IDENTIFYING PREDICTORS OF REVERSION FROM MILD COGNITIVE IMPAIRMENT TO NORMAL COGNITION

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DEDICATION

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Studies on mild cognitive impairment (MCI) have focused on identifying predictors of progression to dementia, yet relatively few studies have examined predictors of reversion from MCI to normal cognition. This retrospective study incorporated data from the National Alzheimer's Coordinating Center Uniform Data Set to examine baseline predictors of MCI reversion. A total of 1,208 participants meeting MCI criteria were evaluated at baseline visit and three subsequent annual visits. Of these, 175 (14%) reverted to normal cognition, 612 (51%) remained MCI, and 421 (35%) progressed to dementia at two-years, with sustained diagnoses at three-years. This study only examined MCI participants who reverted to normal cognition (175)

and progressed to dementia (421) for a final total of 596 participants. Baseline predictors of MCI reversion were categorized into the clusters of demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms. Binary stepwise logistic regression models were used to identify significant predictors of MCI reversion compared to MCI progression for each cluster, which were then entered into a final comprehensive model to find the overall significant predictor(s). Receiver operating characteristic (ROC) curves were then used to determine cut-off scores for the continuous predictors most significant for MCI reversion. The variables most significantly associated with MCI reversion were younger age, being unmarried, having zero copies of the *APOE* ε4 allele, lower Clinical Dementia Rating Sum of Boxes scores, and higher test scores on Logical Memory Delayed Recall, Vegetable Fluency, and Boston Naming Test at baseline. ROC curve results revealed a standard *z*-score of -1.16 or better on Logical Memory Delayed Recall as an accurate classification of the MCI reversion group from the MCI progression group, with 89% sensitivity and 73% specificity. Results suggest that demographic, global functioning, and neuropsychological factors are significantly associated with MCI reversion. Future longitudinal studies on MCI reversion, with a multifactorial approach, are necessary to increase understanding of MCI reversion. Findings could help educate patients and families on clinical outcomes of MCI, better inform healthcare providers on treatment management and clinical prognosis, and increase precision of findings in early intervention studies of dementia.

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LIST OF DEFINITIONS

Aβ – Beta-amyloid

AD – Alzheimer's Disease

ADC- Alzheimer's Disease Center

ADLs – Activities of Daily Living

ADNI – Alzheimer's Disease Neuroimaging Initiative

APOE – Apolipoprotein E

AUC – Area Under the Curve

CAIDE - Cardiovascular Risk Factors, Aging and Dementia

CDR – Clinical Dementia Rating

CDR-SOB – Clinical Dementia Rating Sum of Boxes

DSM – Diagnostic and Statistical Manual of Mental Disorders

GDS – Geriatric Depression Scale

FAQ – Functional Assessment Questionnaire

IADLs – Instrumental Activities of Daily Living

IWG – International Working Group

MCI – Mild Cognitive Impairment

MMSE – Mini Mental State Exam

MNCD – Mild Neurocognitive Disorder

MRI – Magnetic Resonance Imaging

NACC – National Alzheimer's Coordinating Center

NIA-AA - National Institute on Aging-Alzheimer's Association

NPI – Neuropsychiatric Inventory

NPI-Q – Neuropsychiatric Inventory Questionnaire

ROC – Receiver Operating Characteristic

TMT – Trail Making Test

UDS – Uniform Data Set

WAIS-R – Wechsler Adult Intelligence Scale-Revised

WMS-R – Wechsler Memory Scale-Revised

CHAPTER ONE

Introduction

Individuals may show signs of cognitive decline as they become older. For some, such decline may occur sooner and progress more rapidly than what is considered normal aging. Dementia describes this abnormal aging and involves a group of symptoms that affect both cognitive and everyday functioning to the point of interfering with daily life activities. There are several types of dementias, with the most common being Alzheimer's disease (AD) within the United States (Alzheimer's Association, 2014). The global prevalence rate of dementia was nearly 24 million in 2005, with an incidence rate of 4.6 million per year, and approximately 70% of the cases were AD-related (Ferri et al., 2005; Reitz & Mayeux, 2014). In the United States, prevalence rate of AD in 2010 was estimated to be near 5 million and is projected to triple by year 2050, with health care costs approximated at $172 billion per year (Alzheimer's Association, 2013; Hebert, Weuve, Scherr, & Evans, 2013; Reitz & Mayeux, 2014). These statistics highlight dementia as a major public health concern and describe a need to understand dementia's prodromal characteristics to help determine whether signs of cognitive decline inevitably lead to AD or other dementias.

Cognitive decline does not typically occur rapidly. Instead there is often a transitional state called *mild cognitive impairment* (MCI), a term that was first coined in the late 1980s to identify individuals who demonstrated cognitive difficulties that were abnormal for their age, yet did not have overt dementia (Fleisher et al., 2005). Research on MCI has been receiving a great amount of attention over the years, particularly for its role in identifying individuals who are at

risk of developing AD or other forms of dementia (Bondi & Smith, 2014; Devanand et al., 2008; Drago et al., 2011; Eckerstrom et al., 2013; Fischer et al., 2007; Fleisher et al., 2005; Gauthier et al., 2006; Gifford et al., 2014; Gomar et al., 2011; Gomar, Conejero-Goldberg, Davies, Goldberg, & Alzheimer's Disease Neuroimaging, 2014; Jak et al., 2009; Lonie et al., 2010; Lopez et al., 2012; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014; Petersen, 2009; Rosenberg et al., 2011; Tabert et al., 2006; Tokuchi et al., 2014; van Rossum et al., 2012; Vellas et al., 2013; Zonderman & Dore, 2014). Furthermore, in clinical settings, the use of MCI as a diagnosis has become increasingly common and important because of a push for early treatment interventions to prevent further cognitive decline (Albert et al., 2011; Fleisher et al., 2005; Jack et al., 2013; Jack et al., 2010; McKhann et al., 2011).

The definition of MCI varies. One set of MCI diagnostic criteria created by a group of researchers at the Mayo Clinic involves: 1) a complaint of memory problems by self or informant; 2) no impairment in daily functioning; 3) preserved general cognitive functioning; 4) impaired memory abilities for age and education; and 5) does not meet criteria for dementia (Petersen et al., 1997). Another set of criteria for MCI created by a group of researchers known as the International Working Group (IWG) included the following: 1) no normal cognition and no dementia; 2) self- and/or informant-reported decline and impairment on objective cognitive testing or evidence of decline over time via objective cognitive testing; and 3) preserved basic activities of daily living or minimal impairment in complex instrumental functions (Winblad et al., 2004). The National Institute on Aging-Alzheimer’s Association’s (NIA-AA) MCI criteria includes: 1) concern from patient or an informant regarding change in the patient’s cognition in comparison to his/her previous level of cognitive functioning; 2) impairment in at least one

cognitive domain (memory, attention, executive function, visuospatial skills, and language) that is greater than what would be expected when considering the patient's age and education level; 3) preservation of, or mild inefficiencies in, performing complex functional tasks (e.g. shopping and paying bills); and 4) no dementia (Albert et al., 2011). The Alzheimer's Disease Neuroimaging Initiative (ADNI) used yet a different set of criteria, which includes: 1) complaint of memory; 2) Mini Mental State Exam (MMSE) score of 24-30 (inclusive); 3) objective memory loss as measured by Wechsler Memory Scale-Revised (WMS-R) Logical Memory subtest (education-adjusted score on delayed recall of one prose passage); 4) Global Clinical Dementia Rating (CDR) score of 0.5; 5) absence of significant impairment in other cognitive domains; 6) preserved activities of daily living; and 7) absence of dementia (Alzheimer's Disease Neuroimaging Initiative, 2014; Petersen, Roberts, et al., 2010). Furthermore, in 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) introduced *Mild Neurocognitive Disorder* (MNCD) as its own diagnostic entity to represent a new framework for MCI diagnosis, where previous editions of the DSM (IV and IV-TR) incorporated MCI under the general category of *Cognitive Disorder Not Otherwise Specified*. DSM-5 MNCD includes: 1) evidence of modest cognitive decline from previous level of performance in at least one cognitive domain (e.g., complex attention, learning and memory, executive function, language, perceptual-motor, and social cognition) based on both standardized neuropsychological testing (or alternate quantified assessment) and concern for decline from the patient, informant, and/or clinician; 2) cognitive impairments not interfering with independent abilities to perform everyday activities; 3) cognitive impairments not occurring in context of a delirium; and 4) cognitive impairments not better explained by another mental disorder, such as depression or

schizophrenia (American Psychiatric Association, 2013). Altogether, these varying MCI definitions suggest that the diagnostic criteria for MCI continue to be in a process of refinement.

Across the current MCI criteria, there are varying definitions on what constitutes cognitive impairment. Originally, MCI mainly involved memory impairments reported among MCI patients, with impaired memory function being 1.5 to 2.0 standard deviations below the normative group and other cognitive domains being relatively impairment-free (Petersen et al., 1997). These memory-impaired patients tended to benefit less from cues that relate to the meaning of the word(s) or phrase(s) (i.e. semantic cuing) during recall on verbal memory tests and show impaired performance on delayed recall (Grober, Buschke, Crystal, Ban, & Dressner, 1988). Additionally, these patients still have intact activities of daily living (e.g., self-care, work performance, household duties, and leisure activities), while being aware of having such memory difficulties (Petersen et al., 1997). However, the concept of MCI has been expanded to include other cognitive difficulties (i.e., non-memory) in the domains of executive function, language, attention, and visuospatial skills (American Psychiatric Association, 2013; Sachdev et al., 2014). For example, executive function declines faster in MCI patients when analyzed against the domains of memory, language, attention, and visuospatial skills, suggesting that decline in non-memory domains could be better predictors of progression than simply a decline in memory (Johnson et al., 2012). Further, the DSM-5 suggests modest cognitive decline (1.0 to 2.0 standard deviations below the normative group) on neuropsychological testing of several cognitive domains for an MCI patient (American Psychiatric Association, 2013; Sachdev et al., 2014). Due to both memory and non-memory presentations of cognitive difficulties, researchers at the Mayo Clinic expanded MCI criteria in 2004 by including four subtypes: 1) amnestic single

domain (impairment only in memory domain), 2) amnestic multi-domain (impairment in memory domain plus one or more non-memory domains: language, attention, executive function, or visuospatial skills), 3) nonamnestic single domain (impairment in either language, attention, executive function, or visuospatial skills), and 4) nonamnestic multi-domain (impairment in two or more domains of language, attention, executive function, or visuospatial skills) (Figure 1) (Petersen, 2004, 2011), although these concepts had not been previously empirically tested. Since the introduction of these concepts, MCI has been categorized into two major subtypes in some studies: amnestic and/or nonamnestic, irrespective of the number of cognitive domains with impairments (i.e., single versus multiple) (Fischer et al., 2007; Reinlieb, Ercoli, Siddarth, St Cyr, & Lavretsky, 2014).

Incidence and prevalence rates of MCI vary widely. Using the original Mayo Clinic MCI criteria (Petersen et al., 1999), incidence rates range from 37 to 77 per 1,000 person-year (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003) with varying prevalence rates being 3% to greater than 20% (Busse et al., 2003; Ganguli et al., 2011). MCI prevalence and incident rates tend to increase among individuals aged 80 years and older, with a 53.5% progression rate to dementia over approximately three years using MCI criteria established in the Cardiovascular Health Study-Cognition Study (Lopez et al., 2012; Lopez et al., 2003). Variable outcomes of progression rates from MCI to dementia are likely due to a number of factors, including differing classifications/definitions of MCI, length of follow-up, and/or sample selection (e.g., clinic- vs. community-based) (Luck, Luppa, Briel, & Riedel-Heller, 2010; Mitchell & Shiri-Feshki, 2009; Ward, Arrighi, Michels, & Cedarbaum, 2012). While annual progression rates were up to 50% (Fischer et al., 2007; Luis, Loewenstein, Acevedo, Barker, & Duara, 2003; Mitchell & Shiri-

Feshki, 2009), other studies revealed slower annual rates of progression, with 10 to 18% by one to 10 years (Bruscoli & Lovestone, 2004; Gauthier et al., 2006; Petersen, 2004; Petersen et al., 1997; Tschanz et al., 2006). In a meta-analysis of 41 MCI studies using Mayo Clinic-defined MCI (all subtypes), the annual progression rate to dementia and AD was 10% and 8% respectively in clinical settings, and 5% and 7% respectively in community settings (Mitchell & Shiri-Feshki, 2009). Hence, the annual progression rate ranges between 5 to 10%, when compared to 1 to 2% per year among healthy controls (Shah, Tangalos, & Petersen, 2000). The relatively low annual MCI progression rate suggests that a large proportion of MCI individuals do not progress to dementia and that MCI is not inevitably an intermediate stage between normal aging and dementia, a finding that may have important implications for clinical management, research, and social policy.

MCI Progression to Dementia

Numerous studies have focused on symptom progression from MCI to dementia and identified a number of factors generally in the areas of demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk scores, and neuropsychiatric symptoms. Findings in each area are summarized below.

Demographic/Genetic Data

From a demographic standpoint, MCI progressors tend to be older, married or cohabited with a partner in mid-life, more frequently female, and have lower levels of education (Devanand et al., 2008; Lee, Ritchie, Yaffe, Stijacic Cenzer, & Barnes, 2014; Tokuchi et al., 2014; van

Rossum et al., 2012). There appears to be no significant association between the participant's race/ethnicity and progression from MCI to a dementia (Lee et al., 2014; Tabert et al., 2006); however, one study noted a correlation between race/ethnicity and source of the study sample, where participants recruited from a community-based population were more likely to be of a minority descent than participants recruited from a clinic-based population (Farias, Mungas, Reed, Harvey, & DeCarli, 2009).

Of the many MCI progression studies, MCI subtype is often investigated to determine which is more likely associated with progression to dementia. Longitudinal studies, with follow-up period ranging from two to six years, indicate that individuals with amnestic MCI (irrespective of single or multiple domain) convert to AD faster that those with nonamnestic MCI (Busse, Angermeyer, & Riedel-Heller, 2006; Fischer et al., 2007; Ravaglia et al., 2006; Tschanz et al., 2006). Additionally, individuals diagnosed with amnestic multi-domain MCI particularly have a higher risk for progression to AD (estimated progression rate of 50%) than those diagnosed with amnestic single domain MCI (estimated progression rate 10%) within a three-year follow-up (Tabert et al., 2006). Altogether, data suggests that both amnestic and nonamnestic MCI are associated with progression to dementia, although the former appears to have a higher likelihood of progression from MCI to a dementia.

