Identifying Mild Cognitive Impairment in Older Adults

by

Lesley Jane Ritchie
B.A., University of Regina, 2000
M.Sc., Carleton University, 2003

A Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

in the Department of Psychology

Supervisory Committee

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Abstract

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The absence of gold standard criteria for mild cognitive impairment (MCI) impedes the comparison of research findings and the development of primary and secondary prevention strategies addressing the possible conversion to dementia. The objective of Study 1 was to compare the predictive ability of different MCI models as markers for incipient dementia in a longitudinal population-based Canadian sample. The utility of well-documented MCI criteria using data from persons who underwent a clinical examination in the second wave of the Canadian Study of Health and Aging (CSHA) was examined. Demographic characteristics, average neuropsychological test performance, and prevalence and conversion rates were calculated for each classification. Receiver operating characteristic (ROC) analyses were employed to assess the predictive power of each cognitive classification. The highest prevalence and conversion rates were associated with case definitions of multiple-domain MCI. The only diagnostic criteria to significantly predict dementia five years later was the Cognitive Impairment, No Dementia (CIND) Type 2 case definition. It is estimated that more restrictive MCI case definitions fail to address the varying temporal increases in decline across different cognitive domains in the progression from normal cognitive functioning to dementia. Using data from the CSHA, the objective of Study 2 was to elucidate the clinical correlates that best differentiate between cognitive classifications. A machine learning algorithm was used to identify the symptoms that best discriminated between: 1) not cognitively impaired (NCI) and CIND; 2) CIND & demented; and 3) converting and non-converting CIND participants. Poor retrieval was consistently a significant predictor of greater cognitive impairment across all three questions. While interactions with other predictors were noted when differentiating CIND from NCI and demented from non-demented participants, retrieval was the sole predictor of conversion to dementia over five years. Importantly, the limited specificity and predictive values of the respective algorithms caution against their use as clinical markers of CIND, dementia, or conversion. Rather, it is recommended that the predictors serve as markers for ongoing monitoring and assessment. Overall, the results of both studies suggest that the architecture of pathological cognitive decline to dementia may not be captured by a single set of diagnostic criteria.

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Acknowledgments

I would like to express my sincere thanks and gratitude to my supervisor, Dr. Holly Tuokko, for her invaluable support and guidance throughout my graduate studies at the University of Victoria. Across our many collaborative projects, Holly has been an extraordinary mentor and an invaluable source of information. I am privileged to have had a supervisor who took both an academic and a personal interest in her students. Many thanks to my other committee members, Drs. Mateer, Smith, Weber-Jahnke, and Small for sharing their diverse expertise and recommendations in the completion of this dissertation. Special thanks to Dr. MacDonald, Dr. Hunter, and Ben Chou for sharing their statistical expertise.

I would like to thank my parents for their continued support in the pursuit of my education. Special thanks to my mom for sharing her superior grammatical skills over the years and her unwavering encouragement in the pursuit of my personal and professional dreams. Thanks also to my sisters and extended family for their words of support and pride in my accomplishments. I would like to thank my friends and colleagues for providing a much needed balance to my school life. Thank you for the memorable long conversations and coffee breaks.

I would like to acknowledge my best friend and husband, Marcello. Together, we have achieved our respective and shared professional and personal dreams. Thank you for your unconditional love, support, encouragement, and patience. Thank you for sharing my dreams and ambitions, and most importantly, for making me laugh.

Finally, I would like to thank the Alzheimer Society of Canada/CIHR Institute of Aging for generously supporting my doctoral training.

Dedications

This dissertation is dedicated to my husband,

Marcello Oddo,

and to my family,

Lynn, John, Janet, & Karen.

Chapter 1

General Introduction

Cognitive impairment, estimated to affect 65% of the population aged 85 years and older, poses a large challenge to the health care system. Mild cognitive impairment, with an estimated population prevalence of 16.8%, refers to cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia (Graham et al., 1997). An accurate conceptualization of mild cognitive impairment is important, as this group of elderly persons is targeted for both pharmaceutical and cognitive interventions (Zaudig, 1992) with the aim of delaying or preventing the progression to dementia. Currently interfering with this goal is the lack of accepted terminology, definitions, and diagnostic criteria for cognitive decline. The absence of a consensus classification renders the comparison of research findings impractical and ultimately limits the conception of potential treatment options. Moreover, developing potential interventions for cognitive impairment necessitates knowledge of its rate of progression. However, this is limited to specific classifications of cognitive decline (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003).

Cognitive Decline and Normal Aging

Historically, there have two approaches to defining cognitive decline with age. First, several researchers have described cognitive decline as occurring as a natural and normal process experienced by the aged. Kral (1962, 1966) introduced the concept of mild cognitive decline associated with age. He described benign senescent forgetfulness (BSF) as an age-related process involving general forgetfulness and difficulty recalling factual information (i.e., names, dates), with preserved global knowledge and intact awareness of deficits. He coined the term malignant senescent forgetfulness (MSF) to describe the rapidly progressing age-related process of memory impairment (both recent and remote memories) and loss of awareness of deficits.

Over time, descriptions of cognitive decline associated with aging have progressed to include detailed diagnostic criteria. For example, believing Kral's description of BSF as age-associated memory disturbances to be inadequate, the National Institute of Mental Health (NIMH) work group proposed a set of criteria for the diagnosis of "age-associated memory impairment" (AAMI; Crook et al., 1986). The proposed criteria for a diagnosis of AAMI require subjective reports of memory difficulties in everyday activities in persons aged 50 years or more and impaired performance on measures of recent or "secondary" memory (i.e., at least 1 standard deviation below the mean performance of young adults). Impaired memory performance must not be attributable to other medical or psychological conditions or substance use.

The NIMH AAMI criteria have been criticized for failing to reflect a decline in cognitive performance and, thus, are not reflective of an age- or disease-related process (Davis & Rockwood, 2004). For example, persons with low premorbid functioning or limited education may qualify for a diagnosis of AAMI (Davis & Rockwood, 2004). Moreover, Bamford and Caine (1988) suggested that, using the proposed criteria, the majority of persons aged 65 years or older would qualify for a diagnosis of AAMI. To improve the diagnostic criteria, Blackford and LaRue (1989) restricted the age range to apply to persons aged 50-79 years and altered the NIMH criteria for AAMI to reflect impaired performance (at least one standard deviation below the mean) on at least one memory test, as compared to young adults. They also created the classifications of age-consistent memory impairment (ACMI) and late-life forgetfulness (LLF). A diagnosis of ACMI requires the presence of memory functioning within 1 standard deviation of the mean, as compared to similarly aged persons on at least 75% of the tests administered. Impaired memory performance (between one and two standard deviations below the mean) on at least 50% of the tests administered, as compared to similarly aged persons, is required for a diagnosis of LLF. For all classifications, at least four measures of memory are required. The authors provide a list of recommended memory measures, as well as exclusion criteria for the diagnoses (e.g., impairment due to the presence of psychological, psychosocial, medical, or substance use disorders).

In a study designed to evaluate the criteria for AAMI, ACMI, and LLF, Smith et al. (1991) examined the memory performance of 527 adults aged 55 to 98. Several problems were associated with the NIMH AAMI criteria, including the exclusion of 35-54% of independently functioning subjects with no complaints of memory dysfunction but whose history included neurological, medical, psychological, or substance abuse conditions. Moreover, the number of subjects who qualified for a diagnosis of NIMH AAMI fluctuated according the memory measures administered. Similar variability was noted for the Blackford & LaRue (1989) revised AAMI criteria. The reliability of the LLF diagnosis was noted to be limited by the unreliability of detecting dementia as an exclusionary criterion. The NIMH (1986) and Blackford & LaRue (1989) AAMI criteria could be applied to 77-98% and 69-83% of the subjects, respectively. It was concluded that the AAMI diagnoses reflect normal memory declines with age; thus, the use of the term *impairment* (italics in original publication) is inappropriate. The authors recommend longitudinal memory assessment given that 16% of the population would qualify for a diagnosis of AAMI simply by performing one standard deviation below the mean at a young age but who do not decline with age.

Levy (1994) also developed criteria for normal age-related cognitive decline. The classification of aging-associated cognitive decline (AACD) requires a decline of at least one standard deviation, compared to age-matched norms, in any area of cognitive functioning. Thus, the AACD diagnostic classification is not limited to a decline in memory functioning.

Cognitive Decline as a Disease Process

The aforementioned conceptualizations of cognitive impairment are based on a model of normal aging, rather than a disease-related process. As such, they fail to address other cognitive and functional abilities necessary for a diagnosis of dementia (Smith et al., 1996), which currently requires the presence memory impairment and impairment in at least one other cognitive domain (i.e., aphasia, apraxia, agnosia, or executive functioning). The impairment in cognitive functioning must represent a decline from previous cognitive function and be severe enough to interfere with occupational and/or social functioning (American Psychiatric Association [APA], 2000). More recently, definitions with specific diagnostic criteria for mild cognitive impairment as a precursor to dementia have been proposed. It is hypothesized that the American, diseased-based, definitions of MCI create more attractive conceptualizations of mild cognitive impairment as a precursor to dementia and introduce the opportunity for intervention (Ritchie, Artero, & Touchon, 2001).

Zaudig (1992) proposed diagnostic criteria for “mild cognitive impairment” stemming from the Diagnostic and Statistical Manual for Mental Disorders’ – Third Edition - Revised (DSM-III-R; APA, 1987) and the International Classification of Diseases’ – Tenth Edition (ICD-10; World Health Organization [WHO], 1992) criteria for dementia. Using the

DSM-III-R criteria, two categories of mild cognitive impairment were recommended. To qualify for a diagnosis of MCI Type 1 (MCI-1), individuals must present with *only* short-term and long-term memory impairment. A diagnosis of MCI Type 2 (MCI-2) is assigned, if an individual exhibits short-term and long-term memory impairment and at least one of: impairment in abstract thinking, impaired judgment, disturbed higher cortical functioning (i.e., aphasia, apraxia, agnosia), and/or changes in personality.

The ICD-10 criteria resulted in three recommended MCI classifications. Type 1 requires evidence of memory impairment, with no specification of type of memory impairment. Type 2 requires both memory impairment and a decline in intellectual functioning. A classification of Type 3 MCI necessitates the presence of memory impairment, intellectual decline, and disturbed emotional control, social behavior, or motivation. ADLs must not be significantly impaired as a result of memory impairment or intellectual decline. Ranges of performance on the Mini-Mental State Exam (MMSE) from a randomly selected sample of 150 elderly subjects for both classifications of MCI were 23-27 and 23-28 for DSM-III-R- and ICD-10-based criteria, respectively. An MMSE score of 22 or less was highly sensitive and specific in differentiating between demented and mildly cognitively impaired individuals.

Perhaps the most prominent classification of mild cognitive impairment is Petersen et al.'s (1999) definition of MCI. The clinical criteria for MCI require the presence of a subjective memory complaint (preferably substantiated by proxy report), objective evidence of memory impairment (as compared to similarly aged and educated peers), intact cognitive function, intact functional abilities (i.e., ADLs), and failure to meet the criteria for dementia

(Petersen et al., 1999). Despite the proposed clinical criteria, the diagnosis of MCI is described as being the result of clinical judgment (Petersen, 2003).

MCI is hypothesized to represent an interim state on a linear continuum between normal and abnormal cognitive functioning. However, this continuum exists only for those persons "*destined to develop dementia*" (Petersen, 2003, p.2; italics in original text). Moreover, the clinical and pathological continuum is gradual in nature, with no specific cut-points between the stages (Petersen, 2006). In 1999, Petersen and colleagues reported a conversion rate of 12% from MCI (as defined by their clinical criteria) to AD, in a clinical population. An evidence-based review of the literature revealed a rate of progression ranging from 6% to 25% (Petersen et al., 2001). Larrieu et al. (2002) subsequently reported a conversion rate of 8.3% in a longitudinal population-based sample.

The contention that MCI is indicative of incipient dementia has received much criticism. It has been suggested that Petersen's (2001) conceptualization of MCI is too stringent and hinders the accurate and early detection of persons exhibiting mild cognitive impairment who subsequently progress to a dementia other than AD (Low et al., 2004). For example, in a longitudinal, population-based study, the MCI classification was found to be a poor predictor of senile dementia, identifying only 11% of persons who went on to dement (Ritchie, Artero, & Touchon, 2001). Moreover, the MCI classification is reported to be unstable, as many (~ 40%) MCI subjects fail to meet MCI criteria the following year and revert to a diagnosis of no cognitive impairment (Ritchie et al., 2001; Larrieu et al., 2002).

Researchers also attribute the instability of the MCI classification to its reliance on impaired memory as the primary symptom (Ritchie et al., 2001). Evidence suggests that the cognitive impairment in MCI often includes deficits in multiple cognitive domains

(Loewenstein, Acevedo, Agron, & Duara, 2007; Morris et al., 2001). Even persons classified as MCI have been found to demonstrate poor performance on measures of executive function, category fluency, and design fluency (Kramer et al., 2006). Moreover, persons exhibiting multiple cognitive impairments have a higher rate of conversion to dementia. Bozoki and colleagues (2001) report two-year conversion rates of 6% for persons with memory impairment only, compared to 48% for those with memory impairment plus deficit in at least one of language, attention, visuospatial function, and executive functioning. Additionally, most individuals diagnosed with MCI exhibit deficits beyond just memory impairment (Busse, Hensel, Gühen, Angermeyer, & Riedel-Heller, 2006).

In response to these findings, Petersen (2003) introduced three types of MCI. He proposed that MCI could be clinically "heterogeneous" (p.3). The first and more prominent classification is amnestic MCI (aMCI). AMCI is described as a significant memory deficit (i.e., at least 1.5 *SD* below age- and education- matched normative data), with the possibility of very mild (i.e., <0.5 *SD* below the mean) deficits in other cognitive domains. In contrast, multiple-domain MCI (MCImd) allows for deficits in multiple cognitive domains (i.e., 0.5-1.0 *SD* below age- and education-matched norms) and modest impairments in ADLs, while still failing to meet the criteria for dementia. For MCImd, no single impairment significantly exceeds deficits in other cognitive domains. The third classification, non-amnestic single domain MCI (naMCIsd) is described as a deficit in a single, non-memory domain (e.g., executive functioning, language, visuospatial impairment).

Each of these three classifications is described as following a preferentially degenerative course. Specifically, Petersen (2003) hypothesized that aMCI typically progresses to AD and reported an annual conversion rate of 12% (Petersen et al., 1999).

MCImd is expressed as mild impairment in multiple cognitive domains and is believed to progress to AD, vascular dementia (VaD) or normal aging. Greater variety in dementia outcomes based on the presenting symptom is proposed for naMCIsd. Possible outcomes include frontotemporal dementia (FTD), Lewy body dementia (LBD), primary progressive aphasia (PPA), and VaD (Petersen, 2003).

The contention that MCI subtypes preferentially progress to specific types of dementia (Petersen, 2004) contradicts the report that the definition of MCI affects the prevalence but not the outcome of MCI. Fisk, Merry, and Rockwood (2003) examined the prevalence and outcomes of MCI case definitions across five years, using data from the Canadian Study of Health and Aging (CSHA). Stringent amnestic MCI criteria requiring the presence of subjective memory complaints and intact ADLs resulted in lower prevalence rates than did amnestic MCI criteria wherein these requirements were relaxed (1% compared to 3%). Note that the prevalence rates are much lower than those previously described. This is likely due to the fact that the CSHA is based on a population sample and has a lower population prevalence rate, compared to studies wherein participants are sampled from a tertiary memory clinic. Despite alterations in the definition of MCI, no significant differences in outcome were noted.

The three types of MCI have been further subdivided based on the presence or absence of a memory deficit. Petersen (2004) proposed an algorithm for diagnosing the clinical subtypes of MCI. A diagnosis of MCI is made when: 1) an individual presents with a cognitive complaint (either subjective or by proxy); 2) after collecting a clinical history and cognitive screen, a determination of abnormal cognitive function (for age and education) is established; 3) the individual's cognitive functioning represents a decline from previous function; and 4) the individual exhibits intact ADLs. Having established a diagnosis of MCI, the clinician must acknowledge the presence or absence of memory impairment, resulting in the classifications of amnestic MCI (aMCI) and non-amnestic MCI (naMCI). AMCI and naMCI are further divided into Amnestic MCI Single Domain (aMCIsd; memory impairment only), Amnestic MCI Multiple Domain (aMCImd; memory impairment plus deficits in other cognitive domains), Non-Amnestic MCI Single Domain (naMCIsd; impairment in a single non-memory cognitive domain), and Non-Amnestic MCI Multiple Domain (naMCImd; multiple impairments in cognitive domains other than memory). The type and etiology of MCI are presumed to be indicative of progression to variable types of dementia.

With a view to empirically validate the four clinical classifications of MCI, Busse et al. (2006) examined a sample of community-dwelling and institutionalized persons aged 75 years and older. Diagnostic classifications based on original criteria (i.e., 1.0 *SD* below age- and education-matched norms) revealed prevalence rates of 4.5%, 5.5%, 2.1%, and 7.1% for aMCIsd, aMCImd, naMCImd, and naMCIsd, respectively. Significantly higher prevalence rates were observed when modified criteria (i.e., omission of the subjective memory complaint requirement) were used (9.3%, 10.9%, 3.9%, and 17.4% for aMCIsd, aMCImd, naMCImd, and naMCIsd, respectively). Increasing the cut-off to 1.5 *SD* below age- and education-matched norms significantly decreased the prevalence rates, under both conditions. Three of the four clinical subtypes preferentially progressed to AD. Persons diagnosed with naMCImd were more likely to progress to a non-AD type of dementia. The highest conversion rate was associated with the amnestic forms of MCI. Similarly, in a study comparing the course of original (i.e., amnestic MCI) and revised (i.e., allowance for non-amnestic forms of MCI and proxy reports) criteria, Storandt, Grant, Miller, and Morris

(2006) found that 100% and 90% of MCI subjects meeting original and revised criteria, respectively, progressed to AD. As in the Busse et al. (2006) study, impairment was defined as performance falling 1.5 *SD* below expected values. These results suggest that the prevalence, course, and outcome of the four clinical subtypes of MCI are the result of the definition of MCI.

The stability of the four clinical subtypes of MCI remains controversial. Busse et al. (2006) report a 20% reversion rate (i.e., participants with a diagnosis of MCI at baseline failed to meet the criteria for MCI at follow-up). Improved cognitive performance was most frequently associated with the non-amnestic MCI subclassifications. Moreover, 4% to 13% of participants had unstable diagnoses and qualified for a different diagnosis at each follow-up. Some researchers suggest that the instability of the MCI diagnosis is attributable to practice effects and intra-individual fluctuation in cognitive performance. In a one-year follow-up study, Loewenstein et al. (2007) observed stable neuropsychological performance among participants diagnosed with MCI at baseline. However, persons in the MCI groups may represent a more cognitively impaired sample given that impairment was defined as performance at least 1.5 *SD* below the norm and the majority of MCI participants demonstrated impairment in multiple cognitive domains.

In addition to being clinically heterogeneous, Petersen (2003) acknowledged that MCI is etiologically heterogeneous. Apart from a degenerative dementing process, cognitive impairments of insufficient severity to warrant a diagnosis of dementia may be the result of head trauma, depression, cerebrovascular disease, anoxia, stroke, Parkinson's disease (PD), medications, and substance abuse, to name a few. Unlike typical applications of Petersen's (1999, 2003, 2004, 2006) criteria for MCI, the classification of Cognitive Impairment, No

Dementia (CIND) does not exclude persons based on the etiology of their cognitive impairments (Ebly, Hogan, & Parhad, 1995). Rather, as used in the CSHA, the classification of CIND includes persons exhibiting cognitive impairment due to delirium, chronic substance abuse (alcohol and drug), depression and other psychiatric illnesses, mental retardation, Parkinson's disease, epilepsy, sensory deficits (e.g., hearing or sight deficits), socio-cultural factors, cerebrovascular disease (CVD), brain tumor, vascular disease, and multiple sclerosis. Eight CIND subclassifications were also identified including: delirium, long-term substance use (alcohol or drugs), depression, psychiatric disorder, mental retardation, and "other" categories. The other category was further subdivided post-hoc into CVD, general vascular disease, epilepsy, brain tumor, multiple sclerosis, sociocultural, blind/deaf, Parkinson's disease, and social isolation (Tuokko, Frerichs, & Kristjansson, 2001).

In the CSHA, classification of the cognitive status of the participants was done according to DSM-III-R criteria. Ratings for each of the DSM-III-R criteria for dementia were available for CIND and dementia participants at CSHA-2. From there, two CIND categories based on Zaudig's (1992) MCI criteria were created. CIND Type 1 ("circumscribed memory impairment") requires the presence of both short- and long-term memory impairments, in the absence of deficits in other cognitive domains. CIND Type 2 ("other cognitive impairment") includes participants exhibiting cognitive impairment in cognitive domains other than memory. Although not a requirement, CIND Type 2 may include memory impairment, as long as impairment in another cognitive domain is present. These CIND categories differ from Zaudig's (1992) MCI classifications as they are based solely on the exclusion of dementia. The cause of the impairment is not cause for exclusion.

Given its less restrictive criteria, the classification of CIND is reported to have a higher population prevalence rate than all the dementias combined (Graham et al., 1997; Di Carlo et al., 2000). In the CSHA, the overall population prevalence of CIND was 16.8%. Age-based prevalence rates ranged from 11% to 30.3% for persons aged 65-74 years and greater than 85 years, respectively (Graham et al., 1997). As expected, the cognitive performance of the CIND group fell between that of the not cognitively impaired (NCI) and the demented group (Tuokko, Frerichs, & Kristjansson, 2001). A prevalence rate of 10.7% for CIND was identified in the Italian population (DiCarlo et al., 2000). Using the MMSE, approximately 15% of persons aged 75 years and older were identified as CIND in the Kungsholmen Project (Palmer, Bäckman, Small, & Fratiglioni, 2006). The highest population prevalence rate for CIND (33.3%) was observed among Australian community-dwelling elderly aged 70-79 years (Low et al., 2004). The observed variability in the population prevalence rates for CIND is hypothesized to reflect differences in the age groups sampled and different inclusion criteria (Low et al., 2004).

Similar to MCI, heterogeneity in the longitudinal outcomes of CIND have been reported. However, a significant proportion of persons with CIND progress to dementia over time. Longitudinal analyses of CIND participants in the Kungsholmen Project revealed that one third remained stable or exhibited improved cognitive performance, one third died, and the remaining one third progressed to dementia (Palmer et al., 2006). In a five-year follow-up study, Tuokko et al. (2003) report higher rates of mortality, institutionalization, and dementia among persons initially classified as CIND, compared to not cognitively impaired (NCI) persons. No significant difference in the progression to dementia was noted between the major CIND subclassifications. In the Kungsholmen Project, the CIND group exhibited a three-fold risk for the development of AD after three years, compared to cognitively intact participants (Monastero, Palmer, Qiu, Winblad, & Fratiglioni, 2006).

Clearly, there exists substantial variability in the conceptualization of mild cognitive impairment. A primary difficulty with research in this area is the lack of a “gold-standard” or consensus definition of MCI. Additional variability in the data comes from the selection of research samples. Research has been limited by small, highly specified clinical samples (e.g., participants selected from tertiary memory clinics), wherein the measures employed to group participants into MCI or dementia categories are also used to examine the relationship between MCI and dementia (Ritchie et al., 2001). Broadly defined, the goals of the following two studies are to examine the validity of existing definitions of mild cognitive impairment and to identify the medical, neurpsychological, psychiatric, social, and/or functional characteristics that distinguish between NCI & CIND, not demented & demented, and non-converting & converting CIND participants in a population-based, longitudinal study of elderly Canadians.

Chapter 2

General Methodology

Overview of the Canadian Study of Health and Aging (CSHA)

The data for the following pair of studies was derived from the CSHA. The CSHA is a multi-center, population-based, longitudinal assessment of elderly Canadians including four objectives addressing dementia in the Canadian population: 1) determine the prevalence of dementia among elderly Canadians; 2) elucidate AD risk factors; 3) explore caregiving and caregiver burden associated with dementia; and 4) develop a database for further evaluation of dementia, with the goal of informing and developing research examining interventions for dementia (CSHA Working Group, 1994). A representative sample of community-dwelling persons, aged 65 years and older, was randomly selected from provincial health insurance databases (with the exception of Ontario). Age-stratified (i.e., 65-74, 75-84, 85+ years) sampling of participants was completed such that more participants were selected for each successive age group, resulting in an over-sampling of the oldest participants. A sample of elderly participants residing in institutions (i.e., nursing homes, chronic care facilities, and group living environments) was also included in the data set. A total of 10,263 persons took part in the CSHA (CSHAWorking Group, 1994; 2000; McDowell, Xi, Lindsay, & Tuokko, 2004). The community-dwelling participants (n = 9008) underwent a screening interview and completed the Modified Mini-Mental State Exam (3MS; Teng & Chui, 1989). Persons scoring below 78 on the 3MS, a random selection of persons scoring above 78 on the 3MS, and persons who could not complete the screening due to physical or other limitations were selected to participate in a clinical examination (n = 1673). Participants living in an institution did not undergo a screening evaluation, but were invited to undergo a clinical evaluation (n = 1255) (CSHA Working Group, 1994).

The clinical evaluation component of the CSHA was designed to determine the presence or absence of cognitive impairment and to assist in the assignment of a clinical diagnosis according to DSM-III-R criteria. The evaluation consisted of four components: 1) the nurse's evaluation involving the re-administration of the 3MS, evaluation of physical and sensory function (i.e., vital signs, vision, hearing), recording of physical features (e.g., height and weight), and completion of Section H of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX; Roth et al., 1988), a measure used to gather a participant's medical and cognitive history from a significant other; 2) persons receiving a score of 50 or greater on the re-administration of the 3MS underwent a neuropsychological evaluation administered by a psychometrician and interpreted by a neuropsychologist; 3) evaluation by a physician, including a brief mental status evaluation and a physical and neurological examination; and 4) blood work (CSHA Working Group, 1994; McDowell et al, 2004).

The neuropsychological component of the clinical evaluation consisted of a battery of neuropsychological measures evaluating the cognitive domains included in a DSM-III-R (APA, 1987) diagnosis of dementia. The domains evaluated included memory, abstract thinking, judgment, aphasia, apraxia, agnosia, and construction (CSHA Working Group, 1994; Tuokko et al., 1995). Upon completion of the clinical evaluations, a consensus conference was held, wherein consensus diagnoses of NCI, CIND, or dementia were determined for each participant. CIND subclassifications and type of dementia were also determined. Five and ten years later, participants who were able and who agreed to participate underwent similar clinical evaluations, with minor modifications (CSHA-2 and CSHA-3, respectively; McDowell et al., 2004). The cognitive status of persons dying prior to completion of the CSHA was estimated according to one of three sources. Participants dying before the completion of CSHA-3 were given a diagnosis of dementia if one of the following was evident: 1) a collateral report of dementia of memory difficulties prior to death, 2) dementia listed on the death certificate as the underlying cause of death, or 3) a greater than 0.95 probability of dementia according to a predictive algorithm (Stewart, McDowell, Hill, & Aylesworth, 2001).

Neuropsychological Measures

Data from the following 12 neuropsychological measures from CSHA-2 was examined in this dissertation research: 1) *Memory* (Benton Visual Retention Test – Multiple Choice form F [BVRT Recognition; Benton, 1974]; Buschke Cued Recall [immediate recall on Trial 1 = Buschke FR1; total free recall score from trials 1-3 = Buschke Retrieval; total free cued recall from trials 1-3 = Buschke Total Cued Recall; Buschke, 1984; Tuokko & Crockett, 1989]; Rey Auditory Verbal Learning Test [trial 1 = RAVLT1; trial 6 = RAVLT6; total score across all 5 trials = RAVLT Total; Rey, 1964]; Wechsler Adult Intelligence Scale – Revised [WAIS-R] Information [Wechsler, 1981]); (2) A*bstract thinking* (WAIS-R Similarities [short form; Wechsler, 1981]); (3) *Judgment* (WAIS-R Comprehension [short form; Wechsler, 1981]); (4) *Aphasia* (Controlled Oral Word Association Test [COWAT; Spreen & Benton, 1977], Animal Naming [Rosen, 1980]); (5) *Apraxia* (WAIS-R Digit Symbol [short form; Wechsler, 1981]); (6) *Agnosia* (Buschke Visual Component [Buschke, 1984]); and (7) *Construction* (WAIS-R Block Design [short form; Wechsler, 1981]). Selection of neuropsychological measures to address the cognitive domains implicated in a diagnosis of dementia according to DSM-III-R was limited by the availability of normative data, clinician familiarity, and availability of bilingual forms. As such, some of the domains (e.g., agnosia, apraxia) were not directly measured, but intact or impaired function was inferred from other measures. In the CSHA, participants undergoing a neuropsychological evaluation were classified at the case conference as impaired or not impaired in each cognitive domain, following review of all information collected as part of the clinical evaluation (Tuokko et al., 1995).

Overview of Research Questions

This dissertation research consists of two separate but related studies designed to elucidate the clinical and cognitive characteristics associated with MCI and the clinical correlates of conversion to dementia. Using data from the CSHA, Study 1 describes the demographic and neuropsychological characteristics of participants meeting Winblad et al.'s (2004), Zaudig's (1992), and the CSHA's (Ebly et al., 1995; Tuokko et al., 2001) criteria for cognitive impairment of insufficient severity to warrant a diagnosis of dementia. Study 1 also identifies the sample frequency of each cognitive classification and compares the ability of each MCI/CIND classification to predict conversion to dementia. Building on the results of the first study, Study 2 was designed to identify the clinical correlates of participants who convert to dementia (in the absence of specific MCI/CIND diagnostic criteria). Demographic, cognitive, frailty/morbidity, social/physical, neuropsychiatric, vascular, and family history (alone and in combination) predictive algorithms distinguishing CIND from NCI, demented from not demented, and converting from non-converting participants were generated. It is believed that the results and conclusions drawn from these two studies will clarify existing MCI classifications and inform the early identification of persons at-risk for conversion to dementia; thus, providing opportunities for patient and caregiver education, planning, and decision-making, and enabling the development and implementation of more targeted intervention strategies.

Chapter 3

Study 1: Patterns of Neuropsychological Decline and Conversion Rates for Three Classification Schemes of Mild Cognitive Impairment

Introduction

Dementia is reported to affect 252,600 (8%) Canadians aged 65 years and older. This number is predicted to increase to 778,000 Canadians 65 years and older by the year 2031 (Canadian Study of Health and Aging [CSHA] Working Group, 1994). This finding illustrates the importance of the early identification of individuals at risk for pathological cognitive decline. In persons "destined" to develop dementia, MCI describes an intermediary stage in the cognitive and pathological continuum between normal and abnormal cognitive function (Petersen, 2003, p.2). Adhering to a continuum model of cognitive decline, the conceptualization of MCI as an intermediary stage establishes a diagnostic entity that, through long-term monitoring and manipulation, may enable the development of interventions that could delay or prevent the progression to dementia.

Unfortunately, as was described in the section on the history of mild cognitive decline, the conceptualization of MCI as a diagnostic entity is controversial. The biggest obstacle confronting the concept of MCI is the absence of consensus criteria for its diagnosis. The lack of "gold-standard" criteria reflects different conceptualizations of the term MCI. For example, based on evidence of intra-individual decline (as inferred from collateral sources) and neuropathological markers of AD, some researchers suggest that MCI represents early-stage AD (Morris, 2006; Morris et al., 2001). In contrast, in a recently published debate addressing the clinical utility of the concept of MCI, Petersen and Knopman

(2006) argue that, on the basis of diagnostic criteria alone, MCI cannot be AD. Rather it is a prodromal state that may progress to dementia.

The stability of the construct of MCI has also come under criticism. Researchers report that a significant percentage of persons meeting Petersen's (1999) original criteria for MCI exhibit improved cognitive functioning at follow-up. Up to 40% of persons with a baseline diagnosis of MCI are noted to improve to receive a diagnosis of NCI at follow-up (Larrieu et al., 2002; Ritchie, Artero, & Touchon, 2001). These findings contradict the hypothesis that MCI is an interim state between NCI and dementia (Petersen, 2003). However, Petersen and Knopman (2006) contend that the reports of MCI instability result from the ad hoc retrofitting of MCI criteria to an existing database and the utilization of a single cognitive measure to make a diagnosis of MCI.

Core Differences Among Existing Diagnostic Definitions

MCI is a concept with many definitions describing a pathological decline in cognitive function that does not meet the criteria for a diagnosis of dementia. Much of the difficulty in comparing research findings is due to the variability in MCI diagnoses. This variability, ultimately, results in different prevalence rates and conversion rates. Outside of the cognitive presentation, three core differences among existing definitions of MCI include: 1) the presence of a subjective memory complaint (a requisite feature of Petersen's [1999, 2003, 2004] and Winblad et al's [2004] MCI criteria), 2) the presence of intact activities of daily living (ADLs; also required for Petersen's [1999, 2003, 2004] and Winblad et al's [2004] MCI classifications), and 3) the inclusion or exclusion of participants based on the etiology of their cognitive deficits.

Subjective Memory Complaint

In recent years, investigation of the contribution of the subjective memory component required for the commonest definition of MCI (i.e., Winblad et al's [2004] MCI algorithm based on Petersen's [2003] criteria) has increased. The proliferation of research in this area may be due to reports that the requirement of a subjective report of memory impairment for a classification of MCI is an anomaly in medicine (Bond & Corner, 2006). As well, subjective reports of memory difficulties have been found to predict incident AD in older adults (Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999), especially in the highly educated (van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). Moreover, it has been hypothesized that subjective memory impairment, with an approximate duration of 15 years, is a pre-MCI stage in the continuum from intact cognition to dementia (Reisberg, 1986).

In contrast, research suggests that individuals who are mildly cognitively impaired do not report more memory problems, compared to cognitively intact persons (Collie et al., 2001; Kumamoto et al., 2000). In fact, while subjective memory complaints have been associated with incipient AD in NCI persons, Geerlings et al. (1999) report an absence of such a relationship among non-demented but cognitively impaired persons. It has been suggested that impaired insight hinders the self-report of persons with cognitive impairment who do not meet the criteria for dementia (Albert et al., 1999). The role of subjective memory impairment in the diagnosis of cognitive impairment and in the prediction of future dementia is further clouded by findings that cognitive complaints (including subjective memory complaints) are associated with the emotional state of older adults, rather than a reflection of previous or future cognitive decline (Jorm et al., 1997).

Conflicting reports of the utility of a subjective memory complaint criterion for the identification of MCI may be due to differences in how this criterion is measured. For instance, broad-based querying of memory difficulties may produce very different results than more in-depth or specific questioning. To address this issue, Clément, Belleville, and Gauthier (2008) compared the nature and severity of subjective memory complaints in normal, MCI, and AD patients. Participants with MCI and AD exhibited significantly more cognitive complaints than normal healthy older adults. Interestingly, MCI patients subjective reports of memory deficits were limited to specific circumstances (i.e., books/movies and conversations) and were associated with their level of general cognitive functioning and not their current memory ability. Thus, the continued use of the subjective memory criterion without specification may fail to capture several persons exhibiting cognitive decline.

Rather than relying on the potentially fallible subjective memory criterion, recommendations for querying significant others have been proposed. Arguments in favor of using collateral informants to gather the patient history suggest that informant reports have more face validity and provide valuable information regarding intra-individual change – evidence that the individual demonstrates a decline in cognitive performance. Evidence of intra-individual change is considered by some researchers to be paramount when making a classification of MCI (Morris & Storandt, 2006) and has been suggested as a tool for identifying AD prior to the MCI stage (Howieson et al., 2008; Storandt, Grant, Miller, & Morris, 2006). A recent report by the International Working Group on MCI recommended acceptance of a family member's impression of cognitive decline, in lieu of self-reported impairment (Winblad et al, 2004).

Activities of Daily Living

Another modification suggested by the Stockholm consensus group included allowances for increased difficulty in functional ability, while maintaining relatively intact ADLs (Winblad et al., 2004). Prior to this meeting, a classification of MCI according to Petersen's (1999, 2003) criteria required "largely intact" functional ability. Information gathered from collateral informants suggests that cognitive deficits often interfere with functional ability in persons with MCI (Morris et al., 2001). This is further supported by reports that, compared to normal healthy older adults, persons with MCI are impaired on complex activities of daily living (e.g., memory of conversations/television programming, location of objects, appointments; Perneczky et al., 2006). The authors reported that all MCI patients exhibited some form of impairment in instrumental activities of daily living (IADLs) requiring memory or cognitive reasoning. In contrast, no differences were noted between MCI and controls in activities of daily living (e.g., dressing, laundry, etc.)

Similarly, functional ability in persons classified as CIND is reported to fall between that of NCI and demented individuals (Graham et al., 1997; Kumamoto et al., 2000), with up to 49% of persons classified as CIND demonstrating some functional difficulties (Graham et al., 1997). Tuokko, Morris, and Ebert (2005) report even higher rates of functional deficits among MCI/CIND, compared to NCI subjects. Overall, 2/3 of the MCI/CIND group exhibited impairment in functional ability (IADLs and walking and showering). Cognitive impairments, especially in memory and psychomotor speed domains, were observed concurrently with functional impairments. When applied in a longitudinal population study, the revised MCI criteria (allowing for increased difficulty in functional ability) were associated with an estimated prevalence rate of 16.6% (Artero, Petersen, Touchon, & Ritchie, 2006), similar to the population prevalence rate of CIND (Graham et al., 1997). Analysis of the revised MCI criteria revealed that cognitively impaired but nondemented persons frequently have difficulty with using the telephone, money, dressing, and appliances (Artero et al., 2006).

These and other studies highlight the potential relevance of impaired functional ability in the prediction of future dementia. Specifically, the presence of one or more impaired IADLs has been identified as a significant predictor for future dementia, in cognitively impaired and cognitively intact persons (Di Carlo et al., 2007). Moreover, individuals with impaired IADLs are more likely to develop impaired ADLs – a criterion for a diagnosis of dementia (Purser, Fillenbaum, Pieper, & Wallace, 2005). Despite these findings, the maximum level of functional impairment for a diagnosis of MCI remains controversial. To date, the commonest criteria for MCI (i.e., Winblad et al., 2004) do not specify assessment measures or cut-off levels for the diagnostic criterion of intact ADLs.

Etiology

MCI definitions also differ according to whether or not they exclude persons on the basis of the etiology of cognitive impairment. The CIND classification is unique in that it does not exclude persons on the basis of the etiology of their cognitive impairments (with the exception of dementia). Rather, CIND is described as an inclusive classification without formal diagnostic criteria (Tuokko, Frerichs, & Kristjansson, 2001). In contrast, most MCI criteria exclude persons whose cognitive decline may be attributed to a pre-existing medical, neurological, psychiatric, or pharmacological condition. As such, these MCI definitions capture fewer persons exhibiting cognitive decline and may, as a result demonstrate lower sensitivity (Ishikawa & Ikeda, 2007). For example, in a five-year follow-up study, the conversion rate for CIND was 47% (Tuokko et al., 2003). The CIND conversion rate is much higher than the conversion rate reported for the original MCI criteria (6%-25%; Petersen et al., 2001). Broadening the definition of cognitive impairment not meeting the criteria for dementia may enhance the prediction of progression to dementia and its subtypes (Ishikawa & Ikeda, 2007).

Diagnostic Criteria and Prediction of Dementia in Population Studies

The aforementioned core differences in the operationalization of MCI criteria have resulted in several MCI definitions and/or subtypes. Understandably, prevalence rates and rates of progression to dementia have been found to differ according to the MCI criteria employed. In fact, large differences in prevalence rates have been reported following the removal of a single criterion. For example, a 53.6% increase in the prevalence of all MCI cases was observed by simply removing the subjective memory criterion from Petersen's (2004) original criteria for four MCI subtypes (Busse, Angermeyer, & Riedel-Heller, 2006). In a previous study, the authors report baseline MCI prevalence rates varying between 0.5 and 15.4% depending on the severity cut-off for CI and the presence or absence of the subjective memory criterion (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003).

CIND and MCI differences in definitions affect the conversion rate to dementia. A recent examination of the application of various MCI definitions, including CIND, to a UK population revealed little outcome congruence. Population prevalence and conversion rates varied according to the definition of mild cognitive impairment. Self-reported memory complaint was noted to have the highest prevalence rate (42%), while moderate cognitive decline (i.e., stage 4 on the Global Deterioration Scale) had the lowest (0.1%; Stephan, Matthews, & McKeith, 2007). The finding of little overlap in participant classification across definitions was argued to represent the heterogeneity of the concept of MCI and the difficulty that this creates when an individual's cognitive status ranges from normal to impaired according the MCI definition employed. These results have important implications for the predictive accuracy of MCI definitions.

