation).

Rationale: Given the current literature, it is largely unknown whether the APoE-e4 genotype confers a stronger, weaker, or a non-existent association with psychiatric and vascular morbidity and risk of further cognitive decline during the pre-dementia period (i.e., prior to AD diagnosis). Although the e4 allele, itself, is non-modifiable, it does have the potential to modify the associations between other risk factors and AD. Therefore, research in this area is of paramount importance as it may lead to more accurate detection of individuals that are at the highest risk of progressing to MCI and eventual AD.

Hypothesis 2.1: The APoE-e4 genotype modifies the association between total NPS score and risk of conversion to MCI and AD.

Hypothesis 2.2: The APoE-e4 genotype modifies the association between vascular risk factors and conversion to MCI and AD. In other words, individuals who have a high

aggregate vascular burden and are APoE-e4 carriers will be at a higher risk of converting to predementia and dementia than those individuals with no vascular risk factors who are non-APoE-e4 carriers.

2.7. Exploring the Relationship between Neuropsychological Domains and Cognitive Risk Factors

Neuropsychological Domains and Neuropsychiatric Symptoms. If neuropsychiatric factors possibly have deleterious effects on cognition, it is important to help elucidate which cognitive domains they may be impacting and whether these cognitive effects are different for cognitively normal, MCI, and AD subgroups. Although the neuropathology of AD appears untreatable at this time, neuropsychiatric symptoms in preclinical phases of AD may be amenable to treatment, and as such, some improvement in cognition may be possible. Mapping on specific areas of cognition with specific neuropsychiatric factors will better enable clinicians to see if improvements in neuropsychiatric factors result in subsequent improvements in cognition.

One study found that among older, healthy adults who were positive for amyloid-beta, individuals with elevated anxiety symptoms (including subthreshold anxiety symptoms) had greater declines in global cognition, verbal memory, executive function, and language during a 4.5-year period relative to amyloid-beta individuals without anxiety. This finding was independent of advancing age, level of education, IQ, APoE genotype, subjective memory complaints, vascular risk factors, and depressive symptoms (Pietrzak et al., 2015). The precise mechanism linking anxiety to amyloid-beta cognitive

decline may be via increased endogenous levels of glucocorticoids, which can damage areas of the brain such as the hippocampus (Beaudreau & O'Hara, 2008).

Among neuropsychiatric symptoms, psychotic symptoms (delusions and/or hallucinations) are frequently reported in AD. Jeste et al. (1992) suggested that AD patients with delusions have worse performances on measures of global cognition (MMSE and Dementia Rating Scale) and executive functioning (Jeste, Wragg, Salmon, Harris, & Thal, 1992). Executive dysfunction in AD patients with psychosis has been further corroborated by other studies (Hopkins & Libon, 2005; Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004), giving rise to the theory that psychosis in AD patients may be largely associated with frontal lobe dysfunction. However, other studies have found an association between hallucinations (visual and/or auditory) and faster decline in memory, visuconstruction/spatial ability, and language (Becker, Hershkowitz, Maidler, Rabinowitz, & Floru, 1994; Quaranta et al., 2015; Wilson, Gilley, Bennett, Beckett, & Evans, 2000), suggesting that the theory of psychotic symptoms exclusively or primarily affecting executive functioning may warrant further attention.

Depression in older adults has been associated with cognitive impairment across a variety of cognitive measures. A longitudinal study of over 2000 elderly women free of cognitive impairment found that persistent elevation in depressive symptoms was associated with greater declines in global cognition, verbal knowledge and fluency, and memory (Goveas et al., 2014). Another longitudinal study found that depressive symptoms in elderly adults had a specific effect on information processing speed, but not memory (Comijs, Jonker, Beekman, & Deeg, 2001). Executive dysfunction, or flexibility in thinking has been found to be more pronounced in older adults with more chronic or

persistent symptoms of depression (Dotson, Resnick, & Zonderman, 2008) as well as in MCI and AD patients experiencing apathy (McPherson, Fairbanks, Tiken, Cummings, & Back-Madruga, 2002).

Neuropsychological Domains and CVD Risk. Although the data is limited, some studies have attempted to capture the unique relationships between hypertension, diabetes, smoking, cholesterol, and specific cognitive abilities. For example, some studies have suggested that hypertension may lead to elevated risk for white matter damage, which in turn, can impact a broad range of areas including attention, executive functioning, visuospatial skills, and working memory (Hannesdottir et al., 2009; Waldstein et al., 1996; Waldstein, Ryan, Polefrone, & Manuck, 1994). Another study showed that patients with diabetes (compared to non-diabetics) had a greater decline over the span of 6 years on digit symbol and the first-letter word fluency tests, which the authors proposed might be due to demyelination or microinfarction in the cerebral white matter (Knopman et al., 2001). Smoking cigarettes has been found to reduce neurogenesis and increase cell death in the dentate gyrus (DG), an area related to memory and learning (Abrous et al., 2002). Current smokers have also demonstrated reduced psychomotor speed and cognitive flexibility compared with never smokers with the effect similar to that of being approximately 4 years older (Sandra Kalmijn, Van Boxtel, Verschuren, Jolles, & Launer, 2002). In addition, total cholesterol levels have been associated with mixed cognitive findings. Some studies have found that higher total cholesterol is associated with poorer performance on tests in the areas of memory and overall cognition (Sparks et al., 2010; Yaffe, Barrett-Connor, Lin, & Grady, 2002), whereas other studies have found that low cholesterol is associated with poor

performances on tests of processing speed (Benton, 1995; Zhang, Muldoon, & McKeown, 2004). One proposed mechanistic hypothesis behind these differing cholesterol outcomes is that lower levels of cholesterol may injure the brain's microstructure and function, whereas higher levels of cholesterol may lead to atherogenesis (Wendell, Waldstein, & Zonderman, 2014).

The Coronary Artery Risk Development in Young Adults study (CARDIA), a multicenter longitudinal study examining the associations between ideal cardiovascular health and cognitive functioning starting in young adulthood, found that ideal cardiovascular health in young adulthood and middle-age is associated with better performances on tests of psychomotor speed, executive function, and verbal memory in midlife (Reis et al., 2013). In a fourteen-year longitudinal study, diabetes and hypertension were independently associated with significant declines in two non-memory tasks (digit symbol substitution and word fluency tests respectively), but smoking status and high cholesterol levels were not (Petrovitch et al., 2000). This study also reported a significant association between APoE-e4 genotype and declines in Delayed Word Recall. In their discussion of these findings, Petrovitch and colleagues discuss the possibility of a "model of pathoanatomic relationships" where risk factors with a strong vascular component (i.e., diabetes and hypertension) may be more associated with attention and executive function deficits, and risk factors associated with more AD-risk (i.e., APoE-e4) may be associated with steeper declines in memory functioning. However, other studies have found that hypertension is associated with attention, executive function, as well as delayed recall memory impairments and a review article found that diabetes was associated with impairments on processing speed, a brief cognitive screening measure,

and verbal memory. This combined with the fact that hypertension and diabetes are linked with greater AD pathology including hippocampal neuritic plaques and neurofibrillary tangles suggest that the "model of pathanatomic relationships" distinction may be too simplistic (Peila, Rodriguez, & Launer, 2002; Petrovitch et al., 2000).

In one of the few studies specifically looking at MCI, vascular risk, and specific neuropsychological outcomes, an MCI group with vascular risk factors (e.g., arterial hypertension, ischemic heart disease, diabetes), was shown to have significantly lower scores than an MCI group without vascular risk factors on measures of learning, recall, and short-term memory as assessed by the Auditory Verbal Learning Test. The authors of this paper highlight that over 60% of the patients with MCI in their sample had the presence of cardiovascular risk factors and that vascular risk factors are more common in patients with MCI relative to non-cognitively impaired individuals (Siuda, Gorzkowska, Opala, & Ochudlo, 2007).

In a large prospective study of over 8500 cognitively normal participants aged 50 and older, associations between individual as well as aggregate vascular risk factors (as assessed by the FSRP index) and cognitive outcomes were estimated at 4-year and 8-year follow-ups. At 4-year follow-up, participants in the highest quartile of FSR had lower global cognition, memory, and executive functioning scores. At 8-year follow-up, systolic blood pressure $\geq$ 160 mmHg was associated with lower global cognition and memory scores. Smoking status was found to be the most consistent vascular risk factor of cognitive decline at both the 4 and 8-year intervals, as it was associated with low global cognitive, memory, and executive functioning scores (Dregan, Stewart, &

Gulliford, 2013). Another study calculated a total Cardiovascular Health score using body mass index, physical activity, diet, smoking, total cholesterol, blood pressure, and fasting plasma glucose. After controlling for age, education, gender, and other psychological and cardiovascular factors (e.g., triglycerides, depression scores, servings per day of food, etc.), significant associations were found between the cardiovascular health score and visual-spatial memory, working memory, scanning and tracking, executive function, and a global composite score (Crichton, Elias, Davey, & Alkerwi, 2014).

Importantly, the majority of the aforementioned studies are limited to cognitively normal individuals free of dementia and most investigate how individual vascular risk factors (e.g., hypertension) affect cognitive functioning. Among one of the only studies comparing aggregate vascular effects on neuropsychological performance in cognitively normal and MCI patients, Jefferson et al. (2015) found that increasing FSRP was related to worse baseline global cognition (MMSE) and worse longitudinal trajectory on naming, information processing speed, and sequencing abilities in cognitively normal individuals. In contrast, increasing FSRP in patients with MCI was only correlated with worse longitudinal delayed memory (Jefferson et al., 2015). These findings give rise to the possibility that vascular risk factors may have a bigger effect on cognitive decline in cognitively normal older adults compared to adults diagnosed with MCI.

2.7.3. Specific Aim 3

Aim 3: Identify the neuropsychological domains that seem to be the most sensitive to the effects of neuropsychiatric and vascular risk factors across time among cognitively normal, MCI, and AD study groups.

Rationale: A fruitful avenue of further investigation is to explore the impact of risk factors on brain function through a more specific neuropsychological perspective. For example, it is possible that there may be specific cognitive correlates of neuropsychiatric and vascular risk factors. However, neuropsychiatric and vascular symptoms have not been fully characterized with respect to their differential contribution on areas of cognition across the entire cognitive spectrum. In other words, a majority of the studies that look at neuropsychiatric and vascular risk factors and neuropsychological profiles are limited to cognitively normal adults only (i.e., individuals free of dementia), and fail to consider the possibility that neuropsychiatric and vascular risk may differentially affect the cognitive profiles of cognitively normal, MCI, and AD patients. Looking across the entire cognitive spectrum within the same study will provide a more comprehensive understanding of how vascular and neuropsychiatric risk can change across cognitive statuses. Also, examining vascular health using an aggregate approach as opposed to exclusively focusing on singular risk factors is important as it provides an opportunity to better capture the complexity of vascular health and its relationship to cognition.

Hypothesis 3.1: Greater total neuropsychiatric scores will be associated with significantly lower scores on global measures of cognition. Neuropsychiatric symptoms

will have a larger negative impact on cognition in cognitively normal individuals relative to MCI and AD groups.

Hypothesis 3.2: Individuals with higher aggregate vascular burden will perform worse on global cognitive measures. Vascular risk will differentially affect the cognitive profiles of cognitively normal, MCI, and AD patients with vascular risk being more detrimental to cognition in cognitively normal patients relative to MCI and AD.