The apolipoprotein E (*APOE*) plays an important genetic role in aging, particularly its major alleles of ε2, ε3, and ε4. *APOE*, an amyloid-binding protein found on chromosome 19, helps control the metabolism of lipoproteins and manage the transport/redistribution of lipids within cells and tissues by binding to the lipids (Weisgraber, 1994). One of two pathways in which *APOE* contributes to the onset of AD includes the binding of *APOE* to beta-amyloid (Aβ),

which is a known protein associated with AD. Specifically, the risk for AD is two to three times higher for individuals with one copy of the *APOE* ε4 (compared to zero copies) and approximately twelve times higher for two copies of the allele (Corder et al., 1993; Roses, 1996; Saunders et al., 1993). In contrast *APOE* ε2 is considered a protective form of the protein by binding to Aβ with the highest affinity and breaking down beta-amyloid accumulation in the brain. *APOE* ε3 is considered "neutral" (Kim & von Gersdorff, 2009; Shi, Han, & Kuniyoshi, 2014).

APOE ε4 is associated with both early and late onset AD (Caselli et al., 2009; Raber, Huang, & Ashford, 2004) and is a significant predictor of progression from MCI to AD (Gomar et al., 2014). Even in the absence of any dementing processes, carriers of *APOE* ε4 in their 50s and 60s demonstrate more rapid memory loss and decreased learning efficiency than non-carriers (Baxter, Caselli, Johnson, Reiman, & Osborne, 2003; Caselli et al., 2004). Further, homozygote carriers of *APOE* ε4 in their 60s, compared to heterozygotes and non-carriers, have higher rates of cognitive decline, which correlate with reduced cerebral metabolism starting about five to 10 years before onset of cognitive symptoms (Caselli et al., 2007). Additionally, *APOE* ε4 carriers can show a greater decline in memory before 60 years of age than non-carriers, with more rapid decline and added cognitive difficulties from having two alleles versus one (Caselli, Chen, Lee, Alexander, & Reiman, 2008). Interestingly, *APOE* ε4 can impact underlying brain structure during very early development (as early as infancy) and predispose to dementia (Dean et al., 2014; Trommsdorff et al., 1999), suggesting possible presence of AD pathology decades before clinical manifestation of the disease.

Global Functioning

Decline in global functioning is associated with MCI progression to dementia (Petersen et al., 1999; Reisberg et al., 1997). Comprehensive measures of global functioning include the assessment of everyday functioning and cognitive screening (Reisberg et al., 1997). Everyday functioning refers to activities people engage in on a regular basis and are divided into two categories. The first category is *activities of daily living* (ADLs), which relates to one's basic self-care abilities in terms of personal hygiene, dressing, mobility, eating/swallowing, and control of bowel movements (Kane & Kane, 1981). The second category is *instrumental activities of daily living* (IADLs), which requires more cognitively advanced skills (i.e. planning, decision-making, problem-solving, and social abilities) for more complex tasks, such as child-rearing, driving, health/financial management, shopping, cooking, and use of electronics (Kane & Kane, 1981; Lawton & Brody, 1969). While ADLs are fundamental to independence, the IADL scales assess higher functional abilities that are required for independent living at home and in the community (Gallo & Paveza, 2005). Everyday functioning assessed on the IADLs is central to the patient's return to independent living and to cope with the demands of everyday life (McColl et al., 1999).

MCI individuals may perform IADLs at a suboptimal level, need more time and effort to maintain independence on the completion of tasks, and use compensatory strategies (Sachdev et al., 2014), such as making lists and reminder notes. Further, individuals with MCI may experience subtle difficulties in performing IADLs two years before dementia diagnosis (Artero, Tierney, Touchon, & Ritchie, 2003), presumably due to reduced awareness (Albert, Tabert, Dienstag, Pelton, & Devanand, 2002).

Level of global functioning is considered to be the main determinant of whether the MCI patient has shown further deterioration towards a dementia (Petersen, 2004; Petersen et al., 1999; Sachdev et al., 2014; Schneider, Insel, & Weiner, 2011). MCI progressors tend to score poorer than non-progressors on a global cognitive screen (MMSE) and on a measure of IADLs (Functional Assessment Questionnaire, FAQ) (Devanand et al., 2008; Gomar et al., 2014). Also, when annually followed for one to four years, MCI individuals show an increase in scores on a measure of dementia symptom severity (CDR) (Gomar et al., 2014; Leow et al., 2009), suggesting an overall decline in functioning and progression toward dementia.

Neuropsychological Functioning

Neuropsychological functioning can be assessed using neuropsychological measures in the domains of memory (verbal and nonverbal), executive function, language, mental processing speed, visuospatial skills, and attention (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Verbal memory, particularly episodic memory (i.e., memory of events/details specific to each individual's experiences) has been identified as a sensitive, age-related indicator of cognitive decline (Ritchie, Touchon, Ledesert, Leibovici, & Gorce, 1997; Small, Stern, Tang, & Mayeux, 1999) and is often one of the first areas of impairment seen in MCI individuals.

A comprehensive review of studies across a 10-year span (2000-2010) demonstrated converging evidence for episodic memory as a strong, reliable marker for progression to dementia from MCI, despite variable follow-up time (1.5 years to six years) (Drago et al., 2011). Generally, lower baseline performances on delayed trials of verbal episodic memory tasks, such as list-learning and prose passages, predict progression to dementia over periods ranging from

two to 10 years (Artero et al., 2003; Bäckman, Jones, Berger, Laukka, & Small, 2005; Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013; Gomar et al., 2011; Gomar et al., 2014; Lonie et al., 2010; Parikh et al., 2014; Tierney et al., 1996).

Other cognitive domains are also strong markers of progression to dementia. For example, longitudinal and cross-sectional studies have indicated that MCI individuals show a decline in visuospatial abilities (Bennett et al., 2002; Economou, Papageorgiou, Karageorgiou, & Vassilopoulos, 2007), and that it is a potential marker of progression to dementia (Fowler, Saling, Conway, Semple, & Louis, 2002). Further, visuospatial difficulties are the first symptom indicators in early-onset AD (Johnson, Storandt, Morris, & Galvin, 2009; Weintraub, Wicklund, & Salmon, 2012) and even accelerate disease progression (Johnson et al., 2009). Another reliable cognitive marker for MCI progression is semantic memory (Drago et al., 2011; Fama et al., 1998; Monsch et al., 1994), which is general world knowledge an individual accumulates over the years.

Researchers have attempted to identify the most significant cognitive marker(s) of progression amongst a combination of domains, including verbal/nonverbal memory, executive function, language, processing speed, and attention. Specifically, Tabert and colleagues (2006) found that MCI progressors performed lower at baseline than non-progressors (albeit unclear group composition) on independent measures of verbal memory, nonverbal memory, executive function, language, and visuospatial skills after a three-year follow-up, but when these significant predictors were combined together, only verbal episodic memory and mental processing speed were the most significant predictors of MCI progression. Another group of researchers revealed that measures of executive function were significantly predictive at the

univariate level after a two-year follow-up period, but when combined with other neuropsychological measures, verbal episodic memory, language, and visuoconstruction/planning abilities were better predictors of progression than executive function (Aretouli, Okonkwo, Samek, & Brandt, 2011). These data suggest that isolating the most significant neuropsychological predictor for MCI progression is difficult since studies, thus far, have shown certain neuropsychological processes have equivocal predictive value in MCI progression to dementia (i.e., one neuropsychological variable is significant at the univariate level but then non-significant at the multivariate level, or vice versa).

Medical Health and Dementia Risk Score

Medical conditions and related treatments can often exacerbate cognitive difficulties in non-healthy adults (Defina et al., 2013; Maslow, 2004), yet data on particular health variables associated with MCI progression to a dementia are limited. Of the available studies, history of hypertension, and to a lesser extent history of ischemic cardiac disease, in elderly patients with MCI (mean age 77 years) has been suggested to be predictive, albeit non-significantly, of progression after approximately 32 months (Jack et al., 1999). Also, at a univariate level, coronary artery disease (i.e., myocardial infarction and angina pectoris) was a significant predictor of MCI progression after approximately 3.5 years among individuals with mean age of 80 years, yet lacked significance in multivariate analyses (Solfrizzi et al., 2004). MCI individuals (aged 75 years and older) with diabetes or pre-diabetes (defined as blood glucose levels of ≥11.0 mmol/l and 7.8-11.0 mmol/l, respectively) are two to four times more likely to progress to dementia over an approximate three-year follow-up (Xu et al., 2010). In contrast,

history of cerebrovascular disease (i.e., presence of one or more lacunar infarcts) was not predictive of progression to dementia among MCI individuals of mean age 72 years (DeCarli et al., 2004; Rusanen et al., 2014). Taken together, these studies suggest that current findings on the association between medical health variables and MCI progression are limited and mixed, which may be due to the heterogeneous nature of certain medical conditions (e.g., history of stroke influenced by history of heart disease).

Combining medical health variables with demographic variables is relevant to assess the risk of dementia. One particular measure is from the population-based Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study (Kivipelto et al., 2006), where researchers developed a scoring system based on demographic (i.e., age, education, gender, physical activity) and cardiovascular (i.e., hypertension, hypercholesterolemia, and obesity) factors to assess the risk of middle-aged adults, who did not have baseline cognitive deficits, developing dementia in late-life. The CAIDE dementia risk score was found to have a valid cutoff value of nine or higher to accurately classify middle-aged adults who develop dementia from those who did not after a follow-up mean period of 20 years. Another group of researchers externally validated the CAIDE risk score's effectiveness at predicting risk of dementia over a 40-year period in cognitively normal adults aged 40 to 55 years (Exalto et al., 2014). While this measure helps to assess the risk of developing dementia in normal aging, no studies have used the CAIDE dementia risk score to evaluate MCI patients' cognitive trajectories, raising questions as to whether this risk score can be used to predict MCI progression (or MCI stability or reversion to normal cognition).

Neuropsychiatric Symptoms

Neuropsychiatric symptoms often accompany cognitive difficulties, including MCI. Several studies have indicated an association between late-life depression and progressive cognitive impairment, to where cognitive deficits remain despite treatment of depressive symptoms (Bhalla et al., 2006; Butters et al., 2000; Diniz et al., 2013; Jorm, 2001; Murphy & Alexopoulos, 2004; Nebes et al., 2000; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006; Paradiso, Lamberty, Garvey, & Robinson, 1997). Findings, though, tend to be conflicting on whether late-life depression is related to increased chance of developing dementia. A few studies found an approximate 50% increase in the possibility of developing dementia, particularly Alzheimer's and vascular types (Diniz et al., 2013; Jorm, 2001; Ownby et al., 2006), while others did not find any association (Becker et al., 2009; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Salbe et al., 2002). Furthermore, risk for MCI or dementia is proportional to the duration and/or cumulative number of depressive episodes in an individual's lifetime (Koenig, Bhalla, & Butters, 2014), with the rate of dementia increased by 13% with every inpatient psychiatric hospitalization from a depressive episode (Kessing & Andersen, 2004).

Other neuropsychiatric symptoms aside from depression are associated with progression to dementia from MCI. Using the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), night-time behavioral disturbance (e.g., frequent awakenings and excessive naps), anxiety, and apathy were independent risk factors for progressing to dementia after a mean follow-up period of four years and approximately doubled the rate of progression to dementia (Somme, Fernandez-Martinez, Molano, & Zarranz, 2013).

MCI Reversion to Normal Cognition

Numerous studies have demonstrated that MCI individuals are at an increased risk for further deterioration; however, MCI does not always lead to dementia (Ganguli, Dodge, Shen, & DeKosky, 2004; Ganguli et al., 2015; Ganguli et al., 2011; Lopez et al., 2012; Mitchell & Shiri-Feshki, 2009; Sachdev et al., 2014). Indeed, rates of incident reversion among MCI individuals aged 65 years and older were up to 16% over one year in a clinic-based study (Koepsell & Monsell, 2012) and 28% to 55% in population-based studies over a two- to 12-year period (Artero et al., 2008; Ganguli et al., 2004; Han et al., 2012; Larrieu et al., 2002; Lopez et al., 2012; Manly et al., 2008; Ravaglia et al., 2008; Roberts et al., 2014; Sachdev et al., 2013). Reasons for these varying high rates of reversion are unknown, although MCI criteria using inclusion of participants with transient medical issues, comorbid neuropsychiatric symptoms, and/or length of follow-up are possible factors.

To date, significantly few studies have systematically focused on predictors of MCI reversion to normal cognition in comparison to the numerous studies on MCI progression to dementia. Of the few available studies of MCI reversion, predictors of reversion have been generally limited in the areas of global functioning, neuropsychological functioning, MCI subtype, genetic/medical health, and aspects of demographic factors. In the first systematic MCI reversion study, Koepsell and Monsell (2012) retrospectively analyzed data from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (Beekly et al., 2007; Morris et al., 2006) for MCI participants, age 65 years or older, who returned for a follow-up evaluation one year later. Demographic variables (age, gender, race, education level, and marital status), source of cognitive complaint (either subject- or informant-reported), performance on a cognitive screen

(MMSE), scores on measures of functional ability (FAQ and CDR-SOB), genetic marker (number of *APOE* ε4 alleles), medical variables (Hachinski Ischemic Score and history of stroke/diabetes), score on a depression measure (Geriatric Depression Scale), and MCI subtype were subjected to χ^2 and logistic regression analyses comparing reverters with non-reverters (defined as those who continued to have a diagnosis of MCI or progressed to a dementia). At one-year follow-up, 16% of the MCI sample reverted to normal cognition, 64% continued to have MCI, and 20% progressed to a dementia. Predictors of MCI reversion included higher MMSE scores, lower CDR-SOB and FAQ scores, and nonamnestic single domain subtype at baseline visit, as well as absence of *APOE* ε4 allele were predictive of reversion to normal cognition. Additionally, individuals who were younger, had more recent symptom onset, and had neither self-reported nor clinician-reported decline in memory showed increased likelihood of reversion at one-year. It should be noted that the authors combined reverters and those meeting criteria for *Impaired/Not MCI* (cognitive impairment that neither fully meets MCI criteria nor represents normal aging) and treated these clinically distinct groups as "<MCI" to denote reversion. Such categorization may potentially affect precision in identifying predictive variables among MCI participants who fully revert to normal cognition, which could also occur when comparing the reversion group to a group that combined individuals who continued to have a diagnosis of MCI with individuals who progressed from MCI to a dementia.