Despite the heterogeneity of MCI classifications, persons with MCI are at a higher risk for developing dementia. Busse et al. (2006) report that 60% to 65% of individuals with MCI will progress to dementia in their lifetimes. Similarly, Di Carlo et al. (2007) report that MCI and CIND increase the risk of dementia at follow-up three-fold. Not surprisingly, researchers are beginning to investigate the predictive ability of existing definitions of MCI for progression to dementia. For example, Visser and Verhey (2008) examined the predictive accuracy of four MCI definitions (i.e., aMCI [single and multiple domain], mild functional impairment [MFI], AACD, and AAMI) for conversion to AD over five years in a large sample of non-demented elderly referred to a memory clinic. Using the area under the curve (AUC) and receiver operating characteristic (ROC) analyses, operationalized definitions of aMCI, MFI, and AAMI significantly predicted AD at follow-up. Moderately high sensitivities (i.e., the probability of meeting the criteria for a specific diagnosis [e.g., aMCI] in persons converting to dementia) and specificities (i.e., the probability of not meeting the criteria for a specific diagnosis in persons not converting to dementia) were noted for aMCI and MFI, while the AAMI and AACD definitions were associated with high sensitivities and low specificities. Age was found to significantly moderate the positive predictive value (i.e., increasing age was associated with a higher positive predictive value for all MCI definitions) and was argued to be a reflection of the age-associated incidence of AD in the population.

The authors contend that the utility of MCI definitions lies in their ability to describe cognitive function, rather than serving as an early symptom of AD.

Even more relevant to the current study are investigations of the accuracy of MCI classifications in the prediction of future dementia in population-based studies. For example, following the introduction of the four subclassifications of MCI (Petersen et al., 2001), Busse and colleagues (2003) sought to empirically validate the definitions of aMCI, multiple domain MCI, and non-amnestic single-domain MCI by identifying their prevalences and predictive ability in a population sample of elderly adults with a three-year follow-up. In addition to Petersen's (2001) original MCI criteria, Busse et al. (2003) applied criteria that modified the subjective memory complaint criterion (i.e., eliminated the requirement) and/or the severity level of cognitive deficit (i.e., groups formed on the basis of performance 1.0, 1.5, and 2.0 standard deviations below age- and education-matched norms). A small proportion of the population-based sample met the inclusion criteria for groups based on original criteria. The progression to dementia over 2.6 years ranged from 10.1 to 54.5% across the MCI groups. With the exception of the modified multiple domain MCI (1.0 *SD*) group, all MCI classifications failed to predict progression to dementia. These results are consistent with the findings of Ritchie et al. (2001) wherein the diagnosis of MCI was a poor predictor of dementia in the general population.

The Busse et al. (2003) study also addressed one of the core contributors to the heterogeneity in the MCI literature: the use of the subjective memory criterion. Fisk, Merry, and Rockwood (2003) contend that subjective memory complaints do not add to the risk of progression to dementia, above and beyond the remaining MCI criteria, in population-based studies. Busse et al. (2003) noted that the removal of the subjective memory criterion resulted in larger baseline prevalences and higher diagnostic sensitivities. However, the consequence of the modification of the original criteria was lower diagnostic specificities and positive predictive values. In comparing these results to those of Fisk et al. (2003), two important methodological differences should be identified. First, Fisk et al. (2003) conducted a follow-up at 5.0 years, compared to Busse et al.'s (2003) 2.6-year follow-up. Additionally, MCI classification in the Fisk et al. (2003) study was based on clinical diagnostic opinion, whereas Busse et al. (2003) based their classification on psychometric cut-points. Given the different outcomes associated with the varied MCI criteria, Busse et al. (2003) contend that the purpose of a diagnosis of MCI should inform the selection of specific MCI criteria.

Purpose

Given the heterogeneity of MCI definitions and the limited literature examining the predictive accuracy of MCI classifications in population-based samples, the purposes of the current study were two-fold. The first purpose was to examine the frequency of existing prominent classifications of MCI in a population-based sample of elderly Canadians. Second, the utility of each classification for the identification of individuals at-risk for progressing to dementia five-years later was evaluated. The following questions were addressed to fulfill the purposes of the study:

1. What is the frequency of each classification in a sample of older adults in the Canadian population?
2. How does changing the definitions of mild cognitive impairment affect the frequency of each classification within the sample?

Based on previous research, it was hypothesized that the highest prevalence and conversion rates would be associated with definitions of multiple-domain MCI and CIND. Moreover, given reports that persons exhibiting memory impairment are at a higher risk for progression to dementia (Tuokko et al., 2003), it was hypothesized that the conversion rate for persons meeting Zaudig's (1992) MCI criteria (i.e., requiring impairment in both short- and long-term memory impairment) would exceed that of the other classifications of cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia.

Objectives

Three objectives were identified for the current study. The first objective was to elucidate the demographic and neuropsychological characteristics of persons meeting the criteria for a diagnosis of mild cognitive impairment according to Winblad et al's (2004) definition of aMCIsd, aMCImd, naMCIsd, and naMCImd, Zaudig's (1992) definition of MCI Type 1 and MCI Type 2, and the CSHA's definition of CIND Type 1 and CIND Type 2. The second objective was to determine frequency of each classification in a longitudinal population study of elderly Canadians. Finally, the third objective was to determine the five-year conversion rate to dementia for each of the eight MCI classifications, with the goal of identifying the utility of the respective classifications as markers for incipient dementia. These classifications of MCI were selected given their prominence in the literature and their significance with respect to the CSHA data set (i.e., the CSHA CIND typology is based on Zaudig's [1992] MCI classifications). This study is believed to be the first study to jointly examine these classifications of MCI in a population sample.

Methodology

Participants

Only participants who underwent a neuropsychological evaluation at CSHA-2 and received a consensus diagnosis of NCI or CIND, with and without missing neuropsychological data at CSHA-2, were included in the analyses (n = 1233). Data gathered from collateral informants and objective neuropsychological data for persons meeting the inclusion criteria for the study were evaluated to determine for which cognitive classifications they qualified.

Definitions of Cognitive Classifications

Data gathered from collateral informants and objective neuropsychological data for persons meeting the inclusion criteria for the study were evaluated to determine for which of nine cognitive classifications they qualified. Participants identified as cognitively intact at CSHA-2 were assigned to the NCI group (n = 698). Examination of the consensus diagnostic opinion of cognitive performance in each of the cognitive domains led to the subsequent exclusion of 177 participants who were identified as exhibiting impaired performance in at least one cognitive domain, despite their consensus diagnosis of NCI. Although this impairment may reflect historic difficulty in cognitive functioning, participants exhibiting any form of impairment were excluded from the Robust NCI group. This procedure was employed to ensure differences between the Robust NCI and CI group and the absence of any MCI participants in the NCI group at CSHA-2. Thus, the Robust NCI sample consisted of 521 participants. The *NCI-Other* group was created to capture the 177 participants with a consensus diagnosis of NCI and to examine their progression to dementia at follow-up.

The remaining 535 participants had a consensus diagnosis of CIND at CSHA-2 and formed a cognitively impaired (CI) group. Participants in the CI group were subsequently subclassified into eight groups according to Winblad et al.'s (2004), Zaudig's (1992) and the CSHA's (Graham et al., 1997) criteria for cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia. Groupings were formed based on information available from the consensus conference, wherein participants were identified as exhibiting intact or impaired performance in each of the following cognitive domains: short-term memory, long-term memory, language, abstract thinking, judgment, motor, visuospatial, higher cortical functioning, recognition, personality, and ADLs. CI subclassifications were non-independent, overlapping groups (i.e., subjects were assigned to each subclassification for which they met the operationalized diagnostic criteria). The operationalized diagnostic criteria are depicted in Table 1.

MCI Groups According to Winblad et al.'s (2004) Criteria

To be included in the aMCIsd group, participants had to exhibit impaired short-term and/or long-term memory and an absence of impairment in other cognitive domains (i.e., abstract thinking, judgment, visuo-spatial functions, higher cortical functions, aphasia, apraxia, agnosia, and personality) at CSHA-2. Petersen (2003) suggests that, in addition to memory impairment, persons diagnosed with aMCI may exhibit minimal impairment (i.e., within 0.5 standard deviations below the mean) in other cognitive domains. However, the recommended clinical standard for diagnosing cognitive impairment is performance falling below two standard deviations from the mean (Lezak, Howieson, & Loring, 2004). As such, participants exhibiting impairment in cognitive domains other than memory were excluded from the aMCIsd classification. In contrast, participants exhibiting impaired short-term and/or long-term memory impairment and impairment in at least one other cognitive domain, as determined at the CSHA-2 consensus conference, were included in the aMCImd group.

***Table 1.* Summary of Group Classification Criteria**

	aMCIsd	aMCImd	naMCIsd	naMCImd	MCI-1	MCI-2	CIND-1	CIND-2
Memory Impairment	X	X	°	°	X	X	X	#
Short-term	*	*	°	°	X	X	*	#
Long-Term	*	*	°	°	X	X	*	#
Abstract Thinking	°	*	Δ	^	°	*	°	*
Judgment	°	*	Δ	^	°	*	°	*
Language	°	*	Δ	^	°	*	°	*
Motor	°	*	Δ	^	°	*	°	*
Recognition	°	*	Δ	^	°	*	°	*
Visuo-spatial	°	*	Δ	^	°	*	°	*
Higher cortical function	°	*	Δ	^	°	*	°	*
Personality	°	*	Δ	^	°	*	°	*
ADLs	°	°	°	°	N/A	N/A	N/A	N/A

NOTE: X = Impaired; ° = Preserved; * = At least one cognitive domain impaired; Δ = Only one cognitive domain impaired; ^ = More than one cognitive domain impaired; # = Possibly impaired; aMCIsd = amnestic MCI single domain; aMCImd = amnestic MCI multiple domain; naMCIsd = non-amnestic MCI single domain; naMCImd = non-amnestic MCI multiple domain; MCI-1 = MCI type 1; MCI-2 = MCI type 2; CIND-1 = CIND type 1; CIND-2 = CIND type 2; ADLs = activities of daily living

To be included in one of the non-amnestic MCI classifications (i.e., naMCIsd and naMCImd), an absence of short-term and long-term memory impairment was required. Inclusion in the naMCIsd group required that participants exhibit impairment in only one non-memory cognitive domain at CSHA-2. In contrast, participants identified as exhibiting impairment in more than one non-memory cognitive domain were included in the naMCImd group.

Given the variable application of Petersen's criteria for MCI in the literature, the controversy surrounding the importance of intact activities of daily living as a diagnostic criterion for MCI, and an absence of an ADL threshold criterion, two approaches were employed when creating the MCI classifications. The approaches involved either *strict* or *lenient* adherence to Petersen's recommendation for intact ADLs. In the current study, persons were included in the *strict* aMCIsd, aMCImd, naMCIsd, and naMCImd classifications if they were able to engage in eating, dressing, self-care, bathing, and toileting behaviors without help. In contrast, participants were included in the *lenient* aMCIsd, aMCImd, naMCIsd, and naMCImd classifications if they were able to engage in eating, dressing, self-care, bathing, and toileting behaviors with or without help. Participants unable to perform these ADLs with or without help were excluded from both the *strict* and *lenient* aMCIsd, aMCImd, naMCIsd, and naMCImd classifications.

Finally, inclusion in any of the aMCIsd, aMCImd, naMCIsd, and naMCImd classifications required a consensus diagnosis of CIND at CSHA-2. Persons with the following etiological bases of CIND, as identified at the consensus conference, were excluded from the aMCIsd, aMCImd, naMCIsd, and naMCImd classifications: delirium, chronic alcohol abuse, chronic drug intoxication, depression, psychiatric disease, mental retardation, cerebrovascular (stroke), general vascular, Parkinson's disease (PD), brain tumor, multiple sclerosis (MS), epilepsy, AD, vascular dementia, other specific dementia (e.g., frontotemporal dementia [FTD], Huntington's disease, Creutzfeldt-Jacob disease [CJD], dementia post-head injury), and unclassifiable dementia. Subjects with a consensus CIND subclassification of other CIND, social isolation, socio-cultural, blind/deaf (i.e., classification may be due to sensory deficits), unknown CIND, and age-associated memory impairment (AAMI) at CSHA-2 were selected for inclusion the aMCIsd, aMCImd, naMCIsd, and naMCImd groups. The addition of these etiological restrictions is in keeping with previous research evaluating the prevalence and predictive accuracy of amnestic MCI, multiple domain MCI, and single domain MCI (e.g., Alexopoulos et al., 2006; Busse et al., 2003; 2006; Fisk et al., 2003; Tierney et al., 1996, Visser & Verhey, 2008).

MCI Type 1 and Type 2

Participants demonstrating impairment in both short-term and long-term memory impairment and an absence of impairment in other cognitive domains at CSHA-2 were included in the MCI Type 1 (MCI-1) group (n = 16). Participants exhibiting both short-term and long-term memory impairment, as well as impairment in at least one other cognitive domain, were included in the MCI Type 2 (MCI-2) group (n = 34). As specified by Zaudig's (1992) MCI criteria, participants with CSHA-2 CIND subclassifications indicative of psychiatric disorder, neurological disorder, acute confusional/delirous state, head trauma, and mental retardation were excluded from the MCI-1 and MCI-2 groups. As such, only persons identified as having the following CIND subclassifications were included in the MCI-1 and MCI-2 groups: other CIND, social isolation, socio-cultural, blind/deaf (i.e., classification may be due to sensory deficits), unknown CIND, and AAMI.

CIND Type 1 and Type 2

Participants were included in the CIND Type 1 (CIND-1) group if they were identified (at the CSHA-2 consensus conference) as having short-term or long-term memory impairment (or both) and an absence of impairment in other cognitive domains (n = 86). Participants identified as exhibiting impairment in cognitive domains, with or without memory impairment, were included in the CIND Type 2 (CIND-2) group (n = 365). Unlike the CI groups based on Winblad et al.'s (2004) and Zaudig's (1992) criteria for MCI, participants in both the CIND-1 and CIND-2 groups were not excluded on the basis of the etiology of their identified cognitive impairment.

Data Analyses

Data analyses were conducted using SPSS-16 (SPSS, Inc., Chicago, Ill.). Given that the groups were overlapping and non-exclusive, quantitative statistical between-group comparisons were not undertaken. Frequency analyses provided percentage prevalence rates for each cognitive classification at CSHA-2. Descriptive statistics were used to elucidate the demographic characteristics and average neuropsychological test performance for each of the thirteen cognitive classifications at CSHA-2. Retrospective (CSHA-1) and prospective (CSHA-3) group membership were assessed according to the same algorithm employed at CSHA-2 (see Table 1). Frequency analyses provided the associated percentage prevalence rates of group membership and dementia status at CSHA-1 and CSHA-3. Receiver operating characteristic (ROC) analyses were employed to assess the predictive power of each of the CIND/MCI cognitive classifications, as well as the NCI and *Other* classifications, in the prediction of future dementia. A Bonferroni correction (.05/15 = .003) was used to control for type I error when interpreting the ROC analyses. Additional outcome measures included the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each cognitive classification.

Results

Overall Baseline Sample Characteristics

Twelve hundred and thirty-three non-demented participants met the identified inclusion criteria for this study at CSHA-2. Demographic characteristics of this baseline sample are listed in Table 2. Overall, participants ranged from 64 to 99 years of age (mean = 76.8, *SD* = 6.8) at the start of the CSHA (i.e., October 1, 1990) and had between 0 and 25 years of education (mean = 9.9 , *SD* = 4.0). With regard to cognitive status, 57% of the participants received a consensus diagnosis of NCI (N = 698), while the remaining 43% exhibited some form of cognitive impairment (CI; N = 535) not meeting the criteria for dementia at CSHA-2.

Table 2. **Baseline (CSHA-2) & Prospective (CSHA-3) Sample Demographics**

	CSHA-2	**CSHA-3**
Sample Size, N	1233	733
Age on Oct. 1, 1990		
Mean (S.D.)	76.8 (6.8)	76.0 (6.7)
Range	64 – 99	64 – 96
Education, mean years (S.D.)	9.9 (4.0)	10.23 (4.0)
3MS Score, Mean (S.D.)	84.6 (10.3)	85.6 (10.3)
Gender (% Female)	58.6	62.9
Institutionalized (%)	13.8	15.4
Married (%)*	36.5	37.0

Note: CSHA = Canadian Study of Health and Aging; Married = married and common-law status

Group sizes and prevalence rates for the 12 MCI/CIND subclassifications within both the sample of not demented participants and CI participants at CSHA-2 are listed in Table 3. Groups formed on the basis of Zaudig's (1992) diagnostic criteria for MCI included 3% and 6% of those identified as CI in the MCI-1 and MCI-2 groups, respectively. Strict application of Winblad et al.'s (2004) MCI criteria resulted in 9%, 18%, 2%, and 2% of the CI participants meeting the criteria for aMCIsd, aMCImd, naMCIsd, and naMCImd, respectively. More lenient application of the ADL criteria for MCI increased the representation of CI participants in the aMCIsd (12%), aMCImd (28%), naMCIsd (2%), and naMCImd (3%). Finally, the most inclusive groups, in terms of the least restrictive inclusion criteria and accounting for the largest percentage of the CI participants, were the CIND-1 (16%) and CIND-2 (68%) classifications.

Table 3. **Group Sizes and Prevalence Rates for MCI Subclassifications**

MCI Classification	**N**	**NDEM % (N/1233)**	**CI % (N/535)**
CIND-2	365	29.6	68.2
Lenient aMCImd	148	12.0	27.7
Strict aMCImd	96	7.8	17.9
CIND-1	86	7.0	16.1
Lenient aMCIsd	63	5.1	11.8
Strict aMCIsd	46	3.7	8.6
MCI-2	34	2.8	6.4
Lenient naMCImd	17	1.4	3.2
MCI-1	16	1.3	3.0
Lenient naMCIsd	10	0.8	1.9
Strict naMCIsd	9	0.7	1.7
Strict naMCImd	9	0.7	1.7

Note: NDEM = Not demented group (NCI + CIND); CI = Cognitively impaired group (CIND only)

Sample Characteristics by Robust NCI & MCI Subclassifications

Demographic characteristics for the Robust NCI group and CI subgroups are listed in Table 4. Demographic characteristics assessed included gender, age on Oct. 1, 1990 (i.e., start of the CSHA), years of education, institutionalization status since CSHA-1, primary language, and marital status (note: for the current study, participants identified as married included participants who were living as common-law partners.) The mean age upon entry to the CSHA at time 1 ranged from 73.3 years (SD = 7.9) for the L_naMCIsd group to 79.2 years (SD = 7.3 & 6.2) for the MCI-2 and L_naMCImd groups, respectively. On average, the Robust NCI group had the greatest number of years of education (mean = 10.5, SD = 4.0). Eleven of the 13 cognitive classifications had a higher representation of females than males, with the highest percentage of females observed in the MCI-2 group (79.4%). Only a small percentage of each group was reported to live in an institution at CSHA-2. The two MCI subclassifications with the highest percentage of institutionalized members were the MCI-2 and CIND-2 classifications (i.e., 23.5% and 22.0%, respectively).

***Table 4.* Sample Demographics by Cognitive Subclassification**

	ADL Status	Mean Age at CSHA-1 (*SD*)	Mean Education Years (*SD*)	Female %	Institution %	English %	Married %
Robust NCI	n/a	75.7 (6.4)	10.5 (4.0)	58.9	8.6	73.5	41.3
CIND-1	n/a	77.9 (6.8)	9.9 (4.1)	53.5	8.2	80.2	38.4
CIND-2	n/a	77.4 (6.7)	8.8 (3.9)	60.3	22.0	71.5	30.4
MCI-1	n/a	79.1 (6.6)	8.9 (4.6)	62.5	12.4	62.5	31.2
MCI-2	n/a	79.2 (7.3)	9.1 (3.6)	79.4	23.5	52.9	11.8
aMCIsd	Strict	76.4 (6.3)	10.0 (4.4)	41.3	2.2	71.7	50.0
	Lenient	78.0 (6.9)	10.1 (4.3)	50.8	9.6	77.8	42.9
aMCImd	Strict	76.2 (6.3)	8.3 (4.1)	58.3	6.2	64.6	36.4
	Lenient	78.3 (6.7)	8.8 (4.3)	64.9	14.3	64.2	25.7
naMCIsd	Strict	73.3 (7.9)	6.4 (3.6)	66.7	0	77.8	11.1
	Lenient	74.9 (8.9)	6.2 (3.5)	60.0	0	80.0	10.0
naMCImd	Strict	78.6 (4.7)	7.0 (2.8)	44.4	0	66.7	44.4
	Lenient	79.2 (6.2)	7.4 (3.2)	64.7	7.7	76.5	29.4

NOTE: ADL = activities of daily living; *SD* = standard deviation; n/a = not applicable

Average Neuropsychological Performance

Average performance on each of the selected neuropsychological measures was calculated for each of the MCI/CIND classifications and the Robust NCI group. The results for average memory performance are listed in Table 5. Average performances on the remaining neuropsychological measures are reported in Table 6. Overall, the Robust NCI group demonstrated the highest average performance all measures, with the exception of categorical naming and total free verbal recall. The Robust NCI subjects' average performance on the Animal Naming and Buschke Recall measures was second to the Strict aMCImd and Strict naMCIsd groups. Minimal variability across groups was noted on the Buschke Visual Identification measures. The lowest mean performance on all of the verbal memory variables was observed in the MCI-1 group. In addition to sharing the lowest mean performance on 2 of the 7 verbal memory variables, the MCI-2 group was noted to have the lowest average performance on measures of categorical naming, judgment, visual memory, and apraxia. Overall, the average performance on measures of construction, abstract thinking, aphasia, and agnosia was the lowest for the broader definitions of cognitive impairment (i.e., MCI-2).

Continuing & Attrited Participants at CSHA-3

At CSHA-3, 20 participants (1.6%) were lost to follow-up (LTF), 454 participants (36.8%) were deceased, and 759 participants (61.6%) were alive. Cognitive status at follow-up was available for 83.1% (n = 631) of surviving participants, compared to 22.0% (n = 100) of deceased participants. The breakdown of continuing versus subjects lost to attrition or insufficient data to determine cognitive status is depicted in Figure 1. Compared to survivors, participants lost to follow-up and for whom it was not possible to determine their cognitive status at CSHA-3 (n = 500) were significantly older [F (1, 1231) = 24.76; $p < .001$; mean = 77.89 (6.60)], had significantly fewer years of education [F (1, 1224) = 12.89; $p < .001$; mean = 9.40 (3.97)], a lower representation of males ($\chi^2 = 13.49$, df = 1, $p < .001$), and demonstrated significantly poorer performance on the 3MS at CSHA-2 [F (1, 1225) = 19.59; $p < .001$; mean = 83.01).

***Table 5.* Mean Neuropsychological Performance by Subclassification: Memory**

		Memory							
	ADL Status	Buschke FR1 (*SD*)	Buschke Retrieval (*SD*)	Buschke Total Cued (*SD*)	WMS Info (*SD*)	RAVLT Trial 1 (*SD*)	RAVLT Trial 6 (*SD*)	RAVLT Total (*SD*)	BVRT (*SD*)
Robust NCI	n/a	7.8 (1.6)	26.3 (4.2)	9.5 (4.0)	5.2 (1.1)	4.4 (1.7)	7.5 (3.5)	38.7 (10.4)	11.9 (2.3)
CIND-1	n/a	5.6 (2.3)	18.5 (6.9)	15.2 (5.4)	4.0 (1.5)	2.9 (1.3)	3.4 (2.7)	25.7 (7.8)	10.3 (2.3)
CIND-2	n/a	6.1 (2.0)	20.0 (6.1)	14.3 (5.2)	3.9 (1.5)	3.1 (1.6)	3.9 (2.9)	27.3 (8.5)	9.1 (3.0)
MCI-1	n/a	5.2 (3.1)	16.2 (9.9)	16.1 (7.8)	2.5 (0.9)	2.5 (1.4)	2.9 (3.4)	23.4 (10.6)	10.0 (1.9)
MCI-2	n/a	5.3 (2.0)	17.4 (6.3)	15.2 (5.4)	2.5 (1.0)	2.9 (1.7)	2.9 (1.6)	24.9 (7.7)	8.7 (2.4)
aMCIsd	Strict	5.4 (2.4)	17.6 (6.6)	15.8 (5.4)	3.9 (1.6)	2.9 (1.4)	3.1 (2.7)	25.0 (7.9)	10.6 (2.5)
	Lenient	5.5 (2.4)	18.0 (6.7)	15.7 (5.4)	4.0 (1.5)	2.9 (1.4)	3.3 (2.6)	25.6 (7.8)	10.5 (2.4)
aMCImd	Strict	6.2 (1.9)	20.0 (5.8)	14.4 (4.9)	4.1 (1.4)	2.9 (1.5)	3.5 (2.2)	26.1 (7.9)	8.7 (3.1)
	Lenient	5.9 (2.0)	19.1 (5.9)	14.7 (4.9)	4.0 (1.4)	2.9 (1.5)	3.5 (2.3)	26.1 (7.6)	8.7 (3.0)
naMCIsd	Strict	7.9 (1.8)	26.6 (3.8)	9.1 (3.6)	5.0 (0.9)	4.2 (2.0)	6.7 (2.8)	33.6 (7.9)	10.2 (1.9)
	Lenient	7.8 (1.7)	26.0 (4.0)	9.5 (3.6)	5.0 (0.8)	4.0 (2.1)	6.4 (2.8)	32.4 (8.3)	10.2 (1.9)
naMCImd	Strict	7.7 (2.1)	25.8 (5.5)	10.1 (5.6)	4.8 (1.6)	4.2 (1.2)	6.1 (3.6)	36.5 (7.7)	8.9 (2.0)
	Lenient	7.4 (1.9)	23.9 (5.3)	11.6 (5.5)	3.9 (1.6)	3.7 (1.3)	5.9 (3.7)	32.8 (9.0)	9.0 (2.1)

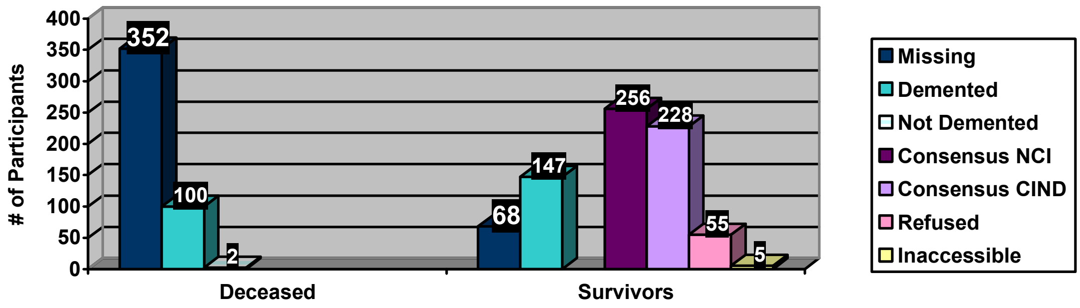
NOTE: Poorest mean scores shaded in grey; ADL = activities of daily living; n/a = not applicable; *SD* = standard deviation; Buschke FR1 = Buschke free recall trial 1 (Buschke, 1984); WMS Information = Wechsler Memory Scale Information subtest (Wechsler, 1974); RAVLT = Rey Auditory Verbal Learning Test (Rey, 1964); BVRT = Benton Visual Retention Test (Benton, 1974)

Table 6. **Mean Neuropsychological Performance by Subclassification: Non-memory Cognitive Measures**

		Abstract Thinking	Judgment	Aphasia		Apraxia	Agnosia	Construction
	ADL Status	WAIS-R Similarities (*SD*)	WAIS-R Comprehension (*SD*)	COWAT (*SD*)	Animal Naming (*SD*)	WAIS-R Digit Symbol (*SD*)	Buschke Visual Identification (*SD*)	WAIS-R Block Design (*SD*)
Robust NCI	n/a	8.0 (4.1)	9.6 (3.1)	28.4 (12.7)	14.9 (4.2)	29.3 (11.4)	11.9 (0.3)	10.0 (4.2)
CIND-1	n/a	6.1 (3.6)	8.4 (2.8)	22.5 (9.5)	12.2 (4.3)	21.6 (10.3)	11.8 (0.7)	8.5 (3.9)
CIND-2	n/a	4.0 (3.5)	7.0 (2.9)	17.1 (9.3)	10.6 (3.7)	17.2 (8.7)	11.9 (0.3)	5.8 (3.9)
MCI-1	n/a	4.5 (3.3)	7.2 (2.8)	18.9 (9.4)	10.5 (2.8)	20.2 (8.8)	11.6 (1.2)	9.3 (3.0)
MCI-2	n/a	2.8 (3.1)	5.7 (2.3)	15.7 (8.3)	9.6 (3.5)	13.8 (7.7)	11.9 (0.5)	4.8 (3.3)
aMCIsd	Strict	6.1 (3.9)	8.6 (2.8)	23.7 (10.4)	12.4 (4.5)	22.6 (11.1)	11.9 (0.4)	9.0 (3.8)
	Lenient	6.2 (3.7)	8.5 (2.8)	23.3 (10.3)	12.7 (4.3)	22.1 (10.3)	11.9 (0.4)	8.7 (3.8)
aMCImd	Strict	3.9 (3.6)	6.6 (2.7)	17.6 (10.8)	17.6 (10.8)	18.6 (8.7)	11.9 (0.5)	6.5 (3.9)
	Lenient	4.0 (3.4)	7.0 (2.7)	17.5 (9.8)	10.3 (3.3)	17.5 (8.6)	11.9 (0.4)	6.2 (3.8)
naMCIsd	Strict	3.3 (2.5)	6.1 (2.3)	12.9 (7.4)	10.8 (2.5)	21.3 (9.2)	12.0 (0.0)	8.0 (3.0)
	Lenient	3.1 (2.5)	6.1 (2.1)	12.9 (7.4)	10.8 (2.3)	21.3 (9.2)	12.0 (0.0)	7.7 (3.3)
naMCImd	Strict	1.0 (1.4)	6.6 (2.9)	16.9 (14.0)	12.0 (3.9)	15.3 (8.8)	11.7 (0.5)	4.3 (3.2)
	Lenient	1.6 (2.4)	5.7 (2.6)	16.0 (10.6)	11.5 (4.3)	16.8 (7.8)	11.9 (0.3)	4.1 (3.6)

NOTE: Poorest mean scores shaded in grey; ADL = activities of daily living; n/a = not applicable; *SD* = standard deviation; WAIS-R Similarities = Wechsler Adult Intelligence Scale – Revised Similarities subtest (short form; Wechsler, 1981); WAIS-R Comprehension subtest (short form; Wechsler, 1981); COWAT = Controlled Oral Word Association Test (Spreen & Benton, 1977); Animal Naming (Rosen, 1980); WAIS-R Digit Symbol subtest (Wechsler, 1981), Buschke Visual Identification (Buschke, 1984); WAIS-R Block Design (short form, Wechsler, 1981)

Figure 1. **Examination at Follow-up**



Cognitive Status at Follow-up (CSHA-3)

Case progression from CSHA-2 to CSHA-3 MCI subclassifications is summarized in Table 7. The addition of the *CI-Other* category allows for the description of participants with a consensus diagnosis of cognitive impairment but who did not meet the criteria for a subclassification of MCI according to algorithms depicted in Table 1. For instance, using Winblad et al.'s (2004) criteria, subjects meeting the criteria for MCI but who demonstrate impairment in activities of daily living are ineligible to be classified as MCI. These participants were, therefore, included in the *CI-Other* (N = 84) group. Similarly, the *NCI-Other* group (N = 177) includes participants with a consensus diagnosis of NCI at CSHA-2 but who exhibited impaired performance in at least one cognitive domain and, therefore, were excluded from the Robust NCI group. MCI criteria requiring the presence of both short-term and long-term memory impairment, as well as impairment in at least one other cognitive domain (i.e., MCI-2), had the lowest rate of improvement (i.e., regression to a diagnosis of NCI) at time 3. The highest rates of regression at time 3 were associated with the multiple-domain, non-amnestic subclassifications (i.e., 17.6% & 22.2% for the L_naMCImd and S_naMCImd groups, respectively). Percent prevalence rates of stability, regression to NCI, and progression to dementia from CSHA-2 to CSHA-3 are depicted in

Figure 2. Note that participants were identified as stable if they maintained a cognitive status of CIND or MCI within a specific classification scheme (e.g., a person classified as L_aMCIsd at CSHA-2 and a classification of L_aMCImd at CSHA-3 was included in the stable group). Percent prevalence rates are calculated as the proportion of participants within an MCI/CIND subclassification at CSHA-2 who (for example) progressed to dementia at CSHA-3 over all subjects within that MCI/CIND subclassification at CSHA-2. Note that the sum of the stable, regressed, and progressed percentages fails to meet 100%. This is due to the presence of participants at CSHA-2 who were subsequently lost to follow-up at CSHA-3 or for whom it was not possible to ascertain their cognitive status at CSHA-3 (e.g., deceased, missing data, etc.).

Table 7. **Progression of MCI/CIND from CSHA-2 to CSHA-3**

	CSHA-2						
CSHA-3	**Robust NCI (n=521)**	**NCI-Other (n = 177)**	**MCI – 1 (n=16)**	**MCI – 2 (n=34)**	**CIND–1 (n=86)**	**CIND–2 (n=365)**	**CI-Other (n=84)**
Survivors	n=384	n = 113	n=10	N=13	n=50	n=182	35
NCI	165	30	1	1	5	16	2
MCI-1	4	0	0	0			0
MCI-2	7	1	0	2			1
CIND-1	25	7			4	1	0
CIND-2	63	19			16	53	3
L_aMCIsd	9	4					0
L_aMCImd	13	2					1
L_naMCIsd	5	1					1
L_naMCImd	4	4					0
S_aMCIsd	17	4					0
S_aMCImd	18	0					1
S_naMCIsd	6	1					0
S_naMCImd	5	3					0
Demented	30	16	4	6	17	62	22
LFT/Unknown	60	22	1	2	6	38	7
Other	41	19	4	2	2	12	1
Deceased	n=126	n=64	n = 4	n = 21	n=34	n=181	n=48
Not Demented	1	1	0	0	0	0	0
Demented	11	16	3	6	10	43	20
LTF/Unknown	114	47	1	15	24	138	28

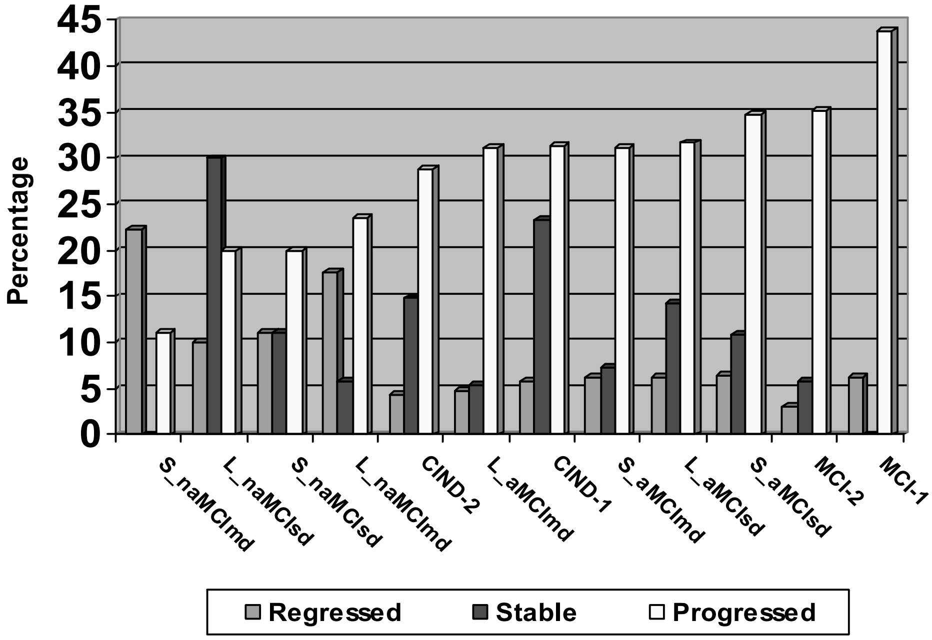
NOTE: LTF = lost to follow-up

Table 7 Continued

CSHA-3	CSHA-2 L_aMCIsd (n=63)	L_aMCImd (n=148)	L_naMCIsd (n=10)	L_naMCImd (n=17)	S_aMCIsd (n=46)	S_aMCImd (n=96)	S_naMCIsd (n=9)	S_naMCImd (n=9)
Survivors	37	77	7	12	31	61	7	7
NCI	4	7	1	3	3	6	1	2
L_aMCIsd	1	0	0	0				
L_aMCImd	8	7	3	1				
L_naMCIsd	0	1	0	0				
L_naMCImd	0	0	0	0				
S_aMCIsd					0	0	0	0
S_aMCImd					5	6	1	0
S_naMCIsd					0	1	0	0
S_naMCImd					0	0	0	0
Demented	12	27	0	3	12	19	0	1
LFT / CSU	5	18	3	1	4	14	3	0
Other	7	17	0	4	7	15	2	4
Deceased	n = 24	n = 70	n = 3	n = 5	n = 14	n = 34	n = 2	n = 2
Not Demented	0	0	0	0	0	0	0	0
Demented	8	19	2	1	4	11	2	0
LTF/Unknown	16	51	1	4	10	23	0	2

NOTE: LTF = lost to follow-up

Figure 2. **Stability, Regression, and Progression Percentage Prevalence Rates at Follow-up**



Note: S_naMCImd = strict nonamnestic MCI multiple domain; L_naMCIsd = lenient nonamnestic MCI single domain; S_naMCIsd = strict nonamnestic MCI single domain; L_naMCImd = lenient nonamnestic MCI multiple domain; CIND-2 = CIND Type 2; L_aMCImd = lenient amnestic MCI multiple domain; CIND-1 = CIND Type 1; S_aMCImd = strict amnestic MCI multiple domain; L_aMCIsd = lenient amnestic MCI single domain; S_aMCIsd = strict amnestic MCI single domain; MCI-2 = MCI Type 2; MCI-1 = MCI Type 1

Table 8 illustrates the percentages of participants in the Robust NCI and each of the twelve MCI/CIND classifications that received a diagnosis of no dementia or dementia at CSHA-3. The column labelled Percent Undetermined reflects the participants that were lost to follow-up or that died between CSHA-2 and CSHA-3 and for whom there was insufficient information to determine cognitive status. MCI classifications requiring the presence of both short-term and long-term memory impairment had the highest conversion rates to dementia (i.e., MCI-1 = 43.8% & MCI-2 = 35.3%). As expected, the Robust NCI group had the lowest conversion rate to dementia (i.e., 7.9%).

Table 8. **Dementia Status at CSHA-3**

	CSHA-3 Diagnosis		
CSHA-2	**% Demented**	**% Not Demented**	**% Undetermined**
Robust NCI	7.9	56.6	35.5
S_naMCImd	11.1	66.7	22.2
L_naMCIsd	20.0	40.0	40.0
S_naMCIsd	22.2	44.4	33.3
L_naMCImd	23.5	47.1	29.4
CIND-2	28.8	22.5	48.8
L_aMCImd	31.1	21.6	47.3
S_aMCImd	31.2	29.2	39.6
CIND-1	31.4	31.4	37.2
L_aMCIsd	31.7	31.7	33.3
S_aMCIsd	34.8	32.6	30.4
MCI-2	35.3	14.7	50.0
MCI-1	43.8	31.2	25.0

Note: S_naMCImd = strict nonamnestic MCI multiple domain; L_naMCIsd = lenient nonamnestic MCI single domain; S_naMCIsd = strict nonamnestic MCI single domain; L_naMCImd = lenient nonamnestic MCI multiple domain; CIND-2 = CIND Type 2; L_aMCImd = lenient amnestic MCI multiple domain; CIND-1 = CIND Type 1; S_aMCImd = strict amnestic MCI multiple domain; L_aMCIsd = lenient amnestic MCI single domain; S_aMCIsd = strict amnestic MCI single domain; MCI-2 = MCI Type 2; MCI-1 = MCI Type 1

Prediction of Dementia

The results of the receiver operating characteristic (ROC) analyses indicate that the majority of MCI/CIND subclassifications failed to predict dementia five years later at CSHA-3 (Table 9 and Figure 3). Of the MCI/CIND classifications with established diagnostic criteria, only the CIND-2 classifications at CSHA-2 was significantly predictive of dementia at CSHA-3 (AUC = .628, $p < .001$), while controlling for type I error. The CIND-2 classification was also associated with the highest sensitivity (42.5%) for the detection of incipient dementia. The *CI-Other* classification (i.e., including participants who had a consensus diagnosis of CIND but who failed to meet the inclusion criteria for any of the 13 MCI/CIND classifications) was also significantly predictive of future dementia (AUC = .579, $p < .001$). With the exception of the strict multiple domain nonamnestic MCI (i.e., S_naMCImd) classification, all multiple domain subclassifications demonstrated higher sensitivity for the detection of dementia, compared to their single domain counterparts. Overall, across the pre-defined MCI/CIND definitions, the sensitivity for the detection of dementia at CSHA-3 ranged from 0.4% in the S_naMCImd group to 42.5% in the CIND-2 group. All MCI/CIND and "Other" definitions had a relatively high specificity (range: 83.1 – 99.2%) for dementia.