2.8 Summary of Aims

Presently, there are 5.4 Americans living with AD, and this estimate is projected to grow to over 7.1 million by 2025 (Alzheimer's Association, 2016). Alzheimer's disease is a chronic and degenerative illness that destroys memory function, but eventually destroys all mental and physical functioning. It is the most expensive condition in the nation (Alzheimer's Association, 2016). Moreover, AD affects not only the individual's health, but also takes a devastating toll on caregiver's health. Caring for a loved one with AD has been associated with downstream negative health outcomes including hypertension (Shaw et al., 1999), cardiovascular illness (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007), and mortality (Schulz & Beach, 1999). Negative psychological consequences associated with caregiving include symptoms of depression (Gallagher, Rose, Rivera, Lovett, & Thompson, 1989) and anxiety (Anthony-Bergstone, Zarit, & Gatz, 1988). Unfortunately treatment efforts for AD, whether via pharmacological methods or psychosocial interventions have shown very limited success.

With these issues in mind, the only way to effectively help combat the current dementia epidemic is to identify the early risk factors that increase the likelihood of getting the disease. Besides the relationship between depression and dementia onset, which has been a popular research interest area, the relationship between other neuropsychiatric symptoms and dementia risk has been largely understudied. Moreover, despite increasing interest in vascular health and cognition, there is still little known about the association between vascular risk factors and risk for dementia. The findings from the extant literature are largely equivocal with some studies reporting a strong positive association between vascular risk and dementia risk, other studies reporting a negative association, and other studies reporting no association. Also, many studies do not look at the effects of aggregate vascular risk on dementia onset.

The current study is an important first step in bridging the gap between the intersection of mental health, physical health, and the impact on cognition by exploring the association between neuropsychiatric and cardiovascular symptoms and the risk of conversion to MCI and AD. One of the benefits of this approach is that it will enable us to gain knowledge about inherent risk for cognitive decline across the entire cognitive spectrum. Moreover, by exploring neuropsychiatric symptom risk, individual cardiovascular risk factors, and aggregate vascular risk, we will be able to see the relationship between each of these factors independently and dementia risk.

The proposed study will also explore how the APoE-e4 genotype, the strongest known genetic risk factor for AD, modifies the association between neuropsychiatric/vascular risk and dementia onset. This design approach will help further elucidate whether APoE-e4 genetic carriers (compared to non- APoE-e4 carriers) are at a

higher risk of progression to dementia when neuropsychiatric and vascular symptoms are present. The ability to identify which groups may have the highest risk of developing dementia will be particularly beneficial as early treatment of modifiable risk factors in these especially vulnerable populations may have substantial health benefits including the possible delay of cognitive impairment.

Given that neuropsychiatric and vascular risk factors may play a strong role in cognition, the third aim of the present study is to identify which neuropsychological domains seem to be sensitive to the effects of neuropsychiatric and cardiovascular risk among the cognitively normal, MCI, and AD subgroups. Examining whether there are specific areas of cognition affected by neuropsychiatric and vascular risk factors will allow us to learn more about their precise role on brain function and may be an important first step in determining whether treatments designed to improve vascular and neuropsychiatric symptoms result in subsequent improvements in certain areas of cognition. The proposed study will expand the knowledge of current research by helping to delineate which specific risk factors may impact risk for dementia, identifying the groups at higher risk, and further elucidating the effects that these risk factors may have on specific areas of cognition. Exploring these aims holds promise in improving targeted treatment early on for individuals at higher risk of developing dementia and has the potential to delay the progression of cognitive impairment in those who are most vulnerable to cognitive decline.

CHAPTER 3: RESEARCH METHOD

3.1 Participants

The current study is a secondary data analysis of 549 volunteers over the age of 65 from the University of California San Diego Shiley-Marcos Alzheimer's Disease Research Center (ADRC). All participants being seen at the ADRC from the year 2006 and beyond were used in the analysis, as this was the first year that the Neuropsychiatric Inventory (NPI) was routinely administered. Two board-certified staff neurologists independently reviewed data from a clinical evaluation and provided a final clinical diagnosis. If the neurologists disagreed on the diagnosis, a third senior neurologist was consulted and a consensus diagnosis was then reached. Criteria for a diagnosis of MCI included a report of change in cognition (from the patient, a well-known informant, or a skilled clinician), impairment in one or more cognitive domains that is greater than expected for the person's age and educational background, and relatively intact activities of daily living (ADLs) (Albert et al., 2011). A diagnosis of probable AD was given using the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). For the purpose of this study, participants were excluded if they had causes of dementia other than AD, a history of severe head injury, or significant alcohol or substance abuse. This study was approved by the UCSD institutional review board and all participants or their caregivers provided written informed consent to participate after a full explanation of the study protocol (approved by the UCSD Human Research Protection Program).

3.2 Procedure

Through the UCSD ADRC longitudinal cohort study, all participants received a clinical evaluation that included a one-hour neurological exam conducted by a senior ADRC neurologist. Then, in a separate session, a trained psychometrist administered a 2-3-hour comprehensive neuropsychological battery and an ADRC nurse practitioner asked questions about medical history, medication use, current or past alcohol or substance use or abuse, and neuropsychiatric functioning. Laboratory tests and APoE genotyping were also performed on all patients.

3.3. Measures

Neuropsychiatric Risk Factors. Informants rated participants neuropsychiatric functioning using the Neuropsychiatric Inventory Questionnaire (NPI) (Cummings, 1997). The NPI is clinician-administered and asks informants about the presence, frequency, and severity of the following neuropsychiatric disturbances within the past year: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. NPI frequency and severity ratings were multiplied to yield a summary score for each of the 12 symptoms, which were then added together to yield a total NPI score (range: 0-144). This scale has been shown to have good psychometric properties including good reliability and validity, high content validity, high inter-rater reliability (93.6% to 100% for different behaviors), and high test-retest reliability (Cummings, 1997).

Depression. Depression was assessed using the Geriatric Depression Scale (GDS)-short form, a 15-item self-rating questionnaire that has been shown to be a reliable and valid tool to assess depression in the elderly. Higher scores were representative of a greater level of endorsed depressive symptoms (Yesavage & Sheikh, 1986).

Individual Vascular Risk Factors. The following individual vascular risk factors were derived from self-report, medical chart review, and physical examination:

Hypertension: Brachial artery systolic and diastolic blood pressure was measured by an ADRC registered nurse while the patient was seated. Hypertension was defined as untreated systolic blood pressure $\geq$ 140 mm Hg, untreated diastolic blood pressure $\geq$ 90 mm Hg, or use of antihypertensive medication (Bangen et al., 2013). In addition, pulse pressure (defined as systolic pressure minus diastolic pressure) was assessed.

Diabetes: Treated diabetes was defined by self-report or use of insulin or hypoglycemic agents.

Smoking: Smoking status information was obtained by patient self-report. Specifically, patients were asked whether or not they smoked within the last 30 days (current smoker) and whether or not they smoked more than 100 cigarettes in their lifetime (past smoker).

Cholesterol: High cholesterol was defined by self-report or the use of cholesterol-lowering agents (Bangen et al., 2015).

Aggregate Vascular Risk Profile. This study calculated aggregate vascular risk by assigning each of the four vascular risk factors (hypertension, diabetes, smoking status, cholesterol) a value of 0 if absent and 1 if present and summing them up to create a composite score (Bangen et al., 2015; Luchsinger et al., 2005). The number of participants with zero, one, two, three, or all four risk factors was then determined.

APoE-e4 Genotype. Using a standardized lab routine, APoE genotype was determined for all patients from peripheral blood. With this information, patients were dichotomized into two groups based on the presence or absence of one or more APoE-e4 alleles.

Neuropsychological Battery. The ADRC neuropsychological battery was comprised of standardized tests of attention, memory, language, visuospatial skills, executive functioning, and processing speed. The six domains are similar to those outlined in a paper by Bangen and colleagues (2010) (Bangen et al., 2010) and included the following measures: (1) *Attention* was assessed with the Digit span subtest of the Wechsler Memory Scale- Revised (WMS-R) and the Attention subscale of the DRS; (2) *Memory* was measured with the Wechsler Memory Scale-revised Logical Memory Subtest (immediate and delayed free recall) (Wechsler, 1984) and the California Verbal Learning Test (CVLT; Trials 1-5 total recall and long delay recall) (Delis, Kramer, Kaplan, & Thompkins, 1987); (3) *Language* was measured with the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and Letter and Category Fluency (FAS and animal and vegetable categories); (4) *Visuospatial Skills* was assessed through simple and complex constructions on the Block Design subtest of the Wechsler Intelligence Scale for Children-Revised (Wechsler, 1974) and the Construction subscale of the DRS; (5) *Executive Functioning* was measured with the Wisconsin Card Sorting Test (WCST-48 card version; number of perseverative errors) (Nelson, 1976) and Trail Making Test Part B (Reitan & Wolfson, 1985); (6) and lastly *Processing Speed* was assessed with the Trail Making Test Part A (Reitan & Wolfson, 1985) and the Digit Symbol subset of the WAIS-

R (Wechsler, 1981). All of the above tests comprising the domains were transformed into standardized z-scores (mean = 0, SD = 1) using the means and standard deviations of the cognitively normal group at baseline. In addition, the z-scores for the individual tests were averaged to create a summary score for each of the cognitive domains. A total neuropsychological composite score was calculated for individuals who had scores for at least ten out of the fifteen neuropsychological tests by summing all of the z-scores from the individual tests together.

3.4. Data Analytic Plan

Analysis for Aim 1. All statistical analyses were performed using SPSS Statistics version 22 (IBM SPSS Statistics). To examine demographic differences at baseline between the groups that progressed to MCI and AD versus the groups that did not (i.e., stable cognitively normal and MCI groups, respectively), independent t-tests and chi-square tests (or Fisher's exact test if cell sizes are too small) will be conducted. Since we are looking at risk of progression to dementia, all participants who were diagnosed with probable or possible AD at baseline will be excluded for the purposes of this analysis. To calculate risk scores, Cox proportional hazards regression models will be used to estimate hazard ratios (HRs) and 95% CI's. Separate analogous models will be conducted for the MCI converters and the AD converters. Time to event variable will be defined as the time from baseline to either diagnosis of MCI or AD. Participants who are stable in their diagnosis will be right-censored at their last visit. Hazard ratios for each of the following neuropsychiatric and vascular variables will be assessed: individual items of the NPI (i.e.,

presence/absence of each of the 12 symptoms), GDS total score, and each vascular risk factor (hypertension, cholesterol, diabetes, smoking). The statistically significant covariates will then be entered into a multivariate predictor model adjusting for age, sex, and years of education. Using the β coefficients from this model, relative risk ratios for each of these factors will be calculated.

To estimate the impact of severity of neuropsychiatric and vascular risk on risk of conversion to MCI and AD, total neuropsychiatric symptoms (scores ranging from 0-144) and aggregate vascular burden will be included into separate Cox proportional hazard regression models. Furthermore, an NPI x aggregate vascular risk interaction term will be tested for each analysis to help determine if neuropsychiatric symptoms and vascular risk factors have an additive effect on risk of conversion in cognitive status.