Sachdev and colleagues (2013) retrospectively studied MCI reversion by selecting a sample of participants (n = 320, age 70 to 90 years) from a previous population-based aging study (Sachdev et al., 2010) that included MCI participants meeting IWG criteria at baseline visit. Variables related to sociodemographic factors (age, gender, education level, and marital

status), lifestyle factors (alcohol use, smoking, and mental/physical/social activity), cardiac health (e.g., coronary artery disease, and blood pressure), physical health (e.g., body mass index, diabetes, and stroke), general health (e.g., smelling ability and visual acuity), *APOE* ε4 status, performance on a cognitive screen (MMSE) and other cognitive tests (where level of performance was categorized as "low," "mildly impaired," "moderately impaired," and "severely impaired" based on cognitive tests used in their 2010 study), source of cognitive complaint (self- or informant-reported), MCI subtype, regions of brain volume (hippocampus, amygdala, caudate, putamen, and cerebellum), and personality factors (neuroticism, openness, and conscientiousness) were analyzed using *t*- or χ^2-tests and logistic regression models. At two-year follow-up, 28% reverted to normal cognition, 5% progressed to a dementia, and 67% continued to have MCI. Comparing the group of reverters with non-reverters (i.e. only MCI stable group), the authors found that reversion was less likely for individuals with multiple-domain MCI, moderately or severely impaired cognitive performance, informant-reported memory complaint, and/or arthritis. Additionally, reversion was more likely for individuals with higher complex mental activity (average number of days per week engaging in activities such as reading books), greater openness to experience, better vision/smelling ability, larger combined left hippocampal and left amygdala volumes, and/or lower diastolic blood pressure.

Robert and colleagues (2014) examined data from a previous, prospective population-based aging study (Petersen, Roberts, et al., 2010; Roberts et al., 2008), where participants were of age 70-89 and had no diagnosis of dementia at initial visit. The primary aim of the study was to determine rates of MCI progression to dementia and rates of MCI reversion to normal cognition, although the authors also secondarily examined factors associated with reversion.

Participants underwent baseline evaluations that consisted of a clinical interview, assessments of functioning (FAQ and CDR-SOB) and mental status (Short Test of Mental Status), neurological exam, and neuropsychological test battery (measuring domains of memory, executive function, language, and visuospatial skills), where the scores were transformed to age-adjusted *z*-scores according to published norms (Ivnik et al., 1992). By using Cox proportional hazards models, they found that 38% of individuals with MCI reverted to normal cognition after a median follow-up period of five years. Predictors of reversion included being married, male gender, having zero copies of the *APOE* ε4 allele, higher global functioning (as assessed by FAQ and CDR-SOB), and higher neuropsychological performance.

Park and Han (2014) examined factors associated with MCI reversion over a two-year period in participants recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). A total of 1,233 participants (median age of 73 years) were separated into "clinically normal" (n = 413, 34%), "MCI reversion" (n = 42, 3%), and "MCI without reversion" (n = 778, 63%) groups based on ADNI MCI diagnostic criteria (Petersen, Aisen, et al., 2010). Of note, the "MCI without reversion" group refers to MCI stability, and there was no MCI progression group used for comparison. Each participant underwent a comprehensive evaluation, including assessment of demographic factors (e.g., age, gender, education level, marital status, MCI subtype, and medication use), AD biomarkers (e.g., *APOE* ε4, cerebrospinal fluid levels of amyloid beta, total number of tau proteins, and levels of phosphorylated tau), brain magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging, and brief cognitive testing (e.g., episodic memory). Despite a relatively small sample size for MCI reversion (n = 42), individuals in this group were

significantly younger, had higher MMSE scores, and lower CDR-SOB scores (suggesting greater global deficits) than the clinically normal group after a two-year follow-up period. Furthermore, the MCI reversion group had significantly fewer *APOE* ε4 alleles, fewer AD biomarkers (cerebrospinal fluid markers of amyloid-beta and tau proteins), larger hippocampal volumes, fewer white matter hyperintensities, and higher neuropsychological test scores than the MCI without reversion group, suggesting that the MCI reverters were more similar to the normal group than the MCI without reversion group (Park & Han, 2014).

Tokuchi and colleagues (2014) looked at predictors of reversion by selecting patients (n = 74, ages 58 to 89 years, median age = 79.0 years, and median education level = 12 years) from a computerized hospital database who had an MCI diagnosis based on ADNI criteria (Petersen, Roberts, et al., 2010). At one-year follow-up, 39.2% (n = 29) of these participants progressed to mild AD, 52.7% (n = 39) remained MCI, and 8.1% (n = 6) reverted to normal cognition. They found higher education level, higher baseline scores on a cognitive screen (MMSE), brain MRI findings of low-grade white matter lesions, and lower parahippocampal gyrus atrophy were associated with reversion from MCI to normal cognition. They also noted that due to a small sample size in this reversion group (n = 6), data was not normally distributed and nonparametric tests (including the use of median instead of mean values) were used to determine statistical significance.

Despite variability in study design (e.g. age group, participant composition, follow-up periods, and MCI definitions) across the above MCI reversion studies, overall findings are not unexpected when considering their reversed direction from the predictors found in MCI progression studies (e.g., higher education level for MCI reversion and lower education level for

MCI progression); yet additional studies are needed to further characterize MCI reversion. Additionally, there is a lack of data on whether endorsements of baseline neuropsychiatric symptoms may influence the likelihood of MCI patients reverting to normal cognition. Specific areas of medical health, such as hypertension, hypercholesterolemia, and body mass index (BMI), have also not been fully examined to determine their potential predictive value in reversion, particularly when combined with demographic variables for an overall dementia risk score (e.g. CAIDE dementia risk score). Furthermore, there appears to be limited research that includes a comprehensive examination of factors that are associated with reversion. Exploration of a comprehensive model including different areas (namely demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms) could improve overall evaluations of MCI patients with potential to revert to normal cognition, as studies of MCI have shown combined baseline factors, versus individual ones, are more accurate and strong in predicting MCI progression (Gomar et al., 2011; Gomar et al., 2014; Vellas et al., 2013).

The primary goal of the current study was to determine if baseline factors of MCI patients may help predict reversion to normal cognition by comparing those who reverted to normal cognition from MCI to those who progressed to a dementia. Of the available reversion studies, most involve a follow-up of less than two years; in contrast, this longitudinal study encompassed a three-year follow-up. Additionally, this study utilized a large, standard dataset (NACC) collected across 34 past and current Alzheimer's Disease Centers (ADCs) in the United States, which may enhance generalizability of findings.

Results from the current study may have several potential implications. First, the findings would help identify which individuals with MCI will be more likely to revert to normal cognition in efforts to further characterize potential protective factors from symptom-progression to dementia. Second, the findings would help patients and their families reduce distress and fears regarding MCI association with future dementia, set appropriate expectations regarding cognitive functioning (e.g. determining how many more years an MCI patient can potentially work before retirement), as well as educate patients and their families regarding the extent to which cognitive symptoms may improve. Third, identifying predictors of reversion may inform healthcare providers the course of clinical management and prognosis (e.g. determining need for anti-dementia medications, frequency of future clinical visits, and level of monitoring required). Fourth, the findings would potentially improve participant selection criteria in early intervention studies of dementia in order to increase robustness (e.g., by excluding MCI patients who are likely to revert) and improve precision of findings. As such the ability to predict MCI patients' likelihood of reverting to normal cognition is important.

CHAPTER TWO

Aims and Hypotheses

To determine potential predictors of MCI reversion to normal cognition, this study examined factors separated into clusters related to baseline demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms. Specifically, a total of six hypotheses were formulated under the following overall aim:

Overall Aim:

To determine if baseline factors in MCI patients may help predict reversion to normal cognition by comparing those who reverted to normal cognition from MCI to those who progressed to a dementia.

Aim 1: To determine whether baseline demographic and genetic characteristics predict reversion.

Hypothesis 1: MCI reverters will be younger, have higher education, are married, have zero copies of the *APOE* ε4 allele, and be diagnosed with nonamnestic MCI subtype at baseline.

Aim 2: To determine whether baseline global functioning scores predict reversion.

Hypothesis 2: Higher Mini Mental State Exam (MMSE) scores, lower Clinical Dementia Rating Sum of Boxes (CDR-SOB) scores, and lower Functional Assessment Questionnaire (FAQ) total scores at baseline will predict reversion to normal cognition.

Aim 3: To determine whether baseline neuropsychological functioning predicts reversion.

Hypothesis 3: Higher baseline standard scores on neuropsychological tests of memory (Logical Memory Story A immediate and delayed recall trials), executive functioning (Trail Making Test Parts A and B), processing speed (Digit Symbol), language (Animal Fluency, Vegetable Fluency, and Boston Naming Test), and attention (Digit Span Forward and Backward total correct trials) will predict reversion to normal cognition.

Aim 4: To determine whether baseline CAIDE dementia risk score (comprised of demographic and medical variables) predicts reversion.

Hypothesis 4: Lower CAIDE dementia risk scores at baseline will predict reversion to normal cognition.

Aim 5: To determine whether baseline symptom severity scores of neuropsychiatric symptoms predict reversion.

Hypothesis 5: Lower baseline symptom severity scores on neuropsychiatric symptoms of depression, anxiety, and apathy in the Neuropsychiatric Inventory Questionnaire (NPI-Q) will predict reversion to normal cognition.

Aim 6: To determine the most the significant predictors derived from each of the above five clusters/hypotheses (demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms), enter them in a comprehensive statistical model, and determine the most significant predictors of MCI reversion to normal cognition.

Hypothesis 6: Younger age, higher education level, zero copies of the *APOE* ε4 allele, nonamnestic MCI, higher levels of global functioning, higher standard scores on neuropsychological tests, lower CAIDE dementia risk scores, and lower symptom severity scores on symptoms of depression/anxiety/apathy at baseline will be the most significant predictors of MCI reversion to normal cognition.

CHAPTER THREE

Methodology

Setting and Participants

The National Alzheimer's Coordinating Center (NACC) resource (NIA U01 AG016976) was established in 1999 and contains data from 34 past and current Alzheimer's Disease Centers (ADCs) across the United States, funded by the National Institute on Aging (NIA). NACC data are freely available to all researchers. Since September 2005, the ADCs have been contributing data to the NACC using a prospective, standardized, and longitudinal clinical evaluation protocol known as Uniform Data Set (UDS). The clinic-based population includes participants with Alzheimer's disease and related disorders (e.g., vascular dementia, Lewy body dementia, and frontotemporal lobar degeneration), as well as cognitively normal subjects and those with MCI. Written informed consent was obtained from all participants and informants by each ADC.

The current longitudinal project utilized a UDS dataset of MCI individuals submitted from each participating ADC to the NACC between September 2005 and July 2013. Full description of the UDS clinical evaluation form packet and documentation are on the NACC web site at https://www.alz.washington.edu/WEB/forms_uds.html in PDF format only.

This study's inclusion criteria included participants who were diagnosed with MCI at baseline visit, and had three annual follow-up visits (i.e., reassessments). NACC used the following standard MCI criteria (Fleisher et al., 2005; Winblad et al., 2004): 1) cognitive concern by the subject or informant; 2) clinician's impression or evidence of cognitive decline via

objective testing; 3) abnormal cognition (neither normal nor demented); and 4) preserved functional activities via consensus or clinician diagnosis of MCI (Figure 1).

Exclusion criteria included participants who were diagnosed with MCI at baseline but subsequently had an evaluation via telephone call (instead of an in-person visit) at 2nd and/or 3rd follow-up visits. Reason for excluding these participants via telephone is the absence of a full set of clinical data (cognitive, neuropsychiatric, and/or functional), resulting in an incomplete UDS protocol and potentially imprecise diagnosis (i.e., not meeting full MCI criteria). The UDS also contains a diagnostic variable known as *Impaired/Not MCI* to describe a subset of participants as falling in an intermediate state between normal cognition and MCI (http://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/tfpguide.pdf, Form D1, section 4e). Because *Impaired/not MCI* appears to represent a poorly-defined diagnostic group, participants categorized with *Impaired/Not MCI* at 2nd and/or 3rd follow-up visits were excluded.

Participants who were diagnosed with MCI at baseline visit and had three subsequent annual follow-up visits were assigned to one of the three clinical outcome groups: 1) *MCI reversion* if they were classified as *normal* (i.e., normal cognition) at both 2nd and 3rd follow-up visits, regardless of the diagnostic status at 1st follow-up visit; 2) *MCI progression* if they were diagnosed at both 2nd and 3rd follow-up visits as demented, regardless of the diagnostic status at 1st follow-up visit; 3) *MCI stability* if they remained diagnosed with MCI at both 2nd and 3rd follow-up visits, regardless of MCI subtype (i.e., amnestic and non-amnestic) or of the diagnostic status at 1st follow-up visit.

Clinical Evaluation

The UDS clinical evaluation form packet includes measures that assess multiple areas, including global functioning, neuropsychological functioning, neuropsychiatric functioning, and medical health variables. The packet also provides information on participant characteristics (e.g., age, gender, ethnicity, education level, marital status, and *APOE* ε4 status), MCI subtype, and source of cognitive complaint (subject- or informant-reported). Selected variables in the UDS packet relevant to the current study are presented in the following clusters below:

Demographic/Genetic Data

The following baseline participant demographic information from UDS form packet (Form A1) was included in the current study: age, gender, ethnicity, level of education, and marital status. In addition, information regarding participant *APOE* ε4 status was obtained via NACC form of *Derived Variables* (https://www.alz.washington.edu/WEB/dervarprev.pdf), which was created by the NACC Research Support Group in order to aid researchers in analysis of NACC data. Specifically, the following *APOE* ε4 status was used: "0" = zero copies of ε4 allele and "1" = at least 1 copy of ε4 allele. MCI diagnosis at baseline visit was also used in the analyses and was subdivided into two subtypes, amnestic versus nonamnestic, irrespective of the number of cognitive domains with impairments (i.e., single versus multiple) (Form B9).