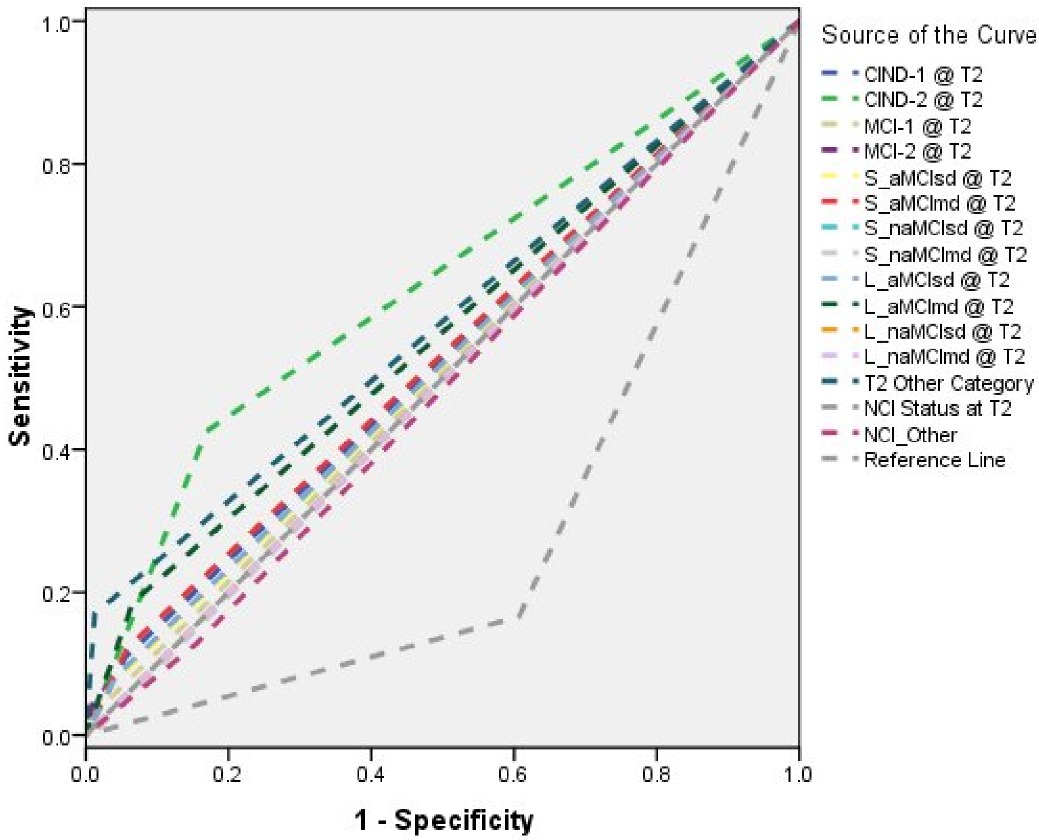
The highest relative predictive power for the progression to dementia at CSHA-3 (i.e., the most favorable relationship between sensitivity and specificity; Busse et al., 2003) and negative predictive power were observed for the CIND-2 group (56.1% and 74.0%, respectively). The CIND-2 classification at CSHA-2 captured 105 of 247 participants who went on to dement at CSHA-3. Of the 142 subjects who did not meet CIND-2 criteria at CSHA-2, 73 participants had a consensus diagnosis of NCI (56.2% of whom were included in the diagnostic classification of Robust NCI). The remaining 69 participants included 19 people who met the criteria for CIND-1 at CSHA-2 and 50 people who failed to meet the inclusion criteria for either of the most inclusive classifications (i.e., CIND-1 and CIND-2). Overall, at most, 42.5% of participants who progressed to dementia at CSHA-3 were identified by an existing definition of MCI/CIND.

***Table 9.* Predictive Power of MCI Criteria for Identifying Conversion at Follow-up**

Group	AUC	S.E.	*p*	95% C.I.	Sensitivity	Specificity	PPV	NPV
CIND-1	.527	.023	.234	.482-.572	.109	.944	.500	.676
CIND-2	.628	.023	.000	.584-.672	.425	.831	.561	.740
MCI-1	.509	.023	.689	.465-.554	.028	.990	.583	.667
MCI-2	.519	.023	.396	.474-.564	.049	.990	.706	.672
S_aMCIsd	.517	.023	.453	.472-.562	.065	.969	.516	.671
S_aMCImd	.532	.023	.157	.487-.577	.121	.942	.517	.679
S_naMCIsd	.500	.023	.998	.456-.544	.008	.992	.333	.663
S_naMCImd	.496	.023	.854	.452-.540	.004	.988	.143	.661
L_aMCIsd	.520	.023	.378	.475-.565	.081	.959	.500	.672
L_aMCImd	.560	.023	.008	.515-.605	.186	.934	.590	.693
L_naMCIsd	.500	.023	.998	.456-.544	.008	.992	.333	.663
L_naMCImd	.500	.023	.995	.456-.544	.016	.984	.333	.663
CI-Other	.579	.023	.000	.533-.624	.170	.988	.875	.701
Robust NCI	.279	.019	.000	.241-.319	.166	.393	.122	.481
NCI-Other	.478	.022	.552	.443-.531	.130	.844	.296	.656

<u>NOTE</u>: AUC = area under the curve; S.E. = standard error; *p* = asymptotic significance; C.I. = confidence interval; PPV = positive predictive value; NPV = negative predictive value; CIND-1 = CIND Type 1; CIND-2 = CIND Type 2; MCI-1 = MCI Type 1; MCI-2 = MCI Type 2; S_aMCIsd = strict amnestic MCI single domain; S_aMCImd = strict amnestic MCI multiple domain; S_naMCIsd = strict nonamnestic MCI single domain; S_naMCImd = strict nonamnestic MCI multiple domain; L_aMCIsd = lenient amnestic MCI single domain; L_aMCImd = lenient amnestic MCI multiple domain; L_naMCIsd = lenient nonamnestic MCI single domain; L_naMCImd = lenient nonamnestic MCI multiple domain; CI-Other = cognitively impaired other group; Robust NCI = robust not cognitively impaired group; NCI-Other = not cognitively impaired other group

Figure 3. **Receiver Operating Curve (ROC) Predicting Conversion**



The type of dementia for participants identified as demented at CSHA-3 is listed in Table 10. For deceased subjects, the type of dementia was not always available, as the information was collected from collateral informants or from the death certificate. As such, not all demented subjects are represented in this table. Clearly, definitions based only on the presence of a memory deficit progressed preferentially to a diagnosis of AD. The CIND-1 classification has some more variability in the progression to AD; however, AD is most highly represented among the types of dementia at CSHA-3. Increased variability in type of dementia at CSHA-3 was noted for definitions requiring

Table 10. **Type of Dementia by MCI Subclassification**

	Group	Survivors	N	Deceased	N
All Cognitive	Robust	36.7% Probable AD	1	18.2% Senile Dementia	2
Domains	NCI	26.7% Possible AD (Vasc)	1	9.1% Unspecified Dementia	1
Intact		16.7% Vascular Dementia	8	72.7% Unknown/Missing	8
		6.7% Possible AD (Coexis)	5		
		6.7% Unclassified Dementia	2		
		3.3% Idiopathic Parkinson's	2		
		3.3% CIND Other	1		
Memory	MCI-1	75% Probable AD	3	33.3% AD	1
Impairment		25% Possible AD (Coexis)	1	66.7 Unknown/Missing	2
Only					
	CIND-1	76.5% Probable AD	1	20% Unspecified Dementia	2
		5.9% Possible AD (Vasc)	3	10% AD	1
		5.9% Possible AD (Coexis)	1	70% Unknown/Missing	7
		5.9% Vascular Dementia	1		
		5.9% Idiopathic Parkinson's	1		
			1		
	S_aMCIsd	91.7% Probable AD	1	25% AD	1
		8.3% Possible AD (Coexis)	1	25% Unspecified Dementia	1
			1	50% Unknown/Missing	2
	L_aMCIsd	91.7 Probable AD	1	25% Unspecified Dementia	2
		8.3% Possible AD (Coexis)	1	12.5% AD	1
			1	62.5% Unknown/Missing	5

Table 10. Continued

		Survivors	N	Deceased	N
Memory-Plus Impairment	MCI-2	50% Vascular Dementia	3	16.7% Other	1
		33.3% Probable AD	2	83.3% Unknown/Missing	5
		16.7% Post-head Injury	1		
	S_aMCImd	31.6% Probable AD	6	27.3% AD	3
		21.1% Vascular Dementia	4	9.1% Senile Dementia	1
		10.5% Possible Atypical AD	2	9.1% Unspecified Dementia	1
		10.5% Possible AD (Vasc.)	2	9.1% Stroke Unspecified	1
		10.5% Possible AD (Coexis)	2	9.1% Other Dementia	1
		5.3% CIND, other	1	36.4% Unknown/Missing	4
		5.3% Post-head Injury	1		
		5.3% Unclassified Dementia	1		
	L_aMCImd	29.6% Probable AD	8	15.8% AD	3
		22.2% Possible AD (Vasc)	6	10.5% Unspecified Dementia	2
		14.8% Vascular Dementia	4	5.3% Senile Dementia	1
		11.1% Possible AD (Coexis)	3	5.3% Stroke Unspecified	1
		7.4% Possible Atypical AD	2	5.3% Other Dementia	1
		7.4% Unclassified Dementia	2	5.3% Other	1
		3.7% Post-head Injury	1	52.6% Unknown/Missing	10
		3.7% CIND, other	1		
	CIND-2	30.6% Vascular Dementia	19	18.6% AD	8
		27.4% Probable AD	17	14% Senile Dementia	6
		12.9% Possible AD (Vasc)	8	11.6% Unspecified Dementia	5
		9.7% Possible AD (Coexis)	6	9.3% Other	4
		6.5% Unclassified Dementia	4	2.3% Vascular Dementia	1
		3.2% Possible Atypical AD	2	2.3% Stroke Unspecified	1
		1.6% Parkinson's Syndrome	1	2.3% Other Dementia	1
		1.6% Idiopathic Parkinson's	1	39.5% Unknown/Missing	17

Table 10. Continued

		1.6% Pick's Disease			
		1.6% Post-head injury	1		
		1.6% Mental Retardation	1		
		1.6% CIND, other	1		
			1		
Non-amnestic Single Domain Impairment	S_naMCIsd	-	0	50.0% AD	1
				50.0% Unknown/Missing	1
	L_naMCIsd	-	0	50.0% AD	1
				50.0% Unknown/Missing	1
Non-amnestic Multiple Domain Impairment	L_naMCImd	66.7 Vascular Dementia	2	100% Vascular Dementia	1
		33.3% Probable AD	1		
	S_naMCImd	100% Vascular Dementia	1	-	0

Note: Vasc = vascular components; Coexis = coexisting disease memory deficits, as well as deficits in at least one other cognitive domain. Overall, classifications that do not exclude participants on the basis of the etiology of their cognitive deficits (i.e., CIND-1 and CIND-2 classifications) were associated with the greatest variability in type of dementia at CSHA-3.

CSHA-1 Cognitive Status for CSHA-3 Demented Participants

Three courses of progression to dementia from CSHA-1 to CSHA-3 were identified. Of those classified as demented at CSHA-3, 136 were not assessed at CSHA-1. That is, they failed to meet the inclusion criteria of a 3MS score of less than 78 and were not members of the group of randomly selected participants with a 3MS score of greater than 77. As such, they are assumed to be of normal cognitive status. When added to the participants with a CSHA-1 consensus diagnosis of NCI, these CSHA-1 cognitively intact participants represent 83.8% (n = 207) of participants who progressed to dementia at CSHA-3, essentially creating a ten-year progression group from NCI to dementia. Thirty-six CSHA-3 dementia participants (14.6%) exhibited a slower ten-year progression, receiving a consensus diagnosis of CIND at CSHA-1. Finally, the remaining 1.6% of CSHA-3 dementia subjects exhibited a fluctuating progression to dementia at CSHA-3. These four participants had a consensus diagnosis of dementia at CSHA-1, a consensus diagnosis of CIND at CSHA-2, and finally a diagnosis of dementia at CSHA-3.

Proxy Report

Petersen’s criteria for MCI (1999, 2003) and Winblad et al.’s (2004) update of Petersen’s criteria specify a report of memory decline by the participant or significant other. In this study, the MCI classifications based on Winblad et al.’s criteria have not addressed the report of memory decline criterion. Participants whose significant other identified great or slight "difficulty remembering short lists" and/or "difficulty remembering recent events" on Section H of the CAMDEX were identified as meeting the report of memory decline requirement. The addition of the proxy report criteria to the strict and lenient MCI classifications reduced the prevalence rate of each MCI classification by 39.7 to 88.9%. Moreover, based on ROC analyses (Table 11), none of the revised strict or lenient MCI groups was significantly predictive of dementia at CSHA-3. The sensitivity of all strict and lenient MCI groups had a reduced or the same sensitivity for the identification of incipient dementia. All groups showed increased specificity and positive predictive values (with the exception of the naMCIsd groups) for the identification of dementia at CSHA-3. More variability (although minimal) in negative predictive values were observed.

***Table 11.* Predictive Power of MCI Criteria with Corresponding Proxy Report**

Group	AUC	S.E.	*p*	95% C.I.	Sensitivity	Specificity	PPV	NPV
S_aMCIsd	.520	.023	.372	.475-.565	.053	.988	.684	.672
S_aMCImd	.522	.023	.328	.477-.567	.069	.975	.586	.673
S_naMCIsd	.499	.023	.964	.455-.543	0	.998	0	.663
S_naMCImd	.502	.023	.929	.458-.546	.004	1.00	1.00	.664
L_aMCIsd	.525	.023	.265	.480-.570	.069	.981	.654	.675
L_aMCImd	.541	.023	.067	.496-.586	.109	.973	.675	.683
L_naMCIsd	.499	.023	.964	.455-.543	0	.998	0	.663
L_naMCImd	.504	.023	.858	.460-.548	.008	1.00	1.00	.665

NOTE: AUC = area under the curve; S.E. = standard error; *p* = asymptotic significance; C.I. = confidence interval; PPV = positive predictive value; NPV = negative predictive value; S_aMCIsd = strict amnestic MCI single domain; S_aMCImd = strict amnestic MCI multiple domain; S_naMCIsd = strict nonamnestic MCI single domain; S_naMCImd = strict nonamnestic MCI multiple domain; L_aMCIsd = lenient amnestic MCI single domain; L_aMCImd = lenient amnestic MCI multiple domain; L_naMCIsd = lenient nonamnestic MCI single domain; L_naMCImd = lenient nonamnestic MCI multiple domain

Discussion

The term mild cognitive impairment typically refers to an interim state of cognitive decline between normal aging and dementia in persons "destined" to progress to dementia (p. 2, Petersen, 2003). It is believed to be a degenerative process, with the amnestic form ultimately culminating in AD (Petersen, 2003). With an approximate duration of up to seven years (Reisberg, 1986) and an annual conversion rate of 10-15% in clinical samples (Petersen et al., 2001), MCI presents a unique research opportunity for the development and study of effective treatment programs for the prevention of dementia. The challenge in developing prevention strategies, however, lies in the selection of MCI criteria with optimal sensitivity and specificity for the prediction of future dementia. The goal of this study was to determine the average demographic and neuropsychological characteristics, as well as the sensitivity, specificity, and predictive accuracy, associated with varied MCI classifications relevant to the sample population.

Demographic Characteristics

Cognitive impairment not meeting the criteria for dementia has been associated with more advanced age, less education, and the female gender (Di Carlo et al., 2000). This finding was supported in the current study wherein 10 of the 12 MCI/CIND groups were noted to have a higher mean age at CSHA-1 entry and a lower mean number of years of education, compared to Robust NCI participants. With the exception of the Strict aMCIsd and naMCImd groups, all groups (including Robust NCI) were found to have a higher representation of females than males. None of the Strict naMCIsd and naMCImd or the Lenient naMCIsd subjects were living in institutions. The MCI-2 classification had the highest rates of institutionalization, reflecting more extensive memory impairment that may impede the maintenance of ADLs requiring memory and executive functioning abilities (Perneczky et al., 2006).

Prevalence & Conversion Rates

The current study confirms the finding that MCI sample prevalence rates and rates of progression to dementia are dependent upon the selection and operationalization of MCI criteria (e.g., Busse et al., 2003, 2006; Fisk et al., 2005; Stephan et al., 2007; Visser & Verhey, 2008). In this study, the broadest definition of mild cognitive impairment, CIND Type 2, including participants exhibiting impairment in non-memory cognitive domains (with or without memory impairment), had the highest overall sample prevalence rate (29.6% of the larger not-demented sample and 68.2% of the CI sample). This result supports previous population-based findings that more encompassing definitions of cognitive impairment, such as CIND, capture a greater percentage of persons with cognitive impairment than do more stringent case definitions (e.g., Fisk et al., 2003; Stephan et al., 2007). The hypothesis that the highest sample prevalence and conversion rates would be observed for definitions of multiple-domain MCI and CIND was partially confirmed by the finding that, overall, the CIND-2 classification captured more than twice as many cognitively impaired participants than the remaining MCI case definitions. However, despite being the only case definition to significantly predict progression to dementia five years later, the CIND-2 classification did not have the highest conversion rate to dementia.

Previous research has found the conversion rate of CIND to exceed that of not cognitively impaired individuals five-fold (Tuokko et al., 2003). In the current study, the CIND conversion rates were 48% and 56% for CIND-1 and CIND-2, after the removal of persons lost to follow-up. This conversion rate is slightly higher than the 43% conversion rate observed by Tuokko et al. (2003) whose CIND classification was likely more heterogeneous as it was not limited to the CIND-2 classification. The finding of a 12% conversion rate for the Robust NCI group (following the exclusion of persons lost to follow-up) is lower than the 18% conversion rate observed by Tuokko et al. (2003). The lower conversion rate in this study is likely a reflection of the stricter NCI criteria (i.e., persons were excluded if the consensus diagnostic opinion revealed any cognitive impairment). Thus, a consequence of our selection criteria may be the creation of a more robust NCI group. This is evident in the much smaller Robust NCI sample size used in the current study. Additionally, in the Tuokko et al. (2003) study, the researchers examined the development of dementia from CSHA-1 to CSHA-2. The current study examined the progression of MCI to dementia from CSHA-2 to CSHA-3.

The second hypothesis (i.e., case definitions requiring impairment in both short- and long-term memory impairment would have the highest conversion rates) was supported by the finding that MCI-1 and MCI-2 groups demonstrated the highest rates of progression to dementia over five years. This finding supports earlier reports of increased cognitive decline three to five years prior to a diagnosis of dementia (Amieva et al., 2005; Hall, Lipton, Sliwinski, & Stewart, 2000) and has significant implications for the role of neuropsychological assessment in the identification of persons at risk for future dementia. Impairment on neuropsychological measures, especially delayed free and cued recall, is a risk factor for future dementia (Petersen, 1999; Tuokko, Vernon-Wilkinson, Weir, & Beattie, 1991). In addition, impaired performance on episodic memory tasks is noted to be a significant predictor of progression to dementia (Blacker et al., 2007). This conclusion was supported by the observation that the lowest mean performance on all verbal memory measures was observed in the MCI-1 group – the group with the highest overall conversion rate to dementia. The finding that the highest conversion rates were associated with the lowest average performance on the RAVLT is consistent with previous research identifying the RAVLT as a highly accurate, sensitive, and specific neuropsychological measure for the prediction of future dementia (i.e., AD, Tierney et al., 1996). Moreover, the conversion rates for all MCI classifications with a requisite memory criterion were greater than 31%, while the non-amnestic, CIND-2, and NCI classifications all had progression rates of 30% or less. Clearly, performance on the memory measures was an important factor in the progression from MCI to dementia. In the current study, individuals at-risk for progression to dementia exhibited difficulty learning new information, despite repeated exposure.

In addition to memory impairment, executive dysfunction is reported to distinguish older adults who will progress to dementia (i.e., AD) from normal healthy older adults and individuals with stable MCI (Albert, Moss, Tanzi, & Jones, 2001; Chen et al., 2001; Talbert et al., 2006), as well as predicting the time to progression (Blacker et al., 2007). Category fluency has been found to have superior sensitivity and specificity for the differentiation between normal healthy older adults and persons with dementia, as well as being more impaired than letter fluency (Crossley, D'Arcy, & Rawson, 1997; Monsch et al., 1992). The Digit Symbol subtest, a measure of psychomotor performance (Lezak et al., 2004), is associated with the multiple-domain subtype of MCI (Lopez et al., 2003) and has been identified as a good predictor of progression to dementia (Berg et al., 1984). Finally, the Number Correct on the BVRT is predictive of cognitive decline in older adults (Berg et al., 1984). In addition to sharing the lowest mean performance on 2 of the 7 verbal memory measures, the average neuropsychological profile of the MCI-2 group (i.e., the group with the second overall highest five-year conversion rate to dementia) was characterized by the lowest average performance on measures of judgment (WAIS-R Comprehension), categorical naming (Animal Naming), visual memory (Benton Visual Retention Test), and apraxia (WAIS-R Digit Symbol); thus confirming the results of previous studies. Although the MCI-1 and MCI-2 groups demonstrated the lowest average performance on many of the neuropsychological measures, between-group statistical comparisons with the other MCI classifications were not undertaken, given the non-independent, overlapping samples.

The higher rate of progression to dementia in the MCI-1 group, compared to the MCI-2 group, contradicts previous research in which 50% of patients with multiple domain cognitive impairment, including memory impairment, progressed to dementia within two years (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001). In the current study, none of the case definitions had conversion rates exceeding 44%. Moreover, higher progression rates for memory-only case definitions of MCI were consistent across all MCI classifications. As well, with the exception of the lenient nonamnestic MCI groups, case definitions of single domain non-amnestic MCI had higher conversion rates than their multiple domain counterparts. These results oppose the conclusion that multiple domain MCI represents a more advanced stage of cognitive decline (Alexopoulos, Gimmer, Perneczky, Domes, & Kurz, 2006), is more likely to progress to dementia, and has higher conversion rates to AD than pure amnestic MCI (Alexopoulos, et al., 2006; Backman, Jones, Berger, Laukka, & Small, 2004; Bozoki et al., 2001;

Gabryelewicz, et al., 2007; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Tabert et al., 2006).

There are several possible explanations for this finding. First, unlike in previous studies, MCI classifications based on Zaudig's (1992) criteria require the presence of both short-term and long-term memory impairment. As such, the high conversion rates associated with the MCI-1 and MCI-2 classifications may illustrate a higher rate of progression to dementia among a more cognitively impaired cohort. The absence of the requirement for intact ADLs associated with the MCI-1 and MCI-2 case definitions further supports this theory. Second, each amnestic multiple domain case definition of MCI had a higher percentage of participants for whom cognitive status was unavailable at CSHA-3. Thus, the higher overall rate of conversion associated with the amnestic single domain case definitions of MCI may be biased in favor of a greater number of available data at CSHA-3. To examine this possibility, the percentage of participants converting to dementia at CSHA-3 was calculated following the exclusion of participants lost to follow-up (Appendix 1 – Table 16). The results reveal that, excluding participants for whom information regarding cognitive status was unavailable at CSHA-3, MCI-2 (an amnestic multiple domain case definition of MCI) had the highest rate of progression (of the predefined case definitions) to dementia at follow-up. These results reflect a previous report examining nonparticipation and attrition in the CSHA between CSHA-1 and CSHA-2 revealing that nonparticipation was associated with poorer cognitive function (Helliwell, Aylesworth, McDowell, Baumgarten, & Sykes, 2001). Overall, both studies affirm the bias that attrition can produce in longitudinal studies of aging (Ritchie & Tuokko, 2007).

The disparity between the conversion rates for the different groups illustrates the importance of the case definition of mild cognitive impairment for the detection of subjects at-risk for developing dementia. Of late, Petersen's (1999, 2003) criteria for MCI have been criticized for their lack of stability (Busse et al., 2003; Ritchie et al., 2001). Specifically, reversion rates of up 40% are reported in population-based studies (Ishikawa & Ikeda, 2007). Similarly, Ritchie et al. (2001) describe high rates of instability with the MCI classification in their three-year population-based study. In the current study, the operationalization of various MCI case definitions resulted in rates of reversion ranging from 3.0% to 22.2%. The highest rates of reversion were observed in the non-amnestic multiple domain MCI classifications (strict = 22.2%, lenient = 17.6%). This finding questions Petersen's (2003) theory that MCI is an interim state between normal cognitive functioning and dementia (Busse et al., 2003). Interestingly, the lowest rates of reversion were noted for MCI-2 and CIND-2 case definitions, which allow for impairment in broad domains of cognitive function and do not require intact ADLs or subjective memory complaints. This finding supports Fisk et al.'s (2003) conclusion that subjective memory impairment and intact ADLs are of limited additive value in population-based studies.

Varying temporal change points have been identified for differing cognitive domains in the progression to dementia (i.e., AD). For example, increasingly impaired performance on measures of episodic memory, executive function, and verbal intelligence are noted 7 years, 2-3 years, and just prior to a diagnosis of dementia, respectively (Grober et al., 2008). These results may have great implications for the predictive validity of various case definitions for MCI. For example, the case definition for amnestic single domain MCI may demonstrate higher predictive accuracy for the progression to dementia approximately seven years post-MCI diagnosis. In contrast, it may be more appropriate to select a case definition of amnestic multiple domain MCI for the prediction of dementia with a shorter follow-up interval. In addition to differences in setting, neuropsychological measures, age range, inclusion and exclusion criteria, and outcome measures, this theory offers a potential explanation for the variability in outcomes associated with studies examining the utility of similarly operationalized MCI criteria. In the current study, classifications emphasizing a decline in short-term and long-term memory impairment demonstrated the highest progression to dementia. With the exclusion of persons lost to follow-up, participants with memory-plus MCI had higher conversion rates than memory-only groups (for the MCI-2, L_aMCImd, S_aMCImd, and CIND-2 groups), confirming their more advanced cognitive decline on the continuum from NCI to dementia.

Proxy Report and Intact ADLs

Despite reports of the limited utility of subjective memory complaints (or proxy reports) in the diagnosis of MCI in community and population-based studies (Fisk et al., 2003; Jorm et al., 1997), it was important to examine the prominence of this feature in the current study for several reasons. First, subjective or proxy reports of memory impairment continue to be included in the commonest MCI criteria. Second, the ongoing controversy surrounding this criterion increases the importance of its examination. Third, the absence of the application of this criterion is a common criticism of population-based studies that retrospectively retrofit MCI criteria to existing data sets (Petersen & O'Brien, 2006). The current study examined the effect of a proxy report of memory difficulty on the prevalence rates and predictive accuracy of MCI classifications based on Petersen's revised (Winblad et al., 2004) criteria. The addition of the proxy report criterion decreased the prevalence rate of each MCI classification by 40 to 89% and did not significantly increase the predictive accuracy of the classifications. Thus, although the purpose of the subjective or proxy report of memory decline is to identify high functioning persons with cognitive decline, to prevent the false-positive diagnosis of persons with premorbid cognitive difficulties, and to identify MCI in the earliest stages wherein performance on cognitive measures may not meet diagnostic cut-points (Morris et al., 2001), these results confirm previous reports questioning the utility of subjective or proxy reports of cognitive decline in population-based studies. However, given that the cognitive classifications were formed on the basis of clinical decision-making following the review of all information collected during the clinical evaluation, the proxy report may not be the sole source of information regarding individual change.

Similarly, although intact ADLs and minimally impaired complex IADLs remain requisite criteria for a classification of MCI according to Winblad et al.'s (2004) criteria, the functional status of persons with MCI remains controversial. Previous research suggests that persons classified as MCI or CIND demonstrate impairment in IADLS, especially those involving memory and psychomotor speed (Tuokko, Morris, & Ebert, 2005). Moreover, reasoning-based IADLs have also been found to be impaired in persons with MCI (Perneczky et al., 2006). In the current study, for the four classifications based on Winblad et al.'s (2004) revised criteria, the lenient application of intact ADL criteria captured a higher percentage of cognitively impaired participants. In contrast, with the exception of the nonamnestic multiple domain MCI group, higher rates of progression to dementia at CSHA-3 were found for classifications based on a strict application of the ADL criterion, compared to the lenient MCI groups. The results of the strict nonamnestic multiple domain group may be a reflection of its small sample size.

Types of Dementia

The various MCI classifications are hypothesized to follow a preferentially degenerative course (Petersen, 2003). However, previous research did not find evidence to support this theory. Specifically, Busse et al. (2003) found that the majority of their cognitively impaired subjects progressed to dementia of the AD type. In the current study, amnestic single domain definitions of MCI progressed primarily to dementia of the AD type (DAT) for surviving participants. Greater variability in dementia type was noted for the CIND case definitions. This is likely a reflection of the heterogeneity of the CIND groups and the multiple etiologies of cognitive impairment for both CIND groups. The multiple domain case definitions of amnestic MCI were also associated with broader types of dementia than their single domain counterparts. Nevertheless, with the exception of the MCI-2 group, the majority (53 – 70%) of surviving participants in the amnestic multiple domain MCI case definitions progressed to a subtype of AD. This finding reflects the memory-plus impairment required for a diagnosis of AD (American Psychiatric Association, 2000). The limited number of complete decedent questionnaires limited the ability to test the preferential progression of various MCI classifications among deceased participants. As a result, a large portion of the deceased participants are identified as having unspecified dementia or dementia of unknown type.

Predictive Accuracy

To date, few studies have examined the accuracy of MCI criteria in the prediction of progression to dementia. Existing research studies, examining original and modified classifications of MCI, AAMI, AACD, and MFI, have been unsuccessful in their attempts to demonstrate the predictive validity of amnestic MCI in population-based samples (Busse et al., 2003; Ritchie et al., 2001). The results of the current study provide similar findings. Overall, the CIND-2 classification was the only predefined case definition to significantly predict dementia at follow-up. This finding replicates Busse et al.'s finding of a modified (i.e., removal of subjective/proxy memory complaint) multiple-domain MCI case definition as the only significant predictor of dementia at a three-year follow-up. In the current study, the commonest MCI classifications (i.e., those based on Winblad et al's [2004] revised MCI criteria), as well as those based on Zaudig's (1992) criteria, failed to significantly predict dementia five years later. Overall, with the exception of the CIND-2 classification, all MCI/CIND case definitions demonstrated poor sensitivity and very high specificity for conversion to dementia, in the non-demented sample. The low sensitivities and predictive values may reflect the low sample prevalence rates of each classification. Specifically, the cognitive classification capturing the largest percentage of cognitively impaired persons not meeting the criteria for dementia (i.e., CIND-2) was the only significant predictor of dementia at follow-up. Note that the ROC analyses exclude participants lost to follow-up and, as a result, the highest predictive value is associated with the case definition (MCI-2) with the highest conversion rate to dementia (after the exclusion of participants lost to follow-up).

Ultimately, when selecting diagnostic criteria for the purposes of implementing intervention strategies, the trade-off between sensitivity and specificity will vary according to the intervention modality. For instance, criteria with a high sensitivity are recommended for screening purposes, while criteria with higher specificities and predictive values are recommended for pharmaceutical interventions (Busse et al., 2003). An objective of the current study was to identify MCI criteria with optimal sensitivities and specificities for the prediction of dementia at follow-up. The MCI/CIND case definition with the best relation between sensitivity and specificity and, as a result, the only case definition that significantly predicted dementia five years later, was the CIND-2 classification. The CIND-2 classification is a very broad and inclusive case definition of MCI that does not exclude individuals on the basis of the etiology of their cognitive impairment. Moreover, CIND-2 does not include criteria requiring the presence of intact ADLs or a subjective/proxy memory complaints. This finding suggests that other existing criteria are too stringent and, as a result, fail to capture many people at-risk for future dementia.

Clearly different operationalizations of MCI capture different proportions of participants, as illustrated by the varied MCI prevalence rates observed in this study. However, MCI criteria often fail to capture several people who will progress to dementia (Rountree et al., 2007). Despite definitional variations ranging from stringent to inclusive, 115 participants who progressed to dementia did not meet the inclusion criteria for any of the MCI case definitions. Approximately 27.8% were identified as not cognitively impaired but were excluded from the Robust NCI group at CSHA-2 (i.e., *NCI_Other*). The remaining 35.6 and 36.5% were identified as not cognitively impaired

(Robust NCI) and *CI-Other* (i.e., had an overall consensus classification of CIND but did not meet the inclusion criteria for specific operationalizations of MCI) at CSHA-2. The 7.9% Robust NCI conversion rate to dementia may illustrate a more rapid conversion rate in a subset of participants. However, it is important to note that progression to dementia was examined across a five-year interval. As such, the annual Robust NCI conversion rate would approximate 1.6% - much lower than the reported 10-15% conversion rate for MCI (Petersen et al., 2001). The failure of the classification criteria to capture the participants falling in the *CI*-O*ther* classification is significant, as this group had the highest overall progression rate to dementia at follow-up. This result suggests that existing criteria for MCI may be too stringent.

Strengths & Limitations

A strength of the current study is the use of clinical diagnostic opinion to classify participants according to various case definitions of MCI. Despite the development of criteria for the identification of persons at-risk for future dementia, clinical judgment is paramount in the identification of MCI (Petersen, 2003). Reliance on neuropsychological performance alone may result in diagnostic errors (Alexopoulos et al., 2006; Stephan et al., 2007), such as the false-positive classification of persons with premorbid cognitive difficulties. As well, the use of different neuropsychological tests, although likely correlated, differentially influences MCI diagnoses (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006). Moreover, basing the cognitive classifications on clinician judgment facilitates comparison to other studies employing different neuropsychological batteries and mimics the clinical diagnostic process (Fisk et al., 2003).

Individuals with mild cognitive impairment are identified as a high-risk group for future dementia. Early identification of MCI, therefore, may enable the implementation of strategies to prevent or delay the progression to dementia. To date, many of the studies examining the progression to dementia among MCI patients have sampled participants from clinical populations. As such, the results may be biased in favor of the progression to dementia, given the more cognitively impaired samples. The current study serves to add to the literature examining MCI from a population perspective. It is important to note that, similar to a previous study using data from the CSHA (Fisk et al., 2003), although overall it is a representative population sample, the clinical sample is not. Secondly, although the longitudinal nature of the CSHA is an asset in the evaluation of the progression of cognitive decline, several participants meeting the criteria for MCI prior to progressing to dementia may have been missed in the current study due to the five-year intervals between follow-ups.

As with several other population studies (e.g., Busse et al., 2003; Fisk et al., 2003; Stephan et al., 2007), cognitive classifications were created by retrospectively applying classification criteria to the population sample. Petersen and O’Brien (2006) argue that, although contributing useful information to the field, the retrospective retrofitting of MCI diagnostic criteria in population-based studies may not accurately depict the concept of MCI as originally defined, as this was not the intent of the study at the outset. The authors suggest that MCI diagnoses may be made in the absence of specific diagnostic criteria, such as informant report of cognitive decline. This was not the case in the current study. Although intentionally not initially included in the classifications, proxy report of memory impairment was examined and, as reported in previous population-based studies (e.g., Fisk et al., 2003), was found to be of minimal additive value. Perhaps it is not the retrofitting of classification criteria that results in greater instability of MCI classifications in population studies, but the lower level of cognitive impairment exhibited by participants, compared to samples drawn from a clinical population.

The results of the current study should be interpreted in the context of its limitations. First, given the overlapping nature of the MCI classifications, between-group statistical analyses were not possible. Nevertheless, it is believed that the comparison of the predictive accuracy of various case definitions of MCI within the same population-based sample outweighs the inability to complete between-group statistical comparisons. Moreover, had MCI classifications been limited to non-overlapping groups, the classifications would likely have been biased by the exclusion of otherwise included participants and the sample sizes would have been too small to be meaningful.

However, interpretation of the results must still consider the small sample sizes. Attempts were made to maintain the largest sample sizes possible (e.g., inclusion of participants with incomplete neuropsychological data; overlapping samples; lenient exclusion criteria), while still adhering to MCI diagnostic criteria. The inclusion of participants with incomplete neuropsychological data is not believed to bias the results of the study, given that all participants underwent a neuropsychological examination and cognitive classifications were made according to clinical judgment. Despite the inclusive nature of the sample selection, sample sizes were limited as a result of the specifications of the diagnostic criteria. For example, by limiting the etiology of the cognitive impairment, many subjects identified as cognitively impaired were excluded from all but the CIND classifications. From a clinical perspective, clinicians employing MCI criteria other than that required for a classification of CIND will likely dismiss many persons exhibiting symptoms of MCI on the basis of etiology.

Finally, the prevalence and progression rates of the Robust NCI group must be interpreted with the knowledge that this group may be more robust than that described in other studies. The Robust NCI group in the current study was further reduced from the consensus diagnosis classification. Some participants clinically judged to be cognitively intact were noted to exhibit impaired functioning in some cognitive domains. Although this impairment may reflect historic difficulty in cognitive functioning, participants exhibiting any form of impairment were excluded from the NCI group. This procedure was employed to ensure differences between the NCI and CI groups.

Conclusions

In summary, the results of the current study confirm that case definitions of multiple-domain MCI are associated with the highest prevalence rates and conversion rates. Additionally, case definitions requiring impairment in both short- and long-term memory impairment demonstrated the highest conversion rates over five years, with the majority of cases preferentially progressing to AD. Confirming results from previous population-based studies, proxy reports of memory deficits and intact ADL diagnostic criteria were found to be of little additive value in the identification of persons exhibiting mild cognitive impairment. Of all the MCI/CIND case definitions examined, the only criteria that significantly predicted dementia five years later was the CIND-2 case definition. This finding suggests that, as a consequence of the overly stringent inclusion criteria of the remaining diagnostic classifications, a large number of people with incipient dementia may be overlooked. It is hypothesized that more restrictive MCI case definitions fail to address the varying temporal increases in decline across different cognitive domains in the progression from normal cognitive functioning and dementia.

Chapter 4

Study 2 - Development of a Clinical Decision Tree for Diagnosing Cognitive Impairment in Older Adults: Comparison with Existing Criteria for Mild Cognitive Impairment

Introduction

The age-associated increase in the prevalence of dementia among Canadians (CSHA Working Group, 1994) highlights the importance of accurately identifying individuals who are at-risk for developing dementia. In persons aged 85 years and older, one in every three persons has a significant risk for cognitive impairment (Petersen, 2003). Persons meeting criteria for mild cognitive impairment (MCI) are identified as being at greater risk for dementia and have conversion rates ranging from 12% with a definition of amnestic MCI (aMCI; Petersen et al, 1999) to 47% with a definition of cognitive impairment, no dementia (CIND; Tuokko et al., 2003). Clearly, there is great inconsistency in the identification of individuals with mild cognitive impairment who will convert to dementia. This inconsistency is supported by variable conversion rates associated with existing case definitions of MCI, as reported in Study 1.

Variable diagnostic stability and resulting discrepant conversion rates may also arise due to different operationalizations and applications of the same diagnostic criteria. Petersen and Storandt (2006) propose that retrofitting diagnostic criteria to existing datasets inadvertently reduces the accuracy of the MCI classification's identification of persons who go on to develop dementia. Nevertheless, it would seem that if the diagnostic criteria have adequate sensitivity and specificity within a population, retrospective application of these criteria should produce fairly accurate accounts of cognitive status.

Variable results and recommendations have emerged for the prediction of conversion. For example, neuropsychological assessment is reported to have a high sensitivity for the identification of persons with cognitive impairment and dementia (Larrea, Fisk, Graham, & Stadnyk, 2000). However, MCI definitions do not specify which neuropsychological measures should be administered when assessing for MCI. Some suggest that the cross-comparison of cognitive research findings would be greatly improved if MCI research were based on a standardized neuropsychological battery (Ritchie, Artero, & Touchon, 2001). Others recommend that neuropsychological batteries with an emphasis on memory assessment be administered to persons at risk for conversion to dementia (i.e., those exhibiting memory deficits) (Petersen et al., 2001). Verbal memory measures are recommended for the identification of memory impairment (Petersen et al., 1999; 2001). However, an estimated 20% of cognitively impaired individuals may be incorrectly excluded from the aMCI classification when only verbal measures are used to determine semantic memory impairment. Moreover, MCImd is more prevalent among persons with both verbal and visual memory deficits (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006). Additionally, as in Study 1, conversion to dementia is reported to be more prominent among nondemented persons who demonstrate mild impairment in memory and other cognitive domains (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001).

