COMPARING THE FREQUENCY, OVERLAP, STABILITY, AND PREDICTIVE UTILITY OF PRECLINICAL DEMENTIA CONSTRUCTS

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ABSTRACT

LAUREN HALF WARREN: Comparing the Frequency, Overlap, Stability, and Predictive Utility of Preclinical Dementia Constructs
(Under the direction of Marilyn Hartman)

Numerous constructs have been proposed to describe the transitional state between normal aging and dementia, but no one set of criteria is consistently referred to as the prodrome to dementia. Although there are many studies of the rates of these constructs, results are hampered by methodological differences. Research examining the overlap and stability of these constructs over time is also lacking, and predictive utility for later dementia remains inconclusive. Moreover, it is unknown whether one construct is superior in predicting later dementia or Alzheimer's disease. The current study addressed these issues using longitudinal clinical and neuropsychological data from a subsample (N=661) of participants in an epidemiological study of aging and dementia, the Cache County Memory Study (CCMS). Results confirmed wide variability in rates of preclinical dementia constructs. Constructs that included measures of functional impairment were the most stable, whereas constructs relying on memory impairment were generally unstable. Using bivariate logistic regression, four of the seven constructs were associated with later dementia, and these constructs either measured multiple cognitive domains or functional impairment. The 'Mild Ambiguous' construct, which includes memory or functional impairment, was statistically superior in predicting later dementia. Although four of the seven constructs were also significant predictors of later AD, no one construct was superior.

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Introduction

As the world population continues to age, the incidence and prevalence of AD and other dementias will continue to rise sharply. A longstanding research focus is on potential risk factors for dementia, with the intent to develop pharmacological agents that may have the potential to slow the progression of AD or reverse neurobiological damage entirely (Rivas-Vazquez, Mendez, Rey, & Carrazana, 2004). Much time and effort have gone into research identifying genetic risk factors for dementia, specifically for AD, such as the APOE _4 allele, and behavioral risk factors, such as head injury or cardiovascular health. In the last twenty years, researchers have also begun to focus on very early and mild cognitive changes that may be indicative of increased risk for later dementia. This transitional state between normal aging and dementia has multiple monikers, including mild cognitive impairment (MCI), cognitive impairment no dementia (CIND), and mild ambiguous/prodromal AD (MA).

In addition to the confusion that results from attempting to compare multiple monikers for the same hypothesized construct (i.e., preclinical dementia), it is also difficult to compare different studies of the same construct, because diagnostic criteria are often not clearly stated or are inconsistently applied across studies. For example, a common criterion is "cognitive impairment" or "memory impairment". However, researchers generally have not specified what cognitive or memory impairment *is*. Sometimes cognitive impairment is determined by clinical consensus (Graham et al., 1997), whereas other times it is determined

by a cutoff score on a neuropsychological test (Blackford & LaRue, 1989). Even when two studies have defined impairment in terms of neuropsychological functioning, they may use different measures (e.g., immediate versus delayed memory), or they may use different cutpoints to define impairment (e.g., 1 SD vs. 1.5 SD below normal). Another common criterion that has been interpreted in multiple ways is "cognitive complaint". Some studies may define this as specifically memory complaints, whereas others may accept complaints in any areas of cognition. Moreover, the complaint may involve self-report or the report of an informant. This latter inconsistency complicates matters because subjective, self-reports of cognitive complaints have often been linked with depression or anxiety (Hänninen et al., 1994), and thus may not be comparable to a complaint by a reliable informant. Measures of cognitive complaint also may differ in how they assess complaint, and may not be interchangeable. In sum, a major difficulty in comparing different constructs is that research studies often differ in measures and specific criteria in defining preclinical dementia.

The contribution of differences in criteria and neuropsychological tests to differences in prevalence rates of preclinical dementia and outcomes (e.g., conversion rates to dementia) has recently become an important area of research. Some studies show major discrepancies in both prevalence rates and outcome when different criteria are used (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003b; Ritchie, Artero, & Touchon, 2001), whereas others show negligible differences (Fisk, Merry, & Rockwood, 2003). Regardless, there is some consensus across studies as to the criteria for definitions and the resulting prevalence.

Definitions and prevalence of transitional states

Since the 1960s, attempts have been made to identify and longitudinally follow individuals believed to be at risk for later occurrence of dementia. Multiple classification

systems have been proposed, but no consensus has been reached as to which criteria best predict AD or dementia or which constructs are the most clinically useful. In a recent brief review, Collie and Maruff (2002) evaluated and compared many of the existing constructs, including several included in the proposed project, and concluded that precise and reliable estimates of frequency and conversion to dementia in the general population had not yet been established. They also noted that inconsistencies in defining, interpreting, and applying diagnostic criteria hampered the accurate interpretation of results, both across studies purporting to use the same construct and between studies comparing different classification systems. In the first section of this review, the prevalence or frequency of each of several of these classification systems will be examined, in an attempt to coalesce the existing literature into a coherent whole.

One of the first modern sets of proposed criteria was that of Crook and colleagues (Crook, Bartus, Ferris, Whitehouse, Cohen, & Gershon, 1986), describing Age-Associated Memory Impairment (AAMI). This constellation was developed not as a description of a dementia prodrome, but rather as stable variant of normal aging. Regardless, it has been also studied as a prodrome to later dementia. This syndrome included people over the age of 50 with a subjective memory complaint and objective memory performance at least one standard deviation below that of younger adults. It excluded individuals with medical, neurological, or psychiatric disorders that could account for the memory disturbance. These criteria have been criticized, both in terms of being overly inclusive (e.g. many cognitively normal older adults are included) and overly exclusive in the medical exclusion criteria (i.e., excluding individuals with most types of medical disorders) (Smith, Ivnik, Petersen, Malec, Kokmen, & Tangalos, 1991).

Reported prevalence rates of AAMI have varied greatly, due mostly to inconsistency in the application of the original criteria, but also to variation in sample characteristics. For example, Koivisto et al. (1995) reported a prevalence rate of 38% in a random sample of 1,049 Finns; Barker, Jones, and Jennison (1995) reported a prevalence rate of 19% in a sample of participants from a local health center; and another study (Coria, Gomez de Caso, Minquez, Rodriguez-Artalejo, & Claveria, 1993) found AAMI present in only 7% of a sample of rural Spaniards. When persons were classified solely on the basis of neuropsychological testing, up to 85% of older adults may be considered to have AAMI (Smith et al., 1991), leading to the criticism that if the majority of older adults "suffer" from this condition, it must be normal aging rather than a pathological condition.

Blackford and La Rue (1989) subsequently proposed changes to the AAMI criteria, including specific tests to measure the objective memory deficit and relaxing the medical exclusion criteria to include people who have common ailments of age that contribute to possible cognitive impairment (e.g., hypertension). They also suggested restricting the age range of people designated as AAMI to between 50 and 79 years of age. This decision was based on the absence of normative data for those above 80 years of age at that time; the authors believed that cognitively normal adults over 80 years old would be categorized as AAMI simply because of poor and inaccurate norms. Although this reasoning appeared sound, there were no suggestions as to what to do with older-old adults who had memory problems that were concerning, but not severe enough to warrant a diagnosis of dementia.

There is only one study of the prevalence of individuals meeting the Blackford and La Rue criteria, and even this study is flawed (Smith et al., 1991). In one part of this study, based on a sample of 136 community-dwelling residents, only 72% had sufficient data to

determine AAMI status. These volunteers were free of medical conditions that could cause cognitive impairment, but importantly, the estimates are not an estimate of the true frequency, because the entire sample in this study was free of cognitive complaints, which is a core criterion. Even without the cognitive complaint criterion, only 9% met full criteria for AAMI. In the same study, a second group of older adults (N=424), all of whom volunteered for a study of cognitive tests and were free of medical conditions that could cause cognitive deterioration, and had no cognitive complaints, only 5% met the full criteria, as proposed by Blackford and LaRue (1989).

Smith et al. (1991) postulated that this conceptualization of AAMI was still not useful, as the medical exclusion criteria were still too stringent. When the researchers classified individuals based solely on the objective memory impairment criterion, however, a very high percentage of them (67-98%, depending on the definition) met this criterion. Moreover, because the sample examined was free of memory complaints, which is a core criterion for both definitions of AAMI, anyone in the community who did have a cognitive complaint was likely to be labeled AAMI because of the high percentage of normal elderly who might exhibit objective "memory impairment" based on these criteria. Additionally, it is well-established that memory complaint may be more related to depression or anxiety, rather than measureable cognitive decline (Smith, Petersen, Ivnik, Malec, & Tangalos, 1996) and is not related to functional impairment or the later development of dementia, indicating its lack of utility as a preclinical dementia variable (Purser, Fillenbaum, & Wallace, 2005).

In sum, although the original AAMI criteria were helpful in setting forth variables the might be useful in detecting the early stages of clinically significant cognitive impairment, there have been many critiques of this construct. Despite improvements that have been

suggested (e.g., Blackford & LaRue, 1989), there is still not one set of criteria that is currently accepted. Medical criteria are thought to be too stringent, whereas comparing older adults' memory abilities to that of younger adults may result in the inclusion of cognitively normal individuals. The use of memory complaint as an integral criterion may be more closely related to psychiatric disturbance and does not appear to correlate with later cognitive decline. Moreover, variations in diagnostic criteria have resulted in prevalence rates ranging from 7-85%, making identification of this population difficult.

Other researchers have included types of cognitive decline in addition to memory in the definition of preclinical dementia. As the name implies, AAMI is defined only in terms of impairments in memory, and not impairments in other cognitive domains, such as language, executive functioning, or visuospatial functioning. Nevertheless, deficits in these other domains are also present in demented persons, and may be of use in detecting early stages of illness. Consequently, Levy (1994), in conjunction with the World Health Organization, set forth criteria for Age-Associated Cognitive Decline (AACD). Major differences from the AAMI criteria include poor performance in one of five cognitive domains, rather than exclusively in memory, and a gradual decline in cognition of at least 6 months. The inclusion of a criterion that required a decline in cognitive functioning from a previously higher level was designed to exclude persons who were functioning at a lower intellectual level initially. Similar to AAMI, additional criteria for AACD include cognitive complaint from the individual or known informant and the absence of medical, neurological, or psychiatric conditions that could account for the cognitive decline. A further important difference between the definitions of AAMI and AACD is that the latter measures cognitive performance relative to age and education-matched peers rather than to younger adults,

eliminating the problem of high percentages of older adults meeting criteria despite being cognitively normal. Additionally, Levy (1994) noted that persons designated as AACD may fall into two separate groups: those who are at risk of declining to dementia, and those whose changes may remain stable, who would thus be better captured by "normal aging".

Because persons with AACD can have impairment in multiple cognitive domains, it would be expected that prevalence rates would be higher than AAMI, which uses age-adjusted norms for memory only, but perhaps lower than AAMIO, which compares older adults to younger adult norms. It might also be expected that the resulting AACD group would have greater heterogeneity, both in composition and in outcome. As with AAMI, methodologically sound studies of the prevalence of AACD are scarce. Nevertheless, three community-based studies using criteria that closely resemble the original construct proposed by Levy (1994) have reported consistent prevalence rates of 20-26% (Hänninen et al., 1996; Ritchie et al., 2001; Schröder, Kratz, Pantel, Minnemann, Lehr, & Sauer, 1998). An additional study (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003a) found a much lower prevalence rate of 9%, with no clear methodological reason for the discrepancy. These estimates are roughly equivalent or slightly lower than estimates of AAMI (Barker et al., 1995; Koivisto et al., 1995; but see Smith et al., 1991 for an exception). Nevertheless, the concept of AACD, while likely representing a more heterogeneous group than AAMI, appears to represent approximately 20-25% of the elderly population.

Another construct, Cognitive Impairment, No Dementia (CIND), which was developed by the Canadian Study of Health and Aging (CHSA), has important similarities to and differences from both AAMI and AACD. Similar to AACD, CIND was developed to denote individuals who are not demented but who are also clearly not cognitively normal.

Also similar to AACD, persons with impairment in any cognitive domain are included; deficits are not limited to just memory. Unlike either construct, CIND diagnosis is established without any specific criteria, by a consensus panel of clinicians. This process may leads to a much more heterogeneous group than either AAMI or AACD. In particular, people are included as CIND when they possess a medical or psychiatric diagnosis that might explain their impairment, or if the impairment is lifelong (e.g., someone with mental retardation), as well as persons for whom there is no explanation for the impairment.