Global Functioning

Baseline scores from the following assessments of global functioning were included: Clinical Dementia Rating Sum-of-Boxes score (CDR-SOB, Form B4), Functional Assessment

Questionnaire (FAQ, Form B7) total score, and Mini Mental State Exam total score (MMSE, Form C1). Detailed descriptions of the CDR-SOB, FAQ, and MMSE are provided in Appendix A.

Neuropsychological Functioning

The neuropsychology test battery in the UDS form packet (Form C1) assesses the domains of episodic memory, attention, working memory (i.e., mental manipulation of information), language (i.e., object naming, verbal fluency, and semantic categorization), executive function (i.e., mental set shifting), processing speed, and visual scanning abilities (Weintraub et al., 2012). Raw scores were demographically adjusted (age, education, and gender) using the published UDS normative data (Shirk et al., 2011) for the following neuropsychological tests: Trail Making Test, Parts A and B (TMT A and B), Wechsler Memory Scale-Revised (WMS-R) Logical Memory Story A, WMS-R Digit Span (forward and backward total correct trials), Animal Fluency, Vegetable Fluency, Boston Naming Test (BNT, 30 items), and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol. See Appendix A for a more detailed description of each measure.

Medical Health/Dementia Risk Score

The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) dementia risk score is comprised of demographic and medical variables that are considered risk factors for dementia. The developers of this measurement assigned a weighted score to each variable: age (score "0" = less than 47 years, "3" = 47-53 years, or "4" = greater than 53 years), education (score "0" =

greater than or equal to 10 years, "2" = 7-9 years, or "3" = 0-6 years), gender (score "0" = female or "1" = male), systolic blood pressure (score "0" = less than or equal to 140 mm Hg or "2" = greater than 140 mm Hg), body mass index (score "0" = less than or equal to 30 kg/m^2 or "2" = greater than 30 kg/m^2), and total cholesterol (score "0" = less than or equal to 6.5 mmol/L or "2" = 6.5 mmol/L) (Kivipelto et al., 2006). CAIDE risk score is calculated by summing the weighted scores across all risk factors, with higher scores representing an increased risk for dementia and lower scores representing a decreased risk for dementia.

Neuropsychiatric Symptoms

The Neuropsychiatric Inventory Questionnaire (NPI-Q) is an informant-based interview assessing the type and severity of neuropsychiatric/behavioral symptoms in dementia patients (Cummings et al., 1994; Kaufer et al., 2000). The NPI-Q includes two scores: a) presence of symptoms ("0" = No and "1" = Yes) and b) symptom severity ("0" = none, "1" = mild, "2" = moderate, and "3" = severe) for each of the following 12 symptoms: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor behaviors (e.g., repetitive activities like pacing, handling buttons, and wrapping string), sleeping behaviors (e.g., awaken during the night, rise too early, and take excessive naps), and appetite (Cummings et al., 1994; Kaufer et al., 2000). For this study, baseline symptom severity scores (ranging from "0" to "3" as described above) for the symptoms of depression, anxiety, and apathy were used. Detailed descriptions for each symptom are found in Form B5 in the UDS packet.

Data Management and Statistical Analyses

Descriptive statistics and comparisons between MCI reversion and progression groups at the univariate level were conducted for baseline data, using two independent sample *t*-tests for continuous variables and χ^2-tests for categorical variables. Mann-Whitney U test as a non-parametric approach was used when variables of measures were not normally distributed. At the multivariate level, a stepwise logistic regression model was used for each cluster, as described below, with selected demographic variables as covariates. To determine which covariates to include, a set of demographic variables (i.e., age, gender, ethnicity, and education) were entered into a separate logistic regression model in a stepwise fashion. All statistical analyses were performed using IBM SPSS Statistics version 21 and two-sided .05 α level was set as a criterion for statistical significance. Missing data were managed via pairwise exclusion.

Hypothesis 1: Demographic/Genetic Data

To examine the hypothesis that MCI reverters will be younger, have higher education, be married, have zero copies of the *APOE* ε4 allele, and be diagnosed with nonamnestic MCI subtype at baseline, a binary stepwise logistic regression model was performed, with the dichotomized MCI outcome variable at three-year follow-up as MCI reversion group versus progression group.

Hypothesis 2: Global Functioning

To examine the hypothesis that higher MMSE scores, lower CDR-SOB scores, and lower FAQ total scores at baseline will predict reversion to normal cognition, a binary stepwise logistic

regression model was performed, with the outcome variable as MCI reversion group versus progression group. Age, gender, ethnicity, and/or education were used as covariates.

Hypothesis 3: Neuropsychological Functioning

It was hypothesized that higher baseline standard scores on neuropsychological tests of memory (Logical Memory Story A immediate and delayed recall trials), executive functioning (Trail Making Test Parts A and B), processing speed (Digit Symbol), language (Animal Fluency, Vegetable Fluency, and Boston Naming Test), and attention (Digit Span Forward and Backward total correct trials) will predict reversion to normal cognition. To determine if baseline neuropsychological test scores predict MCI reversion, demographically adjusted scores were entered in a stepwise fashion in a binary logistic regression model, with the outcome variable as MCI reversion group versus progression group. Demographic covariates were not used since all neuropsychological test scores have been demographically adjusted (Shirk et al., 2011).

Hypothesis 4: Medical Health/Dementia Risk Score

To test the hypothesis that lower CAIDE dementia risk scores at baseline will predict reversion to normal cognition, a binary stepwise logistic regression model was performed, with the outcome variable as MCI reversion group versus progression group. Demographic covariates were not used since age, gender, and education are variables contributing to the overall CAIDE dementia risk score.

Hypothesis 5: Neuropsychiatric Symptoms

To examine the hypothesis that lower baseline symptom severity scores on neuropsychiatric symptoms of depression, anxiety, and apathy in the Neuropsychiatric Inventory Questionnaire (NPI-Q) will predict reversion to normal cognition, a binary stepwise logistic regression model was performed, with the outcome variable as MCI reversion group versus progression group. Age, gender, ethnicity, and/or education were used as covariates.

Hypothesis 6: Comprehensive Model of Prediction

Younger age, higher education level, zero copies of the *APOE* ε4 allele, nonamnestic MCI, higher levels of global functioning, higher standard scores on neuropsychological tests, lower CAIDE dementia risk scores, and lower symptom severity scores of depression/anxiety/apathy at baseline were hypothesized to be the most significant predictors of MCI reversion to normal cognition. This was examined using a binary logistic regression model with the outcome variable as MCI reversion group versus progression group. Furthermore, receiver operating characteristic (ROC) curves were used to determine cut-off scores for the continuous predictors and evaluate their prognostic value for reversion from MCI to normal cognition.

For the ROC curves, an area under the curve (AUC) of 0.50-0.60 was considered as a "failed" test at discriminating the MCI reversion group from the progression group, while an AUC of 0.60-0.70 was considered as "poor," 0.70-0.80 as "fair," 0.80-0.90 as a "good," and 1.0 as "perfect" classification (Greiner, Pfeiffer, & Smith, 2000; Swets, 1988).

CHAPTER FOUR

Results

A study flowchart that describes the selection of the final sample is presented in Figure 2. A total of 1,778 participants were diagnosed with MCI at baseline visit, from which 1,208 participants (68%) were selected for this study after inclusion and exclusion criteria were applied. Of these 1,208 participants, 175 (14%) reverted from MCI to normal cognition at 2nd follow-up visit and remained normal at 3rd follow-up visit (*MCI reversion*), 612 (51%) remained MCI at 2nd follow-up visit and had sustained MCI diagnosis at 3rd follow-up visit (*MCI stability*), and 421 (35%) progressed to dementia at 2nd follow-up visit and remained demented at 3rd follow-up visit (*MCI progression*).

Of the 570 (32%) participants who were excluded, 93 underwent an evaluation via telephone call at 2nd and/or 3rd follow-up visits, 146 received a diagnosis of *Impaired/Not MCI* at 2nd and/or 3rd follow-up visits, and 331 did not have the same diagnostic classification during their 2nd and 3rd follow-up visits (e.g., classified under *MCI reversion* during 2nd follow-up visit but then as *MCI stability* during 3rd follow-up visit). Because the purpose of this study is to examine baseline predictors of MCI reversion compared to MCI progression, participants who remained diagnostically stable (i.e., *MCI stability*, n = 612) were excluded. Therefore, a total of 1,182 (66%) participants from the initial 1,778 MCI participants at baseline visit were excluded from the study, and a final sample of 596 (34%) participants was used for univariate and multivariate analyses. Among these final 596 MCI participants, 175 (29%) were in the *MCI reversion* group and 421 (71%) in the *MCI progression* group.

Of note, no participant in this final sample underwent an evaluation via telephone call at baseline visit. Baseline demographic characteristics are presented in Table 1. Specific types of dementia for the MCI progression group are presented in Table 2. Outcome variable in the multivariate analysis was a binary classification of diagnostic status: MCI reversion or progression.

Univariate Analyses

Demographic/Genetic Data

There were no significant differences in terms of education level and ethnicity between the MCI reversion and progression groups. However, the MCI reversion group was significantly younger at baseline visit, had fewer females, had fewer copies of the *APOE* ε4 allele, and had more participants with nonamnestic MCI subtype than the MCI progression group (Table 1).

Global Functioning

There were significant differences between the MCI reversion and progression groups at baseline for CDR-SOB, FAQ, and MMSE (Table 3). The MCI reversion group had lower scores on CDR-SOB and FAQ and higher scores on MMSE than the MCI progression group.

Neuropsychological Functioning

The MCI reversion group had significantly higher baseline standard scores across all neuropsychological tests (i.e., Logical Memory Story A immediate and delayed recall trials, Trail Making Test Parts A and B, Digit Symbol Test, Animal Fluency, Vegetable Fluency, Boston

Naming Test, and Digit Span Forward and Backward total correct trials) than the MCI progression group (Table 4).

Medical Health/Dementia Risk Score

There were no significant differences for the baseline CAIDE dementia risk score between MCI reversion (M = 6.85, SD = 1.88) and progression (M = 6.71, SD = 1.90) groups, $t(522) = -0.77$, $p = 0.44$.

Neuropsychiatric Symptoms

There were no significant differences for baseline symptom severity scores on depression, anxiety, and apathy between MCI reversion and progression groups (Table 5).

Multivariate Analyses

Covariates

Age, gender, ethnicity, and education were entered into a binary stepwise logistic regression model. Results showed that age, gender, and ethnicity were significantly associated with the MCI groups of reversion and progression. Thus, they were selected as covariates in the stepwise logistic regression models for each of the clusters further described below (Table 6).

Demographic/Genetic Data

The binary stepwise logistic regression model of demographic/genetic data showed that younger age, female gender, being unmarried, diagnosed as nonamnestic MCI, and having zero

copies of the *APOE* ε4 allele at baseline were significantly associated with MCI reversion (Table 7). Age, gender, and ethnicity were not used as covariates because these variables were already entered into this model.

Global Functioning

Lower CDR-SOB and FAQ scores and higher MMSE scores at baseline were significantly associated with reversion when entered into a binary stepwise logistic regression model with age, gender, and ethnicity as covariates. Of the covariates in this model, younger age and Hispanic ethnicity were significantly associated with MCI reversion (Table 8).

Neuropsychological Functioning

Of the neuropsychological tests scores entered into a binary stepwise logistic regression model, higher scores on WMS-R Logical Memory Story A Delayed Recall, Vegetable Fluency, WAIS-R Digit Symbol, and Boston Naming Test at baseline were significantly associated with MCI reversion (Table 9). Age, gender, and ethnicity were not entered as covariates because all neuropsychological test scores have been adjusted using demographic information of gender, age, and education (Shirk et al., 2011).

Medical Health/Dementia Risk Score

The binary stepwise logistic regression model for CAIDE dementia risk score showed that CAIDE risk score at baseline was not significantly associated with MCI reversion (OR =

1.04; 95% CI = 0.94-1.15). Age, gender, and ethnicity were not entered as covariates in the model because age and gender are variables contributing to the overall CAIDE risk score.

Neuropsychiatric Symptoms

The binary stepwise logistic regression model for neuropsychiatric symptoms showed that lower symptom severity scores on depression, anxiety, and apathy at baseline were significantly associated with MCI reversion, after adjusting for the covariates of age, gender, and ethnicity. Among these covariates, younger age and female were significantly associated with MCI reversion (Table 10).

Comprehensive Model of Prediction

The overall binary stepwise logistic regression model included the significant predictors from the above five clusters: demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms. Results revealed that younger age, being unmarried, having zero copies of the *APOE* ε4 allele, lower CDR-SOB scores, and higher test scores on WMS-R Logical Memory Story A Delayed Recall, Vegetable Fluency, and Boston Naming Test at baseline were the overall factors that were significantly associated with MCI reversion (Table 11).

Figures 3, 4, and 5 show the results of receiver operating characteristic (ROC) curves for the continuous variables that were significantly associated with MCI reversion found in the comprehensive model (i.e., age, CDR-SOB, WMS-R Logical Memory Story A Delayed Recall, Vegetable Fluency and Boston Naming Test). ROC curve results showed that WMS-R Logical

Memory Story A Delayed Recall standard *z*-score of -1.16 or better would accurately classify the MCI reversion group from the MCI progression group with 89% sensitivity and 73% specificity (Figure 5). Thus, a *z*-score of -1.16 is considered a valid cutoff value for Logical Memory Story A Delayed Recall standard test score and as a diagnostic criterion for discriminating the MCI reversion group from the progression group. While CDR-SOB had an AUC of 0.85 (95% CI = 0.81-0.88), which is considered a "good" test at discriminating the MCI reversion group from the progression group, the small range of scores led to a skewed distribution of values for the ROC curve (Figure 4); therefore, a cutoff value was not established for this variable. Also, while Vegetable Fluency had an AUC of 0.72 (95% CI = 0.68-0.77), which is considered a "fair" test, a cutoff score was not appropriate in this study due to a very low sensitivity (41%) and high specificity (89%) (Figure 5).

ROC curve analyses for age (AUC = 0.62 [95% CI = 0.57-0.67], Figure 3) and Boston Naming Test (AUC = 0.62 [95% CI = 0.57-0.67], Figure 5) showed AUC values within the range of 0.60-0.70, which indicates "poor" classification of the MCI reversion group from the progression group; therefore, cutoff scores were not reported for these two variables in this study.