The operationalization of cognitive decline is related to the topic of utilizing neuropsychological testing as a means of identifying cognitively impaired individuals. Some suggest that a single evaluation of memory functioning provides insufficient evidence of memory impairment, as test performance may be influenced by psychiatric and neurological conditions, or normal fluctuations in individual performance. Examination of memory performance over two-years revealed the possibility of identifying memory decline in healthy elderly individuals, prior to a classification of MCI or dementia. As such, longitudinal monitoring of cognitive function by means of repeated neuropsychological assessment is recommended (Collie et al., 2001). However, Morris and Storandt (2006) argue that repeated neuropsychological assessment is unfeasible for research given the recommended one-year interval between repeated neuropsychological evaluations. Instead, these researchers recommend referring to reports from collateral informants (e.g., spouse, child, close friend) for evidence of cognitive decline. The focus on intra-individual change in cognitive performance as an indicator of cognitive decline has recently been included in the revised criteria for mild cognitive impairment (Petersen, 2004; Winblad et al., 2004). However, the results of Study 1 confirm reports of the limited contribution of the proxy report in identifying cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia in longitudinal population-based samples such as the CSHA (Fisk, Merry, & Rockwood, 2003).

Variability in the prevalence and conversion rates associated with different diagnostic criteria of MCI limits the identification of persons who will go on to dement. Aside from impaired neuropsychological performance, several demographic factors have been identified as risk factors for dementia. For example, increasing age is a prominent risk factor for cognitive decline and is associated with increased prevalence (CSHA, 2000) and incidence rates (Launer et al., 1999; Ravaglia et al., 2005) for dementia. Advancing age is also significantly related to the prevalence of CIND (Di Carlo et al., 2000; Lindsay, Sykes, McDowell, Verreault, & Laurin, 2004; Low et al., 2004). Gender is also related to the development of dementia, with women being at greater risk for AD. In contrast, men have a heightened risk of vascular dementia (VaD; Yamada et al., 1999). A third demographic variable identified as a risk factor for dementia is education. Low education is associated with an increased risk of developing dementia (Mortimer, Snowdon, & Markesbery, 2003), whereas higher educational attainment is reported to delay the onset of dementia by increasing one's cognitive reserve (Cummings, Vinters, Cole, & Khachaturian, 1998).

Biological and familial characteristics are also identified as markers of incipient dementia. Vascular risk factors for dementia include diabetes (Hassing et al., 2002; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004, Hayden et al., 2006), hypertention and obesity (Hayden et al., 2006), and hypotention (Verghese, Lipton, Hall, Kullansky, & Katz, 2003). A family history of dementia increases the risk two-fold for AD and VaD (Boston, Dennis, & Jagger, 1999). Neurodegenerative risk factors typically include genetic mutations or an increased presence of the apolipoprotein E (ApoE) ε4 allele, which is significantly more prevalent among persons with dementia (Frikke-Schmidt, Nordestgaardm, Thudium, Moes Grøholdt, & Tybjærg-Hansen, 2001; Hsiung, Sadonick, & Feldman, 2004; Baum et al., 2006) and among individuals who progress from CIND to dementia (Hsiung et al., 2004).

Advances in neuroimaging have facilitated the examination of biological markers for the progression to dementia among persons with MCI. Elevated levels of phosphorylated tau in the cerebral spinal fluid (CSF) have been linked with progressive cognitive decline (Buerger et al., 2005; Fellgiebel, Scheurich, Bartenstein, & Müller, 2007). Positron emission tomography (PET), combined with the radioactive tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), has identified reduced cortical glucose metabolism as a predictor of conversion (Fellgiebel et al., 2007). Increased risk of progression from MCI to dementia within three years is reported for persons with atrophy of the medial temporal lobe, as measured by magnetic resonance imaging (MRI; DeCarli et al., 2007). Moreover, the risk of conversion among MCI patients with both medial temporal lobe atrophy and pathological CSF biomarkers is four times that of patients with only one marker (Bouwman, Schoonenboom, & van der Flier, 2007).

Depression is the most prominent neuropsychiatric condition associated with cognitive impairment. In a previous study using data from the Canadian Study of Health and Aging (CSHA), higher rates of proxy-reported depression, loss of interest, and changes in personality and mood were noted among cognitively impaired (CI), compared to not cognitively impaired (NCI), persons. The presence of depression or loss of interest at CSHA-2 significantly predicted cognitive impairment (i.e., MCI, dementia, and AD) at follow-up (Stepaniuk, Ritchie, & Tuokko, 2008). Impaired neuropsychological performance is common among individuals with depression (Lockwood, Alexopoulos, & van Gorp, 2002). Despite frequent comorbidity, the sequence of onset of presenting symptoms has yet to be identified (Barberger-Gateau, Fabrigoule, Amieva, Helmer, & Dartigues, 2002).

Despite the abundance of risk factors, research has identified factors that appear to protect against cognitive decline. For example, maintaining an active lifestyle in old age is reported to postpone the development of cognitive deficits (Weuve et al., 2004). Additionally, cognitive stimulation, through education, social interaction, or occupational achievements, serves to promote neural synaptogenesis (Churchill et al., 2002). These risk and protective factors do not necessarily occur in isolation. For example, vascular risk factors are reported to vary according to gender (Hayden et al., 2006) and the protective effects of education are limited by age (McDowell, Xi, Lindsay, & Tuokko, 2004).

Many studies examining the risk factors for cognitive impairment focus on one or two of the aforementioned clinical domains. Recently, Monastero, Palmer, Qiu, Winblad and Fratiglioni (2007) examined four research hypotheses, each reflecting a separate pathophysiological mechanism, with the goal of identifying factors related to CIND and the progression to dementia. The frailty hypothesis proposed that frailty-related factors (e.g., sensory deficits, functional dependence, chronic disease) are related to cognitive impairment. The vascular hypothesis held that cognitive impairment is related to vascular disease factors (e.g., hypertention, diabetes). The neuropsychiatric hypothesis proposed that depression, psychotropic drugs, and psychosis are risk factors for cognitive impairment. Finally, the social hypothesis held that cognitive impairment is related to limited social and physical activities. Each hypothesis was evaluated separately using logistic regression. An increased risk of CIND was reported for psychosis, polypharmacy, and hip fracture. Participants identified as CIND were found to be at-risk for progression to dementia. Monastero et al. concluded that CIND is associated with heterogeneous risk factors. These results, also, likely reflect the heterogeneous nature of the CIND case definition itself.

Despite evidence identifying a variety of risk and protective factors, much of the research examining mild cognitive impairment has focused on differences in the prevalence and conversion rates for various definitions of cognitive impairment and has been limited to the examination of cognitive and functional abilities. The results of Study 1 suggest that existing diagnostic criteria may be overly stringent and, as a result, fail to capture several persons at risk for incipient dementia. The CSHA data provide the opportunity to examine the longitudinal course of the progression from normal cognitive status to dementia and enable an exploration of the MCI concept as an intermediary stage in the continuum of cognitive decline. The objective of Study 2 was to examine the characteristics and conditions that best discriminate between i) NCI and CIND (Question 1), ii) not demented (i.e., NCI + CIND) and demented participants (Question 2), and iii) stable and progressing (i.e., to dementia) CIND participants (Question 3). Information regarding which factors are associated with a diagnosis of MCI, how these factors interact, and whether these factors can be used to identify individuals who will progress to dementia will be sought. The purpose of the study is to elucidate the risk factors and clinical correlates of MCI and to identify the factors that predict different outcomes, with the goal of informing clinical practice and research toward primary and secondary intervention. This is believed to be the first study in the field of MCI to derive criteria *from* the data, rather than applying criteria *to* the data.

Methodology

Participants

Inclusion criteria for Questions 1 – 3 required subjects to have completed the neuropsychological component of the clinical evaluation at CSHA-2 (n = 1466). To ensure a maximum and sufficient number of participants, subjects with and without missing neuropsychological data were included in the sample. Participants were included in the baseline sample for Question 1 if they received a CSHA-2 consensus diagnosis of NCI or CIND. The baseline sample for Question 2 included participants with CSHA-2 consensus diagnoses of NCI, CIND, or dementia. Finally, in addition to a CSHA-2 consensus diagnosis of CIND, information regarding participants' CSHA-3 cognitive status (i.e., not demented [NCI or CIND] and demented) was required for Question 3.

Predictor Variables

The CSHA consists of over 2000 clinical variables for each time point (Lindsay et al., 2004). The aforementioned research identifying risk and protective factors for cognitive decline was used to select CSHA variables for use in this study. Categories of predictor variables were formulated based on Monastero et al.'s (2007) frailty, vascular, neuropsychiatric, and social hypotheses. Three additional categories of predictors (demographic, cognitive, and family history) were also created. Table 12 lists the categories and associated predictor variables. The same variables were used in the development of classification trees for questions 1 through 3.

Data Analyses

Sample characteristics for each of the three questions were derived using SPSS-16 (SPSS, Inc., Chicago, Ill.). T-tests for continuous variables and chi-square tests for nominal variables were used to identify differences in baseline sample demographic characteristics for each question. A machine learning algorithm (Quick, Unbiased, and Efficient Statistical Tree [QUEST]; SPSS, 1999; Low & Shih, 1997) was used to identify the symptoms that best discriminated between i) NCI and CIND, ii) not demented (i.e., NCI + CIND) and demented participants, and iii) stable and progressing (i.e., to dementia) CIND participants. This search algorithm has been successfully employed to explore patterns in complex data sets from various research domains. For example, QUEST has been used to determine the most important clinical features for the diagnosis of headaches and migraines; thus, enabling the development of highly reliable and valid screening instrument to differentiate between headaches and migraines (Pryse-Phillips et al., 2002). In the field of aging and cognitive decline, the QUEST algorithm was used to identify the symptoms that optimally differentiated nondemented persons from participants with possible and probable AD. From more than 40 available symptom variables, eight informant-reported symptoms were ultimately identified as maximizing the differentiation between nondemented and demented participants. The binary classification tree was subsequently used to structure a discussion among a gerontologist, a psychologist, a neuropsychologist, and a psychiatrist in the development of a dementia screening instrument intended for use in the general population (Mundt, Freed, & Greist, 2000).

This exploratory statistical analysis recursively partitions variables to form a hierarchical binary decision tree. Recursive partitioning performs as well as logistic regression in the prediction of cognitive impairment and the decision trees are practical for clinical settings (James, White, & Kraemer, 2005). For each split in the tree, analysis of variance (ANOVA) F tests or Levene's test, or the Pearson chi-square test, are used to determine the relation between the dependent variable (i.e., cognitive classifications) and continuous/nominal and ordinal variables, respectively (SPSS, 1999). Splitting occurs with the predictor variable identified as having the highest association with the dependent variable. Quadratic discriminant analysis is used to select the cut-point for the predictor variable. This process is repeated until either no further splitting is possible or until ad-hoc stopping rules are reached. The current study employed the following ad-hoc user-defined stopping rules: recursive partitioning continued until 1) $p > 0.05$; 2); the minimum number of cases in the parent node (n = 10) or the child node (n = 5) were met; and/or 3) the tree reached a maximum depth of 5 levels below the root node. Pruning (i.e., the removal of unnecessary splits from the tree to avoid over-fitting) proceeded using the default standard error rule (*SE* = 1.0) where the subtree with the smallest risk (i.e., smallest number of misclassified participants) is grown. Independent classification trees were developed for each category of predictor variables and all predictor variables together. Consensus diagnostic opinion at CSHA-2 (Questions 1 and 2) and CSHA-3 (Question 3) served as the dependent variables for the analyses. Figures illustrating the results of the pruned trees are reported for each category of predictors. Figures illustrating the results for both the unpruned and pruned classification trees are provided for trees generated using all available predictors. The remaining unpruned classification trees are depicted in Appendix 2. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each pruned tree are reported.

***Table 12.* Variable Selection by Category, Description & Rationale**

Domain	Measure	Description/Rationale	Criterion
Demographic	Age on October 1, 1990	Participant age recorded at the start of CSHA-1, irrespective of inclusion in the clinical component of CSHA-1	Years
	Sex	Participant gender	Male, Female
	Education	Participant total years of education	Years
Cognitive	CAMDEX – Section H	Structured interview with the participant's significant other (i.e., informant) addressing the subject's history 1. Memory changes 2. Changes in general mental function	Yes, No
	Wilson-Barona Index Formula	Measure of premorbid intelligence.	Estimated IQ; Max score = 122
	WMS Information	Measure of long-term recall	Total score; Max score = 6
	Buschke Selective Memory Test	Measure of short-term visual memory; free and cued recall conditions 1. Free recall: trial 1 2. Total cued recall: sum of cued recall trials 1-3 3. Total free recall: sum of free recall trials 1-3	Total score; Max scores: Free = 12; Total cued = 36; Total free = 36
	WAIS-R Block Design	Measure of visuospatial ability, construction, and motor function (short version [items 1-9]; odd items only)	Total score Max score = 30
	WAIS-R Similarities	Measure of abstract thinking and verbal problem-solving (short version [items 1-13]; odd questions only)	Total score Max score = 14
	WAIS-R Comprehension	Verbal measure of judgment (short version [items 1-15]; odd questions only)	Total score; Max score = 15

Table 12. Continued.

Domain	Measure	Description/Rationale	Criterion
	Rey Auditory-Verbal Learning Test	Measure of short-term verbal memory 1. List A: trial 1 2. List A: trial 6 3. Total recall list A: sum of trials 1-5	Total score; Max scores: Trials 1 = 15; Trial 6 = 15; Total = 75
	Controlled Oral Word Association Test	Measure of verbal fluency and cognitive flexibility (total number of words generated for words beginning with the letters F, A, and S).	Total score
	Animal Naming	Measure of categorical verbal fluency	Total score
	Benton Visual Retention Test (multiple choice)	Measure of non-verbal memory	Number correct; Max score = 16
	WAIS-R Digit Symbol Test	Measure of attention, problem-solving, and processing speed	Total score; Max score = 93
Frailty/Morbidity	Hearing	Screening for impaired hearing ("adequate" = <u>intact</u>; "borderline" &"inadequate" = <u>compromised</u>)	Intact, Compromised
	Vision	Screening for impaired vision ("adequate" = <u>intact</u>; "borderline" &"inadequate" = <u>compromised</u>)	Intact, Compromised
	Polypharmacy	Total number of medications	Total Max score = 24
	CAMDEX – Section H	Mobility Impairment	Yes, No, Questionable
Social/Physical	Marital Status	Marital status of participant at CSHA-2	Never married, married, common-law, divorced, separated, widowed
	Place of Residence	Participant's place of residence at CSHA-2	Community, Institution

Table 12. Continued.

Domain	**Measure**	**Description/Rationale**	**Criterion**
Social/Physical	Activities of Daily Living (ADLs)	Composite variable identifying intact (eating, dressing, self-care, toileting, and bathing activities all done without help) or compromised ADLs	Intact, compromised
	Instrumental ADLs (IADLs)	Composite variable identifying intact (able to use telephone, get to places outside of walking distance, shop, prepare meals, do housework, take medicine, and handle money without help) or compromised IADLs	Intact, compromised
Neuropsychiatric	Alcohol Abuse	As determined by the clinician's history evaluation	Yes. No, Questionable
	CAMDEX – Section H	1. Depressed? 2. Substance Dependence – composite variable for the detection of substance dependence (if answered yes to tranquilizers, hypnotics, stimulants, barbiturates) 3. Changes in personality 4. Changes in mood 5. More or less irritable or angry 6. Complained of persecution (i.e., delusions) 7. Troubled by voices or visions (i.e., hallucinations)	Yes, No
Vascular History	Arterial Hypertension	As determined by the clinician's history evaluation.	Yes. No, Questionable
	Hachinski Ischemic Score	Total score	0-6 or 7+
	Heart Disease	Composite score of presence or absence of heart disease (myocardial infarction, aarythmia, angina, congestive heart failure), as determined by the clinician's history evaluation.	Yes, No

Table 12. Continued.

Domain	Measure	Description/Rationale	Criterion
Vascular History	CAMDEX – Section H	Heavy smoker?	Yes, No
Family History	Family History	As determined by the nurse's evaluation of family history for: 1. Dementia (combined AD & dementia) 2. Stroke with memory loss 3. Parkinson's disease with memory loss 4. Psychiatric illness (combined depression and bipolar disease) 5. Other psychiatric or neurological disease	Yes, No

Question 1 Results: What clinical correlates best differentiate between persons with NCI and CIND at CSHA-2?

Baseline Sample Characteristics

The baseline sample for Question 1 included 698 and 535 participants identified as NCI and CIND, respectively, at the CSHA-2 consensus conference. Demographic characteristics for each group are listed in Table 13. Participants classified as CIND at CSHA-2 were significantly older (t [1231] = -4.67, p < .001), had fewer years of education (t [1224] = 5.95, p < .001), and scored lower on the Modified Mini-Mental State Exam (3MS; t [1225] = 21.8, p < .001), than did NCI persons. The NCI and CIND groups significantly differed in place of residence at CSHA-2, χ^2 (2, N = 1233) = 39.62, p < .001, and marital status, χ^2 (2, N = 1229) = 13.35, p < .001. At CSHA-2, the CIND group consisted of fewer married participants and more participants residing in institutions, compared to the NCI group.

***Table 13.* Baseline Sample Demographics for Question 1**

	NCI	CIND
Mean Age on Oct. 1, 1990 (*SD*)*	76.0 (6.5)	77.8 (6.9)
Years of Education, Mean (*SD*)*	10.5 (4.0)	9.1 (3.9)
3MS Score, Mean (*SD*)*	89.3 (8.1)	78.4 (9.6)
Gender (% Female)	57.2	60.6
Institutionalized (%)*	8.3	20.7
Married (%)*	44.1	31.0

Note: * significant at p < .001; *SD* = standard deviation; Married = married & common-law

Classification Trees

The root node (i.e., Node 0) describes the summary statistics for the sample. Subsequent nodes illustrate the number of participants belonging to each classification and describe predictor split information.

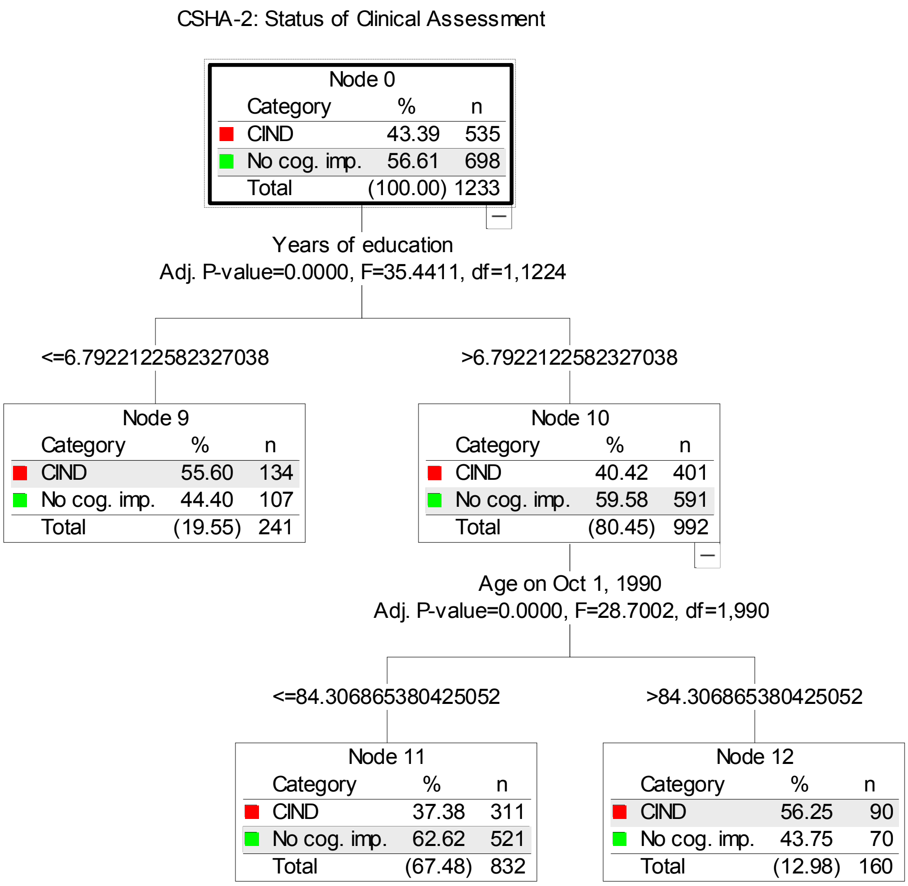
Demographic Predictors

In the pruned classification tree, Years of Education was the first demographic variable selected to differentiate between participants identified as NCI and CIND (Figure 4). A CIND classification was predicted for participants with less than or equal to 6.8 years of education (Node 1; 55.6% correct classification). Participants with more than 6.8 years of education were predicted as CIND if they were older than 84.3 years of age (Node 4; 56.25% correct classification). The sensitivity (i.e., the proportion of correctly identified CIND cases relative to the total number CIND cases), specificity (i.e., the proportion of correctly identified NCI cases relative to the total number NCI cases), PPV (i.e., the proportion of participants predicted to be CIND who are correctly classified), and NPV (i.e., the proportion of participants predicted to be NCI who are correctly classified) for the pruned demographic classification tree were 0.419, 0.746, 0.559, and 0.626, respectively. Overall, the demographic classification tree misclassified 39.6% of the not demented (i.e., NCI & CIND) participants. The model more accurately predicted the NCI classification, compared to the CIND classification.

Cognitive Predictors

The pruned cognitive classification tree correctly classified approximately 79.1% of the not demented sample (i.e., CIND & NCI; Figure 5). Seventy-three percent of the NCI group had none or questionable reports of memory changes according to Section H

Figure 4. **Demographic Classification Tree Differentiating CIND from NCI**



of the CAMDEX, had a total score greater than 19.8 on the Buschke Free Recall measure, and scored greater than 1.04 on the WAIS-R Similarities subtest. The combination of a positive proxy report of memory changes and a total score of less than or equal to 37.2 on the Rey Auditory Verbal Learning Test (RAVLT) captured the largest percentage of CIND participants (Node 5). Node 3 (none or questionable proxy report of memory changes and total free recall score of ≤ 19.8 on the Buschke Selective Reminding Test), Node 5 (positive proxy report of memory changes and total score of ≤ 37.2 on the

RAVLT) and Node 13 (positive proxy report of memory changes, and total score of >37.2 on the RAVLT, and total score of ≤ 3.5 on the WMS Information subtest) had the highest proportion of participants within the target classification (i.e., CIND), therefore becoming nodes of interest in the differentiation between NCI and CIND. The sensitivity, specificity, PPV, and NPV of the pruned classification tree were 0.778, 0.801, 0.750, and 0.824, respectively. The pruned classification tree excluded unnecessary splits on WAIS-R Block Design, RAVLT (total score), Buschke Free Recall (total recall), and verbal fluency (total score).

Frailty/Morbidity Predictors

Using predictors of frailty/morbidity, 54.6 % of CIND participants were correctly classified. Specific predictors and conditions associated with a correct CIND classification were: 1) positive or questionable proxy report of mobility impairment on Section H of the CAMDEX (n = 168; Figure 6, node 1) and 2) negative proxy report of mobility impairment on Section H of the CAMDEX but compromised hearing (n = 124; Figure 6, node 5). This pruned classification tree correctly classified 62.8% of NCI and CIND participants. The sensitivity, specificity, PPV, and NPV of the pruned classification tree were 0.546, 0.691, 0.574, and 0.665, respectively. The pruning procedure removed unnecessary splits on both the left (total number of medications) and right sides (vision) of the tree.

Social/Physical Predictors

The pruned classification tree for the social/physical predictors is depicted in Figure 7. The pruned and unpruned social/physical classification trees were identical, correctly classifying approximately 64.1% of the non-demented sample. Overall, compromised instrumental activities of daily living (IADLs) and activities of daily living (ADLs) were noted to be the best combination of predictors in the correct classification of CIND participants (Node 3). The sensitivity, specificity, PPV, and NPV for the classification tree were 0.398, 0.827, 0.638, and 0.642, respectively. Thus, while compromised IADL and ADL status correctly identified approximately 40% of CIND participants, the model was more successful at identifying participants with no cognitive impairment.

Neuropsychiatric Predictors

The pruned neuropsychiatric classification tree was more effective at predicting the NCI classification, compared to the CIND classification (Figure 8). Overall, the classification tree correctly classified 60.9% of the not demented sample. However, the misclassification rate for the CIND group was approximately 67.1%. The pruning process eliminated splits on the persecution variable (left side of the tree) and the depression variable (right side of the tree). The sensitivity, specificity, PPV, and NPV for the pruned classification tree were 0.329, 0.824, 0.589, and 0.824, respectively.

Figure 5. **Cognitive Classification Tree Differentiating CIND from NCI**

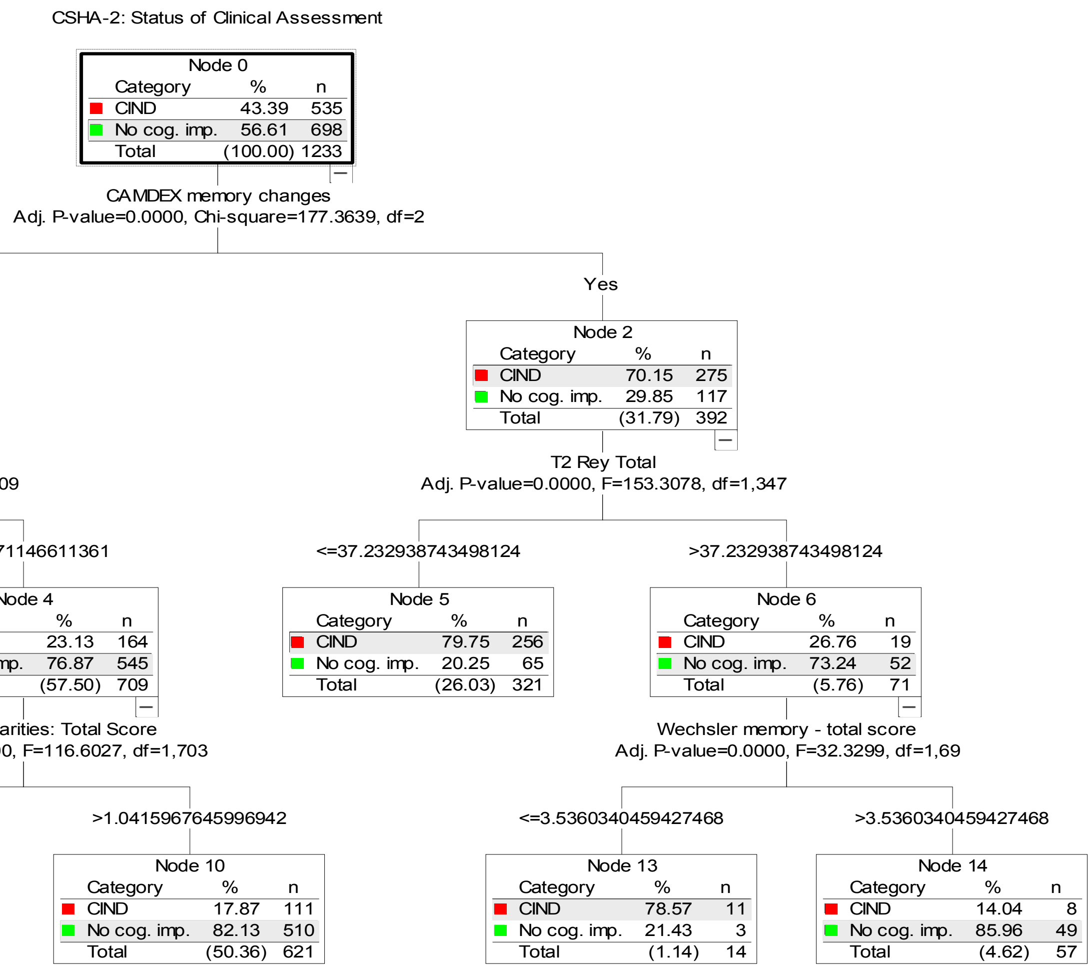


Figure 6. **Frailty/Morbidity Classification Tree Differentiating CIND from NCI**

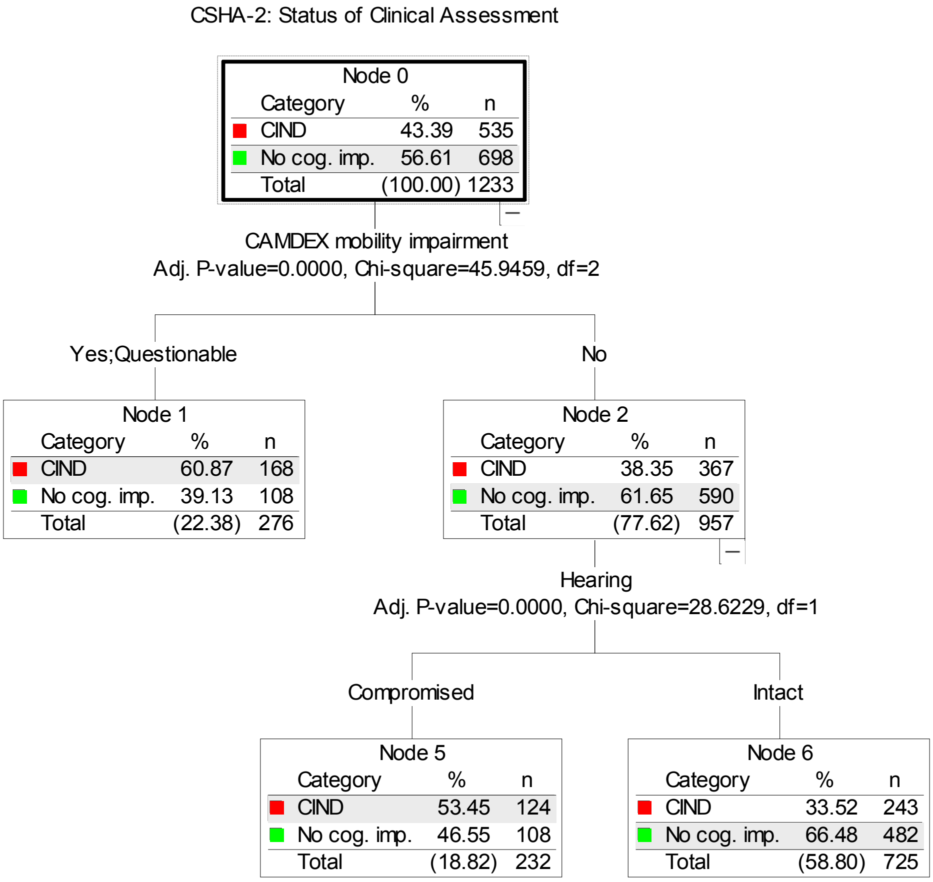


Figure 7. **Social/Physical Classification Tree Differentiating CIND from NCI**

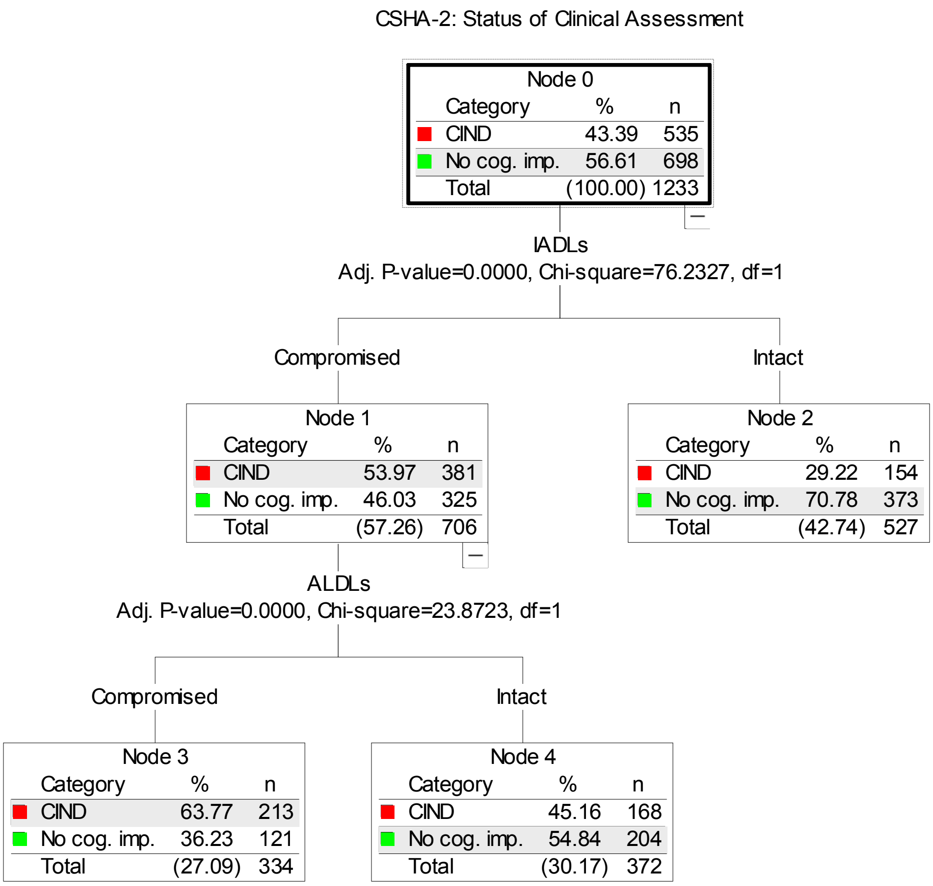
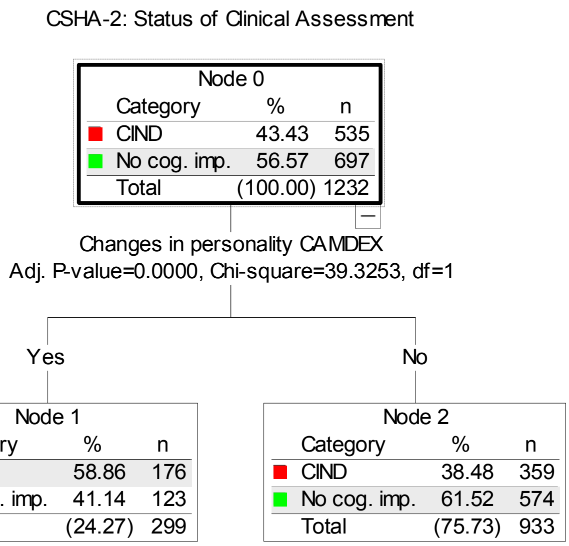


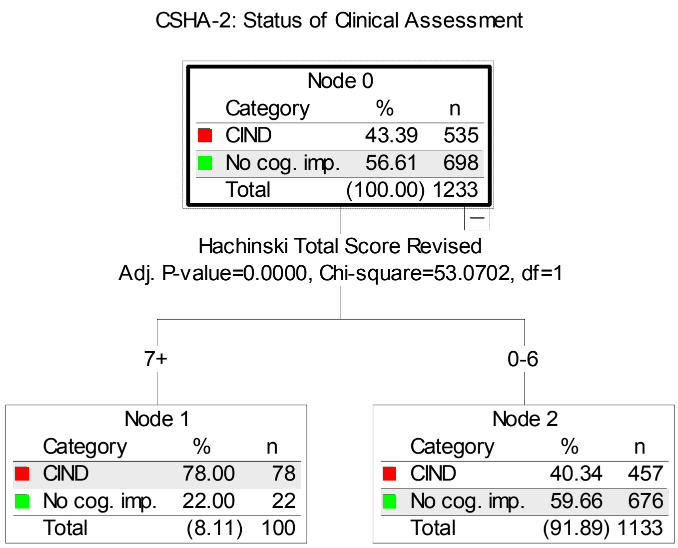
Figure 8. **Neuropsychiatric Classification Tree Differentiating CIND from NCI**



Vascular Predictors

Similar to the neuropsychiatric classification tree, the classification tree grown using vascular predictors more accurately predicted the NCI classification (96.8%), compared to the CIND classification (14.6%). As illustrated in Figure 9, the only significant split in the pruned classification tree was based on participants' total score on the Hachinski Ischemia Scale. A score of seven or more on the Hachinski Ischemia Scale captured a significantly greater proportion of participants with CIND (Node 1; 78%), compared to those with NCI (22%). Both the pruned and unpruned tree were identical and had misclassification rates of 38.8%. The sensitivity, specificity, PPV, and NPV for the pruned classification tree were 0.146, 0.968, 0.780, and 0.597, respectively.

Figure 9. **Vascular Classification Tree Differentiating CIND from NCI**



Family History Predictors

The pruned classification tree examining the ability of family history predictors to discriminate between CIND and NCI participants did not include any splits. The pruned classification tree, consisting solely of the root node, misclassified 42.2% of the not demented sample (i.e., all of the participants with an actual classification of CIND). Comparatively, the unpruned tree included a split on the family history of psychiatric illness predictor but still classified all participants as NCI.

All Predictors

The unpruned and pruned classification trees predicting NCI and CIND classification using all available predictors are depicted in Figures 10 through 12. The pruned tree correctly classified 80.5% of the non-demented sample. The combination of variables correctly classifying the largest percentage (32.5%) of participants with a CIND diagnosis at a terminal node (Figure 12, node 11) included a positive proxy report of memory changes on the Section H of the CAMDEX and a total score of less than 28.0 on the RAVLT. Nodes 3, 13, 17, 11, and 19 captured increasingly larger percentages of CIND participants (ranging from 60.2% to 100%), compared to NCI participants. The sensitivity, specificity, PPV, and NPV for the pruned classification tree were 0.735, 0.858, 0.799, and 0.808, respectively. Pruning of the classification tree removed two unnecessary splits on the WAIS-R Block Design predictor (below Node 3).