Analysis for Aim 2. To explore whether or not the APoE-e4 genotype modifies the association between neuropsychiatric and vascular symptoms and risk of conversion to MCI and AD, interaction terms for all significant covariates from the multivariate predictor model listed in Aim 1 will be applied to Cox proportional hazard ratio models. Specifically, depending on which covariates are significant, the following interaction terms may be tested: Each individual significant symptom from the NPI (out of 12 possible symptoms) x APoE-e4, GDS x APoE-e4, hypertension x APoE-e4, cholesterol x APoE-e4, diabetes x APoE-e4, smoking x APoE-e4, NPI total score x APoE-e4, and vascular burden x APoE-e4. To help correct for multiple comparisons, the Bonferonni correction method will be applied.

Analysis for Aim 3. To identify the neuropsychological domains that seem to be the most sensitive to the effects of neuropsychiatric and vascular risk factors, 145

cognitively normal, 23 MCI, and 296 AD patients who remain unchanged in their diagnosis throughout the duration of the study will be used in the analyses.

To assess longitudinal data, multilevel modeling analyses will be performed separately for the cognitively normal, MCI, and AD groups (with random intercepts included to account for within-subject correlation). Within and between person variables for each of the diagnostic groups will be created for neuropsychiatric and mood measures (total NPI score and GDS score). For the within-person scores, each participant's total NPI or GDS at a given visit will be expressed in terms of deviation from the mean of his or her total NPI or GDS scores across all study visits. This variable will isolate within person change so that change in neuropsychiatric and depressive symptoms can be correlated with change in cognition. For between-person scores, each participant's mean NPI and GDS score across all study visits will be calculated and then that score will be expressed in terms of deviation from the mean of all patients in the same diagnostic group. This will enable us to explore average (long-term) neuropsychiatric and depressive levels and their relation to cognition intercepts over time. These within and between variables will then be entered into a multilevel model analysis with random intercepts and age, education, and either NPI within and between or GDS within and between total scores entered as the fixed effects. Separate analyses will be conducted for each of the following cognition variables: Attention, Memory, Language, Visuospatial Skills, Executive Functioning, Processing Speed, and a Neuropsychological Composite Score (which includes summed z-scores for individuals that have at least 10/15 of the tests) to explore whether age, education, and neuropsychiatric and depressive symptoms explain within or between differences in cognitive performance. Due to the exploratory nature of

this aim and the large number of comparisons, the False Discovery Rate procedure (Benjamini & Hochberg, 1995) will be used to help minimize the risk of Type I error.

The exact same procedure outlined above will be used to assess how vascular burden correlates with change in cognition within cognitively normal, MCI, and AD subgroups. In particular, each patient will be coded as having 0, 1, 2, 3, or all 4 vascular risk factors and within and between variables will be created for the vascular burden factor for each diagnostic group (cognitively normal, MCI, and AD). Separate analyses will be conducted for each of the cognitive domains and the neuropsychological composite score.

CHAPTER 4: RESULTS

4.1 Descriptive Statistics

For the first analysis, 149 cognitively normal individuals, 25 individuals who remained MCI throughout their enrollment in the study, 22 individuals who converted to MCI, and 57 individuals who converted to AD were included. The mean average time of follow-up was 4.61 years (SD = 2.43). Group differences in baseline demographics can be seen in Table 1. As a whole, the sample was mostly Caucasian and highly educated (mean years of education for all groups was greater than 14 years). The full sample generally endorsed a low number of mean aggregate vascular risk factors and total neuropsychiatric symptoms. Neuropsychiatric Inventory data at baseline was missing for 9 normal controls, 3 MCI converters, 1 individual that stayed MCI, and 5 AD converters.

Compared to normal controls, the MCI converters were older at baseline (mean age 79.91 versus 74.12, $p = 0.002$) and more racially diverse ($p = 0.046$). For the variable of race (Caucasian versus Non-Caucasian), Fisher's exact tests were used instead of chi-square tests due to small cell sizes. Compared to individuals that stayed MCI, AD converters were older (mean age 79.49 versus 74.48, $p = 0.015$), had a larger proportion of females ($p = 0.034$), and endorsed less motor disturbance at baseline ($p = 0.001$).

4.2 Survival Analysis (Aim 1)

Risk of MCI. There were 22 individuals who converted to MCI during the study. After adjusting for age, sex, and education, apathy at baseline was found to significantly

increase the risk of MCI (p = 0.017). Importantly, however, there was a power issue on this particular covariate in that only four individuals endorsed having apathy, one of which converted to MCI. Therefore, the results of this finding should be considered preliminary and interpreted with caution. Vascular risk factors, depression, anxiety, disinhibition, irritability, and nighttime and appetite disturbance were not associated with increase risk of MCI. Moreover, there was no significant interaction effect of neuropsychiatric symptoms and vascular risk on MCI conversion (HR = 1.123, 95%CI [0.929, 1.359], p = 0.230). A summary of HRs can be seen in Table 2. Since none of the MCI converters endorsed having diabetes, currently smoking, delusions, hallucinations, agitation, elation, or motor disturbance, hazard ratios could not be calculated for these variables.

Risk of Incident AD. There were 57 individuals that converted to AD during the course of the study. After adjusting for age, sex, and education, agitation and total scores on the GDS at baseline were found to significantly increase the risk of AD. At baseline, there were twelve people that endorsed the presence of agitation, 11 of which converted to AD. According to the model, individuals that endorsed agitation were more than two times as likely to convert to AD (HR = 2.118, 95% CI [1.062, 4.226], p = 0.033). In addition, for every one-point increase on the GDS, risk of conversion to AD increased by 11%. Since scores greater than or equal to 5 on the GDS-15 item scale have been used to indicate depression (Almeida & Almeida, 1999), depression was also recoded into a categorical variable where scores less than 5 were coded 0 and scores greater than or equal to 5 were coded 1. Using this categorical GDS variable, individuals that endorsed at least mild depression (scores $\geq$ 5) were almost 2.5 times as likely to convert to AD (HR =

2.481, 95%CI [1.163, 5.294], p = 0.019) compared to individuals who did not endorse depression. Survival plots for agitation and categorical depression can be seen in Figures 1 and 2.

When entered into a multivariate predictor model (continuing to adjust for age, sex, and education), both agitation and GDS (linear variable) remained significant (HR = 2.289, 95%CI [1.140, 4.593], p = 0.020 and HR = 1.124, 95%CI [1.021, 1.238], p = 0.017, respectively). Vascular risk factors, depression as assessed using just the presence/absence question on the NPI, anxiety, disinhibition, irritability, and nighttime and appetite disturbance were not associated with increase risk of AD. Moreover, there was no significant interaction effect of neuropsychiatric symptoms and vascular risk on AD conversion (HR = 0.986, 95 % CI [0.942, 1.032], p = 0.542). A summary of HRs can be seen in Table 3. None of the AD converters endorsed elation or motor disturbance, therefore hazard ratios could not be calculated for these variables.

4.3 APoE-e4 Interactions (Aim 2)

The next aim of this study was to examine whether the presence of at least one APoE-e4 genotype moderated the association between the significant neuropsychiatric covariates from the multivariate predictor models in Aim 1 and risk of conversion to MCI and AD.

Of those individuals that converted to MCI, 8 (36.4%) had at least one APoE-e4 allele (2 of these individuals had two e4 alleles). Since only apathy was a significant predictor of conversion to MCI, and so few individuals endorsed apathy, an interaction between apathy and APoE-e4 could not be tested.

Of the individuals that converted to AD, 28 (50%) had at least one APoE-e4 allele (6 individuals had two e4 alleles). One of the individuals that converted to AD was missing genotype data. There were no significant interactions between Agitation x APoE-e4 (HR = 0.454, 95%CI [0.109, 1.896], p = 0.279) or between GDS x APoE-e4 (HR = 1.078, 95%CI [0.881, 1.318], p = 0.467). Therefore, our findings suggest that the APoE-e4 genotype did not significantly moderate the effect of agitation and depression on AD conversion rate.

4.4 Multilevel Modeling Analysis (Aim 3):

To examine whether neuropsychiatric symptoms or vascular risk factors may be associated with cognition over time, multilevel model analyses were performed for 145 cognitively normal, 23 MCI patients, and 296 AD patients who remained stable in their diagnosis throughout their enrollment in the study. Demographic characteristics of each of these three diagnostic groups can be seen in Table 4. In general, cognitively normal participants were younger and endorsed fewer neuropsychiatric and depressive symptoms at baseline relative to the MCI and AD groups. Age and education were used as covariates when conducting all of the within and between group analyses. Since there were multiple models being tested, the adjusted p-value of 0.002 and below was considered statistically significant using the False Discovery Rate procedure by Benjamini and Hochberg (Benjamini & Hochberg, 1995) to help correct for Type 1 error.

Within and Between Participant Differences for Cognitively Normal Group over time

Neuropsychiatric Symptoms. As shown in Table 5a, within-person change in neuropsychiatric symptoms (as assessed by the NPI) in cognitively normal participants was not associated with cognitive performance on measures of attention, memory, language, visuospatial skills, executive functioning, processing speed, or overall cognition. Furthermore, there were no significant differences over time between cognitively normal participants with higher versus lower mean levels of neuropsychiatric symptoms on any of the six cognitive domains or on an overall neuropsychological composite score.

Depression. The association between depressive symptoms and cognition within the cognitively normal group was also examined. A significant negative relationship was found within patients when looking at severity of depression (as assessed by the GDS) and memory and executive functioning. In other words, within-person increases in depressive symptoms were significantly related to decreases on memory (B = -0.068, S.E. = 0.022, t = -3.133, p = 0.002, 95% CI [-0.111, -0.025]) and executive functioning performance (B = -0.065, S.E. = 0.021, t = -3.124, p = 0.002, 95% CI [-0.107, -0.024]) (see Table 6).

Between-participant depression (which represents each cognitively normal individual's overall mean level of depression across the total number of assessments completed compared to the mean of the cognitively normal group) was not found to be a significant predictor of change in cognitive functioning (Table 5b).

Aggregate Vascular Risk. Changes within cognitively normal individuals on vascular risk factors was also not associated with significant changes in cognition.

Moreover, there were no statistical cognitive changes found between cognitively normal participants with higher versus lower mean levels of vascular risk factors across time (see Table 5c).

Within and Between Participant Differences for the MCI Group over time

Neuropsychiatric Symptoms. As shown in Table 6a, within-person change in neuropsychiatric symptoms in MCI participants did not impact cognitive performance over time. Furthermore, there were no significant differences between MCI participants with higher versus lower mean levels of neuropsychiatric symptoms over time on any of the six cognitive domains or on an overall neuropsychological composite.

Depression. Within-person change and between-participant levels of depressive symptoms also did not impact cognitive performance in patients with MCI (Table 6b).

Aggregate Vascular Risk. Changes within MCI individuals on vascular risk factors was not associated with significant changes in cognition. Moreover, there were no statistical cognitive changes found between MCI individuals with higher versus lower mean levels of vascular risk factors (see Table 6c).

Within and Between Participant Differences for the AD Group over time

Neuropsychiatric Symptoms. Within-person change in neuropsychiatric symptoms in AD patients impacted several cognitive domains (see Table 7a). Specifically, higher levels of neuropsychiatric symptoms within patients was significantly associated with worse performance on measures of attention (B = -0.057, S.E. = 0.009, t = -6.191, $p < 0.001$, 95% CI [-0.075, -0.039]), language (B = -0.016, S.E. = 0.003, t = -5.109, $p > 0.001$, 95% CI [-0.023, -0.010]), visuospatial skills (B = -0.021, S.E. = 0.004, t

= -4.583, p < 0.001, 95% CI [-0.029, -0.012]), and processing speed (B = -0.027, S.E. = 0.006, t = -4.544, p < 0.001, 95% CI [-0.039, -0.015]).