Because of the broader inclusion criteria and lack of medical exclusion criteria for CIND, it might be expected that prevalence rates would be higher than those of AACD or AAMI; however, two independent studies show prevalence rates of between 10-16% (DiCarlo et al., 2000; Graham et al., 1997), lower than both AAMIO (19-38%) and AACD (20-26%) estimates. One possible explanation for this unexpected result is the potential inconsistency in what constitutes "cognitive impairment". The criteria for AAMI and AACD both specifically state that performance 1 SD below normal is considered "impaired", whereas the CIND studies cited state only that impairment was denoted through clinical consensus. Consequently, it may be that the investigators in studies that use CIND required more impairment before classifying an individual as impaired. Indeed, this issue has been addressed regarding CIND (Tuokko, Frerichs, & Kristjansson, 2001), and 1.5 SD was suggested as an appropriate cutoff point to use on neuropsychological tests. Another possible explanation for the lower than expected prevalence rates is that both studies used screening instruments and cutoff scores for detecting cases, and these scores, although optimal for detecting cases of dementia, likely were insensitive to the mild degree of cognitive impairment that characterizes people with CIND. That is to say, it is likely that many people

who scored above the cutoffs and were perceived as "normal", did in fact evidence cognitive impairment. Indeed, in another CSHA study (Ebly, Hogan, & Parhad, 1995), AAMI and AACD were diagnosed in some members of the control group, who had *not* been denoted as CIND by consensus.

The term that is perhaps most commonly used and misused is Mild Cognitive Impairment (MCI). This term has most recently been adapted by Petersen and his colleagues (Petersen et al., 1995; Petersen, Smith, Waring, Ivnik, Tangalos, & Kokmen, 1999; Petersen et al., 2001), as well as Morris and his colleagues (Morris et al., 2001) to describe prodromal AD. Although these researchers have established specific criteria for their conceptualization of the transitional state between normal aging and AD, MCI has also been used more generally by others to refer to all persons not meeting criteria for dementia or normal aging. Consequently, many studies that indicate prevalence and outcome that vary substantially from the Petersen group results likely do so secondary to significantly different definitions of MCI (e.g., Frisoni, Fratiglioni, Fastbom, Guo, Viitanen, & Winblad, 2000).

The Petersen group set forth their definition of MCI specifically as a way to classify those persons at high risk of developing AD (Petersen et al., 1995); indeed, it was expected that those with MCI had prodromal AD, and with enough follow up, would develop the disease. Similar to CIND, Petersen's group has generally diagnosed MCI based on clinical consensus, although there are also criteria that are often followed in other studies (Petersen et al., 1999). The criteria include cognitive complaint, preferably corroborated by an informant, intact Instrumental Activities of Daily Living (IADLs), memory test performance typically 1.5 SD below age and education corrected norms, and intact general cognitive functioning. Because of the lack of specificity in how to operationalize these criteria (e.g, some have

operationalized "intact general cognitive functioning" using the WAIS, whereas others have used the MMSE), it has been difficult to compare studies using this construct.

Despite the difficulty in operationalizing the definition of MCI, there have probably been more prevalence studies with the Petersen definition of MCI than any other. Unlike the other constructs discussed thus far, prevalence rates have been consistent and low, ranging from 1.0% (Fisk et al., 2003) to 5.3% (Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002). Other studies have demonstrated prevalence rates in between these rates (2.5%, Busse et al., 2003a; 3.5%, Larrieu et al., 2002; 1.7%, Lopez et al., 2003; 3.2%, Ritchie et al., 2001). All of these studies are population-based studies and all used approximately the same definition for MCI.

One critical issue that has been raised with respect to the criteria for MCI is that of cognitive impairment in domains other than memory. The Petersen criteria specify that although memory is impaired, other cognitive domains such as visuospatial processing or language are generally intact. However, memory loss in the absence of other cognitive impairment is rare in a clinical population, and rarer still in the general population, and consequently this criterion may be overly specific with a significant loss of sensitivity (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Ritchie et al., 2001). As a response to this concern, Petersen and his colleagues at a consensus conference proposed subsets of MCI, including MCI-amnestic, which is the traditional definition of MCI and includes people who have impairment only in memory; MCI-multiple deficits, which includes those people who have mild impairments in two or more cognitive domains; and MCI-single non-memory domain, for those people who demonstrate impairment in at least one domain other than memory, such as language or visuospatial functioning (Petersen et al., 2001).

Two population-based studies have examined the prevalence of these subclassifications, and interestingly, prevalence rates for MCI-multiple deficits and MCI-single non-memory domain are not substantially higher than those found for the MCI-amnestic subtype (Busse et al., 2003b; Lopez et al., 2003). Lopez et al. (2003), using a sample from the Cardiovascular Health Study, found a prevalence rate of 4.7% for MCI-multiple cognitive deficits subtype, as compared to 1.7% for the MCI-amnestic subtype. They did not examine the subtype of MCI-single non-memory domain. Overall prevalence of MCI including all definitions was 19%, but this number also included those persons with "possible MCI", and a definition of possible MCI is inconsistent with the Petersen et al. criteria because a cognitive complaint is not required. Similarly, a second study examining the subtypes of MCI comes from the Leipzig Longitudinal Study of the Aged (LEILA), a longitudinal study of persons age 75 and older (Busse et al., 2003b). Using similar neuropsychological criteria to the Petersen group, the researchers reported a prevalence rate of 1.8% for MCI-multiple cognitive deficits subtype, and a prevalence of 4.2% for MCI-single non-memory domain, as compared to a rate of 2.5% for amnestic MCI. Overall prevalence of MCI including amnestic, multiple deficits, and non-memory deficits, was 8.5% (Busse et al., 2003b).

Two community-based studies have also demonstrated no differences between the rates of aMCI as compared to multiple-deficits MCI (Manly, Bell-McGinty, Tang, Schupf, Stern, & Mayeux, 2005; Zanetti, Ballabio, Abbate, Cutaia, Vergani, & Bergamaschini, 2006), although one memory clinic-based study showed a higher rate of aMCI and multiple deficit MCI than single non-memory MCI (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006). Overall, it appears that the estimated prevalence of MCI-multiple cognitive deficits

and MCI-single memory domain is similar to that of amnestic MCI. However, including others previously excluded from amnestic MCI (e.g., those with multiple or non-memory deficits) clearly increases the prevalence, although rates are still substantially lower than that of other preclinical dementia constructs.

Despite recent attempts to broaden the cognitive deficits acceptable for inclusion into aMCI, it appears as though the prevalence rates are much lower than those shown for AACD, CIND, or AAMI, which has been interpreted as sacrificing sensitivity for specificity in prediction of later AD. MCI has also been criticized for its lack of practical application and poor predictive validity in a community setting (Ritchie et al., 2001). Regardless of these limitations, Petersen's conceptualization of prodromal or preclinical AD appears to have become common parlance within the preclinical dementia literature.

As noted above, other researchers have adopted the term MCI but used a different definition. In contrast to Petersen's definition, others have focused more on functional impairment and informant report (Morris et al., 2001). Morris's group does not use neuropsychological testing results to establish an MCI diagnosis; instead, diagnosis is based entirely on functional impairment as measured by the Clinical Dementia Rating (CDR) scale, a semi-structured clinical interview (Morris, 1993). Persons who score 0.5 overall are considered as having either MCI or early dementia, depending on the level of functional impairment. Morris and his colleagues also believe that those persons with MCI actually have very mild AD, and that the difference between the MCI and very early dementia groups is a negligible one of degree. In order to test this hypothesis, they studied participants with a CDR score of 0.5 who were clinically assessed as MCI and not demented. In all but one of the 25 participants, there was neuropathological evidence of AD. These results were

interpreted to mean that these participants did, in fact, have very mild dementia. No prevalence studies using this definition are present in the literature, although multiple studies indicate the importance of functional impairment in preclinical dementia identification (Tabert et al., 2002; Ebly et al., 1995).

One final diagnostic term is Mild Ambiguous/Prodromal AD (MA), which is a term that has been used in the Cache County Memory Study (CCMS) to denote participants who showed cognitive decline but were not demented, similar to CIND in the CHSA (Breitner et al., 1995). Unlike patients with CIND, however, patients denoted as having MA were thought to be in the preclinical stages of AD, similar to aMCI, and those who had cognitive impairment secondary to a medical or psychiatric disorders were not given this designation. Although the MA diagnosis does not have formal inclusion criteria, and has instead been determined by clinical consensus, criteria are being developed in the hopes of better capturing those participants who are in the prodrome of dementia and AD (Warren et al., 2004). Current research criteria combine elements of both the Petersen and Morris conceptualizations of MCI, and include the presence of memory and/or functional impairment. Also similar to MCI and AACD, participants having MA also lack medical or psychiatric conditions thought to be contributory to deficits, and similar to AACD, a gradual decline in functioning is necessary for the diagnosis of MA. In the CCMS baseline evaluation, approximately 2% of those who completed a screening exam for dementia were classified as MA. Based on these rates, it might be expected that MA is more likely to overlap with aMCI than CIND, AACD, or AAMI, but this has yet to be established.

In sum, the five constructs discussed above (AAMI, AACD, CIND, MCI, and MA) all differ from each other in important ways, and may represent either overlapping or

independent measures of preclinical dementia. In addition, alternate definitions of AAMI (Blackford & LaRue, 1989) and MCI (Morris et al., 2001) constitute important changes to the original criteria. Although there are multiple other nosologies that have been proposed as transitional states between normal aging and AD, these seven different definitions constitute the focus of the present study.

Determining the relative frequency of the constructs is important because it is exceptionally difficult to compare the results of different studies, as estimates can vary based on sample characteristics, methodologies, and sensitivity of the measures used to assess cognitive impairment. By examining studies that look at more than one construct, it can be said with greater confidence which constructs are more commonly found. As an example, it is difficult to conclude that AAMI occurs more frequently than aMCI if Study A shows that AAMI occurs in 10% of the population and Study B states that aMCI occurs in 40% of the population. There is no way to know if large portions of variance in either or both of these studies are not due to sample characteristics, different criteria, or dissimilar tests. Because comparison studies assess different definitions within the same sample, the effects of sample and methodological differences are equalized. Although no research has compared the prevalence or frequency of all these constructs within a single study, a few studies have compared two or three different definitions.

Minimal research has been conducted examining the relative frequencies of predementia constructs, but the extant studies show a clear pattern of results. Three studies have examined the relative frequencies of AAMI and AACD (Richards, Touchon, Ledesert, & Ritchie, 1999; Schröder et al., 1998; Ebly et al., 1995). In all three, the frequency with which AACD occurred exceeded the number of people classified as AAMI. This result is not

unexpected, as the diagnostic criteria for AACD allow persons with a wider variety of cognitive impairments into the nosology. Two additional studies compared the frequency with which AACD and MCI occur (Busse et al., 2003a; Ritchie et al., 2001). In both studies, the prevalence for AACD exceeded that of MCI (both groups used criteria based on Petersen et al., 2001). The remaining study examined the relative frequencies of AAMI and MCI (Bartrés-Faz et al., 2001) and found that the frequency with which AAMI occurred exceeded that of MCI. However, the way in which they defined MCI somewhat deviated from Petersen's criteria, and the way in which subjects were deemed impaired on memory tests was poorly specified. One additional study examined the frequency of AAMI and AACD in a group of subjects already designated as CIND (Ebly et al., 1995), and they found that 65% of participants characterized as CIND could not be classified as AAMI or AACD. In those who could be classified, the number categorized as AACD exceeded those who were characterized as AAMI, consistent with the other studies. This study also suggests that CIND represents a much broader group than any of the other definitions. There are no comparison studies that have included fMCI or MA in the comparisons. Regardless, from the literature examining relative frequencies of the various constructs, it appears that the frequency with which CIND occurs is greater than that of AACD, which is greater than that of AAMI, which in turn exceeds the number of people who meet criteria for aMCI.

In addition to examining relative frequency, it is also important to understand the degree of overlap among the constructs. If there is a large amount of overlap between two categorizations, it is fairly certain that they are measuring the same underlying construct, and there is no need for two names. It may also be that as cognition declines, people categorized with one construct (e.g., AAMI) may be better represented by another (e.g., MCI), and there

may be very little overlap between the groups at any given point in time. That is, mutual exclusion may simply represent different points along a continuum of cognitive decline. Lack of overlap may also signify two distinct trajectories. There may be a subgroup that meet criteria for a construct whose cognition remains stable and another subgroup that progresses to dementia. Examining the overlap among constructs can also help explain discrepancies in prevalence and conversion rates to dementia in the literature, as different constructs may be measuring completely different populations (e.g., one stable and one declining). Unfortunately, an even smaller number of the studies that have reviewed multiple constructs have examined the overlap among the different constructs. That is, it would be useful to determine, for example, how many people who meet criteria for AAMI also meet criteria for MCI.