Figure 10. **Left Side of Unpruned Classification Tree Differentiating CIND from NCI – All Predictors**

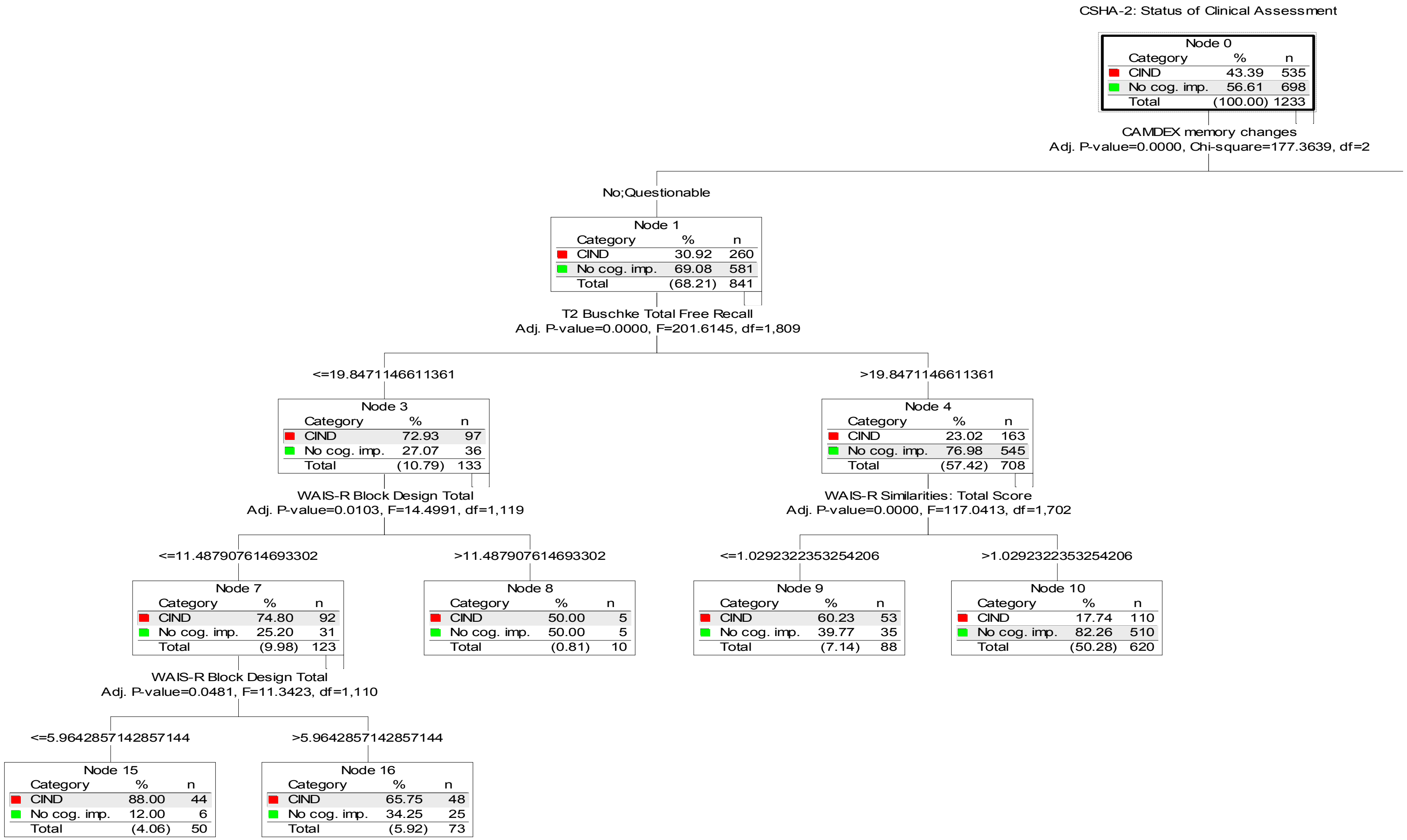


Figure 11. **Right Side of Unpruned Classification Tree Differentiating CIND from NCI – All Predictors**

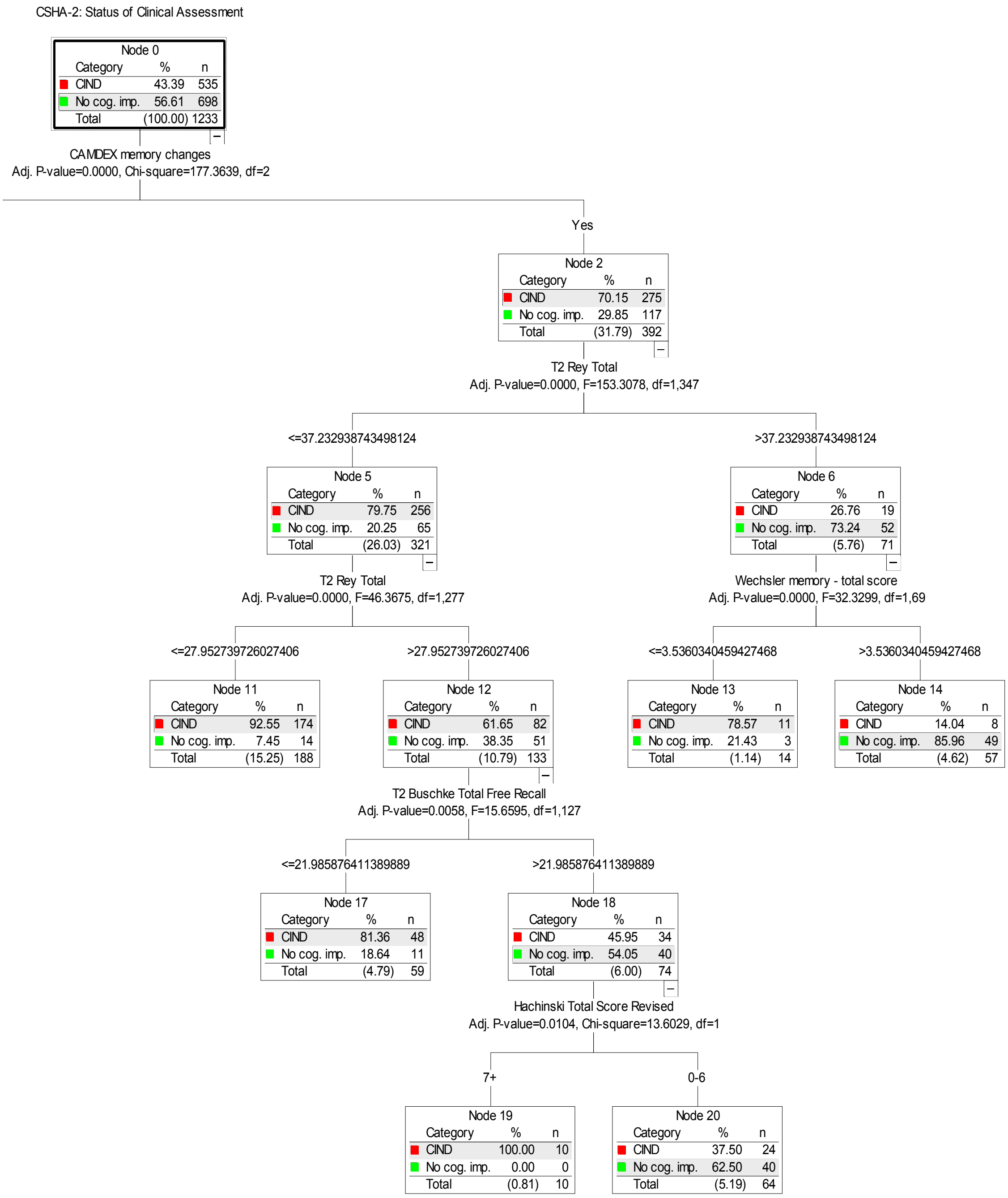
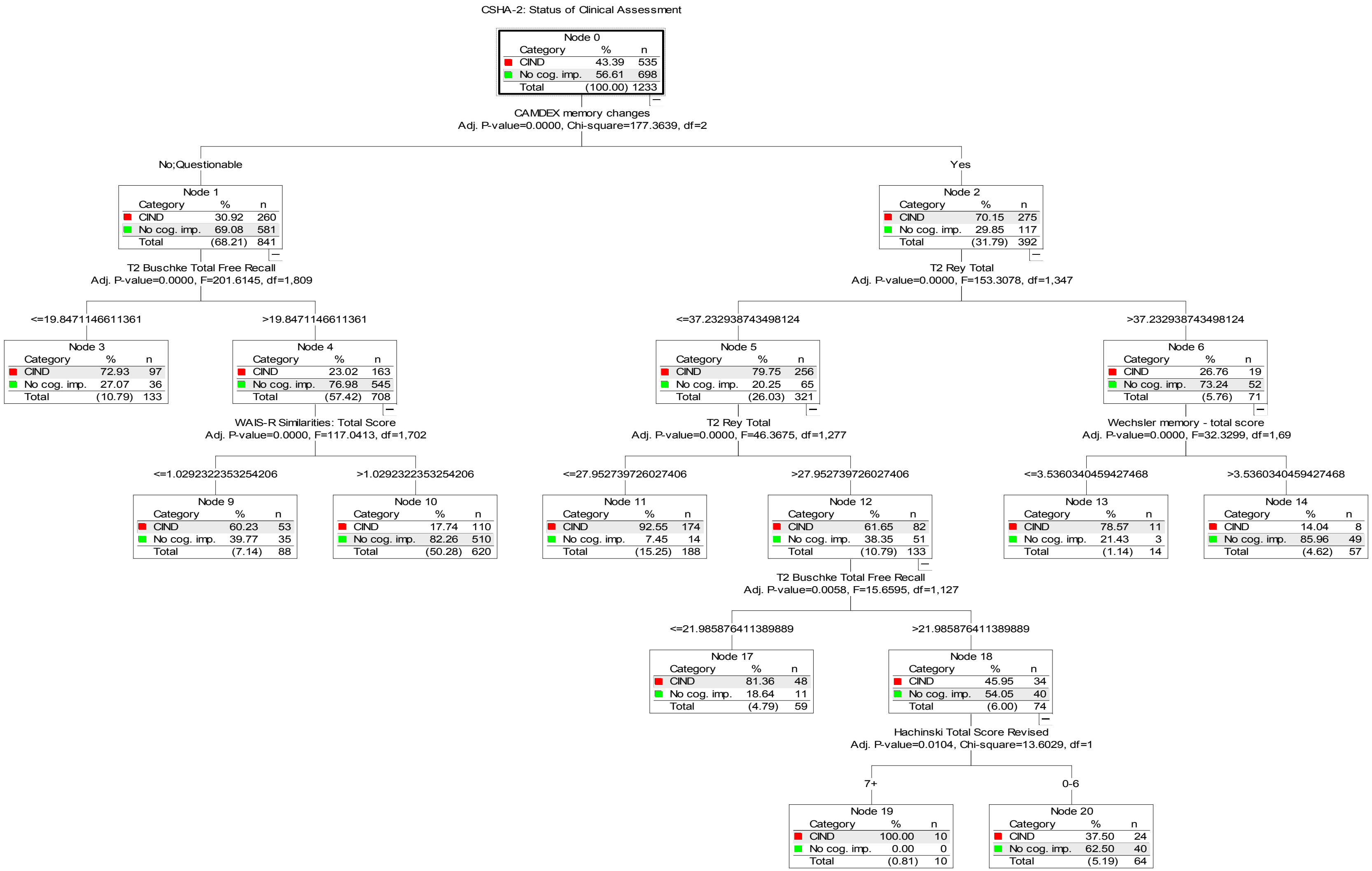


Figure 12. **Pruned Classification Tree Differentiating CIND from NCI – All Predictors**



Question 2 Results: What clinical correlates best differentiate between not demented (NCI + CIND) and demented persons at CSHA-2?

Baseline Sample Characteristics

The baseline sample for Question 2 included 1233 not demented participants (i.e., 698 NCI and 535 CIND participants) and 233 demented participants, as determined at the CSHA-2 consensus conference. Demographic characteristics associated with each of the not demented and demented groups are listed in Table 14. Compared to not demented persons, participants classified as demented were significantly older ($t[1464] = -3.76$, $p < .001$) and scored significantly lower on the 3MS ($t[1457] = 26.59$, $p < .001$). Additionally, a significantly greater proportion of the demented group was residing in an institution at CSHA-2, χ^2 (2, N = 1466) = 73.43, $p < .001$, compared to the not demented group.

Table 14. **Baseline Sample Demographics for Question 2**

	Not Demented	**Demented**
Mean Age on Oct. 1, 1990 (*SD*)*	76.8 (6.8)	78.5 (6.2)
Years of Education, Mean (*SD*)	9.9 (4.0)	9.4 (3.8)
3MS Score, Mean (*SD*)*	84.6 (10.3)	65.2 (9.7)
Gender (% Female)	58.6	58.4
Institutionalized (%)*	13.7	36.9
Married (%)	36.7	31.9

Note: * significant at $p < .001$; *SD* = standard deviation; Married = married & common-law

Classification Trees

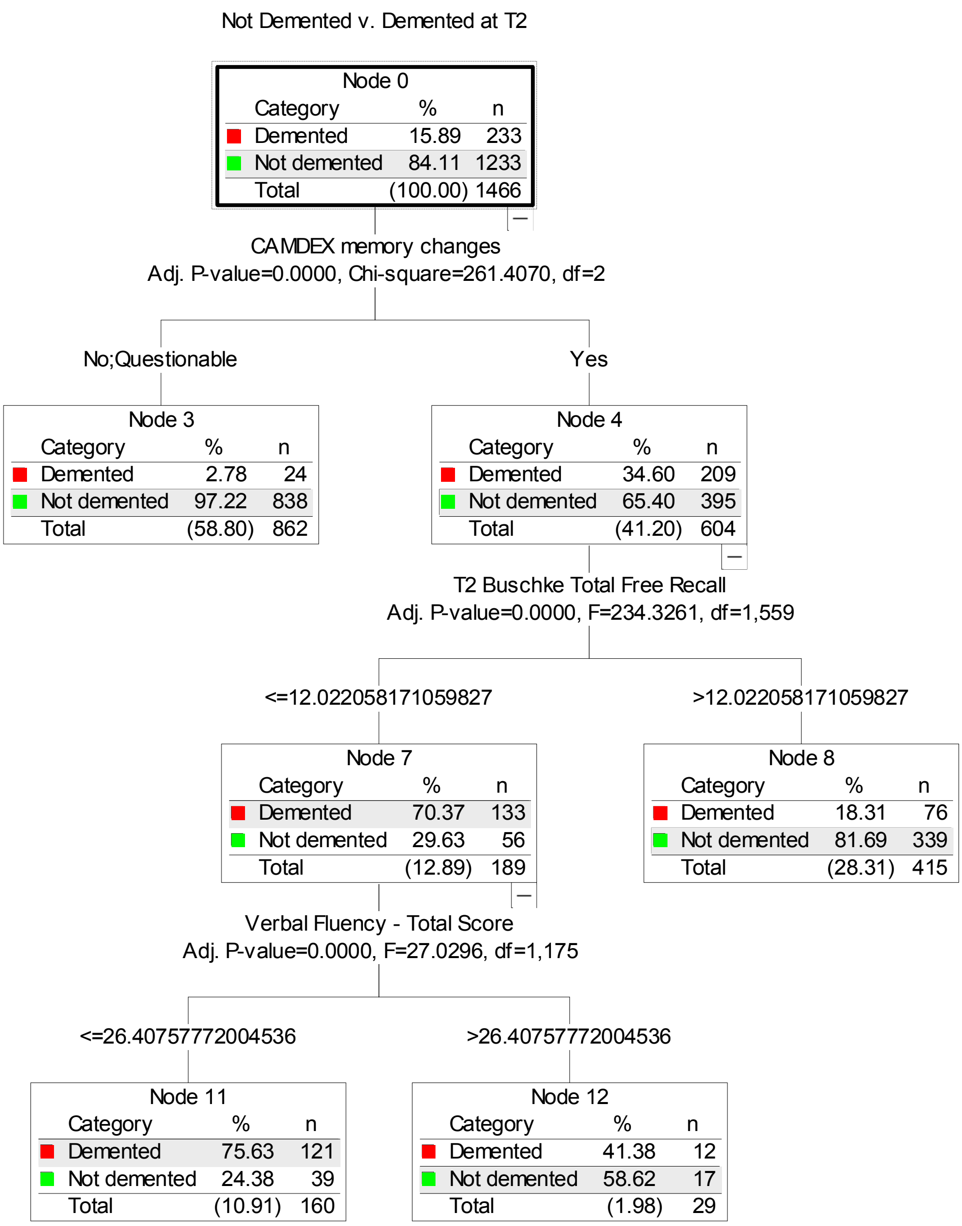
Demographic Predictors

The pruned demographic classification tree for differentiating the not demented (i.e., NCI + CIND) and demented groups at CSHA-2 did not extend beyond the root node. The pruned and unpruned trees misclassified 15.9% and 15.7% of the sample, respectively, the majority of which were not demented. The sensitivity, specificity, PPV, and NPV of the pruned tree were 0.00, 1.00, 0.00, and 0.841, respectively.

Cognitive Predictors

The pruned cognitive classification tree (Figure 13) correctly classified 89.7% of the sample. The first variable to differentiate between the non-demented and demented participants was the CAMDEX memory changes predictor. Specifically, a larger proportion of demented participants (89.7%) had a positive proxy report of memory changes, compared to the non-demented participants (32.0%). Additionally, demented participants were more likely to have a total free recall score below 12.0 on the Buschke visual memory test (Node 7) and generate less than 26.4 words on the measure of verbal fluency (i.e., Controlled Oral Word Learning Test [COWAT]). The pruning procedure removed unnecessary splits below node 3 (Buschke Total Free Recall, Wechsler Memory Information subtest total score), node 11 (performance on Trial 6 of the RAVLT), node 12 (Wechsler Memory Information subtest total score), and node 8 (RAVLT total score, Animal Naming test, total correct on the Benton Visual Retention Test [BVRT], WAIS-R Digit Symbol). The sensitivity, sensitivity, PPV, and NPV for the pruned tree were 0.519, 0.968, 0.756, and 0.914, respectively.

Figure 13. **Cognitive Classification Tree Differentiating Demented from Not Demented Participants**



Frailty/Morbidity Predictors

The pruned frailty/morbidity classification tree predicting not demented and demented cognitive status at CSHA-2 did not extend beyond the root node. The pruning process eliminated unnecessary splits on the following predictors: CAMDEX mobility impairment and vision. In both the pruned and unpruned classification trees, all participants were predicted to be not demented at CSHA-2, resulting in a misclassification rate of 15.9%.

Social/Physical Predictors

The pruned classification tree using social and physical independent variables for predicting not demented and demented cognitive status at CSHA-2 did not extend beyond the root node. The pruning process eliminated unnecessary splits on the following predictors: IADLs, place of residence, and ADLs. In both the pruned and unpruned classification trees, all participants were predicted to be not demented at CSHA-2, resulting in a misclassification rate of 15.9%.

Neuropsychiatric Predictors

Similar to the pruned social/physical classification tree addressing Question 2, the pruned neuropsychiatric classification tree did not extend beyond the root node. Compared to the unpruned tree which misclassified approximately 15.6% of the sample, the pruned tree misclassification rate was approximately 15.9%. The pruning process removed unnecessary splits on the following predictors: CAMDEX changes in personality, CAMDEX hallucinations, CAMDEX depression, and CAMDEX persecution.

Vascular & Family History Predictors

The pruned vascular classification tree consisted solely of a root node. The pruning process removed an unnecessary split on the Hachinski total score predictor. Both the pruned and unpruned trees predicted a non-demented cognitive status for all participants and had misclassification rates of 15.9%. The same misclassification rate was associated with the family history classification trees. The unpruned classification tree did not extend beyond the root node; thus, neither did the pruned tree. The family history predictors, therefore, did not contribute to the differentiation between not demented and demented participants.

All Predictors

The unpruned and pruned classification tree predicting not demented and demented cognitive status at CSHA-2 are depicted in Figures 14, 15, and 16. Despite the larger number of splits, the unpruned tree only correctly predicted two additional demented participants, compared to the pruned tree. The unpruned and pruned classification trees correctly classified 90.4% and 89.4% of the sample, respectively. In the pruned tree, demented participants were correctly classified if they had a positive proxy report of memory changes on Section H of the CAMDEX and a free recall total score below 12.0 on the Buschke measure of short-term visual memory. The sensitivity, specificity, PPV, and NPV of the pruned tree were 0.571, 0.955, 0.704, and 0.922, respectively.

Figure 14. **Left Side of Unpruned Classification Tree Differentiating Not Demented from Demented Participants – All Predictors**

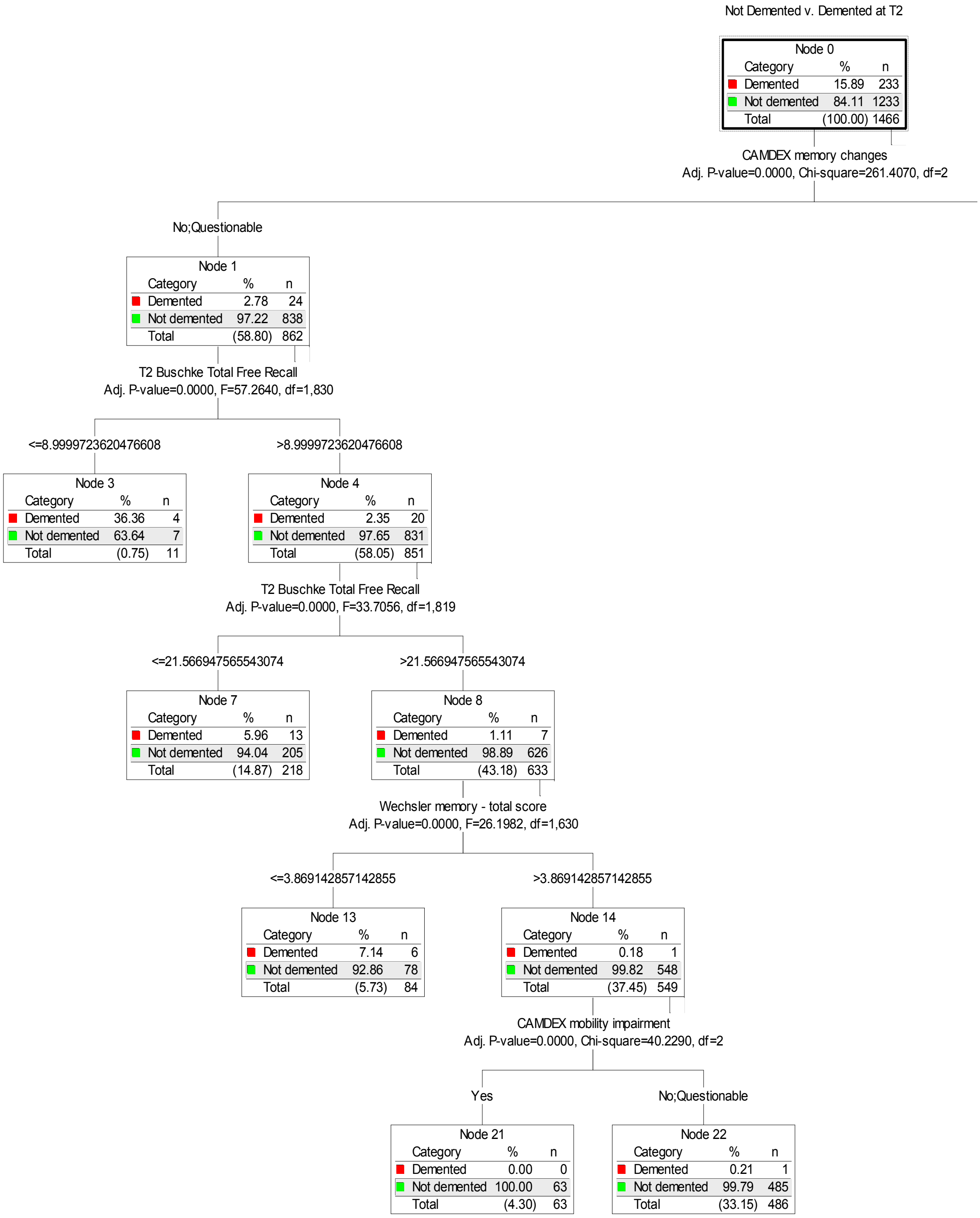


Figure 15. **Right Side of Unpruned Classification Tree Differentiating Not Demented from Demented Participants – All Predictors**

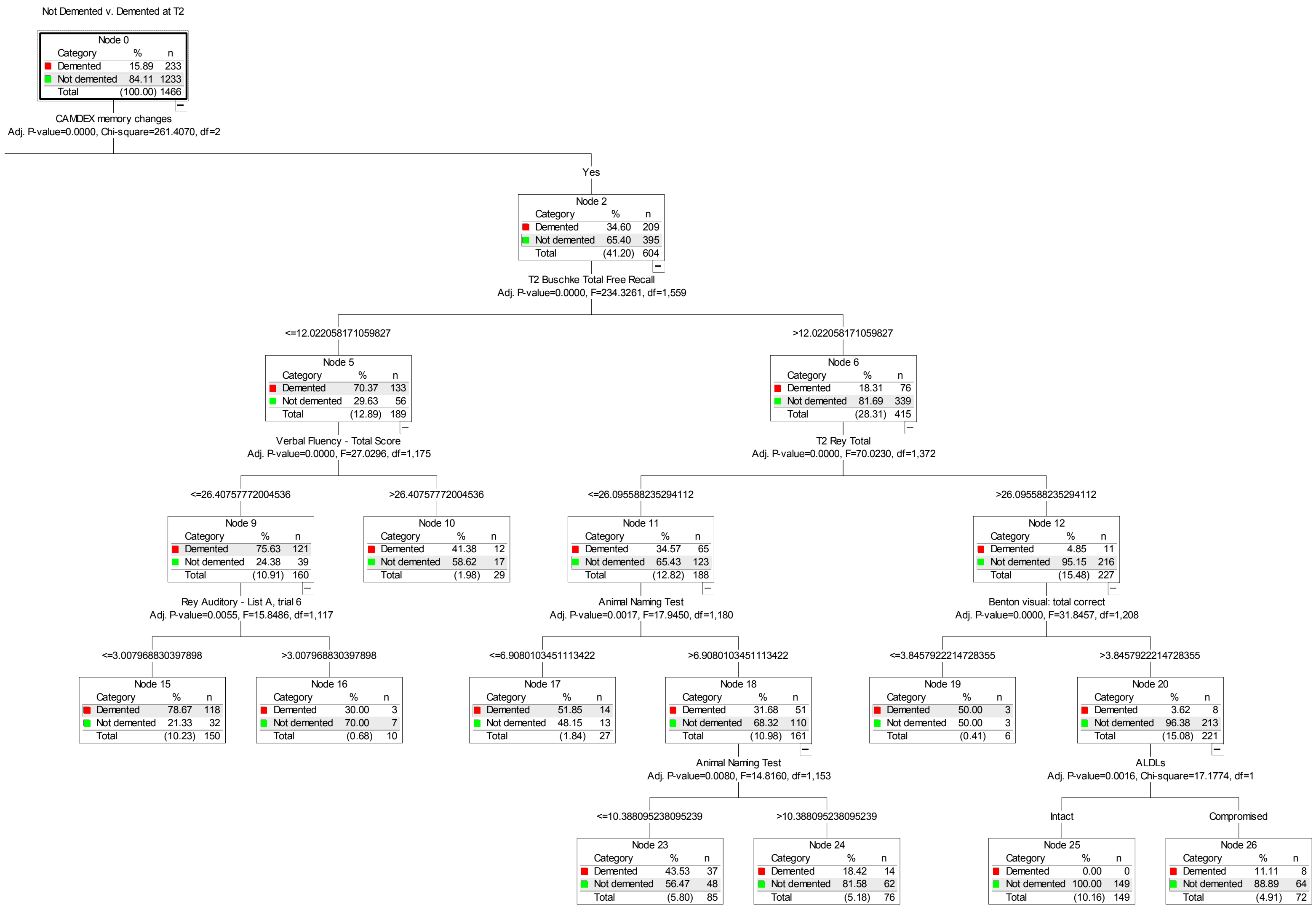
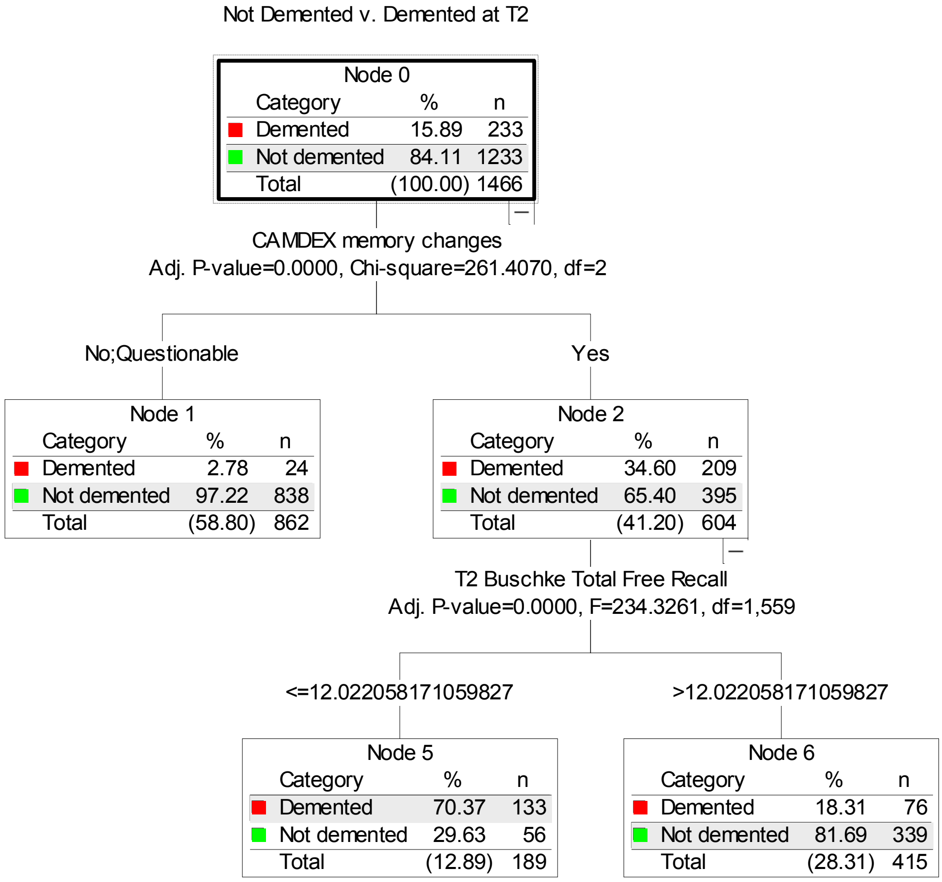


Figure 16. **Pruned Classification Tree Differentiating Not Demented from Demented Participants – All Predictors**



Question 3 Results: What clinical correlates best discriminate between stable and progressive cognitive impairment?

Baseline Sample Characteristics

The baseline sample for Question 3 included 289 participants with a consensus diagnosis of CIND at CSHA-2. Of these, 174 participants progressed to dementia five years later at CSHA-3. Baseline demographic characteristics for Converters (N = 174) and Non-converters (N = 115) are listed in Table 15. Overall, the Converters were significantly older ($t[287] = -4.15$, $p < .001$), more educated ($t[286] = -3.33$, $p = .001$), and produced significantly lower scores on the 3MS ($t[285] = 3.36$, $p = .001$).

Table 15. **Baseline Sample Demographics for Question 3**

	Non-converters	**Converters**
Mean Age on Oct. 1, 1990 (*SD*)*	75.3 (78.7)	78.7 (7.1)
Years of Education, Mean (*SD*)*	8.4 (3.8)	9.9 (4.0)
3MS Score, Mean (*SD*)*	81.1 (8.2)	77.1 (10.8)
Gender (% Female)	66.1	67.8
Institutionalized (%)	15.7	22.4
Married (%)	34.8	25.3

Note: * significant at $p \leq .001$; *SD* = standard deviation; Married = married & common-law

Classification Trees

Demographic Predictors

The pruned classification tree examining the utility of demographic predictors in the identification of persons with CIND at CSHA-2 who converted to dementia at CSHA-3 did not include any demographic predictors. The pruned tree, consisting solely of the root node, misclassified 40% of the baseline sample (i.e., all of the non-converters). In comparison, the unpruned tree, including splits on age and education, misclassified 37% of the baseline sample. Thus, age and education were identified as unnecessary splits and were removed from the tree.

Cognitive Predictors

The pruned classification tree depicting the utility of proxy reports of memory and general cognitive function, as well as neuropsychological test scores, in identifying CIND persons who will convert to dementia over five years is illustrated in Figure 17. The sum of trials 1-3 on the Buschke Free Recall measure (i.e., Total Buschke Free Recall) was the best predictor of conversion. Approximately 71.3% of persons who converted to dementia at CSHA-3 had a total score of less than 21.9 on the Buschke Free Recall test of short-term visual memory. Approximately 21.3% of converters scored between 21.9 and 25.3 on this measure. Overall, the sensitivity, specificity, PPV, and NPV associated with the cognitive classification tree were 0.925, 0.365, 0.688, and 0.764, respectively.

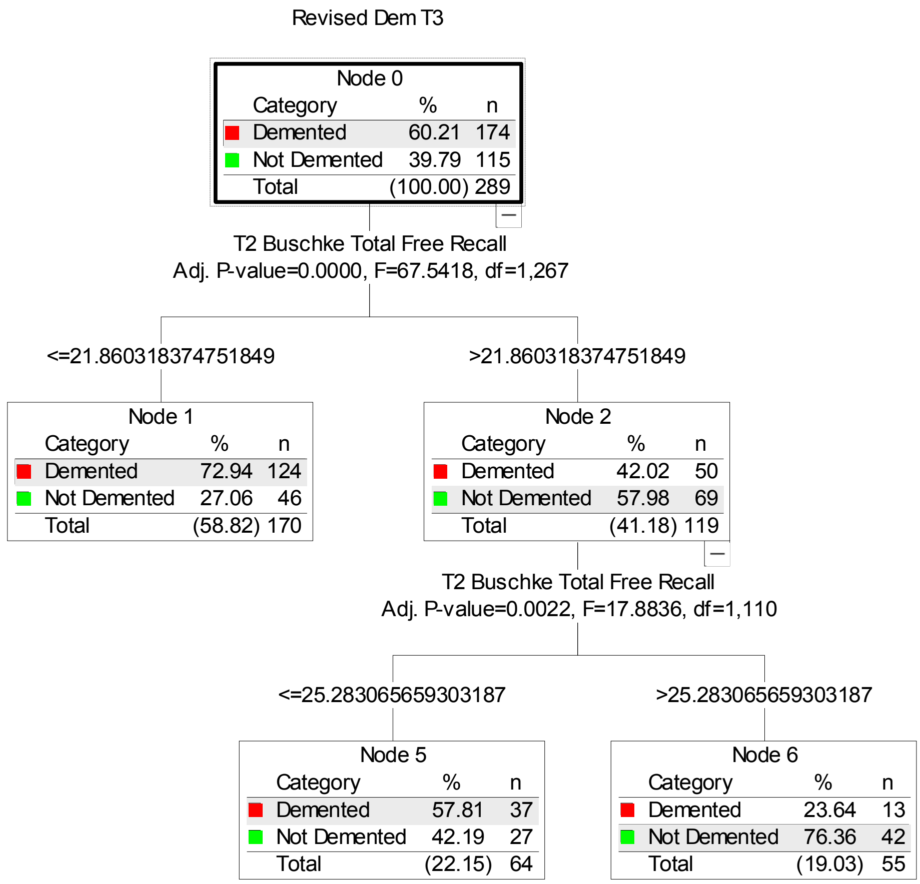
Frailty/Morbidity Predictors

None of the selected Frailty/Morbidity predictors were successful in generating a pruned classification tree that extended beyond the root node. Both the pruned and the unpruned trees (consisting solely of the CAMDEX mobility impairment predictor) misclassified 40% of the baseline sample.

Social/Physical Predictors

Compromised instrumental activities of daily living significantly discriminated between persons who progressed to dementia and those that did not. Specifically, 76.4% of those who progressed to dementia had compromised IADLs (Figure 18). The sensitivity, specificity, PPV, and NPV associated with the Social/Physical classification

***Figure 17.* Cognitive Classification Tree Differentiating Converters v. Non-Converters**

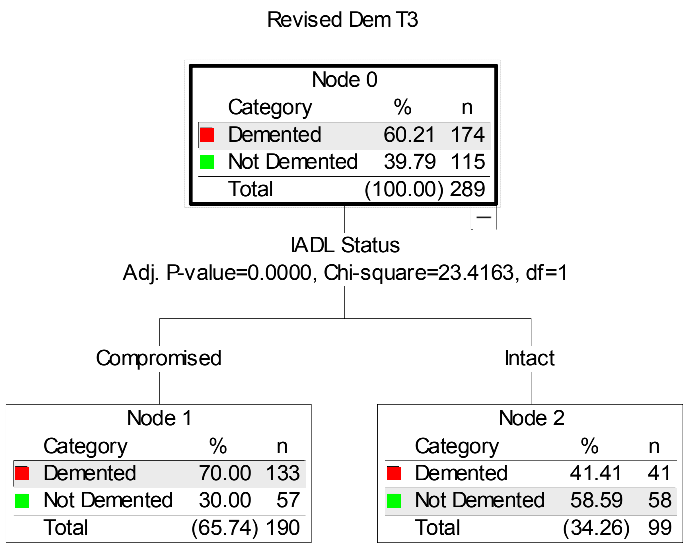


tree were 0.764, 0.504, 0.700, and 0.504, respectively. The same results were observed for the pruned and unpruned trees.

Neuropsychiatric, Vascular, and Family History Predictors

None of the pruned Neuropsychiatric, Vascular, or Family History classification trees extended beyond the root node. Each pruned tree misclassified approximately 40% of the baseline sample (i.e., the predicted classification for each participant was demented). Unlike the unpruned Neuropsychiatric classification tree which included a single split on a proxy report of changes in mood that was subsequently identified as an unnecessary split (i.e., same misclassification rate as the pruned tree), no differences were noted between the pruned and unpruned Vascular and Family History classification trees.

Figure 18. **Social/Physical Classification Tree Differentiating Converters v. Non-Converters**



<u>All Predictors</u>

Both the unpruned and pruned classification trees are reported for trees generated using all predictors. While the unpruned tree (Figure 19) includes more splits, it is less sensitive (0.851) than the pruned tree (see below). The pruned classification tree generated using all of the selected predictors is listed in Figure 20. Note that these results are an exact replication of those observed when the predictors were limited to cognitive predictors, indicating that, in this sample, performance on a measure of short-term visual memory is the predictor that best discriminates between stable and progressive cognitive impairment. The sensitivity, specificity, PPV, and NPV for this model were 0.925, 0.365, 0.688, and 0.764, respectively. The classification tree misclassified 29.8% of the sample – of this, 84.9% had an actual classification of not demented and were incorrectly classified as demented.

Figure 19. **Unpruned Classification Tree Differentiating Converters v. Non-Converters – All Predictors**

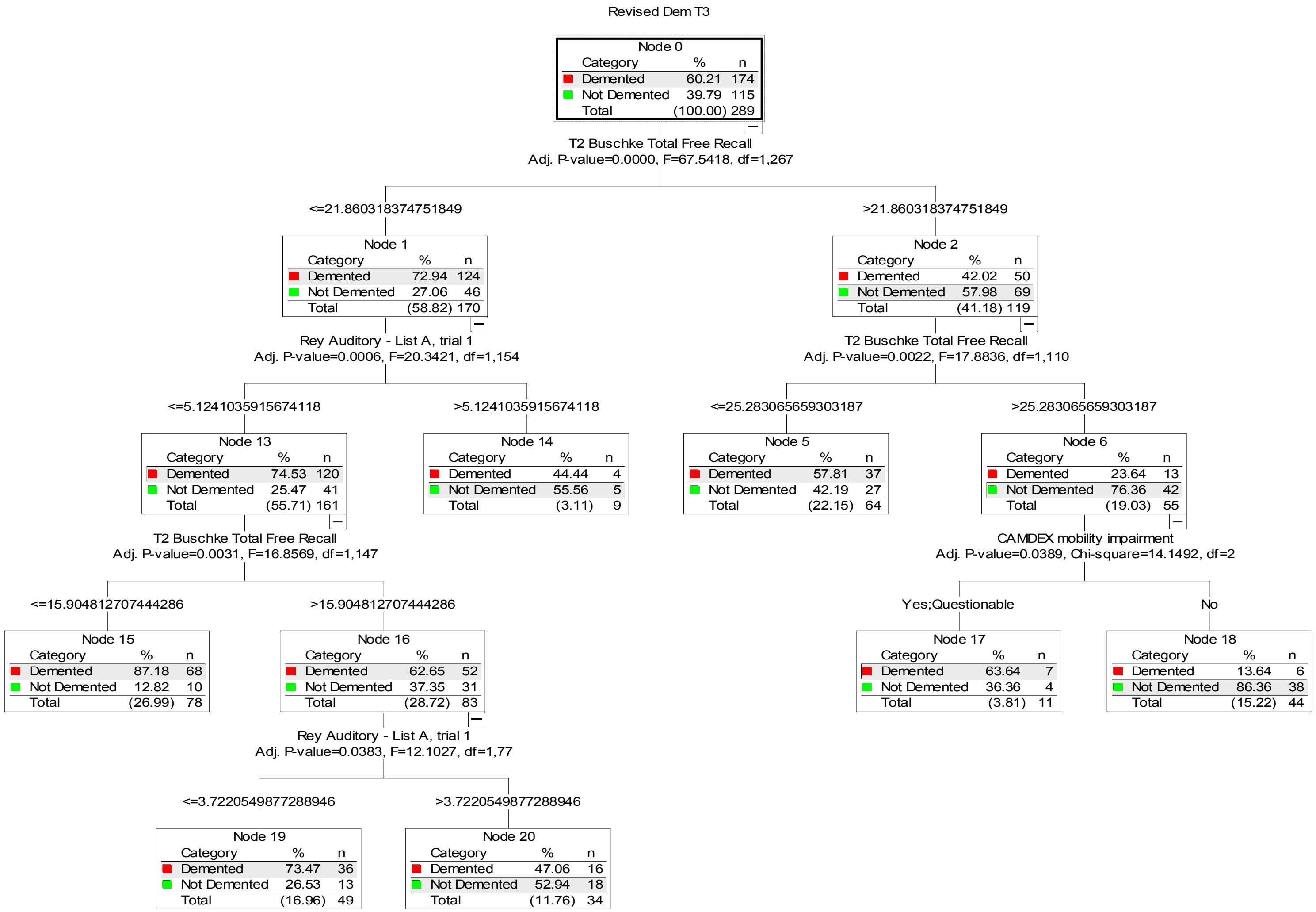
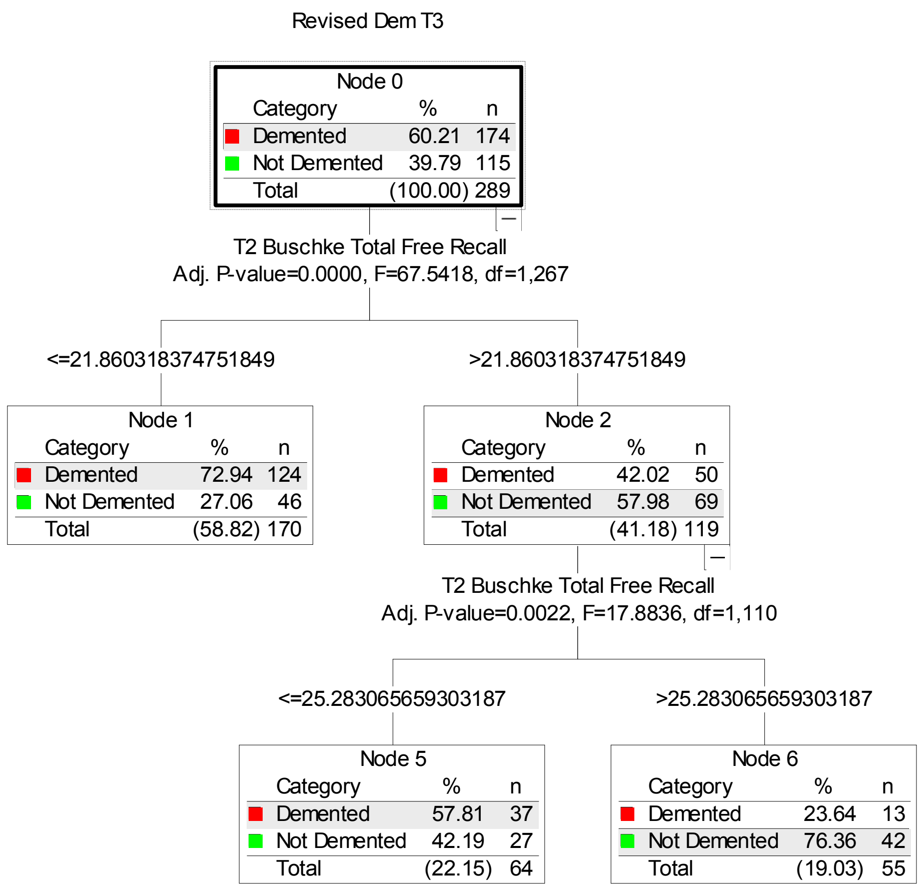


Figure 20. **Pruned Classification Tree Differentiating Converters v. Non-Converters – All Predictors**



Discussion

The identification of persons with incipient dementia is limited by the case definition of MCI or CIND employed. For example, in Study 1, participants with cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia according to criteria from the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychological Association [APA], 1987), but who did not meet the inclusion criteria for any of 13 MCI or CIND case diagnoses, had the highest conversion rates to dementia at follow-up. These results suggest that existing MCI and CIND case definitions fail to capture a large percentage of cognitively impaired persons who will progress to dementia. The purpose of Study 2 was to examine the ability of previously identified risk factors for cognitive impairment and dementia to differentiate between NCI and CIND participants, not demented (i.e., NCI + CIND) and demented participants, and stable and progressing CIND using data from a longitudinal sample of Canadian elderly. The goal of this study was to inform the identification of persons at-risk for dementia to enhance primary and secondary prevention strategies. This study is unique in that it extends beyond previous research that focuses on a limited number or category of predictors and it employs an inclusive case definition of cognitive impairment that does not meet the criteria for dementia.