Between-participant change in neuropsychiatric symptoms in AD patients was a significant predictor of executive functioning (Table 7a). Specifically, AD patients with higher levels of neuropsychiatric symptoms across time performed significantly worse on tests of executive functioning (B = -0.048, S.E. = 0.015, t = -3.198, p = 0.002, 95% CI [-0.077, -0.018]) relative to AD patients with lower levels of neuropsychiatric symptoms.

Depression. Within patient fluctuations over time and the average long-term effect of depressive symptoms between AD patients was not associated with significant changes in cognition (see Table 7b).

Aggregate Vascular Risk. Changes within AD patients on vascular risk factors was also not associated with significant changes in cognition. Moreover, there were no statistical cognitive changes found between AD individuals with higher versus lower mean levels of vascular risk factors across time (see Table 7c).

CHAPTER 5: DISCUSSION

One of the major challenges in studying AD is finding important risk factors and intervening before the disease process is well underway. Therefore, this study sought to explore whether premorbid neuropsychiatric and vascular factors (both of which have the potential to be modifiable) may be associated with increased risk of MCI and AD. In addition, because APoE-e4 has been widely recognized as an established genetic risk factor for AD, this study investigated whether there was an interaction between APoE-e4 and significant neuropsychiatric and vascular symptoms in predicting the outcome of MCI or incident AD. Finally, as a more exploratory aim, this study evaluated whether neuropsychiatric symptoms and cardiovascular risk factors were associated with specific cognitive changes across time in cognitively normal, MCI, and AD patients.

Overall, results indicated that apathy at baseline significantly increased risk of progression to MCI. However, due to the fact that so few cognitively normal individuals in our study endorsed apathy at baseline (i.e., only 4 individuals, one of which converted to MCI), these results should be considered preliminary until they are further corroborated by future studies with larger, more symptomatic samples of individuals. Despite the small number of apathy reports in our study, however, this finding does seem to be consistent with other studies highlighting the importance of identifying apathy as a risk factor for future cognitive decline. For example, in a population based study of 1,587 cognitively normal individuals who underwent at least one follow-up visit, Geda and colleagues reported that individuals with apathy were more than 2x at risk of progressing to MCI (HR = 2.26; 95% CI = 1.49-3.41) (Geda et al., 2014). In this study, which also measured baseline neuropsychiatric symptoms using the informant-based NPI, 57

individuals had apathy at baseline, 25 of which progressed to MCI (Geda et al., 2014). Furthermore, a longitudinal study using the Clinical Dementia Rating scale and data from the Alzheimer's Disease Neuroimaging Initiative found apathy to be associated with greater current and future global functional impairment in normal controls (as well as patients with MCI and mild AD) (Wadsworth et al., 2012). Moreover, apathy has recently been associated with lower thickness of the inferior temporal cortex in both cognitively normal and MCI individuals, suggesting that apathy-associated atrophy may begin during the preclinical stages of AD (Guercio et al., 2015). Taken together, although our study lacked power on the apathy item due to a low number of reported apathy events, our findings in combination with the larger literature suggest that more accurate detection of apathy in cognitively normal individuals may help facilitate more accurate detection of possible risk for MCI.

This study also found that individuals with baseline agitation were more than two times as likely to convert to AD and for every one point increase on the GDS, risk of conversion to AD increased by 11%. Furthermore, when the GDS was recoded into a categorical variable comparing patients with at least mild depression to patients without depression, individuals with at least mild depression were almost 2.5 times as likely to convert to AD. Of note, while the GDS was significantly associated with increased risk of progressing to AD, the depression domain of the NPI in this study did not show any association. This is consistent with other studies (Rosenberg et al., 2013), and likely reflects the higher sensitivity of the GDS instrument to detect depression compared to the one-item screener on the NPI which does not assess for vegetative symptoms, social withdrawal, or psychomotor retardation aspects of depression. Recently, a large

population based study of 332 patients with MCI found results similar to those reported in this study in that baseline agitation and depression significantly increased risk of incident dementia (Pink et al., 2015). Meta-analyses and additional cohort studies have also supported the strong link between depression and increased risk of AD (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby et al., 2006; Teng, Lu, & Cummings, 2007), with some researchers reporting that depressed patients with a poor response to antidepressants (Modrego & Ferrandez, 2004) and patients with multi-domain MCI (as opposed to amnestic MCI) show an even greater risk of conversion to AD (Gabryelewicz et al., 2007).

Inconsistent with other studies, this study did not find a significant association between baseline apathy and risk of AD (although as reported above, it did find apathy to be a risk factor for MCI) (Palmer et al., 2010; Pink et al., 2015; Teng et al., 2007; Chilovi et al., 2009). This discrepancy in findings could be due to methodological differences, such as our smaller sample size, which limited power. Furthermore, some studies with significant apathy findings limited their sample to only amnestic MCI patients (Palmer et al., 2010) or used a different assessment tool to assess apathy than the one item on the NPI (e.g., Marin's diagnostic criteria) (Vicini Chilovi et al., 2009).

The present study also did not find an association between any cardiovascular risk factor or aggregate cardiovascular risk and progression to AD. A recent meta-analysis synthesizing evidence from 76 eligible articles corroborated these null findings reporting that hypertension, smoking (when controlling for age), and high cholesterol do not seem to be associated with risk of conversion from MCI to all-cause dementia (diabetes in this meta-analysis, including prediabetes was associated with increased risk of conversion)

(Cooper, Sommerlad, Lyketsos, & Livingston, 2015). However, these results are inconsistent with several other review papers (de Bruijn & Ikram, 2014; Fillit, Nash, Rundek, & Zuckerman, 2008; Rosendorff, Beeri, & Silverman, 2007), which document a strong relationship between cardiovascular risk and AD risk.

Part of the reason for these conflicting findings could be due to the variability and complexity of how vascular risk is defined across studies. For example, cholesterol alone can be defined by self-report, the use of cholesterol-lowering medications, total cholesterol levels, or low-density lipoprotein (LDL) levels. Also, an increasing amount of studies are highlighting the importance of *midlife* cardiovascular risk factors and risk of dementia, rather than late-life cardiovascular risk factors, which occur far more frequently and may have less damaging long-term effects (Kivipelto et al., 2001; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). Adding to this complexity is the effect of pharmacological treatment and risk of AD with some studies showing a reduced rate of AD in statin users (Jick, Zornberg, Jick, Seshadri, & Drachman, 2000) and antihypertensive users (Johnson et al., 2012) and other studies finding no reduction in dementia risk based on taking medications used to control vascular risk factors (Peters & Beckett, 2009; Zhou, Teramukai, & Fukushima, 2007).

Contrary to the *a priori* hypothesis of our second aim, the APoE-e4 genotype did not moderate the association between significant neuropsychiatric symptoms such as agitation and depression and risk of conversion to AD. Previous reports have found significant additive interactions between neuropsychiatric symptoms such as apathy, depression, and psychosis and APoE-e4 in increasing the risk of MCI and incident

dementia (Geda et al., 2006; Pink et al., 2015), however these same studies did not show significant multiplicative interactions.

Unfortunately, interactions in the present study could not be tested for vascular risk factors and conversion to MCI or AD due to the lack of significant associations on these variables in our sample. Despite this study's inability to tests these interactions in predicting the outcome of dementia, there is evidence that the presence of the APoE-e4 allele increases risk of not only AD, but also atherosclerotic complications and predisposition to coronary artery disease (Davignon, Gregg, & Sing, 1988). Moreover, in the Honolulu Asia Aging Study, a larger concentration of neurotic plaques and neurofibrillary tangles were found in participants with diabetes who carried the APoE-e4 allele compared to those who did not have either risk factor (Peila et al., 2002). More research is needed to test whether neuropsychiatric symptoms and vascular risk factors interact to increase AD risk. The outcomes of these findings may have great clinical relevance as high-risk subgroups can be identified and improved screenings and interventions can take place to provide high-risk individuals with the opportunity to take actions in preclinical phases to help mitigate cognitive decline.

For the third aim of the study, it was hypothesized that greater neuropsychiatric scores would be associated with lower scores in cognition and would have a larger net impact on the cognitively normal group, relative to the MCI and AD groups. This hypothesis was partially confirmed by the results of this study. While overall neuropsychiatric symptom scores did not significantly impact cognition for the cognitively normal participants, higher reports of depressive symptoms within cognitively normal participants was associated with worse memory and executive

functioning performance. This finding may be clinically meaningful for future intervention studies, as the majority of the cognitively normal sample in the present study was not clinically depressed (at baseline, only 4.8% (n = 7) had GDS scores $\geq$ 5), yet still showed worse cognitive performance over time when they endorsed higher than their own average level of depression. In other words, cognitively normal individuals feeling "more depressed than their respective average" may want to be mindful that their mood may impact their cognitive functioning. Both pharmacological and non-phamacological interventions targeting depression have been associated with improvements in cognition (Baune & Renger, 2014)

Other studies have also found depression in older adults to be associated with worse performance on memory and executive functioning tasks (McDermott & Ebmeier, 2009; Reppermund et al., 2011). Some possible explanations for the origin of these deficits was provided by a review paper by Porter et al (2007) (Porter, Bourke, & Gallagher, 2007) which maintained that higher depression involves a reduction on motivation for tasks that involve effortful processing (such as working memory tasks), as well as frontostriatal-limbic dysfunction which can impact executive functioning, particularly in the elderly.

Unlike the cognitively normal sample, it is interesting that greater depression and neuropsychiatric symptoms did not impact cognition in the present study's MCI sample. This could be due to a small sample size of MCI patients that remained unchanged in diagnosis throughout the study or due to the generally low level of reported depressive symptomatology [(prior reports have reported that 36%-63% of patients with MCI suffer from depression (Palmer et al., 2007; Solfrizzi et al., 2007), whereas at baseline, only

4.3% of the MCI patients that stayed MCI in our study had scores ≥5 on the GDS)]. Also, the neuropsychological tests in this study were divided into cognitive domains based on previous studies and the opinion of practicing neuropsychologists. However, there is still some debate regarding what particular brain function is being assessed by each individual neuropsychological test, as there is much overlap and each cognitive test reasonably taps into a number of different complex cognitive processes.

Within AD patients, increased levels of neuropsychiatric symptoms were associated with worse cognitive functioning across a broad range of cognitive domains including attention, language, visuospatial skills, and processing speed. Moreover, between patients, higher average long-term neuropsychiatric symptoms was associated with accelerated cognitive decline in executive functioning. The temporal sequence of these associations and differentiating between cause and effect is complicated, as it is unknown whether worsened neuropsychiatric symptoms lead to cognitive decline in AD patients or if cognitive decline as a result of AD leads to worsened neuropsychiatric symptoms. Pharmacological treatments used to treat major psychiatric disorders (e.g., depression, psychosis) have shown limited efficacy and can have adverse side effects (Gauthier et al., 2010; Irizarry et al., 1999). However, systematic reviews have shown that nonpharmacological or psychosocial interventions (e.g., aromatherapy, psychoeducation, teaching caregivers and staff how to change their interactions with patients) can be effective in reducing behavioral and neuropsychiatric symptoms in persons with dementia (Brodaty & Arasaratnam, 2012; Livingston, Johnston, Katona, Paton, & Lyketsos, 2005; O'Connor, Ames, Gardner, & King, 2009). One recent study found that music therapy in patients with mild-moderate Alzheimer’s disease resulted in

significant improvement in several neuropsychiatric symptoms as well as memory and orientation (Gomez Gallego & Gomez Garcia, 2016). In clinical or research contexts, when working with patients with AD that have a large number of neuropsychiatric symptoms, it will be important for providers to recognize that these individuals may have more pronounced cognitive deficits. It will also be important for future studies to explore whether reduction in neuropsychiatric symptoms may result in subsequent improvements in cognitive performance in patients with AD.