Studies examining the overlap between AAMI and AACD show a variable degree of overlap between them. In one study, approximately half of each group that met criteria for AAMI and AACD could also be classified as the other diagnosis (Richards et al., 1999). That is, of the 37 people classified as AAMI, 20 could also be classified as AACD, suggesting moderate overlap among the two groups. Similarly, in another study (Schröder et al., 1998), 63% of people classified as AAMI also met AACD criteria. In a third study (Ebly et al., 1995), nearly everyone classified as AAMI (96%) was also classified as AACD. Together, these studies suggest moderately strong but variable degrees of overlap between AAMI and AACD. This conclusion appears somewhat counterintuitive, as the prevalence studies suggest that AACD is a much broader concept with a potentially more heterogeneous makeup than those classified as AAMI. With respect to overlap of other constructs, there are

unfortunately no other known studies, and consequently, the relation among other pairs of constructs is not yet known at this point.

Stability of constructs over time

An underlying assumption regarding preclinical dementia syndromes is that cognition declines along a continuum during aging, from normal to dementia status (Katzman, 1976). Although this is often the case, it is not necessarily so, as at least one study has shown cognitive stability in older adults for up to fifteen years (Rubin et al., 1998; Storandt, Grant, Miller, & Morris, 2002). Thus, it is likely that there are separate groups of people who do and do not decline along a cognitive continuum. Moreover, some individuals who do decline may not decline enough to warrant a diagnosis of dementia. Indeed, one of the constructs examined in the current study was developed specifically to account for stable age-related changes (AAMI). Although the researchers who developed the remaining constructs assume that a higher percentage of people who meet criteria will convert to dementia compared to a control group who do not meet criteria, there may still be a large percentage of older adults who remain stable over time, or may even convert back to "normal" cognitive status. Many factors can impact the classification of whether someone declines, improves, or remains stable over time, including subject characteristics, such as genotype (Petersen et al., 1995), methodological factors, such as length of follow up time (Petersen et al., 1999), or the sensitivity of measures used to measure cognitive change (Smith et al., 1991; Storandt et al., 2002).

Examining the stability of preclinical dementia constructs over time has recently emerged as an important area for research (Fisk et al., 2003; Ritchie et al., 2001). Although the cognitive status of many persons classified as MCI, CIND, or other types of preclinical

dementia constructs are expected to decline to dementia with adequate follow up periods, others' cognition may remain stable or even improve to within normal limits with respect to their age and educational level. Temporary decline in cognitive functioning may be due to many factors, including medical problems such as TIAs or thyroid problems, stress or bereavement, or low levels of effort during testing. Single time point test scores can also be affected by practice effects and regression to the mean. Most cognitively normal people do perform at a stable level on reliable tests, however, when these scores are corrected for age (Morris et al., 1989).

One way to examine stability over time is to compare the rates at which persons classified as the different constructs convert back to "normal" cognitive status. Thus, higher rates of conversion back to normal at follow-up are indicative of instability of the construct. Comparisons could also be made within a single construct regarding the number of persons converting back to normal versus converting to dementia. If the percentage of the sample that converts back to normal is greater than the percentage that converts to dementia, the construct may be deemed unstable over time, and potentially not very useful clinically.

One reason why some constructs may be less stable than others is rooted in the variability of cognitive performance over time, which likely increases as people age (Ylikoski, Ylikoski, Keskivaara, Tilvis, Sulkava, & Erkinjuntti, 1999). In support of this idea, when healthy older adults were examined semi-annually to determine the temporal stability of objective memory impairment, very few were consistently impaired across examinations (Collie, Maruff, & Currie, 2002). Of 174 healthy elders, only 13% were consistently memory impaired across three annual examinations, and just under half of the sample was within normal limits on all examinations. The remaining 37% of participants showed memory

impairment on only one or two of the three evaluations, indicating temporal instability in memory impairment over a year's time. It is possible that the consistently memory-impaired decline at a faster rate or have a higher rate of conversion to dementia, but this was not examined. An important point to take from this study is that those persons classified at any one point in time as memory-impaired may in fact not be consistently so, and the presence of these participants in an MCI group will decrease the ability to predict conversion to dementia. Results such as these may pose a problem for preclinical dementia classification systems in which memory impairment is a core criterion (AAMI, aMCI, and MA).

Despite the apparent instability of memory performance over time, studies examining the stability of AAMI and AACD have shown them both to be more stable than other preclinical dementia constructs. In one study, 64% of those classified as AAMI still had that diagnosis 18 months later (Helkala et al., 1997). Over the same time period, 22% had improvements in either objective or subjective cognition, whereas 6% declined and no longer met AAMI criteria. It is unknown how many individuals would have progressed to dementia or remained cognitively stable with a longer follow-up period. Even with longer follow up, AACD also appears to be a moderately stable condition (Ritchie et al., 2001). After three years, 58% remained classified as AACD, in comparison to 29% who declined to dementia. It is unknown how many improved over time.

The stability of aMCI has not fared as well. Despite similar conversion rates to dementia in comparison to AACD, a much higher percentage of aMCI people are likely to improve upon follow-up assessment. Only 7-14% of people classified as aMCI remain classified as such after 2-3 years of follow up (Fisk et al., 2003; Larrieu et al., 2002; Ritchie et al., 2001), with one study reporting that 41% of those classified as aMCI reverted back to

normal cognitive status (Larrieu et al., 2002). When these results are compared to an average annual conversion rate to dementia of 10-15% (Petersen et al., 1999), these studies seem to provide strong evidence that aMCI is an unstable diagnosis.

In sum, studies that have examined stability of preclinical dementia constructs over time are few. Those that exist indicate that AAMI and AACD have the highest numbers of people who remain stable over time, rather than convert to dementia or evidence improved cognition. In contrast, aMCI is fairly unstable, and a higher percentage of people may convert back to "normal" cognition in comparison with how many convert to dementia or remain classified as MCI.

Utility of transitional states to predict later onset of dementia

It is clear that there is considerable confusion regarding the number of different preclinical dementia constructs, how to best define them, and how much overlap there is among the constructs. Regardless, there is overwhelming evidence that diagnosis of many of these constructs yields a higher chance of converting to later dementia compared to control groups (Fisk et al., 2003; Petersen et al., 1995; Ritchie et al., 2001; Tuokko et al., 2003). Indeed, many existing preclinical dementia projects were initiated as a way to identify early manifestations of dementia, in the hopes that preventative intervention might be implemented. However, some constructs may be better than others at predicting who will decline over time. In this section, each construct will be reviewed as to its efficacy in predicting later onset of dementia.

Studies examining AAMI as a risk factor for later dementia show mixed results. Because AAMI was originally conceptualized as a normal variant of aging, and not as a precursor to dementia, it might be expected that there would be no difference in rates to

decline to dementia between those with AAMI and those without, and that result has been shown in at least one study (Snowdon & Lane, 1994). Another study indicated that 9% of those diagnosed as AAMI declined to dementia over 3.5 years, but there was no control group included to assess whether this rate was significantly higher than the control group conversion rate (Hänninen et al., 1995). In contrast to Snowdon & Lane (1994), one study followed community volunteers who met AAMI criteria over a period of three years and found a large discrepancy between the rates of conversion to dementia in those with AAMI and those who were deemed cognitively normal (Goldman & Morris, 2001). At the follow-up examination in this study, 31-42% of those with AAMI had progressed to dementia, compared with 9-16% of those who were deemed cognitively normal. The variations in rates reflect conservative and liberal definitions, respectively, of who was deemed intellectually intact using the Short Blessed Test (Goldman & Morris, 2001). Taken together, these results suggest that there is as of yet no consensus as to whether those persons categorized as AAMI do in fact progress to dementia at a faster rate than those deemed cognitively normal.

Rates for conversion to dementia in those classified as AACD vary somewhat as well, although the results of the two relevant studies indicate an increased risk of dementia (Ritchie et al., 2001; Busse et al., 2003a). In the first study (Ritchie et al., 2001), 29% of those classified as AACD converted to dementia within three years. There was no control group in this study for comparison. ROC analysis, which provides a more stringent test of prediction, revealed 95% sensitivity and 54% specificity of the AACD diagnosis in predicting later dementia. This indicates that the AACD diagnosis captures a high percentage of those who will eventually convert to dementia, but also includes a large number of persons who do not convert. In the second study (Busse et al., 2003a), 47% of persons classified as AACD

developed dementia within a three-year period, as compared to 5% in a control group. Interestingly, and in stark contrast with Ritchie et al., specificity was much higher (95%) than sensitivity (37%), indicating that in this study, a high percentage of those categorized as AACD developed dementia on follow up, but the AACD diagnosis did not adequately capture a large percentage of the overall group who eventually converted to dementia. Thus far, no studies have been conducted that have found equal rates of progression to dementia in those categorized as AACD and controls, and consequently categorization as AACD appears to be a strong risk factor.

Follow-up studies of those diagnosed with CIND also show an increased risk for dementia as compared to similarly aged controls. In one study, 47% of participants with CIND converted to dementia within five years, a significantly higher rate than that seen in the control group (15%; Tuokko et al., 2003). Even when CIND diagnosis was based solely on global cognitive functioning, which may be an insensitive way to determine cognitive impairment or may be capturing those who are already on the cusp of converting to dementia, rates of conversion to dementia were still higher (35-50%) than in a control group after three years (Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002). Taken together, these rates show that CIND, whether defined clinically or psychometrically, confers an increased risk of conversion to dementia.

With respect to MCI, a number of longitudinal studies show that the diagnosis of aMCI incurs an increased risk of developing dementia during follow up periods ranging from two to nine years (Busse et al., 2003a; Busse et al., 2003b; Fisk et al., 2003; Larrieu et al., 2002; Morris et al., 2001; Petersen et al., 1995; Petersen et al., 1999; Ritchie et al., 2001). Annual conversion rates to dementia generally converge on 10-15% per year, although

somewhat lower rates have also been reported (Ritchie et al., 2001). These rates are in comparison to 1-3% per year in similarly aged controls. Although there is little controversy that those who are diagnosed as impaired according to aMCI criteria are at increased risk for dementia, the predictive ability of the diagnostic category remains uncertain. Examination of the specificity and sensitivity of the aMCI criteria show good specificity (92-98%), but very poor sensitivity (5-10%) to predict later dementia diagnosis (Busse et al., 2003a; Ritchie et al., 2001). That is, although those diagnosed with aMCI may indeed progress at a higher rate to diagnosis of dementia, the criteria are so selective that they miss out on most individuals who do in fact progress.

Similar to MCI, the MA designation of preclinical dementia was initially used to indicate suspected incipient AD cases. In an early examination of these patients, only 15% converted to dementia within five years (Breitner et al., 1995); however, the sample in that study was quite young (62-73 years old). More recent research (Tschanz, Welsh-Bohmer, Norton, Corcoran, Toone, & Breitner, 2003), however, included individuals age 65 and older, and demonstrated the predictive utility of this conceptualization, with conversion rates of 43% to dementia over a three-year period. These rates are much higher than those seen in a similarly aged control group (3%) over the same time period.

In sum, prediction of later dementia diagnosis is a key issue when considering the utility of the various preclinical categorization constructs. Although aMCI shows a consistent increase in the risk for later dementia, its predictive utility has been called into question on multiple occasions due to poor sensitivity, and AACD has emerged as a more efficient way to identify preclinical cases of dementia (Busse et al., 2003a; Ritchie et al., 2001). CIND and MA are also associated with an increased risk of later dementia (Tschanz et al., 2003;

Tuokko et al., 2003). With regard to AAMI, some studies (Hänninen et al., 1995; Snowdon & Lane, 1994) have shown no difference between rates of conversion in normals and those with AAMI, whereas others demonstrated much higher conversion rates than cognitively unimpaired subjects (Goldman & Morris, 2001).

Interestingly, when progression rates to dementia are compared among the constructs, there appears little difference between them. For example, people with aMCI generally convert to dementia at about 10-15% per year (Petersen et al., 2001). Annual conversion rates for AAMI can be estimated at 10-14% (Goldman & Morris, 2001), although much lower rates have also been reported. In studies of AACD, CIND, and MA, the annual conversion rate is around 14-16% (Ritchie et al., 2001; Tschanz et al., 2003; Tuokko et al., 2003). Although these results contradict studies that have found superior predictive utility of one construct over another (Busse et al., 2003a; Ritchie et al., 2001), at least one study has shown no difference in predictive ability with different MCI definitions (Fisk et al., 2003). It remains unknown whether any one construct is superior at identifying who will progress to dementia.