CHAPTER FIVE

Discussion

Limited studies have characterized reversion from MCI to normal cognition. The overall aim of this retrospective, clinic-based study, using data from past/current 34 ADCs across the country, was to examine a variety of factors in order to identify predictors of MCI reversion over three-years.

A total of 1,778 were diagnosed with MCI at baseline visit. After applying inclusion and exclusion criteria, 1,208 participants were selected for this study. At two-year follow-up, 175 (14%) of these participants reverted from MCI to normal cognition and remained normal at three-year follow-up, 612 (51%) remained MCI and had a sustained diagnosis at three-year follow-up, and 421 (35%) progressed to dementia and remained demented at three-year follow-up. This study specifically focused on MCI reversion and progression groups (596 total participants).

The incident rate of reversion at two-years was 14% of the 1,208 MCI participants, with continued normal cognition at three-year follow-up. This incident reversion rate of 14% is within the rates of reversion found in other clinic-based MCI studies ranging from 3% to 16% (Koepsell & Monsell, 2012; Park & Han, 2014; Tokuchi et al., 2014) and is similar to the reversion rate of 16% found by Koepsell and colleagues (2012) over one-year follow-up. There are several possible reasons for a relatively large range of reversion rates (3% to 16%) across studies. One reason why the reversion rate may be higher in the current study than the other MCI reversion studies is due to the incorporation of a large sample size of only patients who

were diagnosed with MCI at baseline visit, compared to Tokuchi and colleagues (2014) who used a relatively small sample size of 74 MCI patients, out of whom 8% reverted to normal cognition. Additionally, the present study did not include cognitively normal individuals in the overall sample, unlike Park and Han (2014) who revealed a reversion rate of 3% with cognitively normal individuals included in their sample. Inclusion of cognitively normal individuals would have likely lowered the rate of reversion in the current study. It is also important to note that this study defined MCI reversion as those being classified as "normal" at 2nd follow-up visit and remaining "normal" at 3rd follow-up visit (and progression as a diagnosis of dementia at 2nd follow-up visit and remaining demented at 3rd follow-up visit) versus Roberts and colleagues' (2014) definition of reversion as the first time an MCI patient reverted within their study's median follow-up period of five years.

A total of 421 (35%) of the 1,208 MCI participants progressed to a dementia after two years and remained demented at three-year follow-up. This finding is lower than a prior study that followed MCI patients over 12 years and found a progression rate of 54% within three years (Lopez et al., 2012). These incident progression rates are discrepant, likely because of the differing populations of interest at baseline visit. The present study is a clinic-based, case-control study that examined individuals diagnosed with MCI at baseline visit, while Lopez and colleagues (2012) created an epidemiological study that examined cognitively normal individuals at baseline visit. Nonetheless, it is likely that if the 421 participants in the MCI progression group of the current study were followed for a longer period of time, the rate of progression would possibly approximate to that of Lopez and colleagues, in context of the proposed annual rate of progression being 10% (Mitchell & Shiri-Feshki, 2009).

Overall, the wide range of reversion and progression rates noted in the MCI literature could be due to a number of factors, such as recruitment method (clinic- versus community-based), the composition of MCI samples (e.g., mixing MCI stable and reversion individuals and treating them as "reverters," combining MCI stable and progression individuals as "non-reverters," or including both amnestic and nonamestic MCI individuals versus amnestic only), differing definitions for MCI diagnosis (e.g., based on IWG/ADNI/NIA-AA/ Mayo Clinic's 1997 or 2004 criteria or CDR Global score), and variable follow-up lengths (one-year to 12-year follow-up). Additionally, MCI studies have varied in their definition of the time point at which MCI reversion or progression occurred. For example, some studies clearly defined these time points as one or two years after MCI diagnosis (Koepsell & Monsell, 2012; Sachdev et al., 2013) while others noted that reversion occurred within a median follow-up period (e.g., median of five years in Roberts et al., 2014) or within a span of time (e.g., 12-year period in Lopez et al., 2012) without reporting the annual reversion (or progression) rate or the specific number of years at which reversion (or progression) occurred. Therefore, determining accurate rates of reversion and progression is difficult because there appears to be a lack of consistency in the literature as to how long after MCI diagnosis these trajectories occurred. Furthermore, the majority of the studies did not report the number of MCI individuals who followed varying trajectories during the follow-up period (e.g., MCI–normal–MCI or MCI–normal–MCI–dementia). These "unstable" trajectories could affect the rates of reversion and progression and warrant further study. Thus far, Lopez and colleagues (2012) and Roberts and colleagues (2014) have reported these "unstable" trajectories among their MCI patient samples, although without reporting the specific time points at which they occurred. Regardless, their findings are a starting point in

understanding how the rates of MCI reversion and progression for their "unstable" courses can differ from their linear trajectories (i.e., MCI to normal cognition or MCI to dementia).

Predictors of MCI Reversion

At the multivariate level, the current study identified a number of factors within the clusters of demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms that were significantly associated with MCI reversion over a three-year follow-up.

Demographic/Genetic Data

Younger age, female gender, being unmarried, diagnosed as nonamnestic MCI subtype, and having zero copies of the *APOE* ε4 allele were significantly associated with MCI reversion and are partially consistent with *Hypothesis 1*: MCI reverters will be younger, have higher education, are married, have zero copies of the *APOE* ε4 allele, and be diagnosed with nonamnestic MCI subtype at baseline. The present results are generally in agreement with previous MCI reversion literature (Koepsell & Monsell, 2012; Park & Han, 2014; Roberts et al., 2014), suggesting that age, non-memory cognitive symptoms, and lack of a genetic predisposition to neurodegenerative processes increase the likelihood of an MCI individual improving in their cognitive functioning.

Level of education was not associated with MCI reversion, which could be due to both the reversion and progression groups having a high level of education (mean of 15 years in each group). Similarly, this finding is consistent with other studies that did not find a relationship

between education and MCI reversion (Koepsell & Monsell, 2012; Park & Han, 2014; Sachdev et al., 2013).

MCI reverters were also more likely to be unmarried, which is in contrast to a previous MCI reversion finding (Roberts et al., 2014) where being married was predictive of reversion. Though Roberts and colleagues did not provide reasons as to why being married was a predictor of MCI reversion, this could possibly be explained by a slower rate of cognitive decline as mediated by a spouse who can provide the patient with social support and intellectual stimulation (Hakansson et al., 2009). However, stressful qualities of the marital relationship (e.g., caregiver stress that patient is not following instructions and patient stress over the belief that the caregiver is not taking sufficient care of them) may independently contribute to cognitive decline (Lee et al., 2014). The current study was not designed to assess the quality of the marital relationship between MCI participants and their spouses because such information was not available. Further, this study defined marital status as "married" or "not married," and did not report the subcomponents of the "not married" category (i.e., "widowed," "divorced," "separated," "never married," "living as married," or "other") due to a low number of individuals within each subcategory.

In regards to gender, the present study found that being female was significantly associated with reversion, which is in contrast to a prior MCI reversion study that found males are associated with reversion (Roberts et al., 2014). This could be due to a higher number of females than males in the current study as compared to higher males than females in the prior study. Since the present study's findings on marital status and gender conflict with available

studies on predictors of MCI reversion, these two variables need further characterization in future MCI reversion research.

Global Functioning

Lower CDR-SOB and FAQ scores and higher MMSE scores at baseline, all of which suggest higher functioning in independent activities of daily living, were significantly associated with MCI reversion and are consistent with *Hypothesis 2*: higher MMSE scores, lower CDR-SOB scores, and lower FAQ total scores at baseline will predict reversion to normal cognition. The current results were also consistent with those of available studies of MCI reversion (Koepsell & Monsell, 2012; Park & Han, 2014; Roberts et al., 2014; Tokuchi et al., 2014). Further, univariate level of analyses indicated that MCI reverters had higher functioning at baseline than MCI progressors as demonstrated by these three measures. This suggests that patients who did not demonstrate global difficulties at baseline were more likely to improve in their cognitive abilities than patients who did have such difficulties, though not to the extent of interfering with ADLs.

Neuropsychological Functioning

Higher baseline standard scores on tests of delayed memory (WMS-R Logical Memory Story A Delayed Recall), language (Vegetable Fluency and Boston Naming Test), and processing speed (WAIS-R Digit Symbol) were significantly associated with MCI reversion and are partially consistent with *Hypothesis 3*: higher baseline standard scores on neuropsychological tests of memory (Logical Memory Story A immediate and delayed recall trials), executive

functioning (Trail Making Test Parts A and B), processing speed (Digit Symbol), language (Animal Fluency, Vegetable Fluency, and Boston Naming Test), and attention (Digit Span Forward and Backward total correct trials) will predict reversion to normal cognition. The current results are consistent with another MCI reversion study (Roberts et al., 2014), which found higher scores on tests of delayed memory (WMS-R Logical Memory Delayed Recall and Visual Reproduction Delayed Recall) and language (Boston Naming Test and category fluency) to be predictive of reversion. Roberts and colleagues (2014) also found tests of executive function (Trail Making Test and WAIS-R Digit Symbol) to be significantly predictive of reversion, though Trail Making Test was not significantly associated in the present study. It should be noted that processing speed was assessed via the WAIS-R Digit Symbol (Weintraub et al., 2009), while Roberts and colleagues utilized this test along with Trail Making Test Part B as measures of executive function. It is difficult to determine reasons for the discrepant findings on the Trail Making Test, but one reason could be that the current study did not combine the time score with the number of errors made in the multivariate model (Ashendorf et al., 2008), and it is unclear if Roberts and colleagues did the same. In general, though, overall findings support the notion that higher performances in multiple cognitive domains are associated with MCI reversion.

Immediate verbal memory (WMS-R Logical Memory Story A immediate recall) at baseline was not significantly associated with MCI reversion at the multivariate level, suggesting that learning/encoding abilities are not significant predictors of reversion. Additionally, attention (WMS-R Digit Span subtest) was not predictive of MCI reversion, likely because such a cognitive skill remains relatively intact even amongst individuals who are mildly demented and

that attention deficiency may become more apparent as the disease progresses (Cherry, Buckwalter, & Henderson, 2002).

In examining semantic verbal fluency tasks, Vegetable Fluency was significantly associated with MCI reversion while Animal Fluency was not. Although these two tests seemingly measure similar constructs (category or semantic fluency), Vegetable Fluency requires more cognitive effort than Animal Fluency (Bayles et al., 1989; Bolla, Gray, Resnick, Galante, & Kawas, 1998; Brandt & Manning, 2009), suggesting that MCI reverters do better on more difficult versions of category fluency tests than progressors.

Medical Health/Dementia Risk Score

To date, no studies have examined the CAIDE dementia risk score's association with MCI reversion or progression, although this score predicts risk of developing dementia in people with normal cognition. This study found that the CAIDE risk score, which is comprised of demographic and medical variables, was not significantly associated with MCI reversion and does not support *Hypothesis 4*: lower CAIDE dementia risk scores at baseline will predict reversion to normal cognition. This non-significant result may be due to a couple of reasons. First, the CAIDE risk score was originally developed by using a sample of middle-aged (mean age 50 years) individuals with normal cognitive functioning who were followed for 20 years, while the current study incorporated MCI individuals with a mean age of 74 years who were followed for three years. As such, it is possible that this risk score is useful in predicting MCI reversion (and progression) if our sample is limited to middle-aged adults who have MCI and are followed longitudinally. Second, other risk scores such as the Framingham vascular risk score

(Elias et al., 2004; Unverzagt et al., 2011) has been shown to be a more superior predictor of dementia than the CAIDE risk score (Kaffashian et al., 2013) and, therefore, may be a better predictor of reversion than CAIDE in the current patient sample. This study used the CAIDE dementia risk score because it is a valid measure in predicting risk of dementia (Exalto et al., 2014; Kivipelto et al., 2006), along with the NACC UDS standardized protocol's inclusion of variables that contributed to the overall risk score.

Neuropsychiatric Symptoms

Lower symptom severity scores on depression, anxiety, and apathy at baseline were significantly associated with MCI reversion, which is consistent with *Hypothesis 5*: lower baseline symptom severity scores on neuropsychiatric symptoms of depression, anxiety, and apathy in the NPI-Q will predict reversion to normal cognition. A number of studies on cognitive decline have revealed that baseline levels of depression, anxiety, and apathy (Diniz et al., 2013; Jorm, 2001; Richard et al., 2013; Somme et al., 2013) are significant predictors of progression towards a dementia, which can be explained by underlying neurodegenerative processes. For example, one study revealed that MCI combined with depressive and anxiety symptoms have an underlying neural mechanism (presence of amyloid plaques and neurofibrillary tangles) that is different from these neuropsychiatric symptoms without MCI (Lavretsky et al., 2009). Another study indicated that lesions in the anterior thalamic radiation are associated with apathy among MCI patients (Torso et al., 2015). Thus, it is possible that relatively less severe mood symptoms in MCI reverters may not have these underlying neuroanatomical or neuropathological changes, although this idea needs empirical support.

The current findings disagree with a previous MCI reversion study on depression as a predictor of reversion. Specifically, Koepsell and colleagues (2012) did not find a significant association between depression and MCI reversion through the use of the Geriatric Depression Scale (GDS 15-item version). However, these varied results may be due to the fact that the present study measured depression via an informant-reported single severity score from the NPI-Q, while the GDS is a self-reported measure that covers 15 symptoms of depression (e.g., sadness, worthlessness, fatigue, etc.). As such, different neuropsychiatric outcomes are possible depending on the neuropsychiatric measurement used and the source from which symptoms are reported (i.e., patient versus informant).

Comprehensive Model of Prediction

Seven baseline variables were found to be significantly associated with MCI reversion among the 15 total significant factors identified from the above five clusters (demographic/genetic data, global functioning, neuropsychological functioning, medical health/dementia risk score, and neuropsychiatric symptoms). They included 1) younger age, 2) being unmarried, 3) having zero copies of the *APOE* ε4 allele, 4) lower CDR-SOB scores, and higher standard test scores on 5) WMS-R Logical Memory Story A Delayed Recall, 6) Vegetable Fluency, and 7) Boston Naming Test. These findings suggest that MCI reversion is a function of a combination of factors from the clusters of demographic/genetic data, global functioning, and neuropsychological functioning.