Contrary to our hypotheses, vascular risk did not appear to predict worse cognition in cognitively normal, MCI, or AD patients. This is contrary to several prior cross-sectional (Wolf, D'Agostino, Belanger, & Kannel, 1991) and longitudinal reports (Elias et al., 2004; Kaffashian, Dugravot, Elbaz, et al., 2013). For example, Jefferson et al. (2015) (Jefferson et al., 2015) found that vascular risk was associated with worse cognitive trajectory, especially in global functioning, naming, and processing speed among normal control elderly. Kaffashian et al., (2013) also demonstrated that higher vascular risk scores were associated with greater cognitive decline over a 10-year period (Kaffashian, Dugravot, Brunner, et al., 2013). Part of the reason the current study did not have similar findings could be due to methodical differences in how vascular risk was defined. The Jefferson and Kaffashian studies both used a Framingham Stroke Risk Profile composite score, whereas the present study calculated an aggregate score based on the presence of four vascular risk factors. Also, many of the vascular risk factors in the current study were being controlled by medication (i.e., at baseline, 88.4% of individuals that self-reported hypertension were on anti-hypertensive medication, 77.6% of individuals that self-reported high cholesterol were on cholesterol lowering drugs, and

83.8% of the individuals that self-reported diabetes were on diabetes medication). It is unknown how medication factors such as medication compliance, duration of time medication is used, and the type of drug class an individual is prescribed may impact cognitive outcomes (e.g., antihypertensive angiotensin receptor blockers and calcium channel blockers have been found to lower dementia risk more than beta-blockers) (Johnson et al., 2012; Rouch et al., 2015). Furthermore, our non-significant findings could be due to the generally low frequency of very elevated cardiovascular risk factors reported in our study (none of the cognitively normal participants had all 4 vascular risk factors and only 6% had 3 vascular risk factors, none of stable MCI patients had more than 2 vascular risk factors, and only 1 AD patient had all four risk factors and 6% had 3 vascular risk factors). It should be noted that this last aim of the study is exploratory. Replication in larger longitudinal prospective studies is warranted to help reconcile differences in study findings and to further parse out whether *individual* neuropsychiatric and cardiovascular risk factors, rather than just composite/aggregate scores, may be associated with cognitive changes across time.

5.1. Strengths and Limitations

This study has several notable strengths. First, this study included individuals spanning the entire cognitive spectrum from cognitively normal to the advanced stages of Alzheimer's disease. One of the benefits of this approach is that it allowed changes in diagnostic status to be captured, with all diagnostic determinations being made by board-certified senior neurologists with expertise in MCI and AD. Another advantage of the study design is that it allowed for the examination of a broad range of neuropsychiatric

and vascular risk factors, and in addition to looking at each individual risk factor and risk of progression to MCI and AD, also explored the complex relationship between multiple neuropsychiatric/vascular risk factors and change in cognitive status. In addition, the longitudinal design enabled investigation of the associations between neuropsychiatric/vascular risk factors and cognitive trajectories across time both within and between patients. One benefit of this latter approach is that it provided some insight into the relationship between neuropsychiatric/vascular health and cognitive prognoses.

Despite these strengths, this study also has several limitations that must be acknowledged. To assess neuropsychiatric symptoms, the NPI was administered to an informant (primarily a spouse), to assess the presence/absence of neuropsychiatric symptoms within the preceding year. Although this instrument has been validated for evaluating psychopathology in dementia, to our knowledge, this instrument has not been validated in cognitively normal individuals or MCI individuals, and may not be as sensitive to capturing neuropsychiatric changes within these groups. Additionally, the Geriatric Depression Scale, a valid self-report measure for depression among more cognitively intact older adults, has been shown to lose its validity when administered to patients with Alzheimer's disease (Burke, Houston, Boust, & Roccaforte, 1989). To define "vascular risk", this study included individuals who had vascular risk factors irrespective of whether or not they were on medications to help treat the risk factors. This was consistent with how previous studies have defined vascular risk (Pilotto et al., 2016; Schneider et al., 2015). Vascular risk was also defined this way because medications are not always effective at treating risk factors, and there is a high likelihood that these risk factors were untreated for some time prior to being identified, which could have resulted

in vascular damage. There are, however, several limitations to assessing vascular risk in this way including not knowing the duration of time patients were exposed to untreated hypertension, cholesterol, and diabetes prior to being put on medication as well as not knowing the severity of each condition which may have a larger negative impact on cognition than just having the presence of the risk factor. It is also important to note that as is the case for all survival analyses, subjects were right-censored if they did not experience a change in diagnostic status for the duration of the time that they were in the study. It is reasonable to suspect that some participants experienced cognitive changes after they stopped participating in the study, however there is unfortunately no method to obtain this information without additional contact. It should also be noted that the current sample was predominantly Caucasian with high levels of education; therefore the findings from this study may not necessarily generalize to other studies using more diverse samples.

5.2 Conclusions and Areas for Further Research

More and more research is coming to light suggesting that dementia may be preceded by a long asymptomatic prodromal phase (Sperling et al., 2011). Although neuropsychiatric symptoms have received less attention than other traditional hallmarks of dementia risk (genetics, neurofibrillary tangles, CSF or imaging markers of amyloid deposition), our study found that apathy, and agitation and depression at baseline are associated with increased risk of future MCI and AD, respectively. As such, clinicians may want to be alert to individuals presenting with cognitive complaints and new neuropsychiatric symptoms, as early establishment of an appropriate treatment for

neuropsychiatric symptoms may have the potential to intervene on neural pathways, thereby reducing the risk for or delaying the progression of MCI or AD. It remains unknown whether neuropsychiatric symptoms independently contribute to the underlying cause of dementia or whether they offer an earlier view of emerging prodromal pathology.

Our study did not find cardiovascular risk factors to be a significant predictor of change in cognitive status, however vascular risk was assessed via self-report or the use of medications to treat vascular risk. Better specification of a mechanistic model for how vascular risk factors may lead to cognitive changes may be warranted as it is possible that the currently used vascular measures in our study may not be sensitive enough to predict dementia, but these measures in combination with neuroimaging, neurochemical biomarkers, plaque index, etc. could more accurately predict conversion to dementia. For example, Buratti et al., (2015) recently found that risk of conversion from MCI to dementia was better qualified by assessment of atherosclerotic changes in the carotid artery (plaque index, intima-media thickness) and breath-holding index (to assess cerebrovascular impairment) than classical vascular risk factors (diabetes, hypertension, obesity and smoking) (Buratti et al., 2015). Future studies that capture baseline "vascular risk" using more objective measures such as those described above or through, for example, cholesterol and hemoglobin A1c levels derived from hematology reports, are clearly warranted and would add a great deal to the existing literature. Also, future studies investigating not only neuropsychiatric and cardiovascular but also other putative risk factors for MCI and AD including but not limited to factors such as chronic stress, disruption of brain metabolism, and early abnormal neuroimaging findings may be of

further benefit to the field. It is also clear that further study is required examining the role of neuropsychiatric and CVD risk factor management in the prevention of dementia. More specifically, there is a great need for large, well-designed multicenter randomized controlled trials to investigate whether successful modification of neuropsychiatric and cardiovascular risk factors alters cognitive trajectories in cognitively normal, MCI, and dementia populations.

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TABLES AND FIGURES

Table 1. *Demographic Differences at Baseline Between Cognitively Normal Participants and MCI Converters and Between Stable MCI Participants and AD Converters*

	Cognitively Normal (n=149)	MCI converters (n=22)	t or X^2	Stayed MCI (n=25)	AD Converter (n=57)	t or X^2
Age	74.12 (8.30)	79.91 (6.67)	t (169) = -3.124; **p = 0.002***	74.48 (7.39)	79.49 (8.83)	t (80) = -2.480; p = **0.015***
Education mean years (SD)	15.46 (3.22)	14.82 (3.65)	t (169) = 0.861; p = 0.390	16.16 (3.35)	14.84 (3.57)	t (80) = 1.567; p = 0.121
Sex n (% female)	97 (24.2%)	10 (45.5%)	$X^2(1) = 3.159$; p = 0.075	9 (36.0%)	35 (61.4%)	$X^2(1) = 4.510$; p = **0.034***
Ethnicity n (% Hispanic)	41 (27.5%)	6 (27.3%)	$X^2(1) = 0.001$; p = 0.981	1 (4.0%)	8 (14.0%)	$X^2(1) = 1.791$; p = 0.181
Race n (% Caucasian)	145 (97.3%)	19 (86.4%)	Fisher's exact**, p = 0.046***	25 (100.0%)	56 (98.2%)	Fisher's exact, p = 0.999
Systolic BP mean (SD)	129.27 (14.86)	129.09 (16.64)	t(165) = 0.052; p = 0.959	132.52 (18.25)	131.82 (17.60)	t (80) = 0.163; p = 0.871
Diastolic BP mean (SD)	75.55 (9.50)	71.41 (9.11)	t(165) = 1.916; p = 0.057	72.36 (9.98)	75.16 (9.93)	t (80) = -1.173; p = 0.244
Pulse Pressure mean (SD)	53.72 (13.09)	57.68 (15.00)	t (165) = -1.298; p = 0.196	60.16 (16.20)	56.67 (17.75)	t (80) = 0.842; p = 0.402
Cholesterol n (% yes)	76 (51.0%)	12 (54.5%)	$X^2(1) = 0.096$; p = 0.822	18 (72.0%)	32 (56.1%)	$X^2(1) = 1.837$; p = 0.175
Diabetes n (% yes)	9 (6.0%)	0 (0.0%)	$X^2(1) = 1.403$; p = 0.236	1 (4.0%)	3 (5.3%)	$X^2(1) = 0.060$; p = 0.807
Aggr. CVD Risk mean (SD)	1.30 (0.83)	1.18 (0.73)	t(169) = 0.610; p = 0.543	1.64 (0.64)	1.39 (0.86)	t (80) = 1.323; p = 0.190
Current smoker n (% yes)	5 (3.4%)	0 (0.0%)	$X^2(1) = 0.760$; p = 0.383	0 (0.0%)	1 (1.8%)	$X^2(1) = 0.444$; p = 0.505
NPI total mean (SD)	2.24 (5.20)	3.21 (9.90)	t(157) = -0.672; p = 0.502	6.67 (9.20)	6.44 (10.85)	t (74) = 0.088; p = 0.930
GDS total mean (SD)	1.11 (1.87)	1.14 (1.28)	t(169) = -0.054; p = 0.957	1.76 (1.92)	2.42 (2.68)	t (80) = -1.113; p = 0.269
Delusions n (% yes)	0 (0.0%)	0 (0.0%)	N/A	1 (4.2%)	3 (5.8%)	$X^2(1) = 0.085$; p = 0.771
Hallucinations n (% yes)	1 (0.7%)	0 (0.0%)	$X^2(1) = 0.137$; p = 0.712	0 (0.0%)	1 (1.9%)	$X^2(1) = 0.468$; p = 0.494
Agitation n (% yes)	10 (7.1%)	0 (0.0%)	$X^2(1) = 1.448$; p = 0.229	1 (4.2%)	11 (21.2%)	$X^2(1) = 3.564$; p = 0.059
Depression n (% yes)	20 (14.3%)	2 (10.5%)	$X^2(1) = 0.198$; p = 0.656	5 (20.8%)	12 (23.1%)	$X^2(1) = 0.048$; p = 0.827
Anxiety n (% yes)	15 (10.7%)	2 (10.5%)	$X^2(1) = 0.001$; p = 0.980	5 (20.8%)	8 (15.4%)	$X^2(1) = 0.344$; p = 0.558
Elation n (% yes)	0 (0.0%)	0 (0.0%)	N/A	0 (0.0%)	0 (0.0%)	N/A
Apathy n (% yes)	3 (2.1%)	1 (5.3%)	$X^2(1) = 0.664$; p = 0.415	4 (16.7%)	7 (13.5%)	$X^2(1) = 0.136$; p = 0.712
Disinhibition n (% yes)	5 (3.6%)	1 (5.3%)	$X^2(1) = 0.132$; p = 0.717	1 (4.2%)	3 (5.8%)	$X^2(1) = 0.085$; p = 0.771
Irritability n (% yes)	14 (10.0%)	3 (15.8%)	$X^2(1) = 0.587$; p = 0.443	5 (20.8%)	16 (30.8%)	$X^2(1) = 0.811$; p = 0.368
Motor Disturb. n (% yes)	0 (0.0%)	0 (0.0%)	N/A	5 (20.8%)	0 (0.0%)	$X^2(1) = 11.596$ p = **0.001***
Nighttime Disturb. n (% yes)	16 (11.4%)	2 (10.5%)	$X^2(1) = 0.014$; p = 0.907	4 (16.7%)	10 (19.2%)	$X^2(1) = 0.072$; p = 0.789
Appetite Changes n (% yes)	6 (4.3%)	2 (10.5%)	$X^2(1) = 1.364$; p = 0.243	3 (12.5%)	4 (7.7%)	$X^2(1) = 0.454$; p = 0.500