A related point concerns the specificity and sensitivity of the constructs. Amnestic MCI has been criticized for extremely poor sensitivity (5-10%) in community- and population-based studies (Busse et al., 2003a; Ritchie et al., 2001), despite excellent specificity (92-98%). Comparison of specificity and sensitivity values in conjunction with rates of conversion to dementia can provide a richer understanding of the relative strengths and weaknesses of preclinical dementia constructs. Specifically, although rates of conversion may be similar, sensitivity and specificity analyses can determine whether a majority of dementia cases are being captured by the diagnostic nosology.

Current study

As is clear from this review, researchers are working to identify a preclinical state of dementia and Alzheimer's disease. There are multiple problems with the existing literature, however. First, exact criteria for inclusion have not always been clearly stated, leading to their inconsistent application across studies. Second, although most researchers have identified which type of cognitive impairment is important for their definitions, they have recommended different neuropsychological tests to measure the same construct (e.g., memory), resulting in difficulty comparing the frequencies/prevalences of various definitions. Third, few studies identifying prodromal states of dementia have included more than one category to compare which better predicts later dementia. Several have compared two of the categories (e.g., Richards et al., 1999), but none has examined all syndromes within the same population. It also remains unclear at this point how much overlap there is between the different syndromes, and whether one category is superior in predicting later dementia. What is needed is a study that compares the baseline clinical and neuropsychological characteristics of persons who meet full criteria for each construct, and then compares the outcomes (e.g., improvement, conversion to dementia) at a follow-up evaluation. Accurate estimates of frequency within a healthy elderly population using each construct can then be studied, which will help to define the overlap among them and determine if they are measuring different syndromes. It will also be possible to use the categorization system to predict later onset of dementia. The current study addresses these issues, as described in the following four goals.

Goal #1: Determine relative frequency of preclinical dementia constructs in the study sample.

In the existing literature, prevalence rates of preclinical dementia constructs vary considerably, from as low as 1% to possibly 80%, when different criteria are used. Moreover, no study to date has examined the prevalence of more than three different definitions of the transitional state within the same sample. Determining the relative frequencies of the constructs within one study is important, because studies typically vary in sample characteristics and the selection of neuropsychological tests used to establish diagnostic criteria. To do so with the seven major conceptualizations of preclinical dementia is the first goal of this study. It is hypothesized that the frequencies with which each construct occurs will vary, and that prevalence rates will replicate what has been reported in the literature. Thus, the prevalence for AAMI is expected to range anywhere from 7-38% of the sample, whereas AACD will likely represent 20-25% of the sample. As CIND is the most inclusive of the diagnoses, it is expected to have the highest frequency (>35%). Amnestic MCI and MA are likely to have the lowest frequencies, with an expected rate for aMCI approximately 1-4%, and for MA, 2-10%. Although there are no studies from which the frequency of fMCI can be estimated, it is theoretically a broader construct than aMCI, but more stringent than CIND, and consequently a rate between 5-35% might be expected. Although population prevalence rates will not be able to be estimated because of the composition of the sample (reasons will be discussed in the Methods section), establishing relative frequencies among the different constructs will eliminate the contributions of sample and methodological differences among studies, and consequently the relationships among constructs can be more clearly examined.

Goal #2: Examine overlap among preclinical dementia constructs.

Examination of the overlap among constructs is useful for two reasons. First, it can provide information regarding whether groups of constructs have underlying similarities. Second, by examining overlap in conjunction with longitudinal analyses, it can be determined whether two constructs represent different time points along a cognitive continuum from normal to pathological aging. The existing literature often uses preclinical dementia terms interchangeably, and consequently very strong overlap should be expected. However, this prediction is not supported in the few studies that have specifically examined overlap between constructs. For example, it can be hypothesized that there will be a moderate degree of overlap between AAMI and AACD. That is, at least 50% of people characterized as one construct can simultaneously categorized as the other. Moreover, a high percentage of people classified as AAMI and AACD will also be able to be categorized as CIND, but the reverse is not expected to be true. Although there is no literature indicating how much overlap there may be among the other constructs, there will likely be overlap between fMCI and MA, as both of them include functional impairment as a core criterion. Additionally, there should be some degree of overlap among aMCI, fMCI, and MA, as all three constructs were developed specifically as a prodromal stage of AD, rather than a broad preclinical dementia construct that might be expected to progress to types of dementia other than AD (e.g., vascular).

Goal #3: Determine the stability of preclinical dementia constructs over a 3-year period.

Stability of preclinical dementia constructs over time has recently emerged as an area of importance. There is an assumption that cognition declines from normal to dementia during aging, but this may not always be the case. Consequently, it is important to evaluate

the different constructs to determine whether any might represent a more stable, non-pathological, cognitive state. Moreover, as noted in Goal #2, an individual's cognition may decline insufficiently to be diagnosed as demented, but enough for the individual to meet criteria for differently-defined preclinical dementia constructs. It appears that although some people classified as AAMI do experience a cognitive decline to dementia, there is also a substantial proportion of individuals (perhaps up to 60%) whose cognition remains stable over a period of years. Diagnosis of AACD is also expected to remain fairly stable (approximately 60%) over the three-year period, consistent with extant studies. In contrast, very few people with aMCI (7-14%) are expected to continue to be classified as such at a 3-year follow up, consistent with literature indicating its instability. Although a percentage of people may decline to dementia, a high percentage of aMCI people are expected to convert back to "normal" cognitive status. There are no strong predictions regarding the stability of fMCI, MA, or CIND.

Goal #4: Compare the predictive validity of preclinical dementia constructs to determine which is superior at predicting later dementia.

The ability to predict later dementia diagnosis from preclinical status has been a key motivation for the development of most of the preclinical dementia constructs. Most of the classification systems reviewed do, in fact, incur an increased risk of later dementia compared to a normal control group, with the possible exception of AAMI, for which there is mixed evidence. Thus, it is expected that classification in any construct will be associated with later dementia diagnosis. Surprisingly, when the annual rates of conversion are compared among different constructs and different studies, they all roughly converge on 10-15% per year. It might be expected, then, that for each construct, approximately 25-40% of

those classified at baseline will convert to dementia by the 3-year follow up examination. These increased rates will be in comparison to unimpaired control groups defined according to the criteria for each classification system. This unimpaired group is expected to show decline to dementia at approximately 1-3% per year.

Despite the expected similarity in conversion rates to dementia, the sensitivities and specificities are expected to differ considerably among the major constructs. Amnestic MCI is expected to have high specificity (e.g., >90%), but very low sensitivity. CIND and AACD are expected to show lower specificity than aMCI (e.g., 65-80%), but much higher sensitivity (e.g., >80%). There are no strong predictions for the sensitivity and specificity of the remaining constructs (AAMI, MA, fMCI), as there is no known literature on this topic.

Method

Study Sample

The Cache County Memory Study (CCMS) is an ongoing longitudinal population-based epidemiological study aimed at identifying the genetic and behavioral precursors to dementia and, more specifically, AD. Currently, three waves of data spaced three years apart, including comprehensive medical and neuropsychological evaluations, have been collected. Details of the study protocol have been published previously (Breitner et al., 1999; Miech, Breitner, Zandi, Khachaturian, Anthony, & Mayer, 2002). All residents aged 65 or older as of January 1, 1995, constituted the population for study (N= 5,677). Participation was refused by 559 individuals, and 26 additional people were deceased by the time of the screening evaluation, leaving 5,092 individuals who completed a cognitive screening evaluation.

The cognitive screen primarily used an adaptation of the modified Mini-Mental State Examination (3MS; Teng & Chui, 1987). Proxy interviews (n=386) were conducted with informants instead of the 3MS when any of the following criteria were met: 1) the individual was unable to complete the 3MS; 2) the individual had poor orientation, as indicated by a score below 15/20 on an early portion of the 3MS; 3) the individual scored less than 60/100 on the 3MS; or 4) the individual's ability to provide a history was deemed unreliable. Proxy interviews screened for cognitive impairment using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 1994), and this interview yielded an overall score ranging from 0 (no impairment) to 5 (extreme impairment).

Of the 5,092 who completed the first step of screening, 1,989 were selected to complete a Dementia Questionnaire (DQ; Breitner et al., 1999) with an informant to further assess cognitive impairment. Individuals who were approached to undergo this assessment met one of four possible scenarios: 1) scored ≤87 on the 3MS or ≥3.27 on the IQCODE (n=939), 2) were 90 years or above (n=77), 3) were referred by a community physician for further assessment (n=13), or 4) were an age- and genotype-matched cognitively normal control (n=960; described below). There were 1,856 participants on whom the DQ was completed. DQs were scored by a consensus of two or more clinicians in the following manner: 1) no impairment; 2) mild memory or other cognitive difficulty; 3) moderate cognitive difficulty insufficient to meet criteria for dementia; 4) questionable dementia; 5) probable dementia. A stratified subsample of the population was created using iterative sampling without replacement in order to carry out a nested case-control study (n=960; Group 4 from above). Each member of this subsample completed a full clinical assessment and diagnostic evaluation, regardless of results on the cognitive screening evaluation or DQ. Members of the subsample included two nondemented individuals matched to each of the prevalent AD cases by sex, 5-year age group, and number of _4 alleles (Breitner et al., 1999).

Individuals who received a score of 4 or 5 on the DQ or were part of the designated control group were selected to undergo a full clinical assessment, described below (n=1196). Of those who completed the full clinical assessment (n=1,033), 335 had a diagnosis of dementia and were excluded from the present study. Dementia diagnosis was established after the clinical examination was completed, and included physical and neurological exams, lab work standard for a dementia evaluation and neuroimaging when deemed appropriate. The diagnosis of dementia was made according to DSM-III-R criteria (American Psychiatric

Association, 1987) and required evidence of both neuropsychological and functional impairment, as well as a clinical history consistent with the diagnosis. Diagnosis of Alzheimer's disease was consistent with the guidelines set forth by the NINCDS-ADRDA (McKhann, Drachman, Folstein, Kathzman, Price, & Stadlan, 1984).

The remaining participants were not demented (n=698), but of this group, 37 were missing more than 50% of their neuropsychological data and were excluded from the present sample, leaving a sample size of 661 for the present study. Data from the three-year follow-up are available for 459 people (69% of the original sample), and include the full screening and neuropsychological evaluations completed at baseline.

Clinical assessment

Clinical assessments were performed in participants' homes by a research nurse and psychometrician, and included information collected from both the participant and an informant. A research nurse collected information from the informant about current cognitive difficulties, medical and psychiatric history, and current medications. A neurological exam was performed and vital signs were taken. A psychometrician interviewed the informant using the Neuropsychiatric Inventory (NPI; Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein., 1994) and assessed functional impairment using the Dementia Severity Rating Scale (DSRS; Clark & Exbank, 1996).

The neuropsychological assessment included the following measures: an interview, including educational, occupational, developmental, and family history information, and language and writing samples; a handedness questionnaire (Oldfield, 1971); the CERAD battery (Morris et al., 1989), which includes semantic (animal) fluency, a 15-item Boston Naming Test, word list learning task with delayed recall and recognition, and a

constructional praxis test with delayed recall; Trails A and B (Reitan, 1986); Logical Memory paragraph recall test, both immediate and delayed (Wechsler, 1987); Controlled Oral Word Association Test, a verbal fluency task (COWA; Benton & Hamsher, 1988); Visual Retention Test, an immediate visual memory task (BVRT; Benton, 1974); Symbol Digit Modalities Test, an executive functioning task (SDMT; Smith, 1982); and the Shipley Institute of Living Scale, vocabulary subtest (Zachary, 1991). Participants' scores were compared to age- and education-corrected normative values.

Diagnostic criteria selection

One of the major problems with the preclinical dementia literature is that diagnostic criteria have been interpreted and applied in different ways, thus rendering it difficult to compare the constructs. Thus, in the current study each criterion of each construct was operationally defined and applied consistently. In order to attain this goal, the primary articles associated with each construct were carefully reviewed (see Table 1), and the core criteria for each construct were listed. Once there was a list of necessary criteria for each entity, the baseline examination data in the CCMS database were examined in order to map available data onto the criteria laid out by the researchers who developed each category. For instance, many of the definitions require a report of cognitive decline, either by the patient or informant. For this variable, a positive response to at least one of four "cognitive complaint" items on the DQ or an IQCODE score of greater than or equal to 3.0 satisfied that criterion.