The significant continuous variables (i.e., age, CDR-SOB score, WMS-R Logical Memory Story A Delayed Recall score, Vegetable Fluency score, and Boston Naming Test

score) were each subjected to ROC analyses to establish cutoff values that would accurately classify MCI reversion from MCI progression, and, in turn, predict reversion. Results indicated Logical Memory Story A Delayed Recall was the sole predictor that could accurately classify MCI individuals into the reversion group versus the progression group, using a cutoff score of $z \geq -1.16$. This result is in agreement with findings by Gomar and colleagues (2011), who used a comprehensive model to predict MCI progression to AD that included demographic/genetic risk factors, global functioning scores, brain volumetrics, and neuropsychological tests. They found that tests of delayed verbal memory (WMS-R Logical Memory and Rey Auditory Verbal Learning Test) and left middle temporal lobe cortical thickness and were the most significant predictors of MCI progression to AD over two-year follow-up. Thus, delayed verbal memory is an important and accurate predictor for both MCI reversion and progression.

While the above variables maintained a significant association with MCI reversion at the comprehensive level of analysis, 1) gender, 2) MCI subtype, 3) FAQ score, 4) MMSE score, 5) WAIS Digit Symbol score, and symptom severity scores for 6) depression, 7) anxiety, and 8) apathy were no longer significantly associated with reversion. Although these eight predictors were significant in the initial separate models for each cluster, the final model's inclusion of all the significant predictors allowed for a multifactorial/dimensional framework that caused certain variables across clusters to correlate with each other. This, in turn, ultimately rendered these eight variables as non-significant because the variance they initially contributed was accounted for by the seven significant variables within the model (i.e., younger age, being unmarried, having zero copies of the *APOE* ε4 allele, lower CDR-SOB scores, and higher standard test scores on WMS-R Logical Memory Story A Delayed Recall, Vegetable Fluency, and Boston

Naming Test). A comprehensive model of prediction is preferred versus individual cluster-based since the present data suggest MCI reversion, like progression (Gomar et al., 2011), is affected by multiple factors. Simply put, a multifactorial/dimensional approach is necessary in understanding MCI reversion.

Study Strengths

There are several strengths in the current study. First, this study is the first to incorporate a large clinical sample with a follow-up period of three years, which is longer than the majority of available MCI reversion studies (Koepsell & Monsell, 2012; Park & Han, 2014; Sachdev et al., 2013; Tokuchi et al., 2014). Second, this study used a standardized protocol (NACC UDS) consisting of a comprehensive, annual evaluation that assessed a wide range of patient factors, including demographic, genetic, and medical information as well as clinical variables of global, neuropsychological, and neuropsychiatric functioning, across 34 past/current ADCs in the country. Third, clear definitions and characterizations of the groups of focus (i.e., reversion and progression) were used by describing how participants for each MCI trajectory were selected: reverted to normal cognition at 2nd follow-up visit and remained normal at 3rd follow-up visit or progressed to dementia at 2nd follow-up visit and remained demented at 3rd follow-up visit. Fourth, the present study used an *a priori* selection of individuals who were diagnosed with MCI at baseline visit. As such, there was no prior knowledge as to which MCI patient variables would predict reversion or progression. The significant differences between the two MCI groups at baseline visit at the univariate level of analysis suggests that some MCI patients had inherent factors that could have affected their group participation by 2nd follow-up visit. For example,

MCI progression patients had exhibited lower neuropsychological performance and poorer global functioning at baseline visit, suggesting that a dementing process was already occurring and leading to a diagnosis of dementia at follow-up. In fact, pathological changes in dementia, such as aggregation of cerebral amyloid-beta, are present 20 to 30 years before the onset of dementia (Bateman et al., 2012; Jack & Holtzman, 2013; Jansen et al., 2015). This reinforces the idea that the current study's sample selection method was not inherently biased and that longitudinal studies for MCI reversion and progression are needed.

Study Limitations

The current study has a few limitations. First, comparisons were made only between an MCI reversion group and progression group without examining individuals who remained MCI or improved to near-normal cognition (i.e., *Impaired/Not MCI*), both of which may have distinct cognitive, demographic, functional, medical, genetic, and neuropsychiatric markers. Future studies should include the latter two groups in MCI studies in order to further understand the dynamic cognitive, functional, and medical markers of MCI's different trajectories that could then help improve accuracy in predicting clinical outcomes and/or diagnoses.

Second, despite the fact that this study clearly defined the MCI groups of interests (i.e., MCI individuals who reverted to normal cognition at 2nd follow-up visit and remained normal at 3rd follow-up visit and those who progressed to a dementia at 2nd follow-up visit and remained demented at 3rd follow-up visit), the diagnosis/classification at the 1st follow-up visit was not explored in order to increase the overall sample size. This lack of exploration would affect the rates of "true" reversion (i.e., reverting to normal cognition at 1st follow-up visit and remaining

normal at 2nd and 3rd follow-up visits) versus "true" progression (i.e., progressing to dementia at 1st follow-up visit and remaining demented at 2nd and 3rd follow-up visits). Inclusion of these "true" reverters and progressors would also affect incident/prevalence rates of reversion and progression in epidemiological studies as well as predictors associated with these trajectories.

Third, the current study did not explore biomarkers or injury markers because the NACC UDS standardized protocol did not include such information at the time of the data request. A few available studies demonstrated larger hippocampal and amygdala volumes, lower parahippocampal gyrus atrophy, fewer white matter lesions, and fewer cerebrospinal fluid markers of amyloid-beta and tau proteins were significantly predictive of MCI reversion (Park & Han, 2014; Sachdev et al., 2013; Tokuchi et al., 2014), although the findings of these studies were hampered by the fact that they differed in their comparison groups (e.g., comparing MCI reverters to only a sustained MCI group or comparing reverters to a group comprised of both cognitively normal and sustained MCI groups). Clearly, additional studies are needed to examine the potential association of these markers with MCI reversion.

Future Directions

The most significant predictors of MCI reversion identified in the final comprehensive model, along with the cutoff score for Logical Memory Story A Delayed Recall, could serve as a starting point in developing a "clinical profile" that helps identify which MCI individuals are more likely to revert to normal cognition than progress to a dementia. A clinical profile may comprise of cutoff scores for the significant continuous predictors with the other significant categorical predictors identified in this study.

Despite the current study being the first large-scale study to examine MCI reversion over three years, future longitudinal studies with a larger scale and follow-up lengths greater than three years are needed, especially since MCI reversion can be a transitional or "unstable" state (e.g., MCI–normal–dementia; MCI– normal–MCI) and that such MCI patients may still be at risk for dementia at a later time (Koepsell & Monsell, 2012; Lopez et al., 2012; Roberts et al., 2014). For example, Lopez and colleagues (2012) found 20% of their incident MCI patient population followed an "unstable" course, with 6% of them eventually progressing to dementia within 12-years. The present study did not try to explore these "unstable" courses of MCI since the data was not examined beyond three years. Also, the current study did not have data on any previous diagnoses in the MCI sample prior to their baseline visit. In this context, it is likely that this MCI sample had a previous history of stable MCI, reversion, or even dementia, which may influence the predictors of MCI trajectories. Ideally, longitudinal prospective studies, with annual visits (Weiner et al., 2012) that preferably begin at mid-life (Bateman et al., 2012; Jack & Holtzman, 2013; Kivipelto et al., 2006) are needed to further understand MCI's various trajectories.

Conclusions

A relatively large number of MCI patients do not progress to dementia and instead improve in their cognitive symptoms. Through a comprehensive model of analysis, this study found that younger age, being unmarried, having zero copies of the *APOE* ε4 allele, higher global functioning, and higher neuropsychological functioning on tests of delayed verbal memory and language were significant predictors of MCI reversion at three-years.

Replications of MCI reversion studies may lead to several potential implications. Educating MCI patients and their families on how these predictors of reversion show a reduced likelihood for future cognitive decline can, in turn, reduce any fears or concerns they may have regarding MCI's association with dementia. Additionally, these predictors of reversion can better inform healthcare providers on the course of clinical management and prognosis. For example, they can better decide whether to prescribe MCI reverters anti-dementia medications, considering their potential adverse effects and futility (Birks & Flicker, 2006; Kavirajan & Schneider, 2007; Lanctot et al., 2003; Tricco et al., 2013). Knowing predictors associated with MCI reversion may also help clinicians reduce the level of monitoring required for a subset of MCI patients who are more likely to revert (e.g., decrease frequency of clinic visits), which could then help reduce treatment costs and healthcare burden. Finally, identifying predictors associated with various MCI trajectories, including MCI reversion, will have implications for early-intervention treatment studies of dementia. Here, researchers can better refine inclusion and exclusion criteria (e.g., removing MCI participants who are more likely to revert to normal cognition than progress to dementia) in order to avoid potential "false positives" and increase the robustness/precision of findings.

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FIGURES

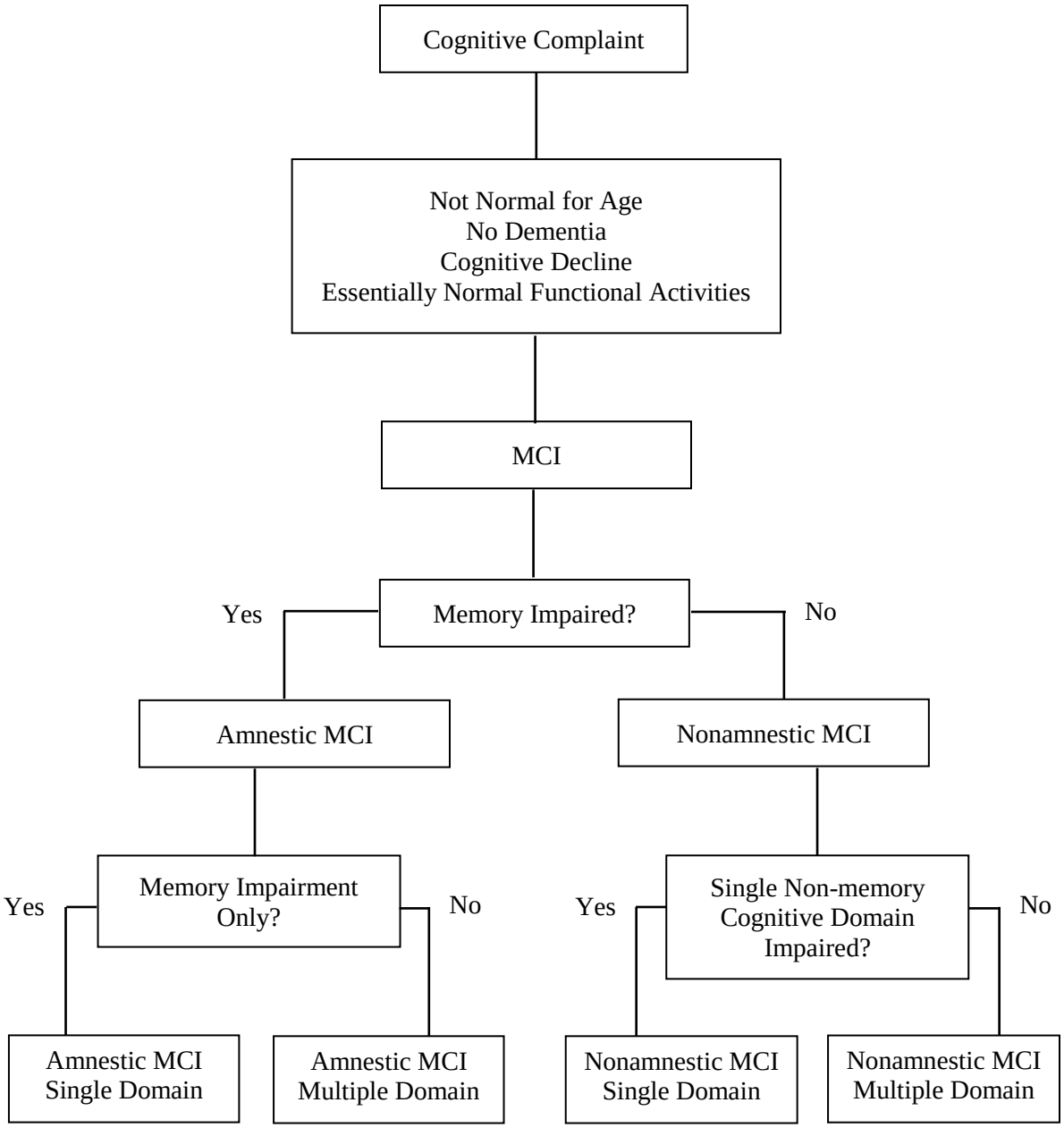

Figure 1: Diagnosis of mild cognitive impairment flowchart (Petersen & Morris, 2005)