*p <0.05

Table 2. *Risk of MCI by Vascular and Neuropsychiatric Symptoms*

Vascular or Psychiatric Variable	HR (95% CI)[a]	p-value
Hypertension or Antihypertensive Use	0.477 (0.189, 1.200)	0.116
Pulse Pressure	1.004 (0.974, 1.034)	0.821
High Cholesterol or on Cholesterol Meds	1.338 (0.562, 3.188)	0.510
Depression	1.067 (0.230, 4.952)	0.934
Anxiety	1.959 (0.424, 9.049)	0.389
Apathy	17.653 (1.681, 185.373)	**0.017***
Disinhibition	3.986 (0.448, 35.468)	0.215
Irritability	1.665 (0.455, 6.089)	0.441
Nighttime Disturbance	1.019 (0.224, 4.626)	0.981
Appetite Disturbance	2.666 (0.601, 11.821)	0.197
NPI Total	1.052 (0.993, 1.115)	0.088
GDS Total	1.058 (0.883, 1.344)	0.643
Aggregate Vascular Risk	0.794 (0.456, 1.381)	0.413

Abbreviations: HR = hazard ratio; CI = confidence interval; Meds = medications; NPI = Neuropsychiatric Inventory; GDS = Geriatric Depression Scale

[a] Adjusted for age, sex, and education

*$p<0.05$

Table 3. *Risk of Incident AD by Vascular and Neuropsychiatric Symptoms Comparing Stable MCI (n = 22) to AD Converters (n = 57)*

Vascular or Psychiatric Variable	HR (95% CI)[a]	p-value
Hypertension or Antihypertensive Use	0.907 (0.468, 1.761)	0.774
Pulse Pressure	0.992 (0.976, 1.008)	0.321
High Cholesterol or on Cholesterol Meds	0.833 (0.472, 1.471)	0.529
Diabetes	1.681 (0.490, 5.762)	0.409
Current Smoker	3.818 (0.480, 30.393)	0.206
Delusions	0.687 (0.211, 2.239)	0.533
Hallucinations	1.064 (0.140, 8.111)	0.952
Agitation	2.118 (1.062, 4.226)	**0.033***
Depression	0.743 (0.376, 1.466)	0.391
Anxiety	1.035 (0.480, 2.230)	0.930
Apathy	1.100 (0.456, 2.654)	0.832
Disinhibition	0.773 (0.234, 2.556)	0.673
Irritability	1.904 (0.994, 3.647)	0.052
Nighttime Disturbance	0.921 (0.443, 1.915)	0.826
Appetite Changes	0.815 (0.247, 1.915)	2.684
NPI Total	1.003 (0.977, 1.029)	0.839
GDS Total	1.111 (1.007, 1.227)	**0.037***
Aggregate Vascular Risk	0.964 (0.682, 1.363)	0.836

Abbreviations: HR = hazard ratio; CI = confidence interval; Meds = medications; NPI = Neuropsychiatric Inventory; GDS = Geriatric Depression Scale

[a] Adjusted for age, sex, and education

*$p<0.05$

Table 4. *Demographic Characteristics, Severity of Symptoms, and Overall Premorbid Cognitive Functioning at Baseline by Diagnosis*

Variable	CN (n = 145)	MCI (n = 23)	AD (n = 296)
Age (years)	73.97 (8.02)	74.91 (7.29)	76.12 (8.59)
Education (years)	15.57 (3.11)	16.22 (3.33)	14.56 (3.67)
Gender (n, % female)	94 (64.8%)	10 (43.5%)	150 (50.7%)
Race (n, % Hispanic)	38 (26.2%)	0 (0.0%)	49 (16.6%)
Ethnicity (n, % Caucasian)	141 (97.2%)	23 (100.0%)	288 (97.3%)
ANART score (at baseline)	119.08 (7.2)	119.26 (5.5)	112.97 (9.2)
NPI total (at baseline)	2.26 (5.27)	4.50 (7.06)	11.57 (13.01)
GDS total (at baseline)	1.07 (1.85)	1.65 (2.01)	2.44 (2.43)
Vascular Risk Aggregate (at baseline)	1.319 (0.83)	1.040 (0.56)	1.297 (0.96)

Note: Values represent means (and SDs) or percentages (where indicated). *ANART = American National Adult Reading Test; NPI = Neuropsychiatric Inventory; GDS = Geriatric Depression Scale.*

Table 5a. *Associations of Cognition and Total Neuropsychiatric Symptoms Within and Between Cognitively Normal Subjects (parameter estimates, standard errors, t-values, and p-values)*

NPI Model	B	S.E	t-value	p-value
Attention				
Intercept	-1.099	0.525	-2.092	0.037
Age	-0.011	0.006	-1.942	0.053
Education (in years)	0.122	0.019	6.554	<0.001
NPI_total_Within	0.011	0.006	1.784	0.075
NPI_total_Between	0.004	0.016	0.267	0.790
Memory				
Intercept	-0.437	0.701	-0.623	0.534
Age	-0.010	0.006	-1.624	0.105
Education (in years)	0.075	0.031	2.397	0.018
NPI_total_Within	0.006	0.005	1.141	0.255
NPI_total_Between	-0.025	0.020	-1.232	0.220
Language				
Intercept	-0.831	0.444	-1.870	0.063
Age	-0.011	0.004	-2.434	0.015
Education (in years)	0.107	0.018	6.072	<0.001
NPI_total_Within	-0.005	0.004	-1.228	0.220
NPI_total_Between	-0.017	0.015	-1.162	0.247
Visuospatial Skills				
Intercept	0.536	0.545	0.983	0.327
Age	-0.025	0.006	-4.291	<0.001
Education (in years)	0.083	0.019	4.273	<0.001
NPI_total_Within	-0.005	0.006	-0.744	0.457
NPI_total_Between	0.011	0.016	0.678	0.499
Executive Functioning				
Intercept	-0.145	0.464	-0.312	0.755
Age	-0.016	0.005	-3.119	0.002
Education (in years)	0.085	0.016	5.393	<0.001
NPI_total_Within	-0.005	0.006	-0.773	0.440
NPI_total_Between	0.001	0.013	0.094	0.925
Processing Speed				
Intercept	1.235	0.547	2.257	0.025
Age	-0.037	0.006	-6.389	<0.001
Education (in years)	0.098	0.020	4.806	<0.001
NPI_total_Within	-0.001	0.005	0.156	0.876
NPI_total_Between	-0.033	0.017	-1.921	0.057
NP Composite				
Intercept	-0.400	0.326	-1.227	0.221
Age	-0.015	0.003	-4.505	<0.001
Education (in years)	0.095	0.013	7.109	<0.001
NPI_total_Within	0.002	0.003	0.636	0.525
NPI_total_Between	-0.011	0.011	-1.041	0.300

Table 5b. *Associations of Cognition and Depression Within and Between Cognitively Normal Subjects (parameter estimates, standard errors, t-values, and p-values)*

GDS Model	B	S.E	t-value	p-value
Attention				
Intercept	-1.110	0.524	-2.116	0.035
Age	-0.010	0.006	-1.781	0.076
Education (in years)	0.118	0.018	6.491	<0.001
GDS_total_Within	-0.020	0.021	-0.940	0.348
GDS_total_Between	-0.005	0.033	-0.141	0.888
Memory				
Intercept	-0.650	0.692	-0.940	0.348
Age	-0.007	0.006	-1.161	0.246
Education (in years)	0.075	0.030	2.537	0.012
GDS_total_Within	-0.068	0.022	-3.133	**0.002***
GDS_total_Between	-0.090	0.043	-2.003	0.047
Language				
Intercept	-0.970	0.440	-2.206	0.028
Age	-0.009	0.004	-1.944	0.052
Education (in years)	0.105	0.017	6.133	<0.001
GDS_total_Within	-0.007	0.014	-0.480	0.631
GDS_total_Between	-0.050	0.031	-1.599	0.112
Visuospatial Skills				
Intercept	0.559	0.554	1.009	0.314
Age	-0.025	0.006	-4.132	<0.001
Education (in years)	0.078	0.019	4.064	<0.001
GDS_total_Within	-0.025	0.022	-1.103	0.270
GDS_total_Between	0.013	0.035	0.376	0.707
Executive Functioning				
Intercept	-0.283	0.462	-0.612	0.541
Age	-0.013	0.005	-2.631	0.009
Education (in years)	0.081	0.015	5.256	<0.001
GDS_total_Within	-0.065	0.021	-3.124	**0.002***
GDS_total_Between	-0.031	0.028	-1.121	0.264
Processing Speed				
Intercept	1.200	0.555	2.163	0.864
Age	-0.035	0.006	-6.002	0.209
Education (in years)	0.090	0.020	4.440	0.164
GDS_total_Within	-0.009	0.019	-0.461	0.701
GDS_total_Between	-0.085	0.037	-2.302	0.023
NP Composite				
Intercept	-0.519	0.324	-1.604	0.110
Age	-0.013	0.003	-3.896	<0.001
Education (in years)	0.093	0.013	7.112	<0.001
GDS_total_Within	-0.025	0.010	-2.585	0.010
GDS_total_Between	-0.047	0.023	-1.989	0.049

***p≤ 0.002**

Table 5c. *Associations of Cognition and Aggregate Vascular Risk Within and Between Cognitively Normal Subjects (parameter estimates, standard errors, t-values, and p-values)*