Table 2 details the criteria used to conceptualize and define each construct. For all the categorizations with the exception of CIND, there was a distinction between required and supportive criteria for inclusion into the category. Supportive criteria were deemed secondary, and were generally established because missing data for these variables would

render a large number of participants unable to be classified. These criteria are noted in Table 2 as *supportive.* For example, the AACD and MA definitions require a gradual onset of symptoms. However, there was much missing data for the disease onset variable because informants were not instructed to estimate the onset date of cognitive decline if they had not endorsed multiple items on the DQ. As a result, for this study, individuals were considered to meet full criteria for AACD of MA if there was no evidence of a sudden onset of symptoms, or if there were missing data for that variable, but they met all other criteria. A similar procedure was adopted when data were missing on the Shipley-Hartford Vocabulary Test in AAMI and aMCI, as well as for the CDR for both MCI definitions. In determining who met neuropsychological criteria, age, education, and gender-corrected norms were used when appropriate.

For each construct, those individuals who did not meet the criteria constituted a heterogeneous group. For instance, they included participants who met all cognitive or functional criteria, but had a medical disorder that kept them from meeting full criteria. Those individuals who did not meet full criteria were split into two groups: those who met all criteria other than the absence of medical, neurological, or psychiatric conditions ("meets inclusion criteria only"), and those who were considered "unimpaired" based on the cognitive and/or functional requirements for each construct. The makeup of each construct's "meets inclusion criteria only" and "unimpaired" groups varied due to variations in definitions in who met full criteria (see Table 2). “Unimpaired” criteria for each construct were developed based upon that construct’s criteria. For example, for AACD, an individual was considered “unimpaired” if he or she scored higher than one standard deviation below age and education corrected norms on each neuropsychological test in all cognitive domains, or if he or she did

not have any cognitive complaints as reported by an informant. For aMCI, a person was considered "unimpaired" if he or she scored higher than 1.5 SD below age and education corrected norms on each *memory* test, if he or she did not have any cognitive complaints, or if a CDR score of 0 was reported. For each construct, there were also some people who could not be classified. Generally, constructs that included only memory impairment (AAMI, aMCI, and MA) or age restrictions (AAMI) had a higher number of participants who could not be classified. For example, a participant who did not show memory impairment, but had objective evidence of impairment in an additional cognitive domain and also had an underlying medical disorder could not be classified under the AAMI definition as meeting full criteria, meeting inclusion criteria only, nor was it appropriate to classify that participant as unimpaired. These numbers will be reported in the results section.

Results

Goal #1: Frequency of preclinical dementia constructs

Frequency analyses were run at both the baseline and 3-year follow up waves to determine the frequency with which preclinical dementia constructs occur in the CCMS sample. Table 3 shows the frequency with which the seven preclinical dementia constructs occurred at the Wave 1 baseline evaluation. Consistent with hypotheses, the frequencies vary widely based on operationalized criteria, with aMCI occurring least frequently (n=10, 1.5% of the sample), and fMCI occurring most often (n=324, 49.0% of the sample). Low rates of preclinical dementia were detected by the two AAMI definitions and aMCI (range of 1.5-3.2% of the sample). There was an intermediate rate as conceptualized by AACD (17.9%), and a higher rate according to CIND, MA, and fMCI (range 31.6-49.0%).

In addition to the frequencies of the full constructs at the baseline evaluation, we also examined the frequency using less stringent criteria by looking at individuals who met inclusion, but not exclusion, criteria. These participants otherwise would fall in the "unable to be classified" group. In this way, we hoped to determine the extent to which overly stringent exclusion criteria (such as a diagnosis of depression) influenced the frequency with which the constructs occur. Thus, Table 3 also includes frequency information for those participants who met inclusion criteria only. By combining those who meet full criteria with those who meet inclusion criteria only into an overall "impaired" group, the rate of preclinical dementia for the two AAMI definitions and AACD more than doubled. For fMCI and MA, the number of individuals in the "meets inclusion criteria only" groups was about

half of the full criteria group, suggesting that overly stringent exclusion criteria have less of an effect on categories that rely on functional impairment as a core criterion. Qualitative examination of the "meets inclusion criteria only" group suggests either that exclusion criteria may be too stringent (e.g., the presence of certain medical conditions that may or may not be related to the individual's cognitive impairment), that medical and psychiatric conditions frequently are associated with cognitive impairment (e.g., Lyketsos et al., 2005), or both. When exclusion criteria were omitted, both fMCI and MA increased in frequency by approximately 50% (e.g., the prevalence rate increased from 49% to 66.5% of the sample).

Table 3 also includes the number of participants who were deemed cognitively normal according to each construct's criteria. These rates ranged between 48-58% of the sample, except for aMCI, which classified nearly 75% of the sample as cognitively normal, and fMCI, in which slightly less than 25% of the sample was considered normal. Finally, Table 3 also indicates those who were unable to be classified based on each constructs' criteria at the baseline evaluation. Participants were unable to be classified either because of missing data, or, more commonly, because the criteria for a particular construct made it difficult to categorize that participant. Specifically, aMCI and both AAMI definitions had high percentages (24-38%) of individuals who could not be classified, primarily including individuals impaired in cognitive domains other than memory.

Table 4 details the same information as Table 3, but for the Wave 2 follow-up examination. Also included in Table 4 are the number and percentage of the sample that at that time were demented, deceased, or refused further examination. When those who refused the follow-up exam or died beforehand were excluded from the analyses (remaining n=459), preclinical dementia rates at Wave 2 were very similar to those at the baseline evaluation,

with the exception of CIND, in which the sample percentage dropped from almost 38% at baseline to 21% at the follow-up examination. All other constructs had frequencies at the follow-up evaluation that were within 3% of the baseline frequency (see Table 5). To determine whether those participants who did not complete the Wave 2 examination (n=270; either because of refusal, death, or dementia) differed from those who did (n=391), *t*-tests compared the two groups on age, education, and baseline 3MS scores, and Chi-square analyses compared the two groups on gender and APOE e4 status. Those who dropped out of the study were older ($t(659) = 4.82$, $p < .001$), less educated ($t(656) = 2.14$, $p = .03$), and had lower 3MS scores (adjusted for education and sensory impairment; $t(655) = 4.97$, $p < .001$) than those who completed the follow-up examination. Those who dropped out were also more likely to be men ($\_^2(1, N=661) = 4.10$, $p = .04$) and have an APOE e4 allele ($\_^2(1, N=660) = 6.44$, $p = .01$). Additional *t*-tests comparing just those who refused the follow-up evaluation (n=94) with those who completed the evaluation revealed that those who refused had lower levels of education ($t(540) = 2.40$, $p=.01$), but no differences based on age, baseline 3MS score, gender, or APOE4 status.

Table 6 shows the sample demographic and neuropsychological characteristics of participants who met full criteria for the seven preclinical dementia constructs at the Wave 1 baseline evaluation, as well as a comparison to the full sample (N=661). Two-sample *t*-tests were conducted between those meeting full criteria against the full sample, minus those in that construct group. Statistically significant differences were present across multiple variables.

Results indicated that the two AAMI groups had a somewhat different profile from the other constructs. Specifically, they had significantly higher MMSE and vocabulary

scores, although vocabulary scores were used in determination of construct categorization. Moreover, their scores on some tests of language (lexical fluency), constructional praxis, and executive functioning (Trails B) were significantly better than that of the full sample. The AAMI group also performed significantly better than the overall sample in visual memory, speeded attention (Trails A), semantic fluency, and an additional measure of executive functioning (Digit Symbol). As expected, the AAMI construct, which limits age to less than 80, was significantly younger than the overall sample. Interestingly, the AAMI group also contained a higher than expected percentage of individuals carrying the APOE e4 allele. Overall, there was no evidence of objective cognitive decline relative to age- and educated-matched peers in either AAMI group, which is much more consistent with a subgroup of normal, rather than pathological, aging.

Individuals classified as CIND were significantly older, were proportionally more female, were less well educated, and had lower vocabulary scores compared to the full sample. They had statistically significantly lower scores on all neuropsychological variables, as expected, given that the categorization criteria included variables in all neuropsychological domains. In contrast, individuals classified as AACD, the definition of which also uses all neuropsychological domains in the definition, but specifies scores 1 SD below the mean, rather than 1.5 SD as in CIND, did not differ from the full sample in demographic characteristics on any tests except for verbal recall.

In the aMCI group, the individuals were also less educated, but had significantly higher vocabulary test scores than the full sample. Unlike the MA group, they were only impaired on a verbal list learning task, as specified in the diagnostic categorization criteria. Similar to the published criteria (Petersen et al., 1999), these participants had

neuropsychological test scores within expected ranges in domains besides memory, and actually had significantly better scores on Trails B, even though this was not specifically designated in the diagnostic criteria for the current study. The fMCI group did not differ from the full sample on any neuropsychological variables, despite being significantly older.

Similar to CIND, the MA group was significantly older and less educated than the full sample. They also performed more poorly on the vocabulary test. In addition to the expected poor performance on memory tests inherent in the definition, these individuals also had lower baseline neuropsychological test scores in the domains of language (lexical and semantic fluency), executive functioning (Trails B and Symbol-Digit), and overall global cognitive functioning (MMSE), even though these scores were not used in assigning the diagnostic classification.

Discussion.

The first goal of the study was to explore the frequency of preclinical dementia constructs in an epidemiological study. Based on the extant literature, rates were expected to vary. This hypothesis was confirmed, as the rates of preclinical dementia in the current study ranged from 1.5% (n=10) to 49% (n=324) of the sample. When exclusion criteria were omitted, frequency rates for the AAMI and AACD constructs more than doubled, suggesting that these constructs in particular have stringent exclusion criteria that affect the rate of occurrence. These findings are not unique; a population-based study of AAMI revealed prevalence rates of 38% with and 54% without exclusion criteria (Koivisto et al., 1995). Whether criteria are considered too stringent or not is very much related to the goal of the study. For example, epidemiological studies (such as this one) may seek to identify anyone who may be at risk for later dementia, and may prefer to emphasis sensitivity over

specificity. In contrast, a pharmaceutical company clinical trial seeking to test the effects of a drug on later development of AD may wish to restrict the sample to a much smaller group that is physically quite healthy and has more pronounced neurocognitive deficits, sacrificing sensitivity for enhanced specificity.

Initially, the AAMI construct and a subset of the AACD construct were thought to represent normal, rather than pathological, aging. The results presented here suggest that stringent exclusion criteria may lead to an overly restrictive sample with low sensitivity to later progression to dementia. Moreover, medical comorbidities are more common in preclinical dementia and dementia samples, in comparison to non-cognitively impaired individuals (Lyketsos et al., 2005). The issue of progression will be discussed within the context of Goal #4.

Based on the rates found in the overall literature, the rates of AAMI were expected to be between 7-38%, much higher than the 3.2% rate found in the current sample. This discrepancy may be related to ongoing methodological differences between our sample and published studies, as our study is the first community sample study of AAMI rates based on the Blackford & LaRue criteria. Even with respect to the original AAMI criteria, however, an epidemiological study in Finland also showed much higher rates (38%) than the current study (Koivisto et al., 1995). The age range in the Finnish study, however, was limited to 60-78, and thus the current sample is significantly older. Although the rate of AAMI in the current sample doubled (7%) when the analysis was limited to those under the age of 80 (n=299), these rates are still far below what would be expected, based on the Koivisto study.

AACD rates in the current study were generally consistent with the extant literature, with a rate of 17.9%, just slightly lower than published rates of 20-25%. As expected, rates of

AACD were higher than those of AAMI, consistent with the broader cognitive inclusion criteria for AACD. The rates of aMCI were also consistent with previous literature in community or population-based studies (Busse et al., 2003a; Fisk et al, 2003; Lopez et al., 2003), with a current estimate of 1.5%, the lowest among the constructs, although some studies found slightly higher rates of between 3-5% (Hanninen et al., 2002; Larrieu et al., 2002; Manly et al., 2005; Ritchie et al., 2001). A very recent population-based study exploring functional impairment (Pérès, Chrysostome, Fabrigoule, Orgogozo, Dartigues, & Barberger-Gateau, 2006) showed an overall prevalence rate of 51.8%, consistent with the rate of 49% of the sample who fit the fMCI categorization in the current study.