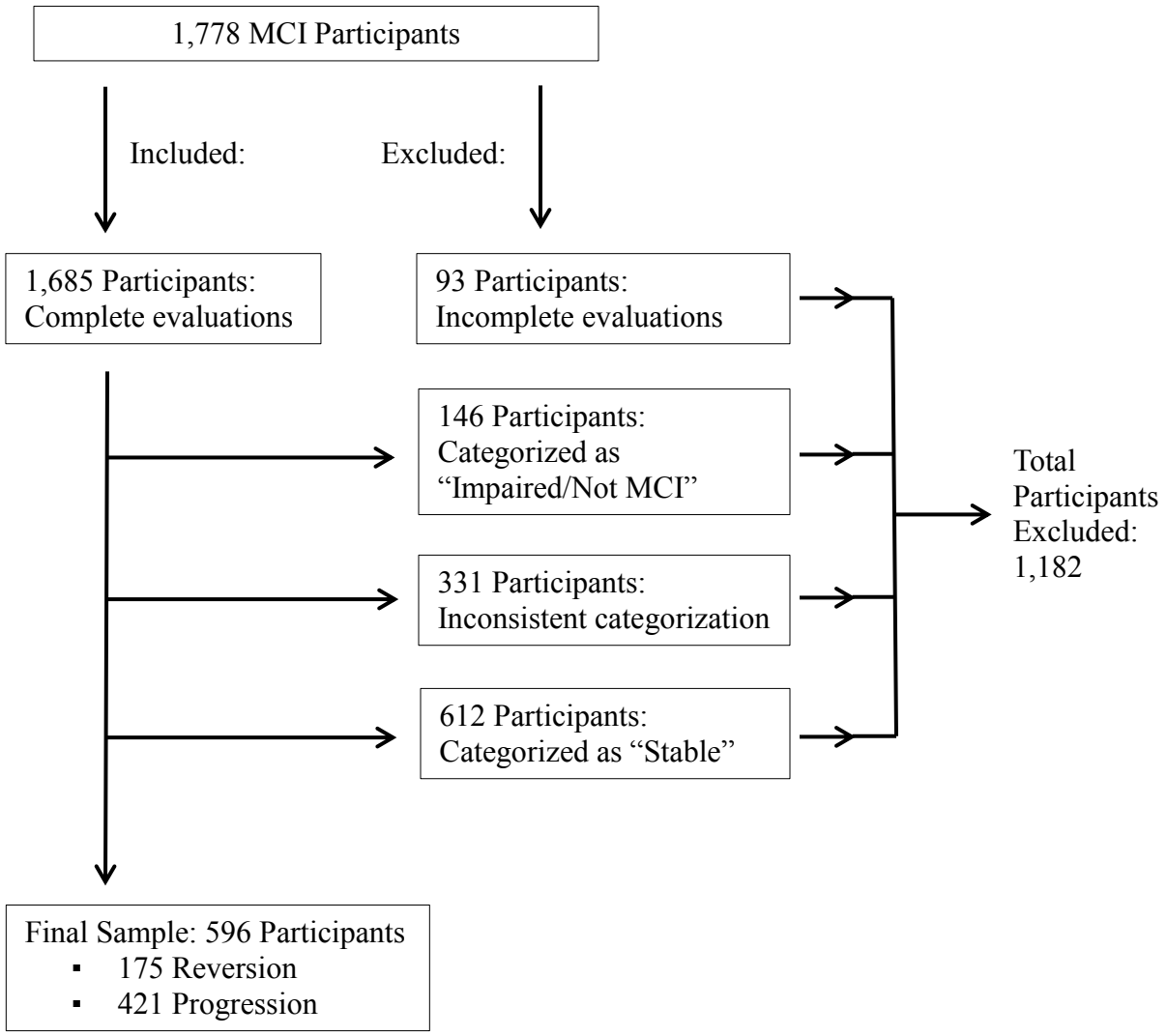

Figure 2: Flowchart depicting selection of final study sample

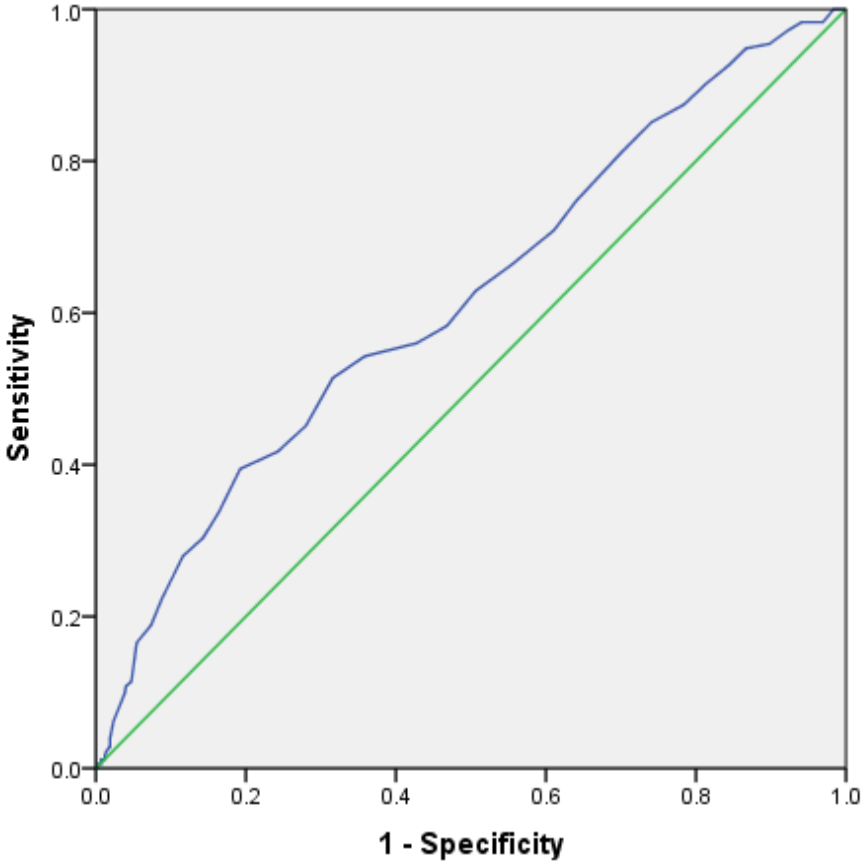

Figure 3: Receiver operating characteristic (ROC) curve for age as a predictor of MCI reversion. Area under the curve (AUC) was 0.62 (95% CI=0.57-0.67).

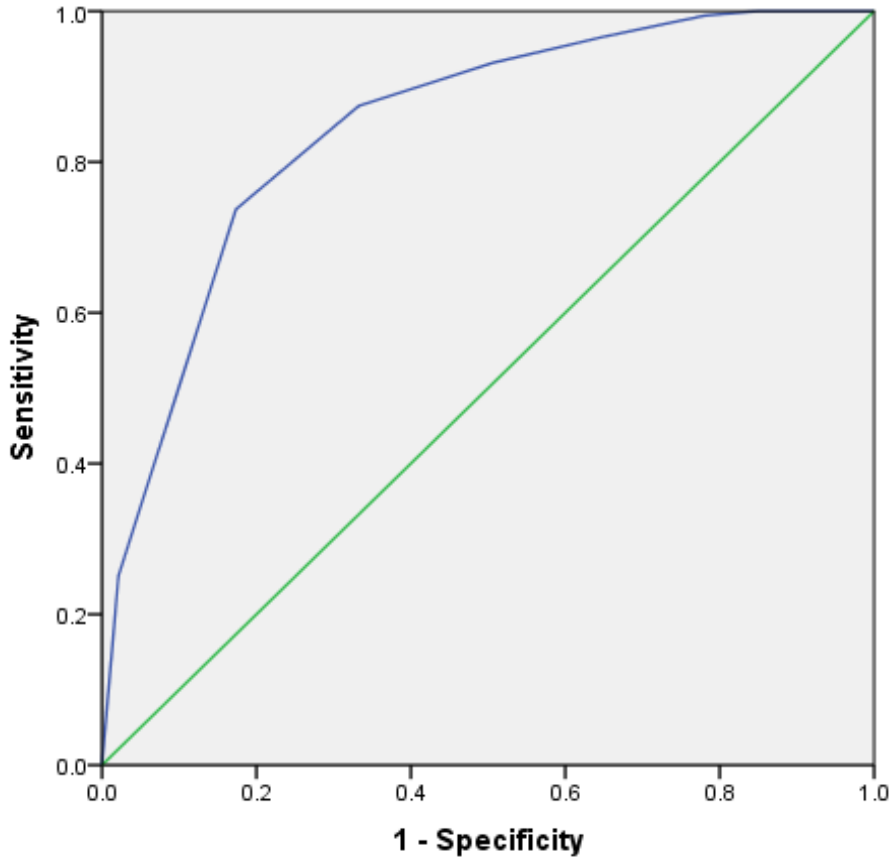

Figure 4. Receiver operating characteristic (ROC) curve for Clinical Dementia Rating Sum of Boxes (CDR-SOB) as a predictor of MCI reversion. Area under the curve (AUC) was 0.85 (95% CI=0.81-0.88).

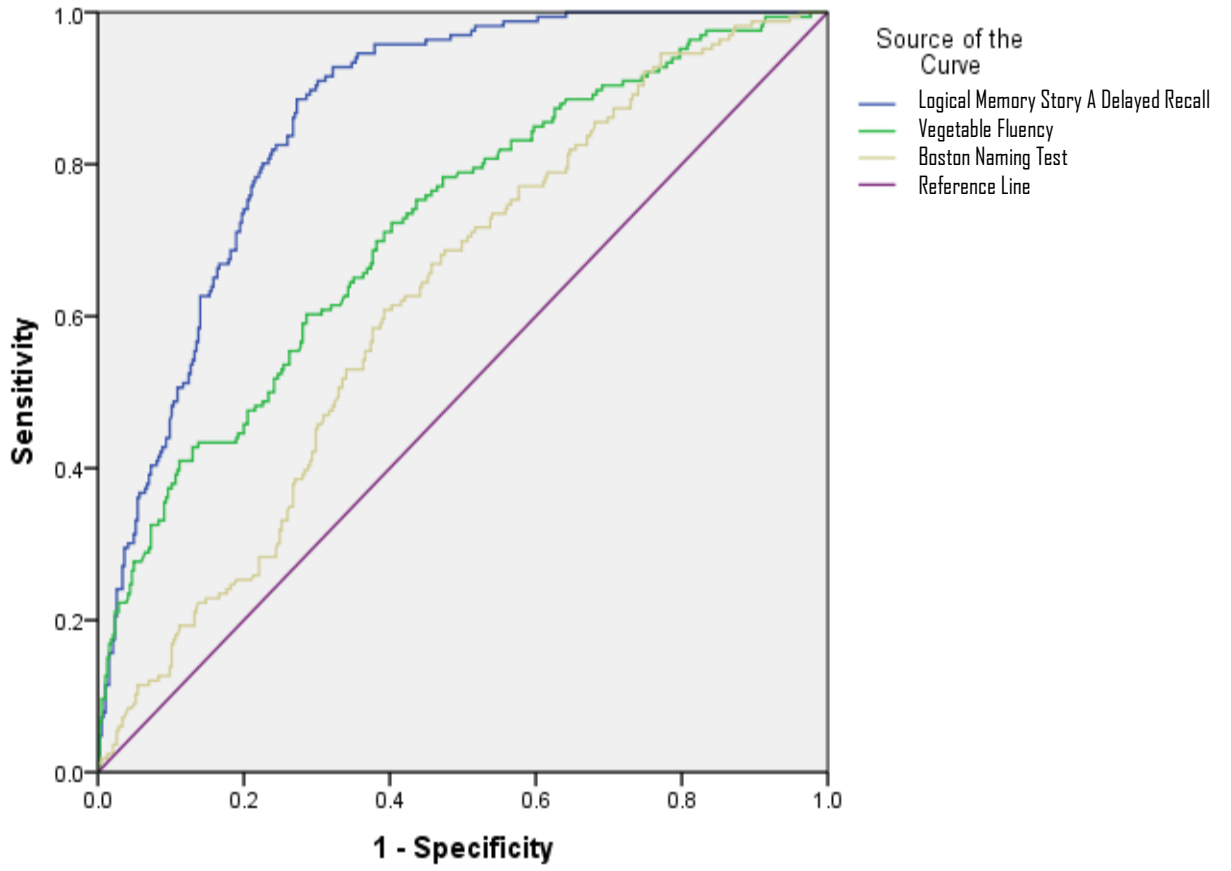

Figure 5: Receiver operating characteristic (ROC) curves for neuropsychological standard test scores of WMS-R Logical Memory Story A Delayed Recall, Vegetable Fluency, and Boston Naming as predictors of MCI reversion. Area under the curve (AUC) for Logical Memory Story A Delayed Recall was 0.86 (95% CI=0.83-0.89). AUC for Vegetable Fluency was 0.72 (95% CI=0.68-0.77). AUC for Boston Naming Test was 0.62 (95% CI=0.57-0.67).

TABLES

Table 1

Baseline Demographic Characteristics for MCI Reversion and Progression Groups

	All Subjects (n = 596, 100%)	Reversion (n = 175, 29.4%)	Progression (n = 421, 70.6%)		
		Mean ± SD or N (%)		*t*	*p*-value
Age (years)	74.07 ± 8.95	71.45 ± 9.07	75.16 ± 8.68	-4.69	<.001
Education (years)*	15.56 ± 3.06	15.75 ± 3.05	15.48 ± 3.07	.96	.336
				χ^2	*p*-value
APOE ϵ4 Allele*				25.88	<.001
0 copies	234 (49.6%)	93 (67.9%)	141 (42.1%)		
≥1 copy	238 (50.4%)	44 (32.1%)	194 (57.9%)		
Gender				7.20	.009
Female	300 (50.3%)	103 (58.9%)	197 (46.8%)		
Male	296 (49.7%)	72 (41.1%)	224 (53.2%)		
Ethnicity				3.70	.076
Hispanic	26 (4.4%)	12 (6.9%)	14 (3.3%)		
Non-Hispanic	570 (95.6%)	163 (93.1%)	407 (96.7%)		
Race*				17.00	.005
White	509 (85.5%)	137 (78.3%)	372 (88.6%)		
Black/African Am.	59 (9.9%)	30 (17.1%)	29 (6.9%)		
Asian	18 (3.0%)	7 (4.0%)	11 (2.7%)		
Native Am./Alaskan	1 (0.2%)	0 (0.0%)	1 (0.2%)		
Native Hawaiian/Pac. Isl.	1 (0.2%)	0 (0.0%)	1 (0.2%)		
Other	7 (1.2%)	1 (0.6%)	6 (1.4%)		
Marital Status*				9.35	.003
Married	422 (70.9%)	108 (62.1%)	314 (74.6%)		

Unmarried	173 (29.1%)	66 (37.9%)	107 (25.4%)		
MCI Subtype				38.69	<.001
Amnestic	504 (84.6%)	123 (70.3%)	381 (90.5%)		
Nonamnestic	92 (15.4%)	52 (29.7%)	40 (9.5%)		
Source of Cognitive Complaint				117.70	<.001
Subject-Report Only	48 (9.5%)	30 (26.8%)	18 (4.6%)		
Informant-Report Only	53 (10.4%)	12 (10.7%)	41 (10.4%)		
Both Subject and Informant	406 (80.1%)	70 (62.5%)	336 (85.0%)		

Note: MCI = Mild Cognitive Impairment; *APOE* ϵ4 = Apolipoprotein E Allele 4.

*Education data for 1 participant, Race data for 1 participant, Marital Status data for 1 participant, and *APOE* ϵ4 data for 124 participants, and Source of Cognitive Complaint data for 89 participants are not available.