Vascular Model	B	S.E	t-value	p-value
Attention				
Intercept	-1.026	0.515	-1.994	0.047
Age	-0.010	0.006	-1.861	0.064
Education (in years)	0.115	0.018	6.420	<0.001
AggregateVascular_Within	0.030	0.051	0.587	0.557
Aggregate_Vascular_Between	-0.121	0.073	-1.654	0.100
Memory				
Intercept	-0.336	0.694	-0.484	0.629
Age	-0.009	0.006	-1.484	0.139
Education (in years)	0.065	0.030	2.185	0.031
AggregateVascular_Within	-0.033	0.046	-0.729	0.466
Aggregate_Vascular_Between	-0.074	0.010	-0.741	0.460
Language				
Intercept	-0.800	0.438	-1.827	0.069
Age	-0.010	0.004	-2.161	0.031
Education (in years)	0.100	0.017	5.809	<0.001
AggregateVascular_Within	-0.010	0.033	-0.313	0.755
Aggregate_Vascular_Between	-0.104	0.070	-1.497	0.137
Visuospatial Skills				
Intercept	0.631	0.548	1.151	0.251
Age	-0.026	0.006	-4.395	<0.001
Education (in years)	0.082	0.019	4.288	<0.001
AggregateVascular_Within	0.073	0.054	1.343	0.180
Aggregate_Vascular_Between	0.084	0.078	1.075	0.284
Executive Functioning				
Intercept	-0.142	0.458	-0.311	0.756
Age	-0.014	0.005	-2.779	0.006
Education (in years)	0.077	0.015	5.014	<0.001
AggregateVascular_Within	0.017	0.052	0.331	0.741
Aggregate_Vascular_Between	-0.093	0.063	-1.464	0.145
Processing Speed				
Intercept	1.454	0.561	2.594	0.010
Age	-0.037	0.006	-6.225	<0.001
Education (in years)	0.084	0.021	4.091	<0.001
AggregateVascular_Within	-0.034	0.048	-0.712	0.477
Aggregate_Vascular_Between	-0.015	0.085	-0.177	0.860
NP Composite				
Intercept	-0.308	0.325	-0.948	0.344
Age	-0.014	0.003	-4.370	<0.001
Education (in years)	0.088	0.013	6.719	<0.001
AggregateVascular_Within	0.009	0.024	0.398	0.691
Aggregate_Vascular_Between	-0.068	0.053	-1.281	0.202

Table 6a. *Associations of Cognition and Total Neuropsychiatric Symptoms Within and Between Mild Cognitive Impairment Subjects (parameter estimates, standard errors, t-values, and p-values)*

NPI Model	B	S.E	t-value	p-value
Attention				
Intercept	0.044	1.495	0.030	0.976
Age	0.002	0.017	0.121	0.905
Education (in years)	-0.008	0.042	-0.184	0.856
NPI_total_Within	0.011	0.007	1.414	0.163
NPI_total_Between	0.011	0.019	0.559	0.582
Memory				
Intercept	0.450	1.724	0.261	0.796
Age	-0.020	0.019	-1.056	0.297
Education (in years)	-0.025	0.049	-0.509	0.617
NPI_total_Within	-0.016	0.008	-1.917	0.061
NPI_total_Between	-0.004	0.023	-0.159	0.875
Language				
Intercept	2.830	1.443	1.961	0.056
Age	-0.038	0.047	-2.448	0.017
Education (in years)	-0.021	0.136	-0.459	0.652
NPI_total_Within	0.001	0.017	0.250	0.804
NPI_total_Between	-0.031	0.062	-1.477	0.156
Visuospatial Skills				
Intercept	2.650	2.179	1.216	0.235
Age	-0.040	0.025	-1.548	0.133
Education (in years)	-0.014	0.057	-0.243	0.811
NPI_total_Within	-0.018	0.014	-1.272	0.209
NPI_total_Between	0.012	0.027	0.440	0.665
Executive Functioning				
Intercept	0.626	1.976	0.316	0.754
Age	-0.029	0.022	-1.293	0.205
Education (in years)	0.080	0.054	1.482	0.157
NPI_total_Within	0.007	0.011	0.616	0.541
NPI_total_Between	-0.001	0.025	-0.027	0.979
Processing Speed				
Intercept	1.057	1.697	0.623	0.537
Age	-0.021	0.019	-1.139	0.261
Education (in years)	0.015	0.049	0.310	0.760
NPI_total_Within	0.002	0.008	0.243	0.809
NPI_total_Between	0.023	0.022	1.010	0.324
NP Composite				
Intercept	1.786	0.900	1.984	0.054
Age	-0.031	0.010	-3.140	0.003
Education (in years)	-0.003	0.027	-0.116	0.909
NPI_total_Within	-0.004	0.004	-1.036	0.305
NPI_total_Between	-0.002	0.012	-0.223	0.826

Table 6b. *Associations of Cognition and Depression Within and Between Mild Cognitive Impairment Subjects (parameter estimates, standard errors, t-values, and p-values)*

GDS Model	B	S.E	t-value	p-value
Attention				
Intercept	0.930	1.480	0.629	0.534
Age	-0.011	0.017	-0.669	0.507
Education (in years)	0.001	0.039	0.013	0.990
GDS_total_Within	0.037	0.029	1.292	0.202
GDS_total_Between	-0.173	0.075	-2.302	0.030
Memory				
Intercept	0.121	1.827	0.066	0.947
Age	-0.015	0.021	-0.727	0.471
Education (in years)	-0.029	0.049	-0.583	0.567
GDS_total_Within	-0.011	0.032	-0.340	0.736
GDS_total_Between	-0.025	0.095	-0.259	0.798
Language				
Intercept	2.296	1.527	1.503	0.139
Age	-0.031	0.016	-1.853	0.068
Education (in years)	-0.025	0.047	-0.530	0.602
GDS_total_Within	0.030	0.021	1.422	0.161
GDS_total_Between	0.067	0.088	0.760	0.455
Visuospatial Skills				
Intercept	3.335	2.284	1.460	0.156
Age	-0.048	0.026	-1.834	0.077
Education (in years)	-0.011	0.057	-0.191	0.850
GDS_total_Within	-0.046	0.052	-0.886	0.380
GDS_total_Between	-0.114	0.113	-1.006	0.325
Executive Functioning				
Intercept	0.991	2.022	0.490	0.628
Age	-0.033	0.023	-1.443	0.158
Education (in years)	0.077	0.052	1.487	0.153
GDS_total_Within	0.016	0.042	0.379	0.706
GDS_total_Between	0.013	0.101	0.131	0.897
Processing Speed				
Intercept	1.270	1.768	0.718	0.477
Age	-0.024	0.020	-1.207	0.234
Education (in years)	0.014	0.048	-0.291	0.774
GDS_total_Within	-0.024	0.030	-0.783	0.437
GDS_total_Between	0.025	0.093	0.275	0.786
NP Composite				
Intercept	1.776	0.919	1.932	0.060
Age	-0.030	0.010	-2.977	0.004
Education (in years)	-0.005	0.026	-0.184	0.856
GDS_total_Within	0.002	0.015	0.169	0.866
GDS_total_Between	-0.034	0.049	-0.689	0.498

Table 6c. *Associations of Cognition and Aggregate Vascular Risk Within and Between Mild Cognitive Impairment (parameter estimates, standard errors, t-values, and p-values)*

Vascular Model	B	S.E	t-value	p-value
Attention				
Intercept	-0.517	1.539	0.336	0.739
Age	-0.005	0.017	-0.302	0.765
Education (in years)	-0.003	0.044	-0.081	0.937
AggregateVascular_Within	-0.142	0.149	-0.958	0.342
Aggregate_Vascular_Between	-0.035	0.193	-0.179	0.860
Memory				
Intercept	-0.457	1.693	-0.270	0.789
Age	-0.005	0.019	-0.282	0.780
Education (in years)	-0.039	0.049	-0.805	0.430
AggregateVascular_Within	0.312	0.160	1.947	0.056
Aggregate_Vascular_Between	-0.237	0.214	-1.112	0.279
Language				
Intercept	3.068	1.490	2.058	0.046
Age	-0.040	0.016	-2.463	0.017
Education (in years)	-0.030	0.048	-0.629	0.537
AggregateVascular_Within	-0.172	0.110	-1.561	0.124
Aggregate_Vascular_Between	-0.091	0.209	-0.435	0.668
Visuospatial Skills				
Intercept	2.944	2.182	1.349	0.190
Age	-0.044	0.025	-1.761	0.090
Education (in years)	-0.007	0.059	-0.123	0.903
AggregateVascular_Within	-0.015	0.265	-0.056	0.955
Aggregate_Vascular_Between	0.124	0.260	0.475	0.641
Executive Functioning				
Intercept	0.629	1.863	0.337	0.739
Age	-0.027	0.021	-1.259	0.218
Education (in years)	0.068	0.051	1.331	0.199
AggregateVascular_Within	0.037	0.215	0.171	0.865
Aggregate_Vascular_Between	-0.271	0.224	-1.207	0.243
Processing Speed				
Intercept	0.937	1.691	0.554	0.583
Age	-0.019	0.019	-0.999	0.324
Education (in years)	0.011	0.049	0.217	0.831
AggregateVascular_Within	0.179	0.154	1.166	0.248
Aggregate_Vascular_Between	-0.112	0.216	-0.517	0.611
NP Composite				
Intercept	1.516	0.869	1.744	0.090
Age	-0.026	0.010	-2.700	0.010
Education (in years)	-0.010	0.026	-0.382	0.707
AggregateVascular_Within	0.054	0.077	0.701	0.486
Aggregate_Vascular_Between	-0.115	0.112	-1.024	0.318

Table 7a. *Associations of Cognition and Total Neuropsychiatric Symptoms Within and Between Alzheimer's disease Subjects (parameter estimates, standard errors, t-values, and p-values)*

NPI Model	B	S.E	t-value	p-value
Attention				
Intercept	-7.903	1.275	-6.197	<0.001
Age	0.057	0.015	3.931	<0.001
Education (in years)	0.098	0.035	2.798	0.006
NPI_total_Within	-0.057	0.009	-6.191	**<0.001***
NPI_total_Between	0.002	0.011	0.145	0.885
Memory				
Intercept	-1.376	0.348	-3.957	<0.001
Age	-0.024	0.004	-6.390	<0.001
Education (in years)	0.016	0.011	1.387	0.167
NPI_total_Within	-0.004	0.016	-2.296	0.022
NPI_total_Between	-0.007	0.003	-2.433	0.016
Language				
Intercept	1.637	0.710	2.306	0.022
Age	-0.062	0.008	-7.735	<0.001
Education (in years)	0.053	0.021	2.563	0.011
NPI_total_Within	-0.016	0.003	-5.109	**<0.001***
NPI_total_Between	-0.008	0.006	-1.267	0.207
Visuospatial Skills				
Intercept	-2.363	0.811	-2.913	0.004
Age	0.000	0.009	0.035	0.972
Education (in years)	0.019	0.023	0.821	0.412
NPI_total_Within	-0.021	0.004	-4.583	**<0.001***
NPI_total_Between	-0.004	0.007	-0.618	0.537
Executive Functioning				
Intercept	-3.580	1.727	-2.073	0.039
Age	-0.040	0.020	-2.023	0.044
Education (in years)	0.207	0.049	4.240	<0.001
NPI_total_Within	0.002	0.012	0.180	0.857
NPI_total_Between	-0.048	0.015	-3.198	**0.002***
Processing Speed				
Intercept	-0.325	1.185	-0.275	0.784
Age	-0.044	0.013	-3.294	0.001
Education (in years)	0.067	0.031	1.933	0.055
NPI_total_Within	-0.027	0.006	-4.544	**<0.001***
NPI_total_Between	-0.018	0.010	-1.691	0.092
NP Composite				
Intercept	-1.793	0.484	-3.708	<0.001
Age	0.020	0.005	-3.610	0.848
Education (in years)	0.061	0.014	4.318	0.054
NPI_total_Within	-0.007	0.003	-2.262	0.024
NPI_total_Between	-0.010	0.004	-2.335	0.020