CIND rates were somewhat higher in the current study than found in the literature (cf. 30% of the CHSA study; Ebly et al., 1995), possibly due to the fact that all constructs in the current study were defined algorithmically, whereas CIND has generally been diagnosed by clinical consensus. Indeed, the rates of algorithmically-derived MA in the current study (n=209; 32% of the sample) differs from the rate of MA (2%) when defined by clinical consensus in the same population (Tschanz et al., 2006), although the clinical consensus rate was based on the entire population, not a subsample as in the current study. In the Tschanz study, which uses the Cache County data as well, 206 individuals were identified as mildly impaired in some way at the baseline evaluation. Only 81 of them overlap with the current study. Regardless of the difference in sample construction, even within the same population studied, the point can be underscored that algorithmic and consensus approaches to diagnosis may vary considerably in the individuals identified for further follow-up.

In summary, frequency rates varied among disparate preclinical dementia constructs. Discrepancies from published studies were present primarily with the AAMI definition, and

are thought to be related to differences in sample composition (for example, clinic vs. epidemiological) and/or specific criteria for the different constructs. Most importantly, the current results lend support to the emerging idea that although there may be a general preclinical dementia syndrome, the terms used in past and present literature to describe this state are not synonymous. That is, because the frequency rates vary so greatly between constructs (e.g., 1.5% to 49%), it would be impossible for these terms to each be identifying the same group of individuals.

Because the frequency results in the current study were also generally within ranges of previous research exploring preclinical dementia constructs in epidemiological, population-based studies (Fisk et al., 2003; Ganguli, Dodge, Shen, & DeKosky, 2004; Manly et al., 2005), the present study appears to be an appropriate and relevant way to compare multiple constructs in this setting.

Goal #2: Overlap among constructs

Table 7 shows the agreement between constructs at the baseline examination using unweighted Kappa statistics. Excellent agreement (≥.70) was present only among the two AAMI constructs. There was good agreement (.40-.70) between a number of pairs of constructs, including AACD with both AAMIs and CIND, and aMCI with both AAMIs, but all other pairings indicated poor agreement. These initial kappa analyses use the difference between the predicted and observed agreement of each construct's 4-prong categorization schema (e.g., meeting full criteria, inclusion criteria only, or cognitively normal criteria, or being unable to classify). As such, poor agreement may be related to differences in exclusion, rather than inclusion, criteria, and may thus be of limited utility (that is, a poor kappa may be due to one construct classifying someone as meeting full criteria and another classifying the

same individual as meeting inclusion criteria only). Thus, Table 8 shows the kappa statistics after combining those participants who met full criteria with those who met inclusion criteria only into one group (impaired), and comparing them with those who were cognitively normal. In this way, the categorization schemas more closely parallel the way in which clinicians diagnose preclinical dementia, by reducing the impact of excluding those with medical conditions that might not necessarily be impacting cognition.

Excellent agreement was seen between the two AAMI constructs (kappa = .96) and between AACD and CIND (kappa = .87). Five pairings achieved "good" agreement, with four of these being between the two AAMI definitions and AACD and CIND. Additionally, CIND and MA had good agreement (kappa = .41). The cluster of good to excellent agreement among the two AAMI definitions, AACD, and CIND may suggest that these constructs are capturing a distinct group separate from that represented by the other three constructs (both MCIs and MA). MA was the only one of the remaining three constructs that had good agreement with any other construct; specifically, with CIND. The two MCI definitions and MA had poor agreement among themselves (kappas ranging from .01-.18), contrary to expectation.

Because both MCIs and MA were developed specifically as prodromal states to Alzheimer's disease, it is surprising that they have such poor overlap. In order to determine the locus of this disagreement, the data were descriptively explored (see Figure 1). By visually examining the raw data, it was determined that 80% (8/10) of those meeting criteria for aMCI also met criteria for fMCI, suggesting that the disagreement was due to the great inequality in sample size. Moreover, *all* of the individuals who met aMCI criteria also met criteria for MA. Disagreement between fMCI and MA was generally attributable to

differences in the way each defined functional impairment (see Tables 2e and 2g). More specifically, of those categorized as MA, three quarters of the group (75.6%) also met criteria for fMCI. However, only 31% of those classified as fMCI met criteria for MA functional impairment. This discrepancy is clearly related to the broader functional criterion for fMCI. Although both constructs include functional impairment as an inclusion criterion, fMCI was operationalized to include those with impairment in both basic ADLs and IADLs, whereas MA specifically included only those with IADL impairment. In addition, 37% of the fMCI group also met the MA memory impairment criterion, and overall, 50% of those classified as fMCI also met full criteria for MA. Taken together, these results suggest that differences in operationalizing functional impairment likely influence the diagnostic categorization process.

Overlap between AACD and CIND was further examined by visually examining the raw data (see Figure 1). Overlap between these two constructs can provide information regarding the role of neuropsychological cutpoints in diagnostic criteria, since both constructs rely on multiple domains of cognition. Moreover, because CIND does not have any exclusion criteria, any differences can be more reliably tied to discrepancies in neuropsychological criteria, particularly when examining the AACD "impaired" group, which does not include exclusion criteria. In the AACD group, 79% met criteria for CIND, and all CIND individuals met AACD neuropsychological criteria. As expected, this suggests strong overlap in neuropsychological impairment between the two groups. Moreover, the comparison of AACD and CIND underscores how exclusion criteria can influence agreement, in that the kappa between the full constructs (including exclusion criteria in AACD) was 0.43, but doubled (0.87) when the AACD criteria did not take exclusion criteria into account.

To further explore the locus of disagreement between constructs originally conceptualized as normal aging (both AAMIs and AACD), the data were descriptively explored by visually examining the raw data (see Figure 1). Although the kappa statistics among these constructs were good to excellent (range 0.41 to 0.80), some interesting observations emerged. For example, 64% of those meeting AACD criteria (75/118) did not meet AAMIO criteria due to an exclusionary medical condition. More than half of the AACD group did not meet the criterion for "intact intellect" for AAMIO (59%; 69/118) or AAMI (54%; 64/118) despite different operationalizations, in that the revised AAMI criteria allow for a much broader definition of "intact intellect" (-0.67 SD to +2.0 SD). Moreover, 61% of those meeting AACD criteria did not meet the AAMI age criterion; these individuals were 80 years and above. Overall, over half of the AACD group (54-61%) did not meet AAMI/AAMIO criteria due to age and intellectual criteria.

In exploring the overlap between the two AAMI definitions, it was found that most discrepancies in classification were related to inclusion or exclusion of individuals with a current medical condition, in particular, cardiovascular and endocrine conditions such as hypertension, diabetes, hypothyroidism, and history of myocardial infarction. Just under half (10/21) of the AAMI group did not meet AAMIO criteria for this reason. Conversely, AAMIO individuals who did not meet AAMI criteria did so because of the age restriction in the latter (9/21).

Overall, these descriptive analyses of both AAMIs and AACD strongly suggest that constitutional factors such as age, premorbid intellectual functioning, and medical conditions affect diagnostic categorization in preclinical dementia groups. Because the AAMI definitions in particular were conceptualized as normal aging, these distinctions may serve to

constrict the group to healthier, younger individuals who are less likely to develop dementia. This issue will be discussed in the fourth section, on prediction.

Discussion.

The goal of exploring overlap among constructs was primarily achieved with descriptive analyses, including kappa statistics and exploration of percentages of constructs meeting other constructs' criteria. The kappa results suggested that the two AAMI definitions and AACD may be capturing a distinct subset of the sample studied; presumably, this group would be more akin to a subset of normal aging as originally conceptualized. Descriptive exploration of the AAMI/AACD overlap suggested an effect of constitutional variables, such as age, medical comorbidities, and premorbid intellectual functioning, on categorization.

Additionally, the kappa analyses revealed very poor overlap among the three constructs conceptualized as early AD (aMCI, fMCI, and MA). Descriptive exploration of these two clusters revealed that the poor kappas in the prodromal AD cluster (e.g., aMCI, fMCI, and MA) were due to the large discrepancy in sample size, with aMCI being completely subsumed by fMCI and MA. Moreover, descriptive analyses showed high levels of overlap among fMCI and MA, and indicated that disagreement was related to differing operationalizations of functional impairment. The overlap analyses thus highlight the importance of the impact of both preexisting constitutional factors in the preclinical dementia syndrome, as well as the conceptualization and practical application of measuring functional decline.

As noted above, the overlap analyses among the "normal aging" constructs (e.g., both AAMIs and AACD) provide evidence of the effects of variations in medical exclusion criteria and "intact intelligence". Low educational level has been shown to be a risk factor for

both MCI (Lopez et al., 2003; Manly et al., 2005) and later development of dementia (Skoog & Gustafson, 2006). Poor cardiovascular health has also been associated with MCI (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Tervo et al., 2004), and thus it is unsurprising that variation in these factors may be related to changes in group categorization rates.

Previous studies exploring overlap between preclinical dementia categories are sparse and primarily limited to AAMI and AACD overlap. Current analyses showed substantial overlap between AAMI and AACD, which was primarily due to the AAMIs being a subset of AACD. There were 6/21 AAMIO and 3/21 AAMI individuals who did *not* meet AACD criteria, and all were due to medical exclusion criteria. These results are consistent with the Canadian Study of Health and Aging overlap analysis, which found that 96% of those categorized as AAMI could also be categorized as AACD (Ebly et al., 1995). A recent study exploring the overlap among aMCI, AACD, and those individuals characterized by a GDS score of 3 revealed that all but one of the individuals could be categorized as AACD (Visser, Kester, Jolles, & Verhey, 2006). That is, almost all the aMCI and GDS3 groups were also AACD. Our results are consistent with this as well, in that the 10 aMCI participants were fully subsumed under AACD (as well as under MA).

As noted above, the results of the overlap analyses also raise the issue of consistency in the operationalization of functional impairment. In the current study, this was assessed by an informant-completed scale, the DSRS. The primary distinction among constructs regarding functional impairment was that fMCI included ADL disability, whereas MA functional impairment was limited to IADL dysfunction. Mild functional problems have recently been thrust into the forefront of the MCI debate, both in terms of who reports

decline (e.g., patient or caregiver) as well as the distinction between instrumental and more basic activities of daily living. Although there is an emerging consensus that individuals with MCI may be functionally limited (Nygard, 2003), IADL impairment was explicitly excluded from the initial MCI conceptualization (Petersen et al., 1999). Recent work has not only shown that individuals with various definitions of MCI show functional impairment (Farias, Mungas, Reed, Harvey, Cahn-Weiner, & DeCarli, 2006; Tabert et al., 2002; Tuokko, Morris, & Ebert, 2005), but has also focused on which domains specifically are impaired. Farias and colleagues (2006) conducted an in-depth assessment of functional impairment in a consensus-diagnosed group of individuals at a memory clinic and determined that the IADL domains most affected included those tasks dependent on everyday memory, such as remembering a list, learning new names, and remembering where objects had been put. Another study also suggested that difficulty in performing housework as the earliest sign of functional decline was related to cognitive impairment five years later (Tuokko, et al., 2005). Thus, in the context of the current study, it would support a distinction between the two definitions of functional impairment and suggest that IADL impairment drives predictive utility (to be discussed in a later section), possibly even before cognitive impairment can be detected. Similarly, it may also be that those individuals with very mild functional impairment are at an earlier stage of decline than those with multiple cognitive deficits (such as those with AACD or CIND as defined in the current study).

Decline in instrumental functions can also be a proxy for underlying cognitive decline that may not yet have been detected due to poor sensitivity of some cognitive tests, as stated above. IADL impairment can not only be related to general neuropsychological integrity, but to specific domains such as memory and processing speed (Tuokko et al., 2005). Although

the temporal relationship between cognitive and functional impairment remains somewhat equivocal, in that they tend to co-occur, there is substantial evidence that, regardless of how IADLs are operationalized, they are an important consideration in any study of MCI and later dementia both because it is often the earliest indicator of problems (Tuokko et al., 2005) as well as an effective predictor of later cognitive decline (Nygard, 2003).

An additional issue in the literature is in regards to who evaluates functional impairment, the patient or a knowledgeable informant. In the current study, the measure of functional impairment (DSRS) was completed by an informant. Informant-completed measures may be influenced by caregiver depression, the relationship with the patient, or caregiver cognitive impairment (Weiner, Gehrmann, Hynan, Saine, & Cullum, 2006). Informants may also under- or overestimate actual abilities, as assessed by direct observation (Wadley, Harrell, & Marson, 2003). The alternative, however, to use problems reported by the patient, may be hampered by cognitive impairment and/or lack of awareness into functional difficulties. Indeed, it has been demonstrated that a discrepancy index between caregiver and self-reported functional decline was strongly predictive of a later diagnosis of AD (Tabert et al., 2002). Direct observational assessment is another way to assess functional abilities; however, this method is prone to error due to variations in patient motivation and can be less ecologically valid than caregiver assessment since the activities observed are not in the natural environment (Marson & Hebert, 2006). Thus, for epidemiological studies in the general population, report by an informant, rather than an individual, appears superior, at least as far as the relationship to actual everyday functioning, and may be more practical than direct observational assessment.