Distinguishing CIND from NCI (Question 1)

The ultimate goal of many research studies addressing pathological cognitive aging is the prevention and/or treatment of dementia. To do so, it is important to accurately identify individuals who are at risk for future dementia as early as possible. The CIND classification is estimated to affect 16.8% of the Canadian population

(Graham et al., 1997) and allows for impairment in any cognitive and functional domain. Moreover, CIND is notably heterogeneous (Tuokko & Frerichs, 2000; Tuokko, Frerichs, & Kristjansson, 2001) and is hypothesized to capture a broader representation of individuals at risk for future dementia (Peters, Graf, Hayden, & Feldman, 2004). For example, the probability of developing dementia is five times greater for individuals identified as CIND, compared to NCI persons (Tuokko et al., 2003). Thus, the ability to correctly differentiate persons with CIND from those with NCI may increase the early identification of persons who will develop dementia. The aim of Question 1 was to elucidate the clinical correlates of CIND with the intent of informing the early identification of incipient dementia.

The heterogeneity of the CIND classification was evident in the classification tree results. The demographic classification tree supported previous associations between cognitive decline, older age, and education (Tuokko et al., 2003). However, although the correct identification of CIND participants was achieved for persons with lower education (≤ 6.8 years) and those with relatively higher education (>6.8 years) but who were older (> 84.3 years of age), the demographic classification tree was a poor predictor of CIND. Specifically, over 50% of CIND participants were misclassified, compared to 25% of NCI participants. This is likely a reflection of the inclusive definition of the CIND classification.

Within the Frailty, Social/Physical, Neuropsychiatric, and Family History classification trees, individual predictors and interactions between predictors significantly differentiated between CIND and NCI groups. Significant predictors of CIND within each category were: 1) Frailty - responses on measures of mobility and hearing; 2)

Social/Physical – compromised IADLs and ADLS; 3) Neuropsychiatric – changes in personality; and 4) Vascular - < 7 on the Hachinski Ischemia Scale. However, similar to the demographic classification tree, the sensitivity of each algorithm was considerably poorer than the associated specificity. Thus, independently, these correlates were of limited value in the identification of persons with CIND.

These results contradict previous reports of frailty and neuropsychiatric risk factors for CIND (Monastero et al., 2007). The disparity in findings may be attributed to differences in study parameters and the case definitions of CIND employed in each study. Specifically, risk factors for CIND in the Monastero et al. (2007) study were identified longitudinally and CIND participants were identified according to performance on the MMSE. In contrast, in the current study, the clinical correlates of CIND were identified through cross-sectional analyses and CIND classification was determined according to clinical judgment. Moreover, Monastero et al. drew their sample from a memory clinic, whereas the sample for the current study was drawn from the general population and may, therefore, consist of participants with less severe cognitive impairment. Nevertheless, the absence of depression as a significant risk factor for CIND is in keeping with the results of the Monastero et al. study, as the relation between CIND and depression was noted to be contingent on future progression to Alzheimer's disease (AD).

In contrast to the limited contributions of the aforementioned categories of variables in discriminating CIND from NCI, the results of the Cognitive classification tree highlight the importance of neuropsychological performance in such a distinction. Specifically, based on proxy report and cognitive performance alone, 78% of CIND participants were correctly classified. Interestingly, the proxy report of memory changes variable served as the first predictor in the classification tree, suggesting that this predictor may be of more value in a more inclusive classification of cognitive impairment, such as CIND, than in more stringent MCI case definitions. However, it is important to note that both positive and negative proxy reports of memory changes informed the correct classification of CIND participants. This finding may explain the reported limited contributions of subjective and proxy reports of memory changes in population based studies of MCI and CIND (Fisk et al. 2003).

Performance on measures of learning and memory and abstract reasoning was significantly related to the prediction of CIND. This is not surprising given that CIND is conceptually a cognitive classification and that performance on neuropsychological measures of learning and memory tend to reflect the largest differences between CIND and NCI individuals (Peters et al., 2004). The Cognitive algorithm partially supported previous logistic regression analyses identifying learning and memory, visuoconstruction, and cognitive flexibility as neuropsychological predictors of CIND (Peters et al., 2004). Moreover, the Cognitive algorithm derived in the current study replicates the sensitivity and has a higher specificity than the Peters et al. study (80.1% versus 64.3%).

A major finding of Question 1 was the observation that, after selecting all available predictors, seven of the eight splits in the classification tree were based on cognitive predictors. The only other predictor included in the final tree was the Hachinski Total Score categorical variable that correctly classified 2% of CIND cases. This finding is in keeping with previous results supporting vascular risk factors in the prediction of CIND (Di Carlo et al., 2000). Overall, these results suggest that neuropsychological measures are the best measures for differentiating between NCI and CIND participants. Further supporting this conclusion was the finding that the Cognitive classification tree correctly classified more CIND participants (i.e., had a higher sensitivity) than the classification tree generated using all available predictors.

In considering the different classification trees generated to differentiate CIND from NCI, it is clear that a single algorithm did not capture all CIND participants. Recall that the CIND classification consists of a heterogeneous sample of persons with cognitive impairment of differing etiologies. Previous attempts to predict CIND status from neuropsychological performance highlight the range of intra-individual variability in cognitive performance across measures. For instance, Peters et al. report that approximately 50% of their CIND sample demonstrated intact cognitive performance on all cognitive measures or were impaired on a single cognitive measure. Thus, caution in interpreting impairment on a single neuropsychological measure as evidence for a diagnosis of CIND is warranted.

This study is unique in its identification of the clinical correlates that serve to differentiate CIND from NCI from a population perspective. Few studies have attempted to differentiate CIND from NCI. The vast majority of existing research has focused on identifying persons with various case definitions of MCI. An advantage of selecting CIND, as opposed to MCI, as the interim cognitive state between NCI and dementia, is the breadth and diversity of participants that are captured by the CIND classification. In contrast, it is impractical to compare the results of this study with those employing a case definition other than CIND. Nevertheless, the results of this study inform the differentiation of CIND from NCI and aid in the identification of a subset of the population at-risk for dementia.

Differentiating Not Demented (NDEM) and Demented (DEM) Participants (Question 2)

This study is believed to be the first study to systematically differentiate NDEM and DEM persons. Previous research has focused on individually differentiating NCI and MCI/CIND from dementia. The creation of a non-demented (NDEM) group by combining the NCI and CIND participants for differentiation from a demented (DEM) group increased the heterogeneity of the comparison group. The heterogeneity of the comparison group (i.e., NDEM), relative to the target group (i.e., DEM), is reflected in the lower sensitivities associated with the classification trees in Question 2. Nevertheless, the DEM group was noted to be significantly older, demonstrated significantly poorer performance on the 3MS, and included a significantly greater proportion of persons residing in institutions, compared to the NDEM group. Additionally, proxy reports of memory changes, learning and memory, and verbal fluency were identified through exploratory statistical analyses to differentiate NDEM from DEM participants. Thus, despite reports of overlapping cognitive performance among NCI and MCI/CIND persons and MCI/CIND and DEM persons along the continuum of cognitive decline (Brayne & Calloway, 1988; Rediess & Caine, 1996), 70-76% of DEM persons were identified using cognitive measures.

Similar sample limitations should be considered when interpreting the results of Question 1 and Question 2. First, both samples consisted of a comparison group (i.e., NCI or NDEM) that was considerably larger than the target group (i.e., CIND or DEM). It should be noted that the unequal sample sizes are a reflection of the resulting sample following the application of the inclusion and exclusion criteria and are not representative of the general population base rates; although similar disparity is present. Second, Question 1 and Question 2 were cross-sectional in nature and inclusion in the cognitive classifications (i.e., NCI and CIND in Question 1 and NDEM and DEM in Question 2) was done according to clinical judgment at the CSHA-2 consensus conference following review of all available clinical data. Thus, the results of the classification trees may be critiqued for their circularity. Circularity occurs when an outcome measure is a product of the variables that, in turn, serve as diagnostic predictors (Tuokko & Frerichs, 2000). However, given the current absence of gold standard diagnostic criteria for cognitive decline and dementia, and the presence of circularity when different cognitive measures are used to create and predict cognitive outcomes (given the correlations between instruments measuring similar cognitive constructs; Tuokko & Frerichs, 2000), circularity will continue to be an instrinsic feature of studies aiming to predict cognitive decline and dementia.

Differentiating Stable versus Progressive CIND (Question 3)

Previous research comparing the conversion rates of pre-existing case definitions of cognitive impairment of insufficient magnitude to warrant a diagnosis of dementia in a population-based sample (i.e., Study 1) reveal substantially greater rates of progression among MCI/CIND case definitions, compared to normal elderly participants. As such, the identification of the clinical correlates that best predict conversion to dementia are of great relevance to the primary and secondary prevention of dementia. The goal of Question 3 was to identify the clinical correlates that best differentiate between stable and progressing CIND prior to the onset of dementia.

The observed five-year conversion rate for CIND participants included in this study (i.e., 60.2%) exceeded those reported in a previous examination of progression to dementia among CIND participants in the CSHA (i.e., 47%; Tuokko et al., 2003). The disparity in findings likely reflects different sample parameters. For instance, Tuokko and colleagues examined CIND conversion from CSHA-1 to CSHA-2, whereas the current study examined the progression to dementia from CSHA-2 to CSHA-3. Moreover, in the current study, only those participants for whom information regarding not demented or demented cognitive status (irrespective of vital status) was available at CSHA-3 were included. Thus, the Question 3 sample may represent participants with greater cognitive impairment at baseline. As such, it was not surprising that the results of the exploratory statistical analyses in Question 3 differed from those reported by Tuokko and colleagues. However, the degree of difference between the predictive models was surprising. While memory impairment was a key prognostic feature in both predictive analyses, the predictive algorithm generated in the Tuokko et al. study (including memory impairment, functional impairment, and proxy report of memory changes) more accurately identified not demented participants (93%) at follow-up, compared to demented participants (32%). That is, the specificity of the researchers' algorithm was substantially greater than the sensitivity. In contrast, the sensitivity and specificity associated with the predictive algorithm (including all predictors) reported in the current study were almost the exact opposite of those reported by Tuokko et al. (2003; 93% and 37%, respectively).

The vast difference in results is likely due to the difference in predictors utilized in each study. In the Tuokko et al. (2003) study, memory-impairment predictors were based on clinical judgment and informant report. The most significant predictor, clinician observed memory impairment, may incorporate clinical judgment regarding the implications of an impaired memory score for each individual participant. For example, Person A may score below age- and education-matched norms and this score may reflect a decline in his memory over the past year. In contrast, Person B may also score below age- and education-matched norms but his performance may reflect premorbid memory difficulties. Thus, based on clinical judgment, Person A may be identified as demonstrating memory impairment, while Person B, although scoring in the impaired range for his age and education, may be identified as NOT memory impaired. Moreover, the memory impairment predictor in Tuokko and colleagues' (2003) study represented impairment as a core feature. That is, it was not reflective of performance on a single memory measure. In contrast, the results of the current study reflect individual performance on each cognitive measure without inference of impairment status. Research examining the performance of CIND participants on neuropsychological measures reveals substantial intra-individual variability in performance across measures, with up to 80% of persons with CIND demonstrating a 2 standard deviation difference between their weakest and best test results (Peters et al., 2004). Thus, while performance on the Buschke free recall measure was identified as the best predictor of conversion in the current study, administration of more than one neuropsychological measure in each domain to confirm the presence of impairment in a specific domain is recommended.

The results of Question 3 confirm previous findings supporting the early identification of persons at-risk for dementia by means of neuropsychological (e.g., Albert, Moss, Tanzi, & Jones, 2001; Devanand, Folz, Gorlyn, Moeller, & Stern, 1997; Fleisher et al., 2007; Griffith et al., 2006; Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999; Perri, Serra, Carlesimo, Caltagirone, & the Early Diagnosis Group of the Italian Interdisciplinary Network on AD, 2007; Tabert et al., 2006; Tierney, Yao, Kiss, & McDowell, 2005; Tuokko et al., 2003) and functional (Rozzini et al., 2007) assessment. Similar to Tabert and colleagues (2006), total immediate recall using a selective reminding test (SRT) at baseline was the best predictor of conversion to dementia at follow-up. In both studies, the ability to learn and recall information across repeated trials significantly differentiated non-converters and converters. Poorer performance on the same enhanced cued recall measure (Buschke, 1984; Tuokko & Crockett, 1989) was noted to differentiate non-demented participants who converted to dementia 12-18 months after baseline assessment ("change group") from those who did not ("no change group"; Tuokko Vernon-Wilkinson, Weir, & Beattie, 1991). Specifically, retrieval (i.e., the total free recall score on Buschke's Cued Recall paradigm) was associated with the best sensitivity, specificity, and predictive values. The utility of the free recall condition on the Buschke SRT as a marker for the development of dementia over five years is reportedly attributable to its promotion of learning while controlling for attention and cognitive processing. Through restricted measurement of the learning process, the free recall condition on the Buschke SRT predicts conversion to dementia over five years by discriminating between persons with age-associated memory impairment who will not progress to dementia and those with memory impairment indicative of incipient dementia (Grober, Lipton, Hall, & Crystal, 2000). Overall, the results of Question 3 are in keeping with previous reports of poorer episodic memory among cognitively impaired persons who convert to dementia, compared to non-converters (Perri et al., 2007; Tuokko et al., 1991). The results of the current study suggest that, in the presence of other significant risk factors, poor episodic memory (specifically retrieval) supersedes all other predictors in the early identification of persons at risk of dementia within the next five years.

The results of the Cognitive classification tree partially confirm previous results obtained in an investigation of the predictive ability of neuropsychological measures in the identification of incident dementia using data from the CSHA. In addition to an episodic memory test (short delayed recall on the RAVLT), Tierney et al. (2005) identified performance on the WMS Information subtest and the Animal Naming measure as significant predictors of conversion to dementia within five years. In contrast with the current study, more pronounced differences on these measures of long-term memory and categorical fluency may have been present in the Tierney et al. study, as (1) their sample excluded persons with neurological conditions and sensory deficits and (2) the researchers were predicting conversion to AD, rather than dementia as a whole.

The absence of significant neuropsychological predictors other than the total score on the Buschke free recall measure may be attributable to the population-based sample, to the inclusive nature of the CIND case definition, or to the five-year span between baseline assessment and follow-up diagnoses. First, population-based studies enable the investigation of mild cognitive impairment, compared to studies in which participants are drawn from a clinical sample (e.g., from a memory clinic) and tend to include participants in more advanced stages along the continuum of pathological cognitive decline (Spaan, Raaijmakers, & Jonker, 2005). Second, the heterogeneity of the CIND sample may mask less robust differences observed between converters and non-converters in studies employing more restrictive exclusion criteria (e.g., Fleisher et al., 2007; Rozzini et al., 2007; Tabert et al., 2006; Tierney et al., 2005). Third, given that participants' neuropsychological results reflect their cognitive functioning five years prior to their classification as converters or non-converters, their performance on neuropsychological measures at CSHA-2 may reflect only the earliest stages of cognitive impairment. This theory is supported by reports that multiple domain MCI represents a more advanced stage of cognitive decline (Alexopoulos, Gimmer, Perneczky, Domes, & Kurz, 2006). Additionally, Grober et al. (2008) report increasingly impaired performance on measures of episodic memory, executive function, and verbal intelligence at 7 years, 2-3 years, and just prior to a diagnosis of dementia, respectively (Grober et al., 2008). Thus, given the five-year interval between baseline assessment and classification of conversion or non-conversion, the presence of cognitive impairment extending beyond the memory domain is unlikely.

In addition to neuropsychological performance, functional ability was a predictor of conversion to dementia. Similar to Rozzini et al. (2007), who identified a decline in IADL functioning among the risk factors for conversion to AD among aMCI persons within one year, impairment of IADL function was predictive of progression to dementia in the current study. Up to 76% of CIND participants who converted to dementia at follow-up demonstrated some form of impaired IADLs. It is important to note that impaired IADL ability was not included in the overall predictive algorithm (i.e., the model including all available predictors). The inability to carry out IADLs is frequently associated with impaired cognitive function. For example, impaired psychomotor and memory functions are associated with impaired IADL functioning, showering, and walking among MCI/CIND persons (Tuokko, Morris, & Ebert, 2005). Thus, the absence of functional impairment as a predictor of conversion to dementia at follow-up in the overall model may be attributable to its association with memory function (which is represented by the total score on the Buschke free recall measure in the overall predictive algorithm). Nevertheless, the results of the Social/Physical algorithm highlight the relevance of acknowledging functional impairments in non-demented elderly persons given their predictive utility in the early identification of persons at-risk for dementia.

The fact that the outcome classifications (i.e., converters v. non-converters) for Question 3 were derived independently of the predictors is a strength. Dementia status at CSHA-3 was determined based on the information attained through the CSHA-3 clinical evaluation, while the predictors represented clinical information from CSHA-2. In contrast, Question 3 may be criticized for its lack of biological markers of dementia, specifically the apolipoprotein E (ApoE) gene, from the list of variables included in the predictive algorithms. Persons with the ApoE ε4 allele are reported to be at increased risk for AD. Moreover, presence of the ApoE ε4 allele is reported to predict the conversion from CIND to dementia in the CSHA. However, the predictive values for the ApoE ε4 allele were insufficient to support its use as a diagnostic marker of conversion from CIND to dementia within five years (Hsiung, Sadovnik, & Feldman, 2004). Moreover, the recent finding that the predictive accuracy of a cognitive model for the conversion from aMCI to dementia only fell from 81% to 80% with the removal of the ApoE ε4 allele as a predictor (Fleisher et al., 2007) confirms reports that the presence of the ApoE ε4 allele is not predictive of cognitive decline or conversion to dementia (Albert et al., 2001; Amieva et al., 2004; Devanand et al., 2005). As such, the absence of

ApoE ε4 allele in the current study is not believed to limit the results or their implications.

Although various predictive algorithms were derived for the identification of persons at risk for conversion to dementia, none of the models produced accurately identified all participants who progressed to dementia at follow-up. Moreover, while the sensitivity of both the Cognitive and Overall classification trees was 92.5%, the specificities and predictive values were less than optimal, confirming reports of limited precision associated with the neuropsychological prediction of conversion (Tian, Bucks, Haworth, & Wilcock, 2003). The low specificities and predictive values may corroborate previous reports that performance on a single neuropsychological measure may be predictive of conversion for some CIND persons but, given the heterogeneity resulting from the CIND case definition and reports of substantial intra-individual variability in neuropsychological performance, several persons who will develop dementia may not be captured using a single neuropsychological measure (Peters et al., 2004). As such, it is recommended that the identified risk factors serve as markers for ongoing monitoring and assessment of functional and cognitive decline, rather than diagnostic markers for incipient dementia.

Overall Strengths and Weaknesses

Unlike many existing studies examining the prediction of conversion to dementia that employ definitions of MCI, the current investigation sampled participants using a definition of CIND. As noted previously, it is hypothesized that the restricted MCI case definitions limit the identification of persons at-risk for dementia. In contrast, CIND captures persons at various stages of cognitive decline, as it allows for cognitive impairment in any cognitive domain (irrespective of etiology). The current study extends beyond previous research predicting conversion to dementia from CIND (i.e., Peters et al., 2004) by examining clinical correlates of conversion including and extending beyond neuropsychological predictors. Similarly, rather than predicting conversion to AD, the current study examined the clinical correlates of progression from CIND to dementia in general. Thus, maintaining the broad exploratory nature of the study.

The evaluation of 45 possible risk factors was made possible with the selection of the QUEST program. Unlike previous examinations of risk factors for cognitive impairment and decline that tend to employ logistic regression analyses, QUEST performs exploratory statistical analyses by recursively partitioning variables to form a hierarchical binary decision tree. Unlike regression analyses, interactions between predictors are automatically calculated by QUEST. Another strength of the QUEST program is its unbiased algorithm. Unlike exhaustive search algorithms, QUEST does not select variables for splitting simply because they enable more splits. Thus, the resulting binary tree is limited by fewer nodes, but is superior given its unbiased node selection (Loh & Shih, 1997). Moreover, QUEST easily and rapidly manages large data sets, such as the CSHA, consisting of nominal, ordinal, and continuous variables. Another strength of this program is its handling of missing data. Using the QUEST algorithm, missing data are not included in the growth of classification trees, but are subsequently classified using surrogate predictors. This process maximizes the number of participants included in each sample.

The current study was designed to be exploratory in nature. Therefore, although it was hypothesized that predictive algorithms for cognitive impairment and cognitive decline would be produced using the QUEST program, no predictions regarding specific risk factors were made. Given its exploratory nature, all predictors were treated equally. As noted by Fleisher et al. (2007), many studies designed to identify risk factors for the conversion from MCI to dementia either disregard the demographic characteristics of their participants or control for them in the predictive model. In the current investigation, the baseline demographic characteristics of the participants were included as predictors in categorical and overall predictive algorithms for conversion to dementia within five years.

The results should be interpreted within the contexts of the study's limitations. First, the results of Questions 1 through 3 are only generalizable to the cognitive case definitions employed. Second, although the data were sampled from the CSHA, a longitudinal, population-based sample of elderly Canadians, only participants who completed the clinical component of CSHA-2 were included in the current study. Therefore, the results are not representative of the population in general. As with all studies, the results of this study should be interpreted relative to its inclusion and exclusion criteria. Third, cognitive ability in some domains (i.e., agnosia, apraxia) was inferred from other measures due to a lack of available normative data, French and English forms, and clinician familiarity (Tuokko et al., 1995). Fourth, the selection of predictors was limited by the clinical variables derived from the CSHA and does not include any biological markers or neuroimaging measures. Finally, although various combinations of neuropsychological measures, cerebrovascular risk factors, and proxy reports of memory changes were identified as significant predictors of cognitive impairment, the specificity and predictive values of the algorithms caution against their use as clinical markers of CIND, dementia, or conversion. Rather, it is recommended that impairment in the identified domains serve as clinical markers for ongoing monitoring and evaluations.

Conclusions

Across the three questions addressed in this study, poor overall performance on Buschke's (1984) enhanced free recall paradigm was consistently identified as a significant predictor. Performance on this retrieval measure was noted to interact with measures of abstract reasoning, long-term memory, cerebrovascular risk factors, and proxy report of memory change in the differentiation of CIND from NCI participants. An interaction with proxy report of memory change was also noted when differentiating demented from non-demented participants. However, retrieval was the sole significant predictor of conversion to dementia over five years, supporting earlier reports that impaired memory performance is the earliest marker of progression to dementia (Albert et al., 2001; Alexopoulos et al., 2006; Grober et al., 2008).

Overall, the results of Questions 1 through 3 are in keeping with the results previous studies examining various case definitions of MCI or questionable dementia revealing the predictive ability of neuropsychological measures of learning and memory and executive function. Future research in this area should include biological markers and neuroimaging results among the predictors as reduced cortical glucose metabolism (Fellgiebel et al., 2007), temporal lobe atrophy and pathological CSF biomarkers (Bouwman et al., 2007) have been identified as significant risk factors for conversion. As this was an exploratory study, replication of the results in a different sample is required. Other related avenues for future research include shorter follow-up intervals and inclusion of a cost/benefit analysis of misclassification. Additionally, as the use of the QUEST algorithm is a novel approach to exploring risk factors and associated patterns of interaction within the field of cognitive impairment and conversion to dementia, comparison with other data-mining approaches is recommended. As with other studies employing the QUEST algorithm (Trenberth & Dewe, 2006), the goal of the present study was to highlight the clinical correlates associated with various cognitive classifications and conversion to dementia to inform future research targeting the development of primary and secondary prevention of CIND and dementia. The results suggest that impairments in memory (especially retrieval) are a key feature in the architecture of pathological cognitive decline.

Chapter 5

General Discussion

Mild cognitive impairment is conceptualized as an intermediary stage in the continuum of pathological cognitive decline. Unfortunately, the absence of gold standard diagnostic criteria has resulted in variable nomenclature, case definitions, outcomes, risk factors, and prognostic utilities. Through the pair of studies reported in Chapter 3 and Chapter 4, (1) the utility of existing case definitions of mild cognitive impairment to identify not demented but cognitively impaired persons and subsequent progression to dementia, and (2) the clinical correlates differentiating between varying cognitive states were examined, respectively, in a population-based sample. While replicating previous findings suggesting that prevalence and conversion rates are dependent upon the case definition of mild cognitive impairment (e.g., Stephan et al., 2007), Study 1 added a description of the demographic and cognitive characteristics of persons captured by each classification and identified a subset of participants with a high conversion rate who failed to meet the criteria for any cognitive classification. The broadest case definition of mild cognitive impairment (i.e., CIND-2) identified the greatest proportion of not demented but cognitively impaired persons, but was not associated with the highest conversion rate – likely due to the heterogeneity of the sample. Nevertheless, the CIND-2 case definition was the only pre-defined cognitive classification to significantly predict dementia at follow-up. After correcting for attrition, conversion rates were highest for participants exhibiting both short-term and long-term memory impairment, as well as impairment in at least one other cognitive domain, confirming reports that multiple domain MCI represents a more advanced stage of pathological cognitive decline (Alexopoulos et al., 2006).

Several cognitively impaired participants did not meet the inclusion criteria for the selected pre-existing MCI diagnostic criteria in Study 1. This study is believed to be the first study to identify this group of persons with a high conversion rate who are not captured by existing criteria. As this group was associated with the highest conversion rate, clearly there is a need for alternative classification criteria, as existing criteria failed to capture this important group of at-risk individuals. To identify the underlying patterns of clinical characteristics that predict conversion to dementia among persons with cognitive impairment but who are not demented (including those who were not captured by existing criteria in Study 1), Study 2 stepped away from the traditional use of existing classification criteria for the identification of persons with MCI. In the absence of diagnostic restrictions, Study 2 investigated the clinical correlates that differentiated between NCI and CIND, not demented (i.e., NCI + CIND) and demented, and CIND non-converters and converters. The results indicated the significant contribution of neuropsychological performance, especially episodic memory functioning, in these distinctions. Performance on the enhanced Buschke free recall paradigm was a significant predictor of the target category in each of the three questions, confirming reports of impaired episodic memory as a predictor of conversion to dementia (Perri et al., 2007; Tierney et al., 2005; Tuokko et al., 1991). Despite greater variability of significant predictors differentiating CIND from NCI (Question 1), the importance of neuropsychological measures in correctly classifying participants was highlighted by the finding that seven of the eight predictors in the overall model were measures of cognitive function.

While the outcomes of specific case definitions of cognitive impairment vary, the importance of memory impairment in the prediction of future dementia was evident from the results of both studies. In Study 1, greater conversion rates were found for case definitions with a requisite memory criterion, compared to nonamnestic case definitions. In Study 2, episodic memory impairment, specifically poorer retrieval ability, significantly differentiated CIND from NCI, demented from not demented participants, and converters from non-converters. Given the five-year interval between baseline assessment and follow-up, these results suggest that retrieval deficits represent an early stage of cognitive impairment in the progression to dementia. The finding that retrieval was the sole significant predictor of conversion, compared to its status as one of several neuropsychological predictors of CIND in Question 1, is in line with reports of increasing impairment in episodic memory in more advanced stages of pathological decline (Mitrushina et al., 1994). Recall that, in Study 1, the majority of participants who progressed to dementia were diagnosed with a dementia of the Alzheimer's type (DAT). Early impairment in episodic memory is consistent with neuropathological changes in bilateral medial temporal regions of the brain associated with early AD (Braak, Griffing, Bohl, Bratzke, & Braak, 1999).

The finding that retrieval was the best and sole predictor of conversion may be explained by reports of accelerated decline in learning, as measured by free recall from an enhanced selective reminding paradigm, prior to a diagnosis of AD. The first point of acceleration is reported to occur approximately seven years prior to a diagnosis of AD, while the second substantial decrease in learning is noted in conjunction with a decline in executive function 2-3 years prior to a diagnosis of AD (Grober et al., 2008). The implicit heterogeneity of the CIND sample likely accounts for the absence of impaired executive function as a significant predictor of conversion. In addition to etiological heterogeneity, temporal heterogeneity of cognitive impairment may also be reflected in the results as the onset of impaired cognitive function was not evaluated.

The results of Study 1 support the report of limited additive value of intact functional ability and subjective reports of memory changes criteria in population-based studies of mild cognitive impairment (Fisk et al., 2003). In contrast, proxy report of memory changes was a significant predictor of cognitive status when differentiating CIND from NCI and demented from not demented participants. Importantly, proxy report of memory changes was not the sole predictor to differentiate between cognitive statuses; rather, interactions with other measures of cognitive ability were noted. Similarly, while functional ability was a significant predictor in the differentiation of CIND from NCI and converters from non-converters, it was not included in the overall predictive algorithms, suggesting that functional disability may be secondary to cognitive decline. This conclusion is supported by previous research using CSHA data wherein, although occurring simultaneously, impaired cognitive function directed the appearance of functional deficits (Tuokko et al., 2005). Overall, these results provide a potential explanation for the variable utility of intact functional ability and proxy report of memory changes as criteria for mild cognitive impairment by suggesting that these criteria are not distinct entities. Rather, intact functional ability and proxy report of memory impairment appear to exist in association with or secondary to other, more significant, predictors.

These studies, comparing pre-existing case definitions of MCI and CIND and identifying the clinical correlates of varying stages of cognitive impairment, are important from both theoretical and clinical perspectives. Theoretically, the development of prevention strategies for the pathological cognitive decline to dementia is reliant on the ability to accurately identify persons at-risk for incipient dementia. Clinically, the early identification of persons at risk for cognitive decline would allow for the implementation of preventative strategies and for the patient and their family to engage in decision-making planning. The results of this pair of studies address the diversity of case definitions of mild cognitive impairment. Overall, while some were better than others, none of the pre-defined MCI or CIND case definitions were associated with 100% accuracy in identifying persons at-risk for incipient dementia in population-based sample. This finding is believed to reflect different temporal stages of cognitive decline among participants. Moreover, while neuropsychological performance, especially retrieval, was significantly predictive of conversion to dementia, none of the algorithms captured all participants who progressed to dementia. As such, it is recommended that these results, specifically the significant predictors of conversion, serve as markers for continued clinical and neuropsychological monitoring; rather than as diagnostic criteria for conversion.

In sum, these results suggest that the architecture of the pathological cognitive decline to dementia may not be captured by a single set of diagnostic criteria. It is important to note that the results of this study are limited by their associated inclusion and exclusion criteria. Replication of these findings in different population and clinical samples is recommended. Moreover, while Study 2 examined several possible risk factors for cognitive impairment, the study is limited by its lack of biological and neuroimaging predictors. These may include elevated phosphorylated tau in the CSF (e.g., Bouwman et al. 2007; Buerger et al., 2005; Fellgiebel et al., 2007), elevated ApoE ε4 allele levels (e.g., Frikke-Schmidt et al., 2001; Hsiung et al., 2004; Baum et al., 2006), MRI for medial temporal atrophy (e.g., Bouwman et al., 2007; DeCarli et al., 2007), and PET-FDG for level of cortical glucose metabolism (Fellgiebel et al., 2007). It is recommended that future studies incorporate these markers among the predictors. Clinicians are cautioned against only monitoring persons who meet existing MCI criteria. For patients failing to meet MCI criteria, it is recommended that clinicians carefully monitor patients demonstrating functional impairments, difficulty with episodic memory, proxy report of memory difficulties or personality changes, sensory impairment, and a history of cerebrovascular incidents. Given the noted importance of neuropsychological predictors of cognitive decline and conversion, referral for neuropsychological evaluation and subsequent monitoring is recommended for persons exhibiting the aforementioned impairments.

Bibliography

Albert, S.M., Michaels, K., Padilla, M., Pelton, G., Bell, K., Marder, K., Stern, Y., & Devanand, D.P. (1999). Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis. *American Journal of Geriatric Psychiatry, 7*, 213-220.

Albert, M.A., Moss, M.B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society, 7*, 631-639.

Alexopoulos, P., Gimmer, T., Perneczky,R., Domes, G., & Kurz, A. (2006). Progression to dementia in clinical subtypes of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 22*, 27-34.

Alladi, S., Arnold, R., Mitchell, J., Nestor, P., & Hodges, J.R. (2006). Mild cognitive impairment: Applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychological Medicine, 36*, 1-9.

American Psychiatric Association. (1987). Diagnostic *and statistical manual of mental disorders (3rd – revised ed.).* Washington, DC: Author.

American Psychiatric Association. (2000). Diagnostic *and statistical manual of mental Disorders: Text Revision (4th ed.).* Washington, DC: American Psychiatric Association

Amieva, H., Jacqmin-Gadda, H., Orgogozo, J.M., Le Carret, N., Helmer, C., Letenneur, L., et al. (2005). The 9 year cognitive decline before dementia of the Alzheimer type : A prospective population-based study. *Brain, 128*, 1093-1101

Artero, S., Petersen, R., Touchon, J., & Ritchie, K. (2006). Revised criteria for mild cognitive impairment: Validation within a longitudinal population study. *Dementia and Geriatric Cognitive Disorders, 22*, 465-470.

Bäckman, L., Jones, S., Berger, A.K., Laukka, E.J., Small, B.J. (2004). Multiple cognitive deficits during transition to Alzheimer's disease. *Journal of Internal Medicine, 256*, 195-204.

Bamford, K.A., & Caine, E.D. (1988). Does "benign senescent forgetfulness" exist? *Clinics in Geriatric Medicine, 4*, 897-916.

Baum, L., Lam, L.C.W., Lee, G., Chiu, H.F.K., Mok, V.C.T., Wong, A., et al. (2006). Apolipoprotein E ε4 allele is associated with vascular dementia. *Dementia and Geriatric Cognitive Disorders, 22*, 301-305.

Benton, A.L. (1974). Revised *Visual Retention Test: Clinical And Experimental Applications*. New York: Psychological Corporation.

Berg, L., Danziger, W., Storandt, M., Coben, L., Gado, M., Hughes, C.P., et al. (1984). Predictive features in mild senile dementia of the Alzheimer type. *Neurology, 34*, 563-569.

Blacker, B., Lee, H., Muzikansky, A., Martin, E.C., Tanzi, R., McArdle, J.J., et al. (2007). Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Archives of Neurology, 64*, 862-871.

Blackford, R.C., & La Rue, A. (1989). Criteria for diagnosing age-associated memory impairment: Proposed improvements from the field. *Developmental Neuropsychology, 5,* 295-306.

Bond, J., & Corner, L. (2006). Mild cognitive impairment: Where does it go from here? *Philosophy, Psychiatry, & Psychology, 13*, 29-30.

Boston, P.F., Dennis, M.S., & Jagger, C. (1999). Factors associated with vascular dementia in an elderly community population. *International Journal of Geriatric Psychiatry, 14*, 761-766.

Bouwman, F.H., Schoonenboom, S.N.M., & van der Flier, W.M. (2007). CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. *Neurobiology of Aging, 28*, 1070-1074.

Bozoki, A., Giordani, B., Heidebrink, J., Berent, S., & Foster, N. L. (2001). Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Archives of Neurology, 58*, 411-416.

Brayne, C., & Calloway, P. (1988). Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: A continuum? *Lancet, 331*, 1265-1267.

Buerger, K., Ewers, M., Andreasen, N., Zinkowski, R., Ishiguro, K., Vanmechelen, E., et al. (2005). Phosphorylated tau predicts rate of cognitive decline in MCI subjects: A comparative CSF study. *Neurology,65*, 1502-1510. Buschke, H. (1984). Cued recall in amnesia. *Journal of Clinical Neuropsychology, 6*, 433-440.

Buschke, H. (1984). Cued recall in amnesia. *Journal of Clinical Neuropsychology, 6*, 433-440.

Busse, A., Angermeyer, M.C., & Riedel-Heller, S.G. (2006). Progression of mild cognitive impairment to dementia: A challenge to current thinking. *British Journal of Psychiatry, 189*, 399-404.

Busse, A., Bischkopf, J., Riedel-Heller, S. G., & Angermeyer, M. C. (2003). Subclassification for mild cognitive impairment: Prevalence and predictive validity. *Psychological Medicine, 33*, 1029-1038.

Busse, A., Hensel, A., Gühen, U., Angermeyer, M.C., & Riedel-Heller, S.G. (2006). Mild cognitive impairment: Long-term course of four clinical subtypes. *Neurology, 67*, 2176-2185.

Canadian Study of Health and Aging Working Group. (1994). Canadian Study of Health and Aging: Study methods and prevalence of dementia. *Canadian Medical Association Journal, 150*(6), 899-913.

Canadian Study of Health and Aging Working Group. (2000). The incidence of dementia in Canada. *Neurology, 55*, 66-73.

Chen, P., Ratcliff, G., Belle, S.H., Cauley, J.A., DeKisky, S.T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease. *Archives of General Psychiatry, 58*, 853-858.

Churchill, J.D., Galvez, R., Colcombe, S., Sain, R.A., Kramer, A.F., & Greenough, W.T. (2002). Exercise, experience and the aging brain. Neurobiology of Aging, 23, 941-955.

Clément, F.C., Belleville, S., & Gauthier, S. (2008). Cognitive complaint in mild cognitive impairment and Alzheimer's disease. *Journal of the International Neuropsychological Society, 14*, 222-232.

Collie, A., Maruff, P., Shariq-Antonacci, R., Smith, M., Hallup, M., Schofield, P.R., Master, C.L., & Currie, J. (2001). Memory decline in healthy older people: Implications for identifying mild cognitive impairment. *Neurology, 56*, 1533-1538.

Crook, T., Bartus, R.T., Ferris, S.H. (1986). Age associated memory impairment: proposed diagnostic criteria and measures of clinical change: Report of a National Institute of Mental Health group. *Developmental Neuropsychology, 2*, 261-276.

Crossley, M., D'Arcy, C., Rawson, N.S.B. (1997). Letter and category fluency in community-dwelling Canadian seniors: A comparison of normal participants to those with dementia of the Alzheimer or vascular type. *Journal of Clinical and Experimental Neuropsychology, 19*, 52-62.

Cummings, J.L., Vinters, H.V., Cole, G.M., & Khachaturian, Z.S. (1998). Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology, 51 (Suppl.1)*, S2-S17.

Davis, H. S., & Rockwood, K. (2004). Conceptualization of mild cognitive impairment: A review. *International Journal of Geriatric Psychiatry, 19*, 313-319.

DeCarli, C., Frisoni, G.B., Clark, C.M., Harvey, D., Grundman, M., Petersen, R.C., et al. (2007). Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Archives of Neurology, 64*, 108-115.

Devanand, D.P., Folz, M., Gorlyn, M, Moeller, J.R., & Stern, Y. (1997). Questionable dementia: Clinical course and predictors of outcome. *Journal of the American Geriatrics Society, 45*, 321-328.