***p≤ 0.002**

Table 7b. *Associations of Cognition and Depression Within and Between Alzheimer's disease Subjects (parameter estimates, standard errors, t-values, and p-values)*

GDS Model	B	S.E	t-value	p-value
Attention				
Intercept	-6.819	1.024	-6.659	<0.001
Age	0.041	0.012	3.545	<0.001
Education (in years)	0.126	0.028	4.483	<0.001
GDS_total_Within	0.039	0.059	0.655	0.513
GDS_total_Between	-0.081	0.053	-1.524	0.129
Memory				
Intercept	-1.524	0.340	-4.479	<0.001
Age	-0.022	0.004	-5.958	<0.001
Education (in years)	0.015	0.012	1.294	0.197
GDS_total_Within	0.012	0.010	1.129	0.260
GDS_total_Between	0.008	0.017	0.444	0.658
Language				
Intercept	1.493	0.682	2.187	0.030
Age	-0.060	0.007	-7.842	<0.001
Education (in years)	0.056	0.020	2.783	0.006
GDS_total_Within	0.058	0.023	2.571	0.010
GDS_total_Between	-0.013	0.036	-0.350	0.727
Visuospatial Skills				
Intercept	-2.304	0.765	-3.012	0.003
Age	0.001	0.009	-0.109	0.913
Education (in years)	0.028	0.022	1.299	0.195
GDS_total_Within	0.050	0.032	1.528	0.127
GDS_total_Between	-0.054	0.040	-1.371	0.171
Executive Functioning				
Intercept	-4.404	1.699	-2.592	0.122
Age	-0.027	0.019	-1.393	0.052
Education (in years)	0.196	0.049	4.005	0.003
GDS_total_Within	0.116	0.085	1.374	0.265
GDS_total_Between	-0.116	0.089	-1.305	0.275
Processing Speed				
Intercept	-0.616	1.146	-0.538	0.591
Age	-0.039	0.013	-3.058	0.002
Education (in years)	0.065	0.034	1.918	0.056
GDS_total_Within	0.036	0.044	0.815	0.416
GDS_total_Between	-0.046	0.059	-0.771	0.441
NP Composite				
Intercept	-1.943	0.469	-4.139	<0.001
Age	-0.017	0.005	-3.323	0.001
Education (in years)	0.060	0.014	4.367	<0.001
GDS_total_Within	0.040	0.020	1.969	0.050
GDS_total_Between	-0.020	0.024	-0.853	0.394

Table 7c. *Associations of Cognition and Aggregate Vascular Risk Within and Between Alzheimer's disease Subjects (parameter estimates, standard errors, t-values, and p-values)*

Vascular Model	B	S.E	t-value	p-value
Attention				
Intercept	-6.814	1.346	-5.060	<0.001
Age	0.040	0.015	2.618	0.009
Education (in years)	0.114	0.038	3.034	0.003
AggregateVascular_Within	-0.187	0.239	-0.783	0.434
Aggregate_Vascular_Between	0.455	0.173	2.636	0.009
Memory				
Intercept	-1.551	0.341	-4.550	<0.001
Age	-0.021	0.004	-5.910	<0.001
Education (in years)	0.016	0.012	1.341	0.181
AggregateVascular_Within	0.027	0.035	0.781	0.435
Aggregate_Vascular_Between	0.016	0.043	0.377	0.706
Language				
Intercept	1.436	0.686	2.092	0.037
Age	-0.060	0.008	-7.738	<0.001
Education (in years)	0.054	0.020	2.669	0.008
AggregateVascular_Within	0.177	0.080	2.201	0.028
Aggregate_Vascular_Between	0.063	0.092	1.762	0.080
Visuospatial Skills				
Intercept	-2.313	0.796	-2.906	0.004
Age	-0.001	0.009	-0.162	0.871
Education (in years)	0.024	0.023	1.055	0.292
AggregateVascular_Within	0.127	0.114	1.114	0.266
Aggregate_Vascular_Between	0.289	0.104	2.779	0.006
Executive Functioning				
Intercept	-4.692	1.695	-2.769	0.006
Age	-0.024	0.019	-1.230	0.220
Education (in years)	0.195	0.049	3.978	<0.001
AggregateVascular_Within	0.064	0.289	0.222	0.824
Aggregate_Vascular_Between	0.209	0.215	0.332	0.332
Processing Speed				
Intercept	-0.699	1.134	-0.616	0.538
Age	-0.039	0.013	-3.100	0.002
Education (in years)	0.067	0.033	2.018	0.045
AggregateVascular_Within	0.271	0.148	1.835	0.067
Aggregate_Vascular_Between	0.284	0.148	1.923	0.056
NP Composite				
Intercept	-2.089	0.464	-4.499	<0.001
Age	-0.016	0.005	-3.039	0.003
Education (in years)	0.060	0.014	4.385	0.000
AggregateVascular_Within	0.043	0.068	0.628	0.530
Aggregate_Vascular_Between	0.121	0.059	2.038	0.043

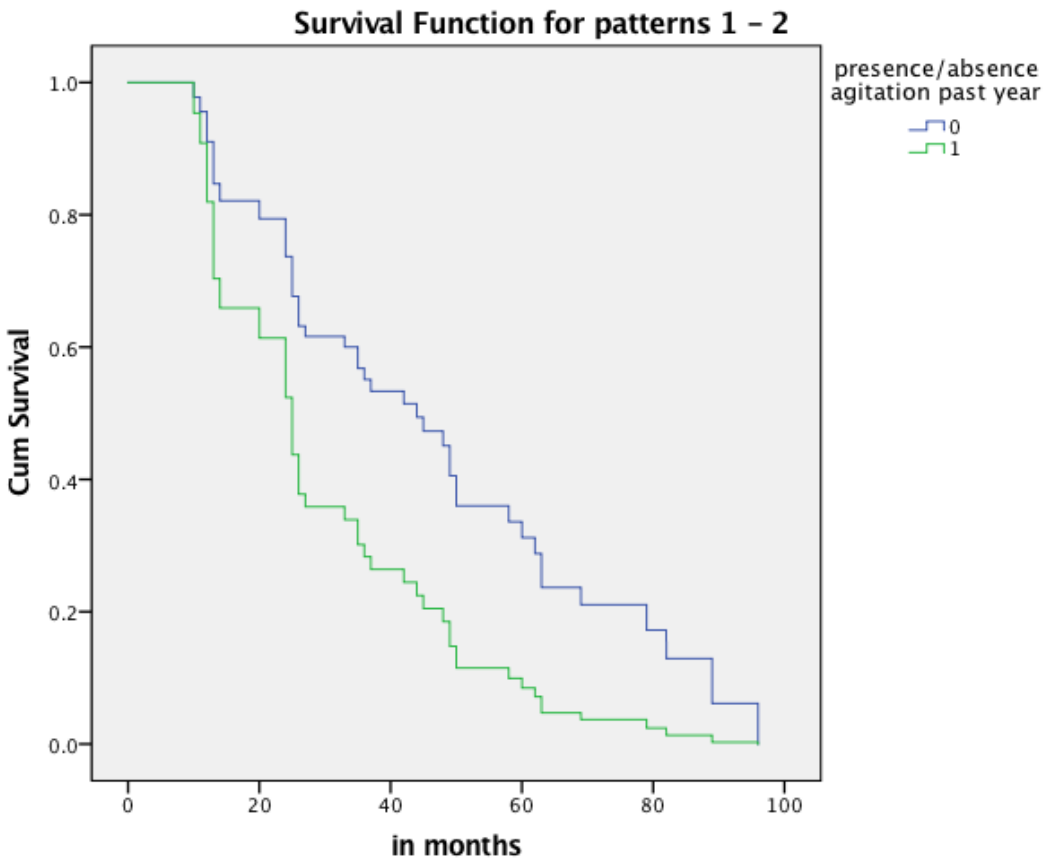

Figure 1. *Estimates of the Survival Curve for MCI Individuals Endorsing Agitation and Conversion to AD*

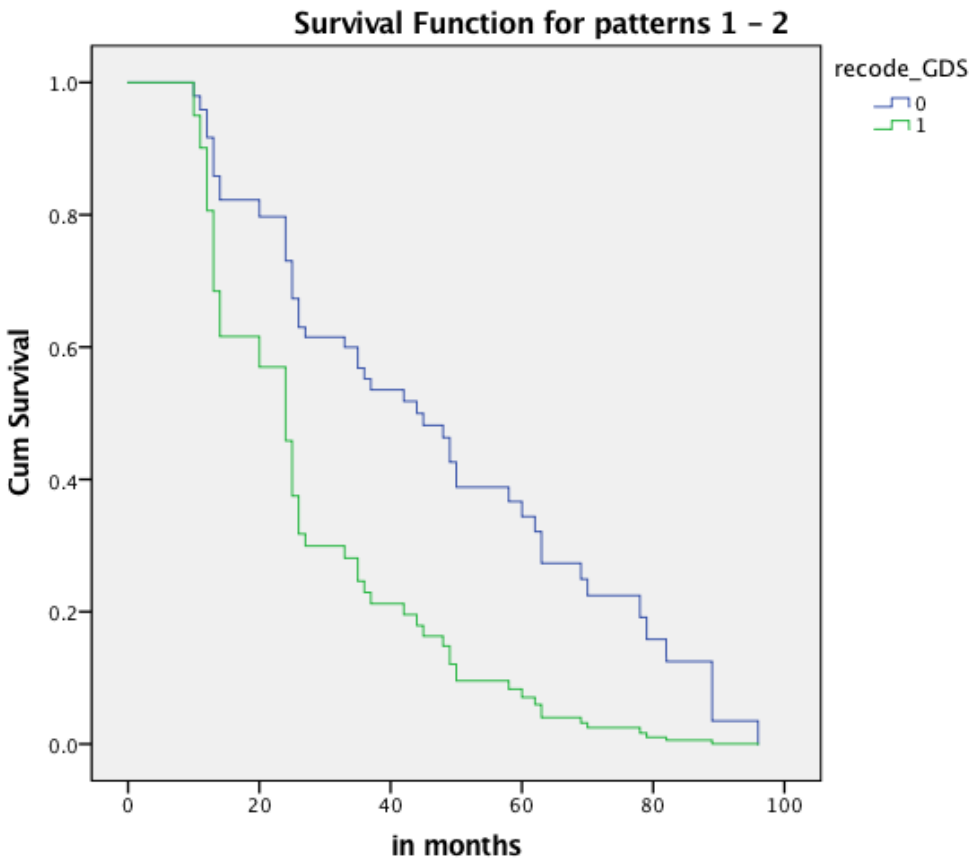

Figure 2. *Estimates of the Survival Curve for MCI Individuals Endorsing Depression (where scores <5 indicate no depression and scores ≥ 5 indicate at least mild depression) and AD Conversion.*