In summary, overlap analyses in the current study revealed that "normal aging" constructs including AAMI may indeed contain individuals who are aging successfully and are less likely to decline to dementia. Criteria that are restrictive, such as limited educational attainment or vocabulary scores, as well as exclusion of common medical comorbidities such as cardiovascular disease, may result in a small group of individuals who do not overlap with other preclinical dementia constructs.

Overlap among hypothesized preclinical AD constructs, including aMCI, fMCI, and MA was hampered by significant discrepancies in subsample sizes, which artificially drove down kappa estimates. Descriptive exploration revealed that these three constructs did overlap quite a bit. Specifically, aMCI was completely subsumed by MA, and differences between MA and fMCI were entirely due to differences in operationalization of functional impairment. Mild impairment or decline in IADLs may be a harbinger of later cognitive decline (Tuokko et al., 2005), or may simply be an ecologically relevant expression of cognitive deficits too mild to be picked up on by current neuropsychological measures.

Goal #3: Stability over time

To examine stability of preclinical dementia constructs over the three-year period, a two step process was undertaken that included grouping the data in two ways. First, outcomes were described for each construct with participants grouped as meeting full criteria, inclusion criteria only, cognitively normal, and unable to be classified. Then, outcomes were examined for each construct after combining the full criteria and inclusion-criteria-only groups into a single "impaired" group. For each of these groupings, stability was examined in two ways. The first way compared percentages of individuals who remain categorized the same way over time (e.g., as meeting full criteria). The second way is based

on the assumption that those initially diagnosed with a preclinical dementia will decline in their functioning over time. Thus, the second approach combined those who maintain the diagnosis with those who progressed to dementia (Alzheimer's disease or other dementia) over the 3-year period (n=68), and compared all of them to those who improved over the same time period. Note that the denominator included those who died and refused further examination, so that percentages do not add up to 100%.

In the AAMIO group, 24% remained categorized as such after three years, whereas 38% reverted to cognitively normal (Table 9). One person (5%) declined to dementia. When the full criteria group was combined with those meeting inclusion criteria only, resulting in an overall "impaired" group, 22% retained this categorization over time, 31% converted back to normal cognitive status, and 12% declined to dementia (Table 10). As such, it appeared that AAMI had generally poor stability, since a greater percentage of individuals were unstable and converted back to normal status, even when exclusion criteria were relaxed. Even when including those who converted to dementia in the group that remained stable, roughly equal percentages (34% v. 31%) remained stable or declined as compared to improved (see Table 10).

In the AAMI group, 24% of those meeting full criteria were stable across the 3-year period, as compared to 52% who converted to cognitively normal. No one carried a dementia diagnosis at the follow-up evaluation. In the combined "impaired" group, 26% remained stable, 41% converted back, and 9% declined to dementia. Thirteen percent died or refused further evaluation. Combining those who remained stable with those who declined did not lead to improved stability, in that more individuals converted back to normal (41%) than

remained stable or declined to dementia (36%). Thus, with respect to the AAMI definitions, it appears that the original criteria are more stable over time than the revised criteria.

Although AACD and CIND rely on multiple cognitive domains, and might thus be expected to be more stable over time, this did not appear to be the case. Only 18% of those meeting full criteria for either definition remained classified as such over time, and similar to the AAMI definitions, 28-35% of these groups converted back to cognitively normal at follow-up, compared to 12-19% who declined to dementia. In comparing rates of those impaired with those who improved, only 13% of AACD remained stable, as compared to 28% who improved (Table 10). Again, 18-19% of those considered impaired at Wave 1 declined to dementia. Rates were somewhat better when those who remained stable or declined to dementia were combined and compared against those who converted back to cognitively normal. Specifically, the rates of stability/decline compared to improvement were roughly equivalent for both AACD and CIND (AACD: 30% stable/declined, 35% improved; CIND: 37% stable/declined, 28% improved).

To further explore the shifting status of the AACD and CIND groups, the data were qualitatively explored. Of the 41 individuals who were categorized as meeting full criteria for AACD at baseline, but were cognitively normal at Wave 2, 32 of them showed improvement on tests of memory and met the criteria for normal memory at the follow-up evaluation. Improvement on measures of attention, thinking, and language was present for 24/41, and 11/41 improved in visuoconstructional test performance. Fourteen individuals improved in at least 3 of the four cognitive domains. Qualitative exploration of the CIND data (n=70) revealed that 32/70 showed improvements in memory, 42/70 improved in attention/executive functioning, 38/70 improved in language, and 17/70 improved in visuoconstructional test

performance. In many cases, scores improved only a point or two. It is likely that performance at the baseline evaluation was just beyond the cutoff, and that when performance improved minimally, this, coupled with an added 3-years to the individual's age, resulted in a score that was just inside what is considered normal.

Amnestic MCI also showed poor stability. None of those characterized as aMCI remained categorized as such at the 3-year follow-up examination, and 60% of them were classified as cognitively normal. One individual (10%) converted to dementia. Even when the impaired group was considered, only 8% remained as aMCI over time, with 50% converting back to normal. Combining the impaired group with those who declined to dementia resulted in a stable/decline percentage of 17%, again in contrast to the 50% of the group who were cognitively normal. Thus, stability of aMCI remains quite poor in epidemiological studies, similar to concerns raised in previous studies (Busse et al., 2003a; Ritchie et al., 2001).

In contrast, fMCI and MA, both of which include a measure of functional impairment, showed better stability than the other constructs. For the individuals meeting full criteria, 27% of MA and 46% of fMCI were stable over time (Table 9). These rates were in contrast to conversion rates back to normal in the sample of 19% and 9%, respectively. Ten to fourteen percent converted to dementia after three years. Utilizing the "impaired" definition yielded similar results. Twenty-nine percent of MA and 45% of fMCI remained stable, in comparison to 16% and 8% of the groups that converted back, and 13-18% converted to dementia. Combining the impaired group with those who declined to dementia resulted in 47% of the MA group remaining stable or declining in contrast to 16% who converted back to normal. For the fMCI group, 57% remained stable or declined, compared to only 8% who converted back to normal.

Qualitative exploration of the MA data revealed that of 40 individuals who improved to cognitively normal at the Wave 2 evaluation, 32/40 showed improvements in memory. Thirteen of forty improved in functional status, 11 of whom also met the criterion for normal memory. Of those 40 individuals, six improved on all three memory tests. No individual in this group of 40 was deemed demented by clinical consensus at Wave 2. For both AAMI definitions as well as aMCI, individuals improved to cognitively normal performance only in memory, as that was the only cognitive domain used for classification purposes. These changes in status may be a result of the practice effects sometimes seen in episodic memory performance in older adults, which can be evident even after five years (Rönnland, Nyberg, Bäckman, & Nilsson, 2005), or may provide a good indication of those individuals who are likely to remain non-demented, at least for the next few years.

Of the 29 individuals who were categorized as meeting full criteria for fMCI at baseline and then met unimpaired criteria at the follow-up examination, 23 had improved only 1 or 2 points on the functional impairment scale (DSRS). The largest change was 5 points of improvement, evidenced by 2 individuals. Thus, it appears that change in status for fMCI was due to individuals on the cusp of impaired/unimpaired as measured by the DSRS. These results may be due to measurement error (e.g., variation in caregiver report) or may very well be a clinically meaningful change.

In summary, most preclinical dementia constructs had poor stability over a 3-year period, as evidenced by equal or greater rates of reverting back to cognitively normal status as opposed to remaining stable or declining to dementia. The original definition of AAMI appeared to have somewhat better stability than the revised criteria, although in both groups, the percentage of those who converted back to normal (31-52%) exceeded the percentage

who remained stable (22-26%). Constructs that relied on multiple domains of cognition (AACD, CIND) did not generally show improved stability relative to those that relied on just memory performance as an indicator of cognitive status (aMCI, AAMI, AAMIO) and had roughly equivalent percentages of individuals who remained stable or declined to dementia in comparison to those who reverted back to normal status. In contrast, constructs that included a measure of functional impairment (fMCI, MA) were more stable over time. The main difference did not appear to be in the percentage of individuals who remained stable over time (although the fMCI group was the highest, at 46%), but rather that a much smaller percentage converted back to normal.

Discussion.

The stability analyses raise several issues worthy of discussion. First, the improved stability in groups that relied on measures of functional impairment (fMCI, MA) is relevant to research exploring the role of functional impairment in early detection of dementia (e.g., Daly, Zaitchik, Copeland, Schmahmann, Gunther, & Albert, 2000). Second, constructs that included memory measures as a primary neuropsychological variable were quite unstable, most notably aMCI. The stability of episodic memory performance in both healthy and preclinical populations will be discussed. Finally, comparison of the current results to existing studies of stability in preclinical dementia will be reviewed.

One noteworthy finding in the stability analyses was that individuals with functional impairment (fMCI and MA) were more stable over the 3-year follow-up period, with only 8-16% converting back to a "normal" group status, in comparison to 31-52% of individuals in definitions that relied on memory impairment (AAMIs, aMCI) who reverted back to normal. These rates are in contrast to a consistent percentage of individuals who declined to dementia

from all groups (8-18%), with the exception of the AAMI definitions, in which only 0-5% of individuals declined.

Few studies have explored the stability of functional measures in healthy elderly. One study explored the short term test-retest reliability of a measure of functional impairment and found it to be very stable over 4-6 weeks (Ottenbacher, Mann, Granger, Tomita, Hurren, & Charvat, 1994), although the sample used was quite small (N=20). A more recent study (Finlayson, Mallinson, & Barbosa, 2005) showed that IADLs and ADLs were generally stable over a period of 13 years in a group of healthy adults over the age of 85. Notably, the four items that showed decline over time were related to cooking and household chores. Similarly, Royall, Palmer, Chiodo, and Polk (2005) repeatedly tested IADL functions in a group of 70 community-dwelling individuals and reported that performance decreased 0.22SD per year. Regrettably, these studies do not address fluctuation in functional status in individuals who were initially considered impaired, but do provide support for general stability of functional measures over a period of time. Studies that have explored the role of functional impairment in the early detection of dementia have shown much lower rates of return to normal status than conversion to dementia (Daly et al., 2000; Pérès et al., 2006). A very recent population-based study also found that 11% of functionally impaired and 35% of functionally unimpaired individuals converted back to normal after 2 years of follow-up (Pérès et al., 2006). These results are remarkably convergent despite a difference in how functional impairment was reported (self vs. informant).

The second issues raised by the stability analyses concerns the instability of memory-based MCI definitions. This issue has been noted to be a concern specifically in population-based studies (as opposed to memory clinic samples), and our findings provide additional

justification for a broader definition of MCI in non-memory clinic samples. Episodic memory has been of particular interest, as it is well-known to be sensitive indicator of preclinical dementia (Petersen et al., 1999). However, in epidemiological and memory clinic samples, categorization as MCI or CIND is frequently based on assessment at one point in time assessment, as in the current study. One study has addressed this issue by exploring cognitive performance in repeat evaluations nine years preceding a diagnosis of AD, as well as a healthy control group (Amieva et al., 2005). In this population-based study, the measure of visual memory (BVRT; similar to that used in the current study) showed very mild decline (from a score of 11.5 to a score of 11) over the nine-year period, suggesting relative stability in visual memory in healthy controls. In the context of the current study, this suggests that a single low score may indeed be indicative of later problems, but that deficits may only emerge with longer follow-up. Alternatively, one low memory score may reflect short-term psychiatric or cardiovascular disturbances, which may then spontaneously resolve over time. Post hoc evaluation of the data supported the latter explanation, as no individual who improved on any test of memory was diagnosed with dementia. Regardless, there does remain the possibility of later decline as noted above.

Both population-based longitudinal and cross-sectional studies of episodic memory measures indicate declines in performance over the age of 60, even when accounting for practice effects (Rönnlund et al., 2005). As such, improvement in memory may be particularly noteworthy, in that it would suggest preservation of cognition at that time point. One caveat about population-based studies, however, is that they likely include some individuals who are in the preclinical stages of dementia. Thus, despite convergent findings in this regard, some caution in interpretation is warranted. Studies of episodic memory in

preclinical AD and dementia frequently show episodic memory deficits, but the stability of these performances has not been investigated as vigorously. One study indicated that the memory deficit in patients who go on to develop AD is stable from 6 to 3 years prior to diagnosis, with a more precipitous decline in the 3-year period immediately preceding conversion to AD (Bäckman, Small & Fratiglioni, 2001), but another study showed much more variable memory performance over a 2-year period in those diagnosed with MCI (Collie et al., 2002). These results may not be contradictory, however, in that it may be that those in the early stages of MCI may vacillate in their performance, with evidence of a more stable memory decline only present closer to the conversion to AD. In the context of the current study, it will be useful to determine cognitive status at an additional time point to address whether those who fluctuate in their memory status eventually do decline to dementia.