Devanand, D.P., Pelton, G.H., Zamora, D., Liu, X., Tabert, M.H., Goodkind, M. (2005). Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Archives of Neurology, 62*, 975-980.

Di Carlo, A., Baldereschi, M., Amaducci, L., Maggi, S., Grigoletto, F., Scarlato, G., et al. (2000). Cognitive impairment without dementia in older people: Prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *Journal of the American Geriatrics Society, 48*, 775-782.

Di Carlo, A., Lamassa, M., Baldereschi, M., Inzitari, M., Scafato, E., Farchi, G., & Inzitari, D. (2007). CIND and MCI in the Italian elderly: Frequency, vascular risk factors, progression to dementia. *Neurology, 68*, 1909-1916.

Ebly, E. M., Hogan, D. B., & Parhad, I. M.1995. Cognitive impairment in the nondemented elderly: Results from the Canadian Study of Health and Aging. *Archives of Neurology, 52*, 612-619.

Fellgiebel, A., Scheurich, A., Bartenstein, P., & Müller, M. (2007). FDG-PET and CSF phospho-tau for prediction of cognitive decline in mild cognitive impairment. *Psychiatry Research: Neuroimaging, 155*, 167-171.

Fisk, J. D., Merry, H. R., & Rockwood, K. (2003). Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology, 61*, 1179-1184.

Fleisher, A.S., Sowell, B.B. Taylor, C., Gamst, A.C., Petersen, R.C., & Thal, L.J. (2007). Clinical predictors of progression to Alzheimer disease in amnestic mild cognitive impairment. *Neurology, 68*, 1588-1595.

Frikke-Schmidt, R., Nordestgaard, B.G., Thudium, D., Moes Grøholdt, M.-L., & Tybjærg-Hansen, A. (2001). APOE genotype predicts AD and other dementia but not ischemic cerebrovascular disease. *Neurology, 56*, 194-200.

Gabryelewicz, T., Styczynska, M., Luczywek, E., Barczak, A., Pfeffer, A., Androsiuk, W., et al. (2007). The rate of conversion of mild cognitive impairment to dementia : Predictive role of depression. *International Journal of Geriatric Psychiatry, 22*, 563-567.

Geerlings, M.I., Jonker, C., Bouter, L.M., Adèr, H.J., & Schmand, B. (1999). Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *American Journal of Psychiatry, 156*, 531-537.

Graham, J.E., Rockwood, K., Beattie, B.L., Eastwood, R., Gauthier, S., Tuokko, H., & McDowell, I. (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet, 349,* 1793-1796.

Griffith, H.R., Netson, K.I., Harrell, L.E., Zamrini, E., Brockington, J.C., & Marson, D.C. (2006). Amnestic mild cognitive impairment: Diagnostic outcomes and clinical prediction over a two-year time period. *Journal of the International Neuropsychological Society, 12*, 166-175.

Grober, E., Hall, C.B., Lipton, R.B., Zonderman, A.B., Resnick, S.M., & Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 14*, 266-278.

Grober, E., Lipton, R., Hall, C., & Crystal, H. (2000). Memory impairment on free and cued selective reminding predicts dementia. *Neurology, 54*, 827-832.

Hall, C.B, Lipton, R.B., Sliwinski, M, & Stewart, W.F. (2000). A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease. *Statistics in Medicine, 19*, 1555-1566.

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

Hayden, K.M., Zandi, P.P., Lyketsos, C.G., Khachaturian, A.S., Bastian, L.A., Charoonruk, G., Tschanz, J.T., et al. (2006). Vascular risk factors for incident Alzheimer disease and vascular dementia: The Cache County Study. *Alzheimer Disease and Associated Disorders, 20*, 93-100.

Helliwell, B, Aylesworth, R., McDowell, I., Baumgarten, M., & Sykes, E. (2001). Correlates of nonparticipation in the Canadian Study of Health and Aging. *International Psychogeriatrics, 13*, 49-56.

Howieson, D.B., Carlson, N.E., Moore, M.M., Wasserman, D., Abendroth, C.D., Payne-Murphy, J., & Kaye, J.A. (2008). Trajectory of mild cognitive impairment. *Journal of the International Neuropsychological Society, 14*, 192-198.

Hsiung, G.R., Sadonick, A.D., & Feldman, H. (2004). Apolipoprotein E 84 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *Canadian Medical Association Journal,171,* 863-867.

Ishikawa, T., & Ikeda, M. (2007). Mild cognitive impairment in a population-based epidemiological study. *Psychogeriatrics, 7*, 104-108.

James, K.E., White, R.F., & Kraemer, H.C. (2005). Repeated split sample validation to assess logistic regression and recursive partitioning: An application to the prediction of cognitive impairment. *Statistics in Medicine, 24*, 3019-3035.

Jorm, A.F., Christensen, H., Korten, A.E., Henderson, A.S., Jacomb, P.A., & MacKinnon, A. (1997). Do cognitive complaints either predict future cognitive decline or reflect past cognitive decline? A longitudinal study of an elderly community sample. *Psychological Medicine, 27*, 91-98.

Kluger, A., Ferris, S.H., Golomb, J., Mittelman, M.S., & Reisberg, B. (1999). Neuropsychological prediction of decline to dementia in nondemented elderly. *Journal of Geriatric Psychiatry and Neurology, 12*, 168-179.

Kral, V. A. (1962). Senescent forgetfulness: Benign and malignant. *Canadian Medical Association Journal, 86*(6), 257-260.

Kral, V. A., & Müller, H. (1966). Memory dysfunction: A prognostic indicator in geriatric patients. *Canadian Psychiatric Association Journal, 11*(4), 343-349.

Kramer, J.H., Nelson, A., Johnson, J.K., Yaffe, K., Glenn, S., Rosen, H.J., & Miller, B.L. (2006). Multiple cognitive deficits in amnestic mild cognitive impairment. *Gementia and Geriatric Cognitive Disorders, 22*, 306-311.

Kumamoto, T., Sannomiya, K., Ueyama, H., Aoki, K., Nakashima, T., Nakamura, R., & Tsuda, T. (2000). Neurological abnormalities in cognitively impaired but not demented elderly. *Acta Neurologica Scandinavica, 102*, 292-298.

Larrea, F.A., Fisk, J.D., Graham, J.E., & Stadnyk, K. (2000). Prevalence of cognitive impairment and dementia as defined by neuropsychological test performance. *Neuroepidemiology, 19*, 121-129.

Larrieu, S., Letenneur, L., Orgogozo, J. M., Fabrigoule, C., Amieva, H., Le Carret, N., et al. (2002). Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology, 59*, 1594-1599.

Launer, L.J., Andersen, K., Dewey, M.E., Letenneur, L., Ott, A., Amaducci, L.A., Brayne, C., et al. (1999). Rates and risk factors for dementia and Alzheimer's disease: Results from the EURODEM pooled analyses. *Neurology, 52*, 78-84.

Levy, R. (1994). Aging-associated cognitive decline. *International Psychogeriatrics, 6*, 63-68.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). Neuropsychological *assessment* (3rd ed.). New York : Oxford University Press.

Lindsay, J., Sykes, E., McDowell, I., Verreault, R., & Laurin, D. (2004). More than the epidemiology of Alzheimer's disease: Contributions of the Canadian Study of Health and Aging. *Canadian Journal of Psychiatry, 49*, 83-91.

Lockwood, K.A., Alexopulos, G.S., & van Gorp, W.G. (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry, 159*, 1119-1126.

Loewenstein, D.A., Acevedo, A., Agron, J., & Duara, R. (2007). Stability of neurocognitive impairment in different subtypes of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 23*, 82-86.

Lopez, O.L., Jagust, W.J., Dulberg, C., Becker, J.T., DeKosky, S.T., Fitzpatrick, A., et al. (2003). Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 2. *Archives of Neurology, 60*, 1394-1399.

Loh, W.-Y., & Shih, Y.-S. (1997). Split selection methods for classification trees. *Statistica Sinica, 7*, 815-840.

Low, L.-F., Brodaty, H., Edwards, R., Kochan, N., Draper, B., Trollor, J., et al. (2004). The prevalence of 'cognitive impairment no dementia' in community-dwelling elderly: A pilot study. *Australian & New Zealand Journal of Psychiatry, 38*, 725-731.

McDowell, I., Xi, G., Lindsay, J., & Tuokko, H. (2004). Canadian Study of Health and Aging: Study description and patterns of early cognitive decline. *Aging, Neuropsychology, and Cognition, 11*, 149-168.

Monastero, R., Palmer, K., Qiu, C., Winblad, B., & Fratiglioni, L. (2007). Heterogeneity in risk factors for cognitive impairment, no dementia: Population-based longitudinal study from the Kungsholmen Project. *American Journal of Geriatric Psychiatry, 15*, 60-69.

Monsch, A.U., Bondi, M.W., Butters, N., Salmon, D.P., Katzman, R., & Thai, L.J. (1992). Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. *Archives of Neurology, 49*, 1253-1258.

Morris, J.C. (2006). Mild cognitive impairment is early-stage Alzheimer disease: Time to revise diagnostic criteria. *Archives of Neurology, 63*, 15-16.

Morris, J.C., & Storandt, M. (2006). Detecting early-stage Alzheimer's disease in MCI and PreMCI: The value of informants. In M. Jucker, K. Beyreuther, C. Haass, & Y. Christen (Eds.). *Alzheimer: 100 Years and Beyond, Research and Perspectives in Alzheimer's Disease* (pp. 392-397). Heidelberg, Berlin: Springer-Verlag.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., & Berg, L. (2001). Mild cognitive impairment represents early-state Alzheimer disease. *Archives of Neurology, 58*, 397-405.

Mortimer, J.A., Snowdon, D.A., & Markesbery, W.R. (2003). Head circumference, education and risk of dementia: Findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology, 25*, 671-679.

Mundt, J.C., Freed, D.M., & Greist, J.H. (2000). Lay person-based screening for early detection of Alzheimer's disease: Development and validation of an instrument. *Journal of Gerontology: Psychological Sciences, 55B*, P163-P170.

Palmer, K., Bäckman, L., Small, B.J., & Fratiglioni, L. (2006). Cognitive impairment in elderly persons without dementia: Findings from the Kungsholmen Project. In H.A. Tuokko & D.F. Hultsch (Eds.), *Mild Cognitive Impairment: International Perspectives* (pp.57-75). New York, NY: Taylor and Francis.

Perri, R., Serra, L., Carlesimo, G.A., Caltagirone, C., & the Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease. Preclinical dementia: An Italian multicentre study on amnestic mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 23*, 289-300.

Perneczky, R., Pohl, C., Sorg, C., Harmann, J., Tosic, N., Grimmer, T., Heitele, S., & Kurz, A. (2006). Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. *International Journal of Geriatric Psychiatry, 21*, 158-162.

Peters, K.R., Graf, P., Hayden, S., & Feldman, H. (2004). Neuropsychological characterization of cognitive-impaired-not-demented (CIND) individuals: Clinical comparison data. *The Clinical Neuropsychologist, 18*, 208-228.

Petersen, R. C. (2003). Conceptual overview. In R. C. Petersen (Ed.), *Mild Cognitive Impairment: Aging to Alzheimer's Disease* (pp. 1-14). London: Oxford University Press.

Petersen, R.C. (2006). Conversion. *Neurology, 67*, S12-S13.

Petersen, R.C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183-194.

Petersen, R.C., & Knopman, D.S. (2006). MCI is a clinically useful concept. *International Psychogeriatrics, 18*, 394-402.

Petersen, R., & O'Brien, J. (2006). Mild cognitive impairment should be considered for DSM-V. *Journal of Geriatric Psychiatry and Neurology, 19*, 147-154.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*, 303-308.

Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., & DeKosky, S.T. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*, 1133-1142.

Pryse-Phillips, W., Aubé, M., Gawel, M., Nelson, R., Purdy, A., & Wilson, K. (2002). A headache diagnosis project. *Headache, 42*, 728-737.

Purser, J.L., Fillenbaum, G.G., Pieper, C.F., & Wallace, R.B. (2005). Mild cognitive impairment and 10-year trajectories of disability in the Iowa Established Populations for Epidemiologic Studies of the Elderly cohort. *Journal of the American Geriatric Society, 53*, 1966-1972.

Rasquin, S.M., Lodder, J., Visser, P.J., Lousberg, R., & Verhey, F.R. (2005). Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment : A 2-year follow-up study. *Dementia and Geriatric Cognitive Disoders, 19*, 113-119.

Ravaglia, G., Forti, F., Maioli, F., Martellia, M., Servadei, L., Brunetti, N., Dalmonte, E., et al. (2005). Incidence and etiology of dementia in a large elderly Italian population. *Neurology, 64*, 1525-1530.

Rediess, S., & Caine, E.D. (1996). Aging, cognition, and DSM-IV. *Aging, Neuropsychology, and Cognition, 3*, 105-117.

Reisberg, B. (1986). Dementia: A systematic approach to identifying reversible causes. *Geriatrics, 41*, 30-46.

Rey, A. (1964). *L'examen clinique en psychologie*. Paris: Presses Universitaires de France.

Ritchie, K., Artero, S., & Touchon, J. (2001). Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology, 56*, 37-42.

Ritchie, L.J., & Tuokko, H. (2007). Neuropsychological prediction of attrition due to death. *Journal of Clinical and Experimental Neuropsychology, 29*, 385-394.

Rosen, W.G. (1980). Verbal fluency in aging and dementia. *Journal of Clinical Neuropsychology, 2*, 135-146.

Roth, M., Huppert, F.A., Tym, E., et al. (1988). CAMDEX*: The Cambridge Examination for Mental Disorders of the Elderly.* Cambridge U Pr, Cambridge, England

Rountree, S.D., Waring, S.C., Chan, W.C., Lupo, P.J., Darby, E.J., & Doody, R.S. (2007). Importance of subtle amnestic and nonamnestic deficits in mild cognitive impairment: Prognosis and conversion to dementia. *Dementia and Geriatric Cognitive Disorders, 24*, 476-482.

Rozzini, L., Chilovi, B.V., Conti, M., Bertoletti, E., Delrio, I., Trabucchi, M., et al. (2007). Conversion of amnestic mild cognitive impairment to dementia of Alzheimer type is independent to memory deterioration. *International Journal of Geriatric Psychiatry, 22*, 1217-1222.

Smith, G., Ivnik, R.J., Petersen, R.C., Malec, J.F., Kokmen, E., & Tangalos, E. (1991). Age-associated memory impairment diagnoses: Problems of reliability and concerns about terminology. *Psychology and Aging, 6*, 551-558.

Smith, G. E., Petersen, R. C., Parisi, J. E., & Ivnik, R. J. (1996). Definition, course, and outcome of mild cognitive impairment. *Aging, Neuropsychology, & Cognition, 3*, 141-147.

Spaan, P.E.J., Raaijmakers, J.G.W., & Jonker, C. (2005). Early assessment of dementia: The contribution of different memory components. *Neuropsychology, 19*, 629-640.

Spreen, O., & Benton, A.L. (1977). Neurosensory *Center Comprehensive Examination for Aphasia: Manual of Instructions*. Victoria, BC.: University of Victoria.

SPSS. (1999). AnswerTree algorithm summary. Retrieved April 22, 2007, from the World Wide Web: http://www,sinster.com.tw/etdc/spss_paper/AnswerTreeAlgorithm.pdf

Stepaniuk, J., Ritchie, L., & Tuokko, H. (2008). Neuropsychiatric impairments as risk factors for Mild Cognitive Impairment and dementia. *American Journal of Alzheimer's Disease and Other Dementias, 23*, 326-333.

Stephan, B.C.M., Matthews, F.E., & KcKeith, I. (2007). Early cognitive change in the general population: How do different definitions work? *Journal of the American Geriatrics Society, 55*, 1534-1540

Stewart, M., McDowell, I., Hill, G., & Aylesworth, R. (2001). Estimating antemortem cognitive status of deceased subjects in a longitudinal study of dementia. *International Psychogeriatrics, 13*, 99-106.

Storandt, M., Grant, E.A., Miller, J.P., & Morris, J.C. (2006). Longitudinal course and neuropathological outcomes in original vs revised MCI and in pre-MCI. *Neurology, 67*, 467-473.

Talbert, M.H., Manly, J.J., Liu, X., Pelton, G., Rosenblum, S., Jacobs, M., et al. (2006). Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Archives of General Psychiatry, 63*, 916-924.

Teng, E.L., & Chui, H.C. (1989). The modified mini-mental state (3MS) examination. *Journal of Clinical Psychiatry, 48*, 314-318.

Tian, J., Bucks, R.S., Haworth, J., & Wilcock, G. (2003). Neuropsychological prediction of conversion to dementia from questionable dementia: Statistically significant but not yet clinically useful. *Journal of Neurology, Neurosurgery, and Psychiatry, 74* 433-438.

Tierney, M.C., Szalai, J.P., Snow, W.G., Fisher, R.H., Nores, A., Nadon, G., et al. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology, 46*, 661-665.

Tierney, M.C., Yao, C., Kiss, A., & McDowell, I. (2005). Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology, 64*, 1853-1859.

Trenberth, L., & Dewe, P. (2006). Understanding the experience of stressors: The use of sequential analysis for exploring the patterns between various work stressors and strain. *Work and Stress, 20*, 191-209.

Tuokko, H., & Crockett, D. (1989). Cued recall and memory disorders in dementia. *Journal of Clinical and Experimental Neuropsychology, 11*, 278-294.

Tuokko, H., & Frerichs, R.J. (2000). Cognitive impairment with no dementia (CIND): Longitudinal studies, the findings and issues. *The Clinical Neuropsychologist, 14*, 1-21.

Tuokko, H., Frerichs, R., Graham, J., Rockwood, K., Kristjansson, B., Fisk, J., Bergman, H., et al. (2003). Five-year follow-up of cognitive impairment with no dementia. *Archives of Neurology, 60*, 577-582.

Tuokko, H.A., Frerichs, R.J., & Kristjansson, B. (2001). Cognitive impairment, no dementia: Concepts and issues. *International Psychogeriatrics, 13 (Suppl.1)*, 183-202.

Tuokko, H., Kristjansson, E., & Miller, J. (1995). Neuropsychological detection of dementia: An overview of the neuropsychological component of the Canadian Study of Health and Aging. *Journal of Clinical and Experimental Neuropsychology, 17*, 352-373.

Tuokko, H., Morris, C., & Ebert, P. (2005). Mild cognitive impairment and everyday functioning in older adults. *Neurocase, 11*, 40-47.

Tuokko, H., Vernon-Wilkinson, R., Weir, J., & Beattie, B.L. (1991). Cued recall and Early identification of dementia. *Journal of Clinical and Experimental Neuropsychology, 13*, 871-879.

van Oijen, M., de Jong, F., Hofman, A., Koudstaal, P.J., & Breteler, M.M.B. (2007). Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimer's and Dementia, 3*, 92-97.

Verghese, J., Lipton, R.B., Hall, C.B., Kullansky, G., & Katz, M.J. (2003). Low blood pressure and the risk of dementia in very old individuals. *Neurology, 61*, 1667-1672.

Visser, P.J., & Verhey, F.R.J. (2008). Mild cognitive impairment as predictor for Alzheimer's disease in clinical practice: Effect of age and diagnostic criteria. *Psychological Medicine, 38*, 113-122.

Wechsler, D. (1974). Wechsler *Memory Scale.* New York: Psychological Corporation.

Wechsler, D. (1981). Wechsler *Adult Intelligence Scale – Revised*. New York: Psychological Corporation.

Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M.B., Ware, J.H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. Journal of the American Medical Association, 292, 1454-1461.

Winblad, B., Palmer, K., Kivipelto, M., Kivipelto, M., Jelic, V., & Fratiglioni, L., Wahlund, L.-O., et al. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*: 240-246.

World Health Organisation. (1992). *International statistical classification of diseases and related health problems* (10^{th} ed.). Geneva: Author.

Xu, W.L., Qiu, C.X., Wahlin, Å., Winblad, B., & Fratiglioni, L. (2004). Diabetes mellitus and risk of dementia in the Kungsholmen project: A 6-year follow-up study. *Neurology, 63*, 1181-1186.

Yamada, M., Sasaki, H., Mimori, Y, Kasagi, F., Sudoh, S., Ikeda, J., Hosoda, Y., et al. (1999). Prevalence and risks of dementia in the Japanese population: RERF's Adult Health Study Hiroshima subjects. *Journal of the American Geriatrics Society, 47*, 189-195.

Zaudig, M. (1992). A new systematic method of measurement and diagnosis of "Mild Cognitive Impairment" and dementia according to ICD-10 and DSM-III-R criteria. International Psychogeriatrics, 4(Suppl. 2), 203-219.

Appendix A

Study 1 – Revised Conversion Rates

Table 16. **Conversion Rates After Removing Participants Lost to Follow-Up**

Case Definition	% Demented
CI-Other	85.7
MCI-2	70.5
L_aMCImd	58.2
CIND-2	55.6
S_aMCImd	50.8
MCI-1	50.0
S_aMCIsd	50.0
CIND-1	48.2
L_aMCIsd	47.6
L_naMCIsd	33.3
S_naMCIsd	33.3
L_naMCImd	33.3
S_naMCImd	14.3
Robust NCI	11.8

Appendix B

Study 2 – Unpruned Classification Trees

Question 1 - Differentiating CIND from NCI

Figure 21. **Unpruned Demographic Classification Tree Differentiating CIND from NCI**

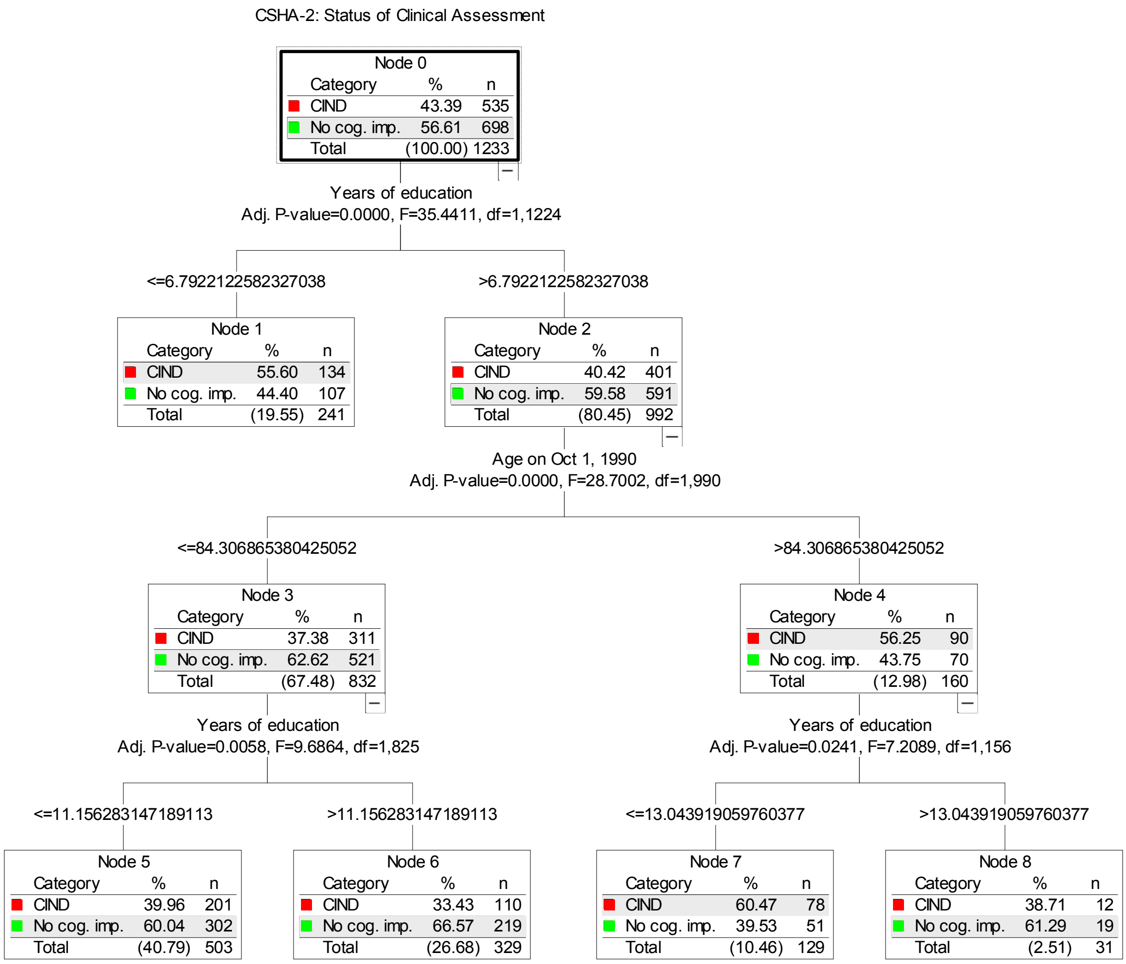


Figure 22. **Left Side of Unpruned Cognitive Classification Tree Differentiating CIND from NCI**

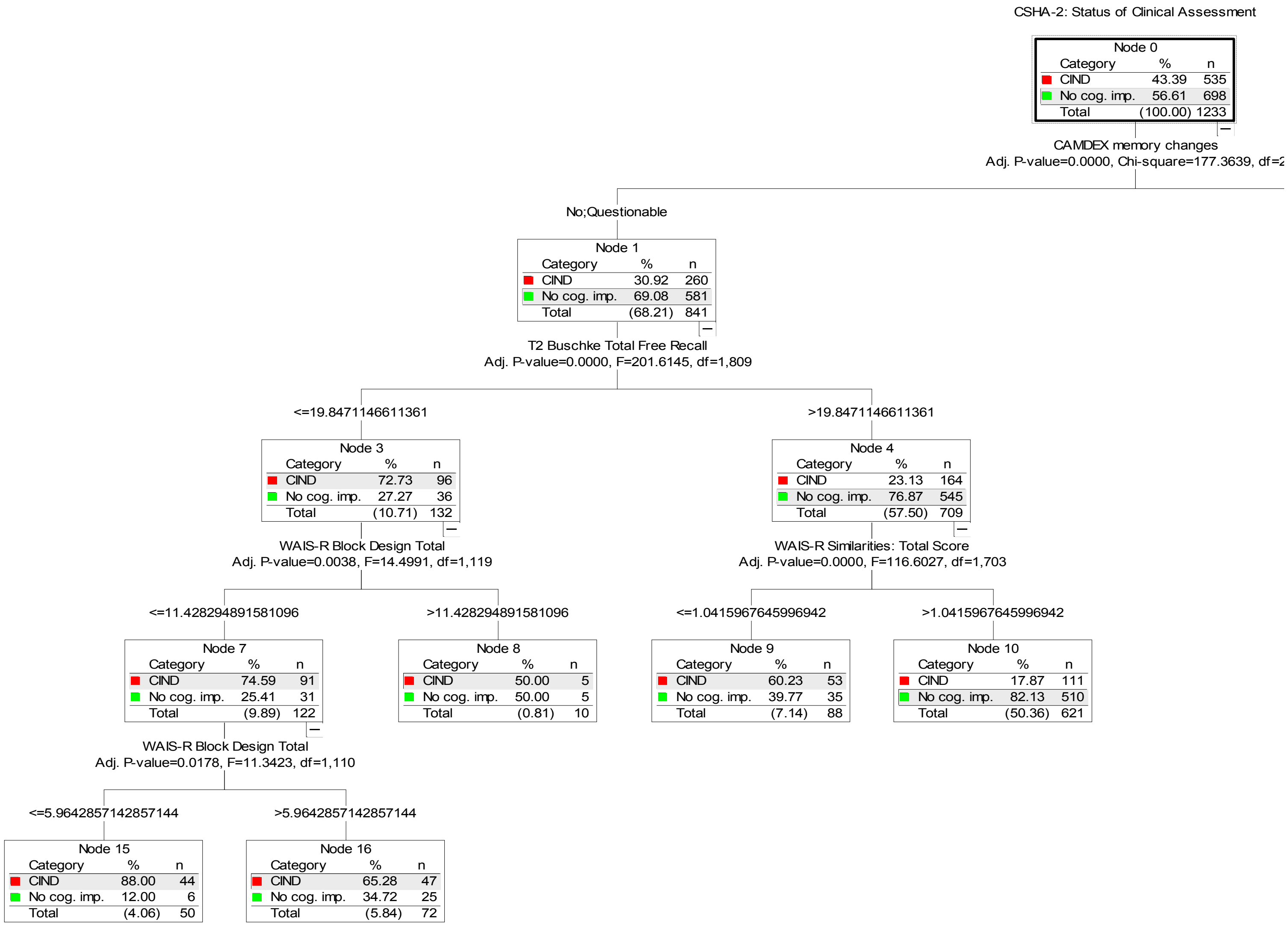


Figure 23. **Right Side of Unpruned Cognitive Classification Tree Differentiating CIND from NCI**

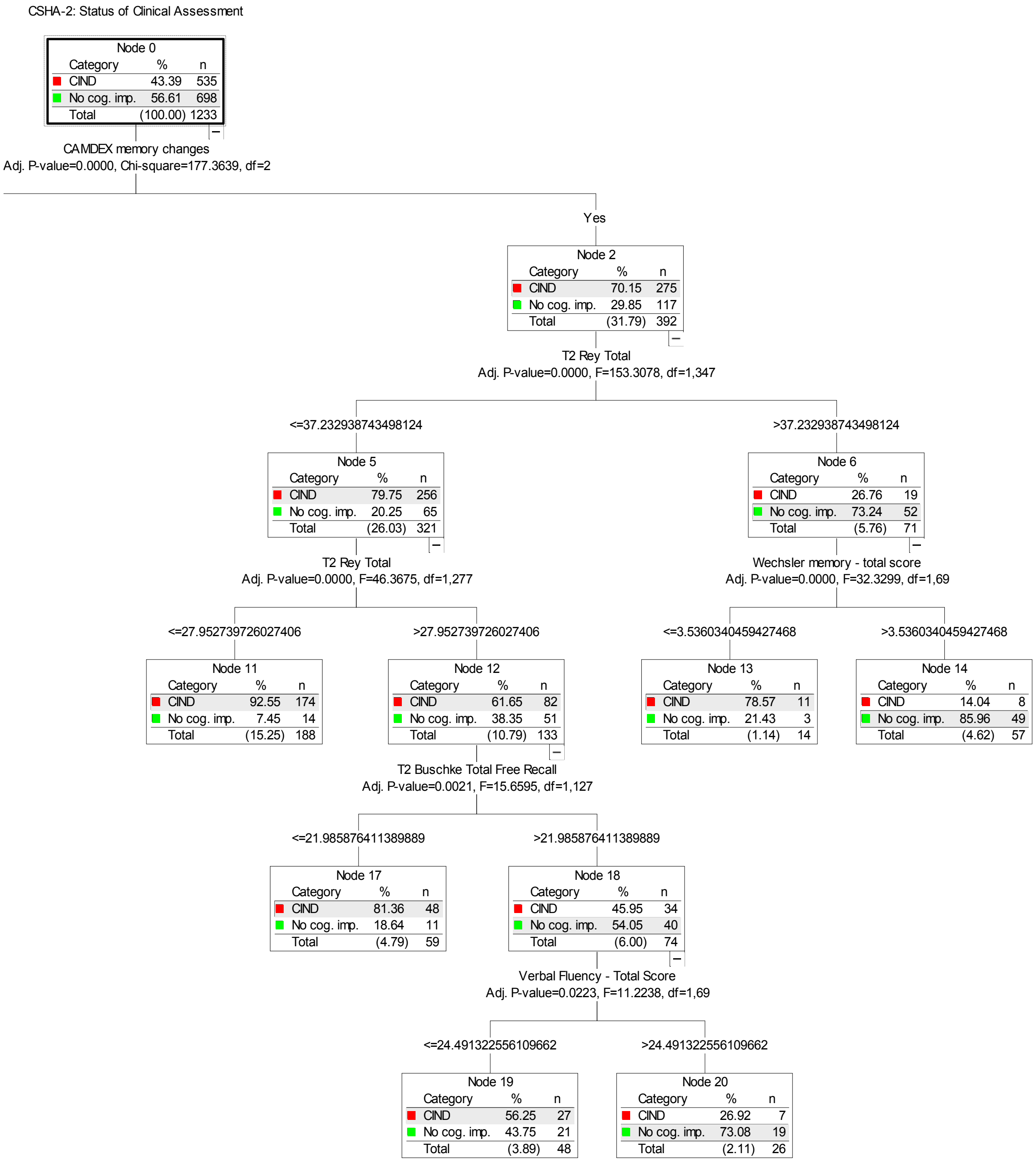


***Figure 24.* Unpruned Frailty/Morbidity Classification Tree Differentiating CIND from NCI**

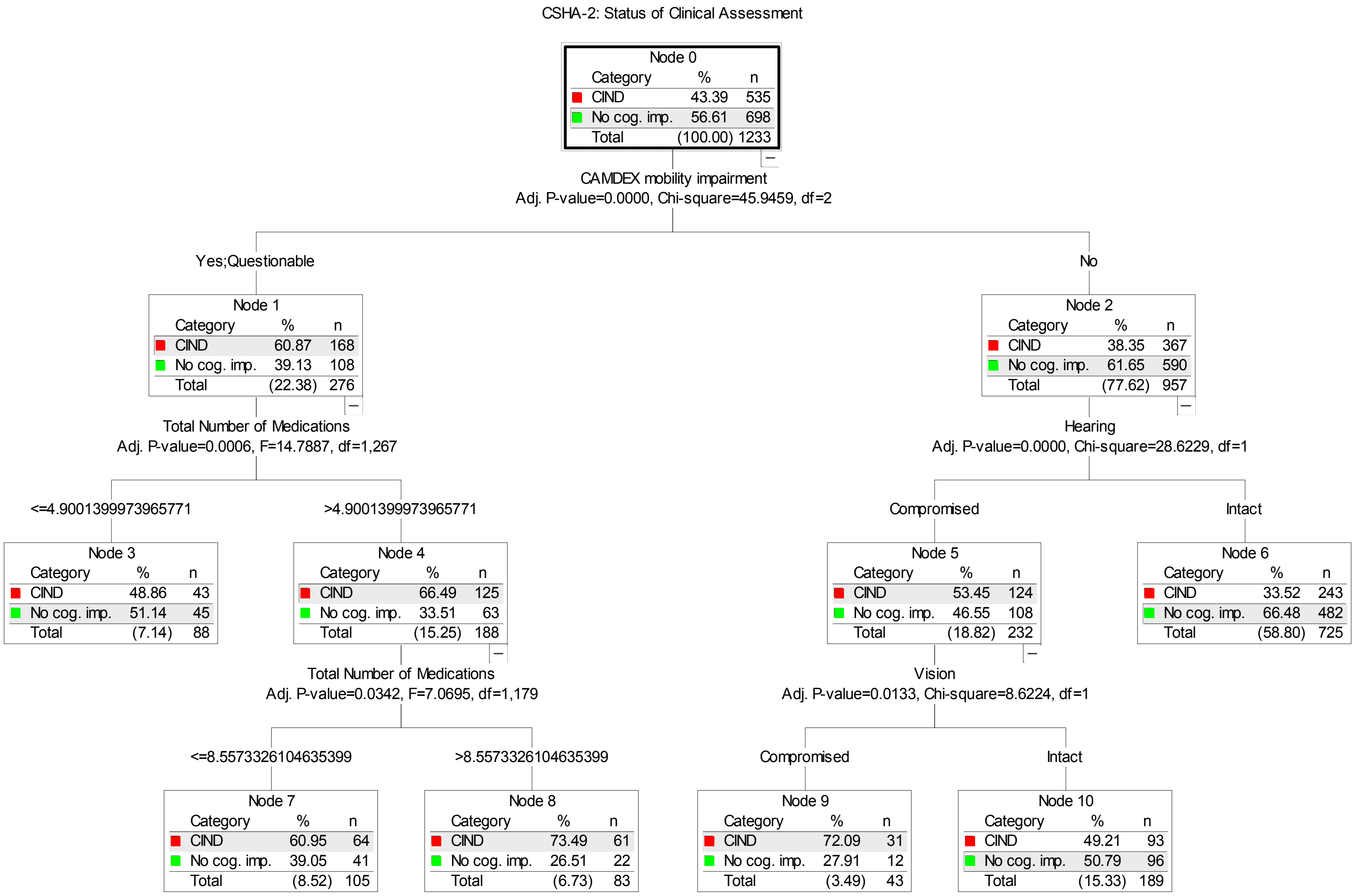


Figure 25. Unpruned Social/Physical Classification Tree Differentiating CIND from NCI

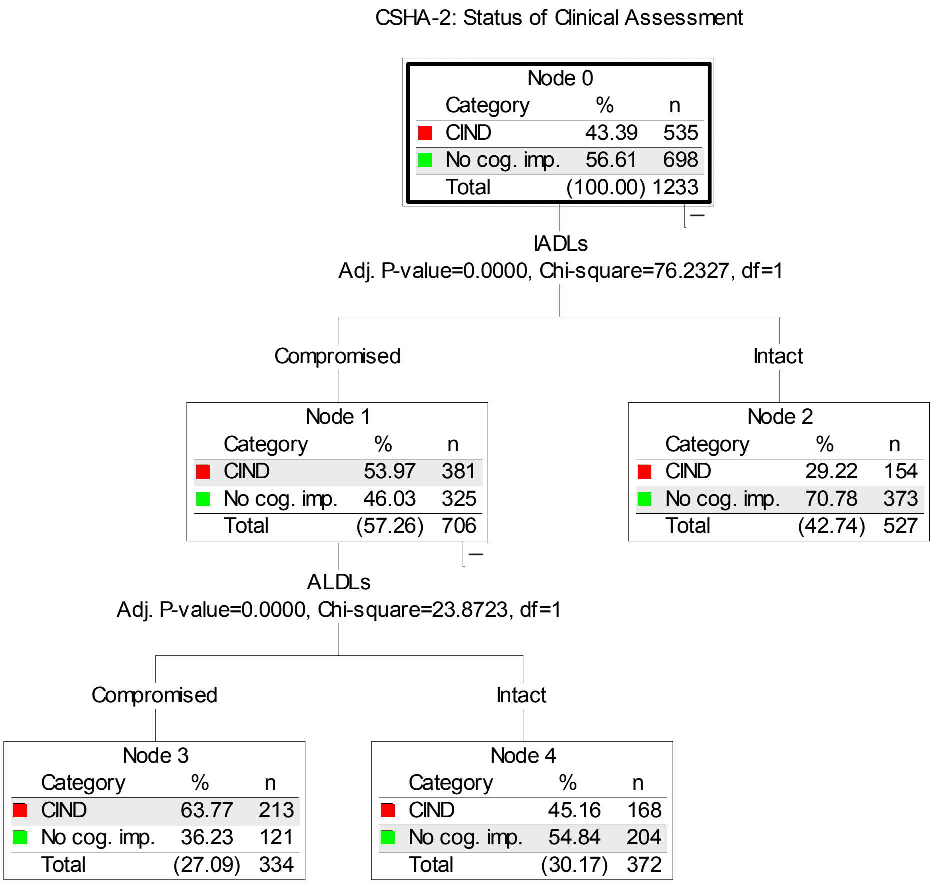


Figure 26. **Unpruned Neuropsychiatric Classification Tree Differentiating CIND from NCI**