Table 2

Types of Dementia in MCI Progression Group at Three-Year Follow-up

	MCI Progression Group (n=421) N (%)
Alzheimer's Disease	148 (35.2%)
Vascular Dementia	99 (23.5%)
Dementia with Lewy Bodies	7 (1.7%)
Primary Progressive Aphasia	4 (1.0%)
Frontotemporal Dementia	1 (0.2%)
Other Dementias	7 (1.7%)

Note: Data not available for 266 participants.

Table 3

Baseline Global Assessments of Functioning Scores for MCI Reversion and Progression Groups

	All Subjects (n = 596, 100%)	Reversion (n = 175, 29.4%)	Progression (n = 421, 70.6%)		
		Mean ± SD		*t*	*p*-value
CDR-SOB	1.58 ± 1.30	0.62 ± 0.61	1.97 ± 1.30	17.20	<.001
FAQ	4.09 ± 5.14	1.05 ± 2.73	5.36 ± 5.38	12.91	<.001
MMSE	26.90 ± 2.45	28.50 ± 1.60	26.24 ± 2.44	-13.101	<.001

Note: CDR-SOB = Clinical Dementia Rating Sum-of-Boxes; FAQ = Functional Assessment Questionnaire; MMSE = Mini Mental State Exam.

Table 4

Baseline Neuropsychological Standard Test Scores for MCI Reversion and Progression Groups

	All Subjects (n = 596, 100%)	Reversion (n = 175, 29.4%)	Progression (n = 421, 70.6%)		
		Mean ± SD		*t*	*p*-value
LM Story A Immediate Recall	-0.97 ± 1.27	0.00 ± 1.03	-1.38 ± 1.13	-13.60	<.001
LM Story A Delayed Recall	-1.13 ± 1.36	0.06 ± 1.08	-1.63 ± 1.14	-16.25	<.001
Digit Span Forward	-0.32 ± 1.04	-0.16 ± 1.04	-0.39 ± 1.03	-2.40	.017
Digit Span Backward	-0.27 ± 1.01	-0.05 ± 1.03	-0.36 ± 0.99	-3.44	.001
Animal Fluency	-0.77 ± 0.95	-0.37 ± 0.97	-0.93 ± 0.89	-6.77	<.001
Vegetable Fluency	-0.07 ± 1.17	0.60 ± 1.16	-0.35 ± 1.06	-9.40	<.001
Trail Making Test Part A	-0.76 ± 1.57	-0.55 ± 1.47	-0.85 ± 1.61	-2.07	.039
Trail Making Test Part B	-1.09 ± 1.62	-0.70 ± 1.41	-1.26 ± 1.68	-4.02	<.001
Digit Symbol Test	-0.51 ± 1.03	-0.09 ± 0.93	-0.69 ± 1.02	-6.35	<.001
Boston Naming Test	-0.94 ± 1.48	-0.46 ± 0.99	-1.15 ± 1.60	-6.15	<.001

Note: LM = Wechsler Memory Scale-R Logical Memory; raw test scores were transformed to standard *z*-scores using demographically-adjusted norms (age, education, and gender) (Shirk et al., 2011); *z*-scores have a mean of 0 and SD of 1.

Table 5

Baseline Neuropsychiatric Symptom Severity Scores for MCI Reversion and Progression Groups

	All Subjects (n = 596, 100%)	Reversion (n = 175, 29.4%)	Progression (n = 421, 70.6%)		
		Mean ± SD		*t*	*p*-value
Anxiety	1.41 ± .55	1.35 ± .57	1.43 ± .55	.61	.541
Apathy	1.49 ± .66	1.46 ± .66	1.49 ± .67	.14	.888
Depression	1.32 ± .50	1.17 ± .38	1.35 ± .52	2.20	.079

Note: Range of symptom severity scores: 0 to 3 (i.e., "0" = none, "1" = mild, "2" = moderate, and "3" = severe).

Table 6

Stepwise Logistic Regression Analyses for Demographic Covariates

Covariates	Odds Ratio	95% CI
Age	0.96	0.94 – 0.98*
Education Level	1.05	0.99 – 1.12
Gender		
Female	1.67	1.15 – 2.42*
Male (reference)	1.00	------
Ethnicity		
Hispanic	2.56	1.08 – 6.09*
Non-Hispanic (reference)	1.00	------

Note: CI = Confidence Interval.
*p<.05

Table 7

Stepwise Logistic Regression Analyses for Baseline Demographic Data

Predictors	Odds Ratio	95% CI
Age	0.93	0.91 – 0.96*
Education Level	1.03	0.95 – 1.11
Gender		
Female	1.76	1.07 – 2.88*
Male (reference)	1.00	------
Ethnicity		
Hispanic	2.28	0.72 – 7.25
Non-Hispanic (reference)	1.00	------
Marital Status		
Married	0.48	0.28 – 0.83*
Unmarried (reference)	1.00	------
MCI Subtype		
Nonamnestic	3.43	1.94 – 6.07*
Amnestic (reference)	1.00	------
APOE ε4 Allele		
≥1 copy	0.27	0.17 – 0.44*
0 copies (reference)	1.00	------

Note: CI = Confidence Interval; MCI = Mild Cognitive Impairment; *APOE* ϵ4 = Apolipoprotein E Allele 4.

*p<.05

Table 8

Stepwise Logistic Regression Analyses for Baseline Global Assessments of Functioning Scores

Predictors	Odds Ratio	95% CI
CDR-SOB	0.31	0.20 – 0.46*
FAQ	0.84	0.76 – 0.94*
MMSE	1.52	1.32 – 1.76*
Covariates		
Age	0.95	0.92 – 0.98*
Gender		
Female	1.30	0.80 – 2.12
Male (reference)		-----
Ethnicity		
Hispanic	4.12	1.16 – 14.61*
Non-Hispanic (reference)		-----

Note: CI = Confidence Interval; CDR-SOB = Clinical Dementia Rating Sum-of-Boxes; FAQ = Functional Assessment Questionnaire; MMSE = Mini Mental State Exam.

*$p<.05$

Table 9

Stepwise Logistic Regression Analyses for Baseline Neuropsychological Standard Test Scores

Predictors	Odds Ratio	95% CI
LM Story A Immediate Recall	1.04	0.70 – 1.55
LM Story A Delayed Recall	2.81	1.93 – 4.09*
Digit Span Forward	1.02	0.78 – 1.33
Digit Span Backward	0.90	0.67 – 1.22
Animal Fluency	1.03	0.74 – 1.42
Vegetable Fluency	1.35	1.04 – 1.75*
Trail Making Test Part A	0.83	0.68 – 1.01
Trail Making Test Part B	1.10	0.90 – 1.35
Digit Symbol Test	1.53	1.10 – 2.13*
Boston Naming Test	1.51	1.19 – 1.91*

Note: CI = Confidence Interval; LM = Wechsler Memory Scale-R Logical Memory; raw test scores were transformed to standard *z*-scores using demographically-adjusted norms (age, education, and gender) (Shirk et al., 2011).

*$p<.05$

Table 10

Stepwise Logistic Regression Analyses for Baseline Neuropsychiatric Symptom Severity Scores

Predictors	Odds Ratio	95% CI
Anxiety	0.67	0.45 – 0.99*
Apathy	0.59	0.38 – 0.92*
Depression	0.52	0.35 – 0.78*
Covariates		
Age	0.94	0.92 – 0.97*
Gender		
Female	1.65	1.11 – 2.43*
Male (reference)		-----
Ethnicity		
Hispanic	1.89	0.70 – 5.08
Non-Hispanic (reference)		-----

Note: CI = Confidence Interval.
*p<.05

Table 11

Stepwise Logistic Regression Analyses for Comprehensive Model of Predictors for MCI Reversion

Predictors	Odds Ratio	95% CI
Age	0.91	0.87 – 0.96*
Gender		
Female	0.35	0.11 – 1.10
Male (reference)	1.00	------
Marital Status		
Married	0.32	0.14 – 0.76*
Unmarried (reference)	1.00	------
MCI Subtype		
Nonamnestic	1.32	0.50 – 3.48
Amnestic (reference)	1.00	------
APOE ε4 Allele		
≥1 copy	0.33	0.15 – 0.71*
0 copies (reference)	1.00	------
CDR-SOB	0.21	0.11 – 0.40*
FAQ	0.97	0.84 – 1.11
MMSE	1.21	0.97 – 1.51
LM Story A Delayed Recall	2.39	1.68 – 3.39*
Vegetable Fluency	1.92	1.17 – 3.14*
Digit Symbol Test	1.36	0.89 – 2.08
Boston Naming Test	1.69	1.16 – 2.47*
Anxiety	0.90	0.41 – 1.98
Apathy	0.84	0.35 – 2.02
Depression	0.61	0.29 – 1.25

Note: CI = Confidence Interval; MCI = Mild Cognitive Impairment; *APOE* ϵ4 = Apolipoprotein E Allele 4; CDR-SOB = Clinical Dementia Rating Sum-of-Boxes; FAQ = Functional Assessment Questionnaire; MMSE = Mini Mental State Exam; LM = Wechsler Memory Scale-R Logical Memory.

*$p<.05$

APPENDIX A

Description of NACC UDS Form Packet

Description of UDS Measures

Assessments of Global Functioning:

Functional Assessment Questionnaire. The Functional Assessment Questionnaire (FAQ) assesses changes in the participant's functional activities in 10 domains (e.g., financial management, shopping, preparing drinks/food, remembering pertinent events, and traveling) that are affected by cognitive difficulties, in comparison to previously attained functional abilities (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). A clinician or trained health professional completes the questionnaire by interviewing an informant for the participant, and responses for each domain are coded as "0" = Normal, "1" = Has difficulty but does by self, "2" = Requires assistance, "3" = Dependent, and "8" = Not applicable (e.g., never did). The score of interest for this study is the total FAQ score, excluding responses coded as "8," with higher scores indicating greater functional impairment.

Clinical Dementia Rating. The Clinical Dementia Rating (CDR) scale evaluates the severity of cognitive impairment. The measure is comprised of six domains: 1) memory; 2) orientation; 3) judgment/problem-solving; 4) community affairs; 5) home and hobbies; and 6) personal care (Morris, 1993). A clinician or trained health professional completes the questionnaire by interviewing an informant of the participant, and responses for each domain are coded using a five-point scale that describes the various stages of impairment: "0" = None (no dysfunction), "0.5" = Questionable, "1" = Mild, "2" = Moderate, and "3" = Severe. The CDR yields two separate scores: Global and Sum of Boxes (SOB). The Global CDR score is

computed via an algorithm or using the Washington University online algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html). The CDR-SOB score is the total score from the six domains. The score of interest for this study is the CDR-SOB, with higher scores indicating greater cognitive and functional impairment.

Mini Mental State Exam. The Mini Mental State Exam (MMSE) is a cognitive screen that assesses several cognitive and functional domains (Folstein, Folstein, & McHugh, 1975). The participant is asked to respond to several questions and tasks in the areas of orientation to place and time, memory (immediate and delayed recall of three words), attention (spelling "WORLD" backwards), language (naming, repetition of phrases, reading, writing, and comprehension of simple instructions), and visual construction (copying of two intersecting pentagons). The score of interest in this study is the total number of correct responses, with lower scores indicating poorer performance.

Neuropsychological Tests:

Test of Memory

Logical Memory Subtest. The Logical Memory Story A subtest from the Wechsler Memory Scale-Revised is a measure of short-term and long-term verbal episodic memory (Wechsler, 1987). The participant is read one, brief story and is asked to recall the details of the story immediately following presentation and following an approximate 20-minute delay. There are two separate scores of interest in this study: the total number of story details recalled immediately and then following the delay. Raw scores will be transformed to demographically

corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).

Tests of Attention and Processing Speed

Digit Span Subtest. The Digit Span subtest from the Wechsler Memory Scale-Revised (Wechsler, 1987) is a measure of attention. In Digit Span Forward, the participant is read a sequence of numbers of increasing length and is asked to repeat the sequence exactly as it was presented. In Digit Span Backward, the participant is also read a sequence of numbers of increasing length, but then is asked to repeat the sequences in reverse order. The scores of interest in this study are the total number of correct trials prior to two consecutive incorrect responses at the same digit length for Digit Span Forward and for Digit Span Backward. Raw scores will be transformed to demographically corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).

Digit Symbol Subtest. The Digit Symbol subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) is a measure of processing speed. The participant is presented with a stimulus page and is asked to fill in as many of the empty boxes associated with the presented numbers in 90 seconds, according to a key provided at the top of the page that shows each number corresponding to a certain symbols (i.e., "marks"). The score of interest in this study is the total number of correct responses. Raw scores will be transformed to demographically corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).

Tests of Language

Verbal Fluency. The Verbal Fluency test is a widely used measure of semantic memory and includes two separate trials in the UDS form packet: Animal Fluency (Goodglass & Kaplan, 1983) and Vegetable Fluency (Bayles et al., 1989). In Animal Fluency, the participant is asked to name as many different exemplars of animals in 60 seconds. In Vegetable Fluency, the participant is asked to name as many different exemplars of vegetables in 60 seconds. The scores of interest in this study are the total number of animals named in the Animal Fluency trial and the total number of vegetables named in the Vegetable Fluency trial. Raw scores will be transformed to demographically corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).

Boston Naming Test. The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) is measure of language that is sensitive to aphasias and deficits in object recognition. Typically a 60-item measure, the participant is asked to name line drawings of objects on only the odd-numbered items (i.e., 30 in total). The score of interest in this study is the total number of correct responses. Raw scores will be transformed to demographically corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).

Tests of Executive Function

Trail Making Test (Parts A and B). The Trail Making Test (TMT) (Reitan & Wolfson, 1995) is a measure of executive function. In TMT Part A, the participant is presented with a stimulus page of numbers (from "1" to "25") and is asked to draw a line from one number to the next in sequential order under a time pressure. In TMT Part B, the participant is presented with a

stimulus page of numbers (from “1” to “13”) and letters (from “A” to “L”) and is asked to draw a line alternating from a number and a letter in sequential/alphabetical order under a time pressure. The scores of interest in this study are the total number of seconds to complete Part A and the total number of seconds to complete Part B. Raw scores will be transformed to demographically corrected *z*-scores (i.e., age, gender, education) using published normative data (Shirk et al., 2011).