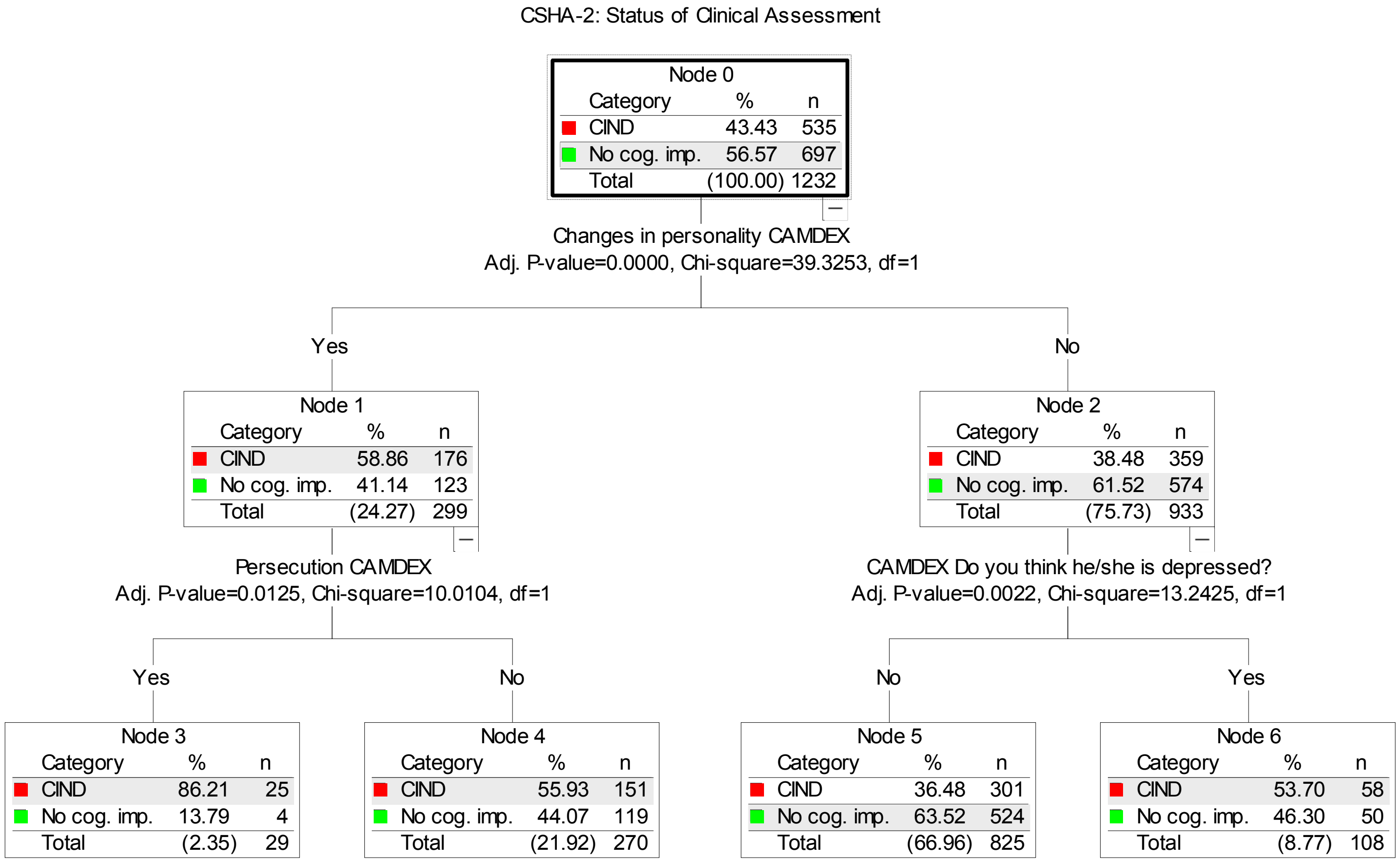


Figure 27. **Unpruned Vascular Classification Tree Differentiating CIND from NCI**

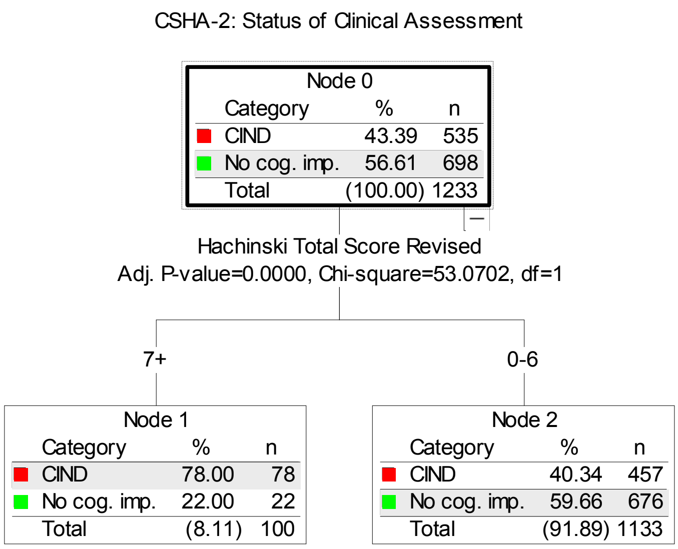
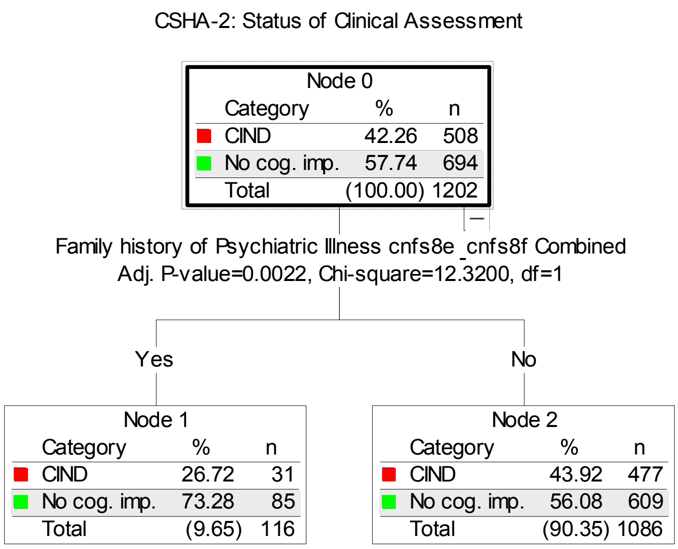


Figure 28. **Unpruned Family History Classification Tree Differentiating CIND from NCI**



Question 2 – Differentiating Demented (DEM) from Not Demented (NDEM) Participants

Figure 29. **Unpruned Demographic Classification Tree Differentiating DEM from NDEM**

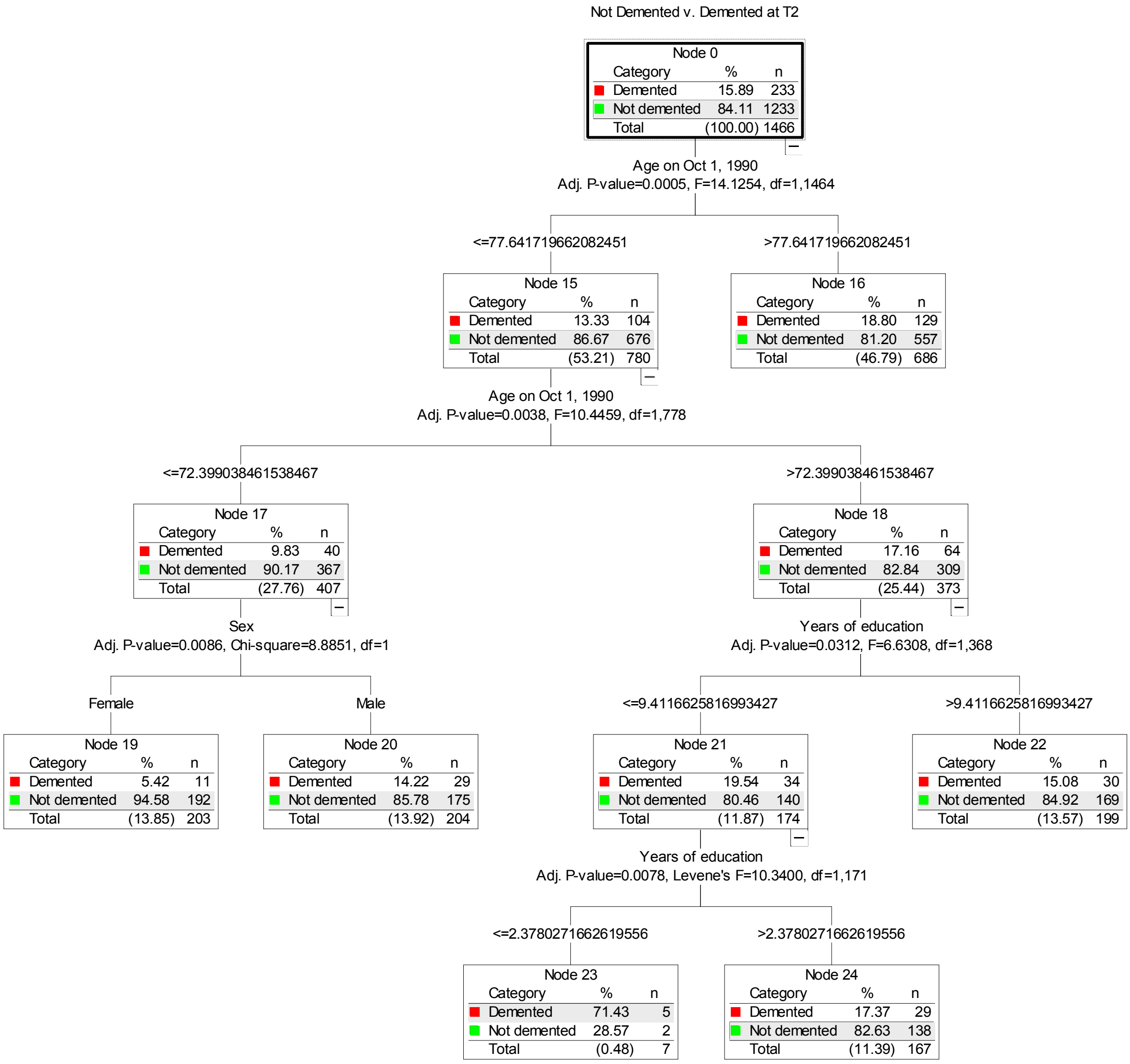


Figure 30. **Left Side of Unpruned Cognitive Classification Tree Differentiating DEM from NDEM**

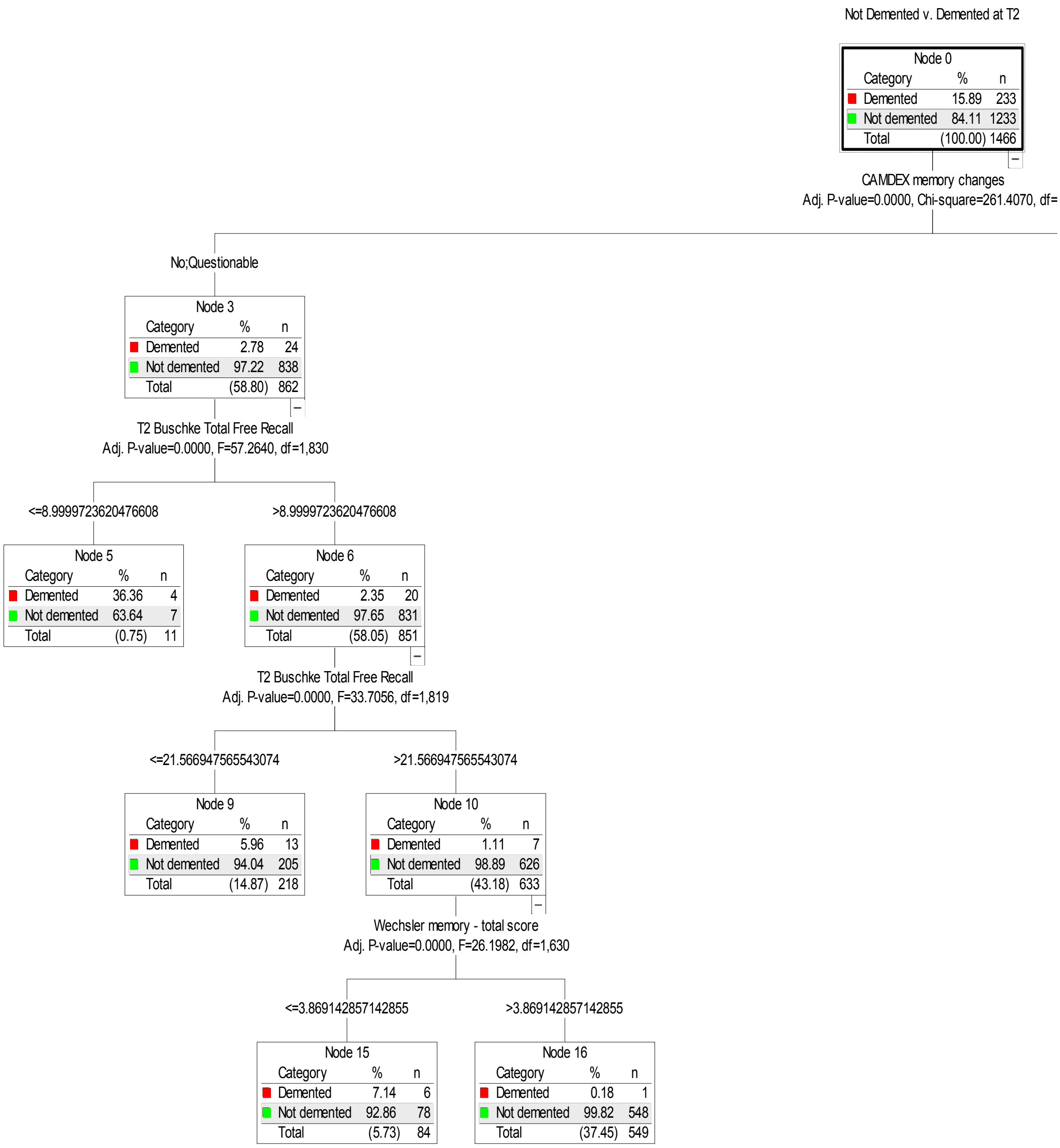


Figure 31. **Right Side of Unpruned Cognitive Classification Tree Differentiating DEM from NDEM**

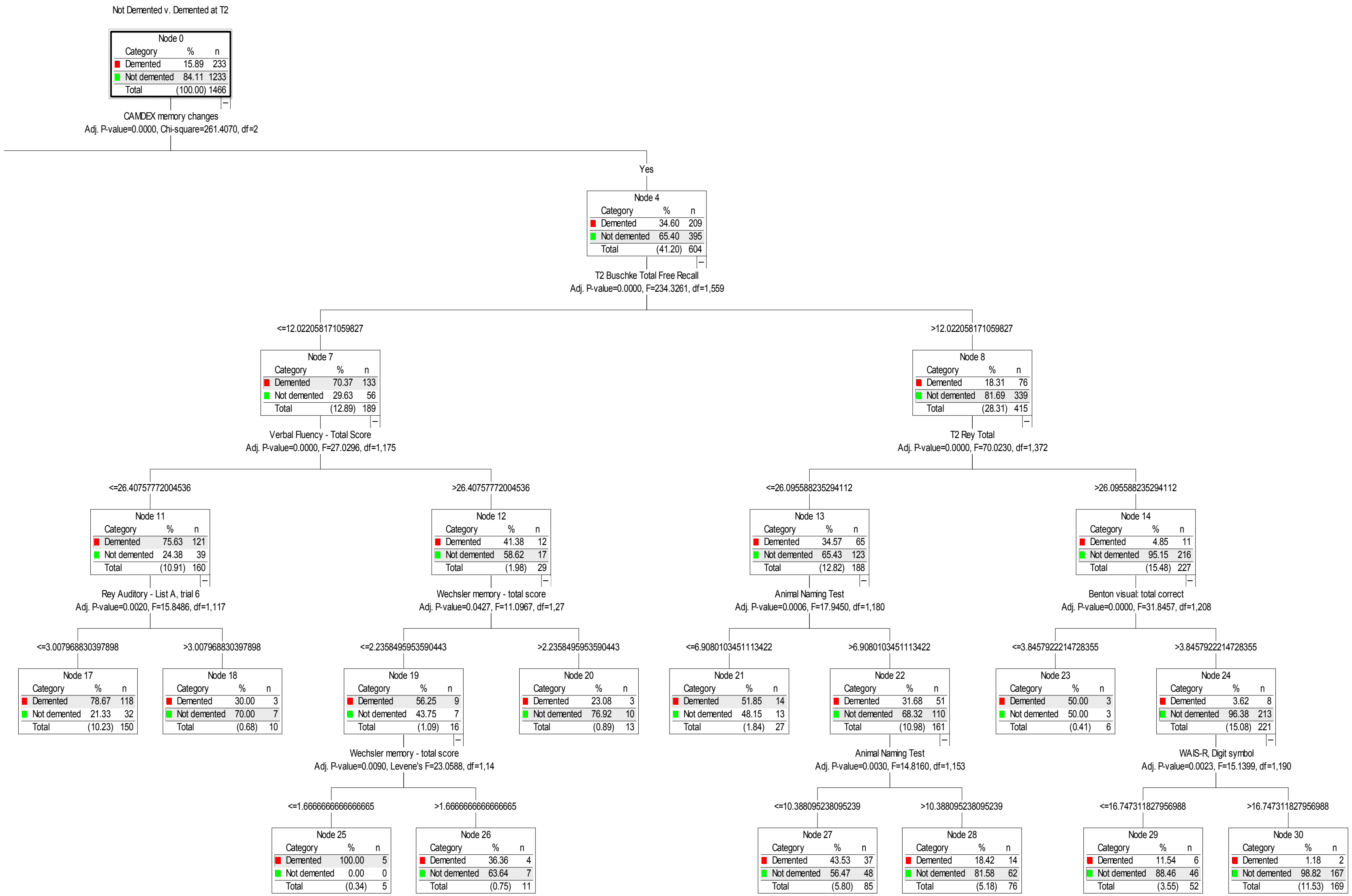


Figure 32. **Unpruned Frailty/Morbidity Classification Tree Differentiating DEM from NDEM**

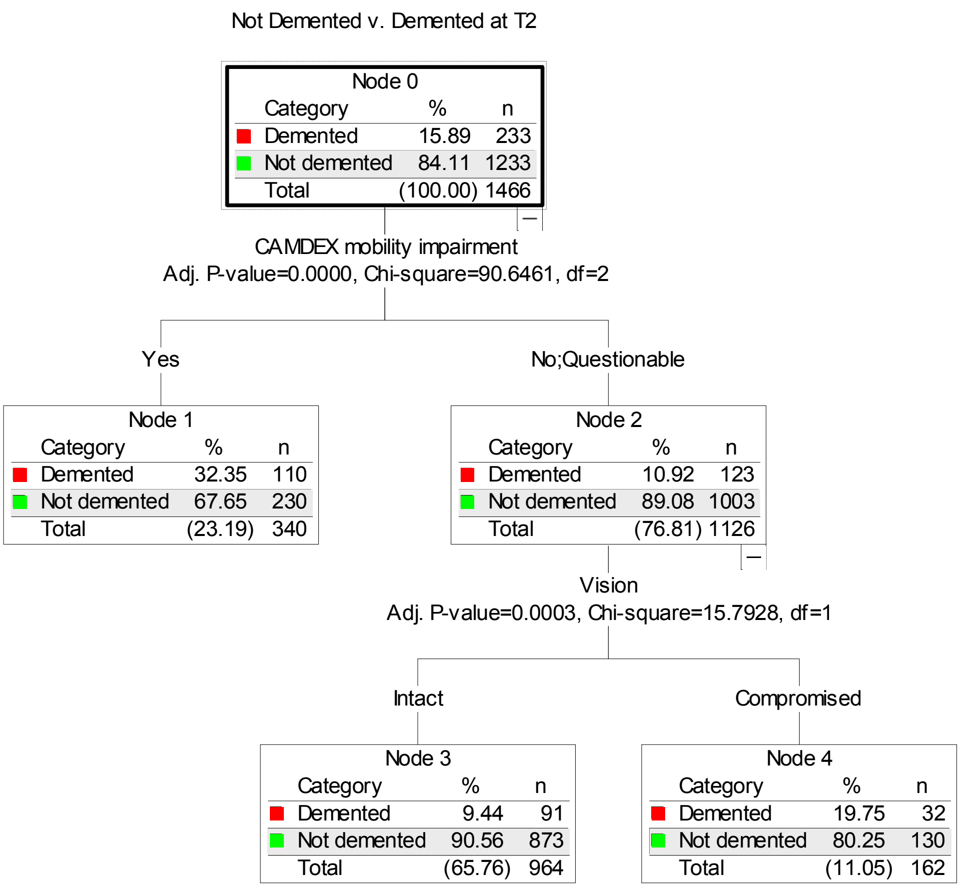


Figure 33. **Unpruned Social/Physical Classification Tree Differentiating DEM from NDEM**

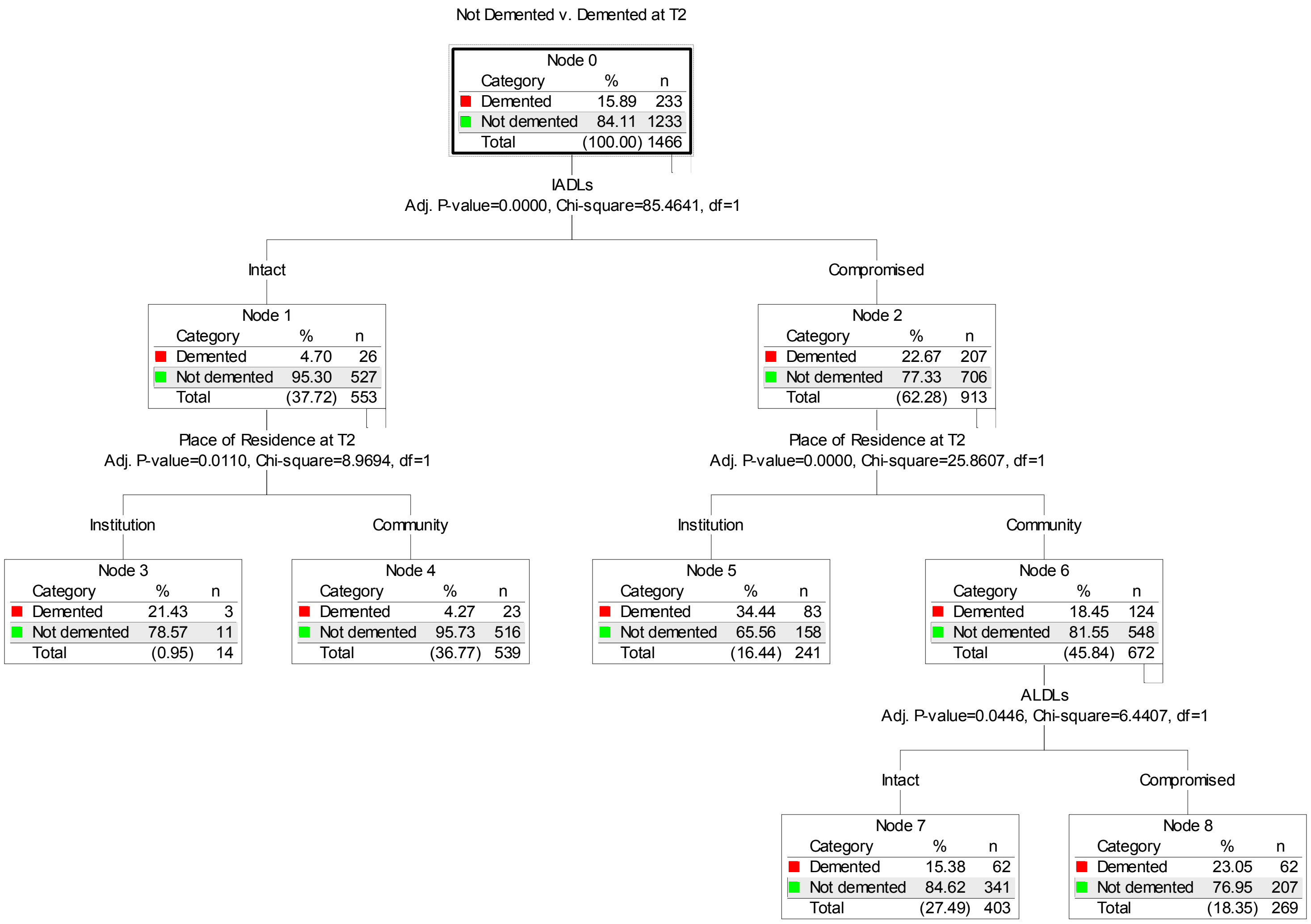


Figure 34. **Unpruned Neuropsychiatric Classification Tree Differentiating DEM from NDEM**

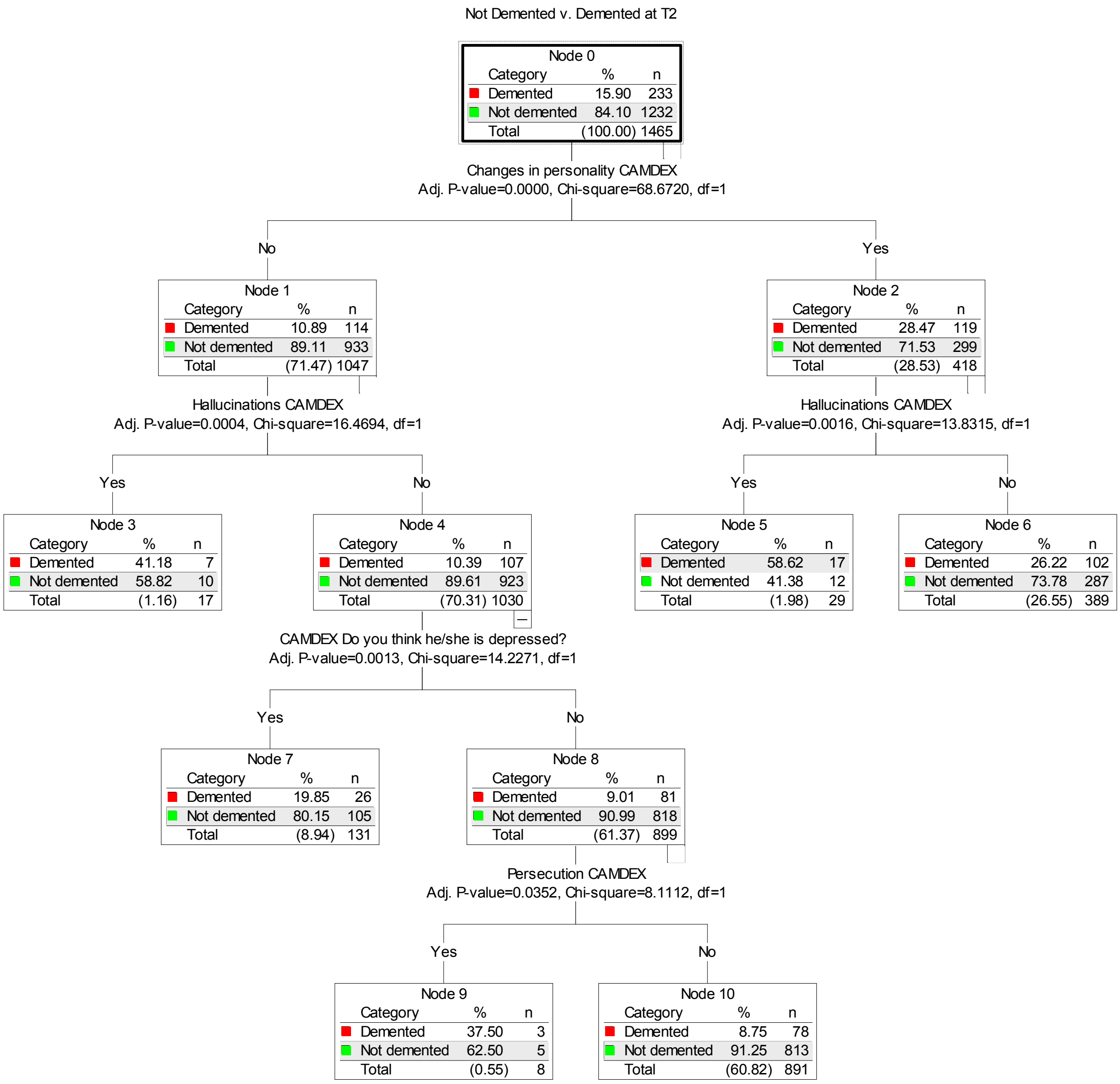


Figure 35. **Unpruned Vascular Classification Tree Differentiating DEM from NDEM**

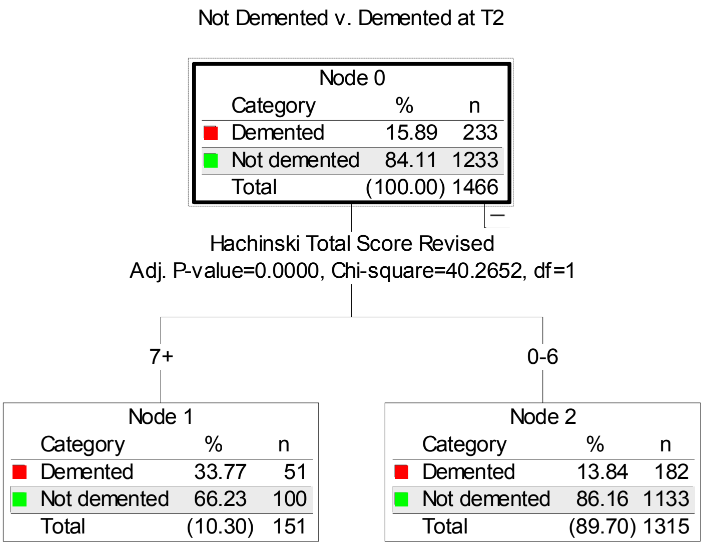


Figure 36. **Unpruned Family History Classification Tree Differentiating DEM from NDEM**

Not Demented v. Demented at T2

Node 0

Category	%	n
Demented	14.14	198
Not demented	85.86	1202
Total	(100.00)	1400

Question 3 – Differentiating Converters from Non-Converters

***Figure 37.* Unpruned Demographic Classification Tree Differentiating Converters from Non-Converters**

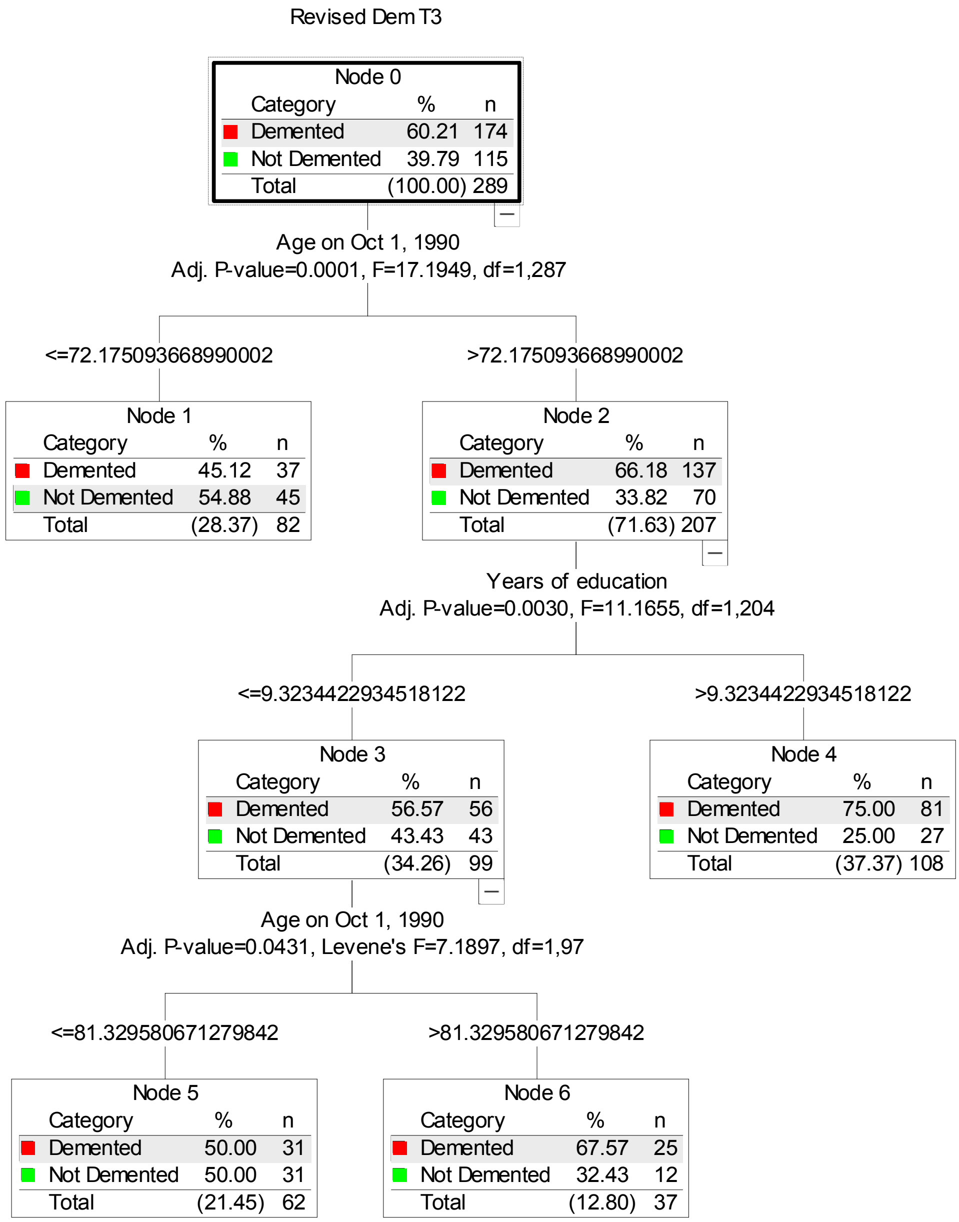


***Figure 38.* Unpruned Cognitive Classification Tree Differentiating Converters from Non-Converters**

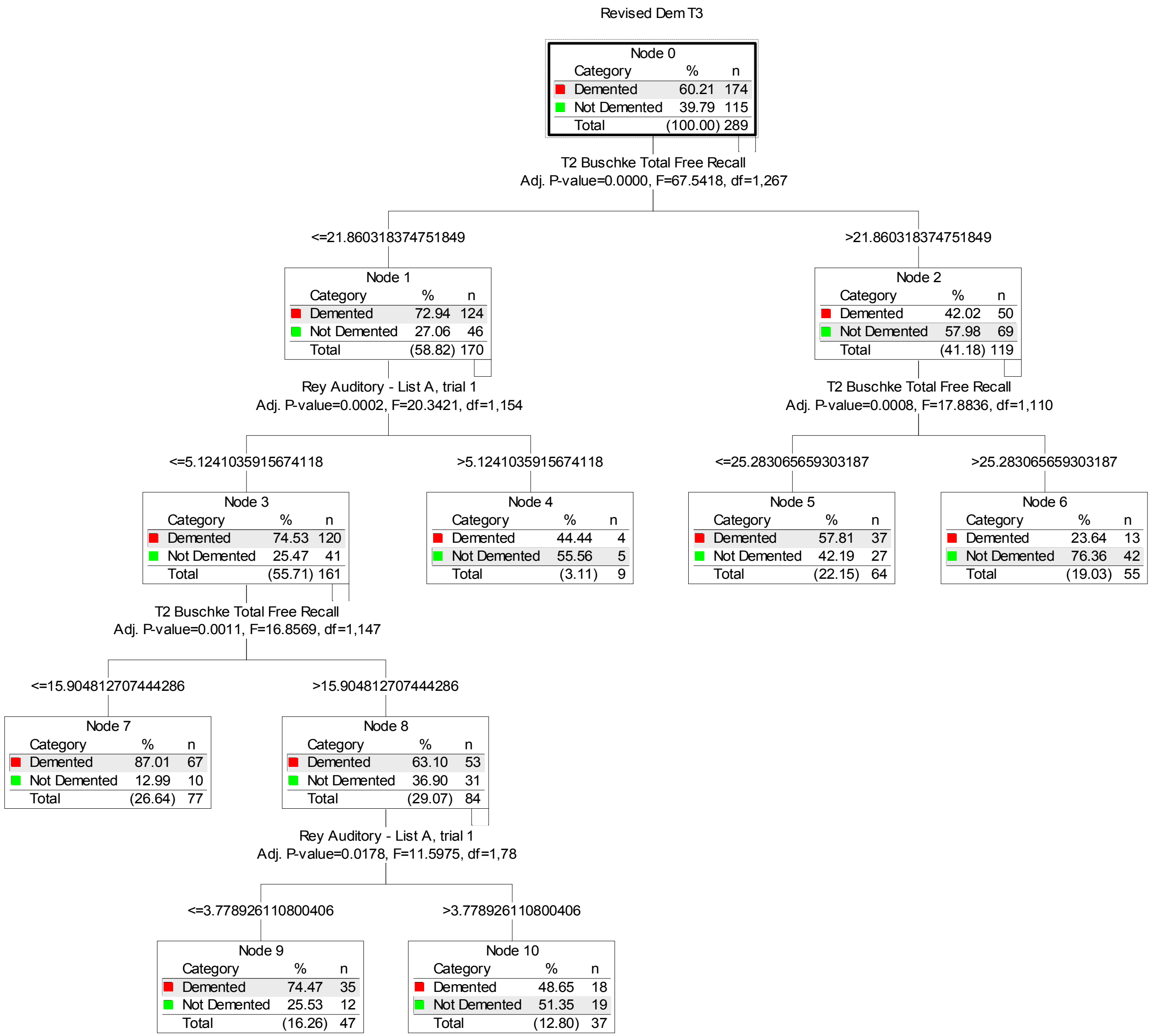


Figure 39. **Unpruned Frailty/Morbidity Classification Tree Differentiating Converters from Non-Converters**

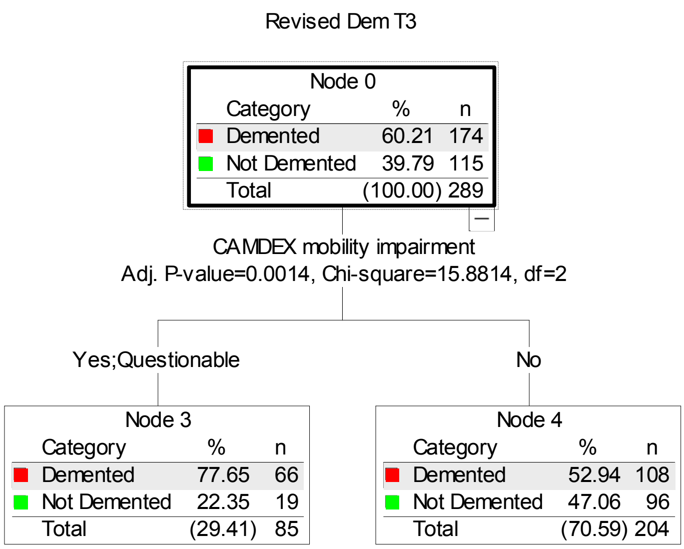


Figure 40. **Unpruned Social/Physical Demographic Classification Tree Differentiating Converters from Non-Converters**

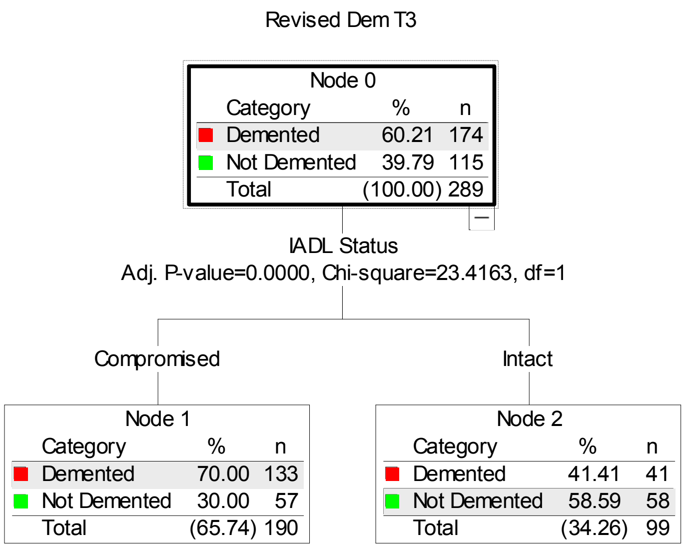


Figure 41. **Unpruned Neuropsychiatric Classification Tree Differentiating Converters from Non-Converters**

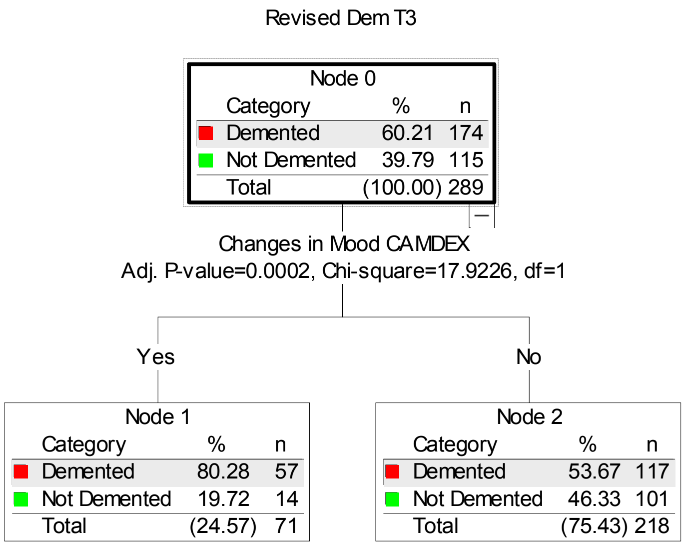


Figure 42. **Unpruned Vascular Classification Tree Differentiating Converters from Non-Converters**

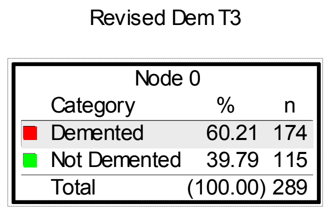


Figure 43. **Unpruned Family History Classification Tree Differentiating Converters from Non-Converters**