The final point of discussion concerns comparison to extant studies of stability, which were generally consistent with the present study's findings. One study found that two different definitions of preclinical dementia had a 32-43% rate of returning to normal after 2 years (Larrieu et al., 2002). In the second study (Palmer et al., 2002), 59% of those with MCI reverted back to cognitively normal. However, cognition in both of these studies was measured solely by the MMSE, and thus may not be comparable to the current study, which used a more comprehensive neuropsychological battery. Stability of aMCI has been a particular focus of recent research (e.g., Fisk et al., 2003; Ritchie et al., 2001), and the current results add additional evidence that as previously conceptualized (Petersen et al., 2001), it is extremely unstable, with 60% of the baseline group converting back to cognitively normal after three years. Our results do not provide support for increased stability using the revised

criteria, which take into account cognitive impairment in multiple domains, as well as one non-memory domain (Petersen, 2004). In the current study, stability in constructs that included multiple cognitive domains (AACD and CIND) was no better than those that relied on memory alone (aMCI, both AAMI definitions).

Goal #4: Prediction of dementia and AD

As shown in Table 4, three years after the baseline evaluation, 459 participants (69.4% of the original sample) completed the follow-up examination. Sixty-eight (10.3%) of the baseline sample were diagnosed with dementia, 45 of whom had diagnoses of AD. The remaining participants did not complete the follow-up evaluation due to death (n=86), refusal (n=94), or moving out of the area (n=22).

Four sets of logistic regression and ROC analyses were conducted in order to determine whether being classified as having one of the preclinical dementia constructs at the baseline examination predicted dementia or Alzheimer's disease at the follow-up examination. All regression models controlled for baseline variables that may affect cognition, including age, sex, education, and the presence of at least one APOE e4 allele. Sensitivity and specificity of constructs were calculated for both dementia and AD.

Table 11 details the odds ratios for prediction of dementia when only those meeting full criteria at the baseline examination were used in the model. Table 12 details the same information as Table 11, but specifically for prediction of AD. Both tables include rows that provide results from a set of analyses using a combined "impaired" group (those meeting full criteria and inclusion criteria only) to predict later dementia or AD status. The cognitively normal group served as the reference group for all logistic regressions. Once these analyses were conducted, the areas under the ROC curves were statistically compared among

significant predictors to determine which construct was superior at predicting later dementia or AD. Sensitivity and specificity values are provided for prediction of dementia (Table 13) and AD (Table 14).

Prediction of dementia.

The first set of logistic regressions examined whether meeting full criteria for preclinical dementia status at the baseline examination predicted dementia three years later after accounting for constitutional variables, including age, sex, education, and APOE _4 allele (Table 11). AACD, CIND, fMCI, and MA were all significant predictors of later dementia diagnosis, conferring an additional two- to eight-fold risk of developing later dementia, as compared to the reference group of cognitively normal individuals.

As multiple constructs were significant predictors of later dementia, areas under the curve (AUCs) in ROC analyses were compared, in order to determine whether any constructs were better at predicting later dementia (e.g., resulted in a statistically significantly larger AUC). AUCs were compared using the method described in Hanley & McNeil (1983). In the ROC analyses for dementia using the full constructs, AUCs ranged from .753 to .843. Among the statistically significant predictors, pairwise comparisons indicated that MA was a better predictor than fMCI ($z = 2.60$), CIND ($z = 2.36$), or AACD ($z = 2.08$), which did not differ (see Figure 2a). Sensitivity of the constructs for detection of dementia ranged from 67-74%, with minimal discrepancy among the constructs. Specificity ranged from 68-80%, with aMCI and MA with the highest specificity (Table 13).

The next set of logistic regressions examined whether being classified as impaired by either meeting full criteria or just the inclusion criteria at the baseline examination predicted dementia three years later, again accounting for constitutional covariates, including age, sex,

educational level, and APOE _4 allele (Tables 11 and 12). Identical to the previous analyses in which only those meeting full criteria were included, AACD, CIND, fMCI, and MA were significant predictors of later dementia diagnosis. In the ROC analyses, AUCs ranged from .705 to .830, and as in the previous analyses, MA was a better predictor than all other constructs (z values ranged from 1.99 to 2.74; Figure 2b). Sensitivity was incrementally improved across constructs, but the resulting loss in specificity was greater (Table 13).

In summary, only four preclinical dementia constructs were associated with an increased risk of later development of dementia, namely AACD, CIND, fMCI, and MA. Among these four, in statistical comparison of AUCs, MA emerged as superior in its ability to account for a larger percentage of cases. Notably, MA is the only construct that allows for either cognitive or functional impairment in determining change from previous status, suggesting an additive effect for a combination of variables in comparison to each one by itself.

Prediction of Alzheimer's Disease.

Prediction of AD was specifically examined because many of the constructs developed in previous research (e.g., aMCI, both AAMI definitions, and MA) were conceptualized specifically as precursors to AD, rather than more to dementia in general. Thus, in addition to analyses predicting dementia, a series of logistic regressions was run to determine which constructs were significant predictors of later AD.

The next set of logistic regressions examined whether meeting full criteria at the baseline examination predicted AD three years later, after accounting for constitutional variables, including age, sex, educational level, and APOE _4 allele (Table 12). AACD, CIND, fMCI, and MA emerged as statistically significant predictors of later AD diagnosis.

In the ROC analyses, AUCs ranged from .757 to .846, and no construct was statistically better at predicting AD diagnosis (Figure 3a). Sensitivity ranged from 68-82%, with MA showing the highest sensitivity to later AD, and specificity ranged from 66-82%, with aMCI showing the highest specificity for later AD.

The next set of logistic regressions examined whether being classified as impaired (either meeting full criteria or just inclusion criteria) at baseline predicted AD three years later, after accounting for age, sex, educational level, and presence of at least one APOE _4 allele (Table 12). Again, AACD, CIND, fMCI, and MA emerged as significant predictors of later AD, as did the original definition of AAMI. In the ROC analyses, AUCs ranged from .716 to .831, all constructs predicted AD better than chance, and no construct was superior to any other at predicting subsequent AD diagnosis (Figure 3b). Sensitivity and specificity values were generally worse when the impaired group predicted AD, as compared to those individuals who met full criteria (Table 14).

These results are similar to the ones for general dementia, in that the same four constructs that were significant predictors of dementia also predicted AD. This is not surprising, as a majority of the dementia cases detected (66%) were consensus-diagnosed as AD, as opposed to vascular or other dementias. However, unlike the general dementia results, none of the constructs was statistically superior at predicting AD based on the AUC. This result is contrary to expectation and particularly interesting in light of the fact that many of the constructs used (e.g., aMCI, fMCI, MA, and both definitions of AAMI) are thought to be preclinical AD. Implications and possible explanations will be explored in the discussion section.

Discussion.

The prediction of conversion to dementia based on neuropsychological and demographic variables has long been an aim of MCI and CIND-based research. In the current study, seven preclinical dementia constructs were compared to determine which was the best predictor of later dementia and AD. Overall rates of progression were roughly consistent across constructs (8-18%), consistent with published studies (Fisk et al., 2003; Ganguli et al., 2004; Ritchie et al., 2001). Using logistic regression, we demonstrated that algorithmically-derived constructs that include indicators of cognitive impairment in multiple domains (AACD, CIND) or rely on informant-reported functional impairment (fMCI, MA) significantly predicted development of dementia and AD in a population-based sample. Constructs that relied solely on memory impairment without complementary functional impairment (AAMIs, aMCI) performed quite poorly and did not significantly predict later dementia or AD. By comparing the AUCs of significant predictors, MA emerged as a better predictor of dementia than the other constructs, but no construct was superior at predicting later AD. Sensitivity and specificity of all demographically-corrected constructs was satisfactory, with both indices generally ranging from 68-85%. Sensitivity was not appreciably improved when those who had previously been excluded for medical reasons were then included.

The current study revealed that disparate constructs were significantly predictive of later dementia, regardless of specific criteria. Indeed, of the four constructs that significantly predicted dementia, two (AACD and CIND) sampled multiple cognitive domains but did not include any measure of functional impairment, one (fMCI) relied solely on functional impairment, and one (MA) allowed impairment in either memory or functional domains. Results are commensurate with a recent study finding that individuals with functional

impairment had higher rates of conversion to dementia than those without (Pérès et al., 2006), although another study found equivalent rates of progression, regardless of the presence of functional impairment (Fisk et al., 2003). In the Fisk study, however, individuals with functional impairment had a higher odds ratio than those with intact IADLs, but the groups were not statistically compared to determine whether one construct was superior. Thus, the results may in fact be consistent with those of the current study.

The current study results also support a viewpoint that individuals with impairment in multiple cognitive domains are more at risk, and may be further along a trajectory towards dementia, than those with impairment in just memory (e.g., Alexopolous et al., 2006). Specifically, in the current study, constructs that included multiple cognitive domains (AACD, CIND) were more highly associated with a dementia outcome than those that relied solely on memory (both AAMIs, aMCI). In support of this view, a population-based study with a 22-year follow-up period (Elias, Beiser, Wolf, Au, White, & D'Agostino, 2000) showed that 10 years prior to diagnosis of AD, only measures of verbal recall and abstract reasoning were associated with preclinical AD diagnosis, whereas five years prior to diagnosis, impairments were notable on those two tests, as well as additional verbal and visual learning tasks. Unfortunately, this study did not include many non-memory measures for comparison, but other studies have noted changes in many areas of cognition in preclinical AD, including executive functioning, processing speed, global cognitive functioning, and visuospatial abilities (see Bäckman, Jones, Berger, Laukka, & Small, 2005, for a review and meta-analysis).

Results are also consistent with the emerging viewpoint that very mild functional impairment is an important variable in the consideration of the development of later dementia

(Daly et al., 2000; Pérès et al., 2006). In the Pérès study, although individuals with MCI with and without functional impairment had an increased risk for later dementia, the risk was higher when there were constricted functional abilities, such as difficulty completing daily chores without assistance or preparing meals. These tasks are thought to reflect cognitive changes that are mild enough that they cannot be reliably discerned on available neuropsychological tests, although at least one study has found strong correlations between functional decline and measures of executive functioning (Royall et al., 2005). A related idea is that functional decline may simply be an ecologically relevant way of detecting underlying cognitive impairment in a population sample.

Recent research (Perneczky et al., 2006) has also focused on developing optimal cutoffs to distinguish between those with MCI and those individuals who are healthy on measures of functional difficulties, consistent with other algorithmic approaches to diagnosing dementia (Tschanz et al., 2000). Moreover, measures of functional impairment may be more ecologically valid than measures of cognition. In other words, compensatory strategies aimed at increasing functional independence may be more practically useful to patients and caregivers than cognitive-based strategies, which may not be as task-relevant. As such, acknowledgement of early functional decline as an important indicator for later development of dementia may facilitate the development of compensatory strategies and other interventional tactics specifically geared towards functional independence (Weiner et al., 2006).

General Discussion

This study utilized extensive descriptive data analyses and logistic regression to explore the frequency, overlap, stability, and predictive utility of seven different preclinical dementia constructs in an epidemiological sample. General themes from the study will be highlighted, and the four goals (frequency, overlap, stability, and predictive utility) will be discussed for each construct separately.

AAMI was originally developed as a subset of "normal aging", and based on the results of the current study, that appears to be an appropriate definition. Frequency analyses were notable for better neuropsychological performance on many tests, suggesting that these groups may in fact be "successful", rather than normal aging or preclinical dementia. Although individuals classified as AAMI had reasonable overlap with the AACD group, they were subsumed by AACD, indicating a lack of unique contribution of this conceptualization. Moreover, neither AAMI definition was a significant predictor of AD or dementia. As such, further studies of those categorized as AAMI may wish to examine this group in the context of healthy or successful aging.

AACD was originally conceptualized as a mixed group of normal and pathological aging, which is consistent with the current study's findings. Although it was a significant predictor of dementia and AD, indicating its utility as a preclinical dementia construct, overlap analyses showed that the AACD group included most of the AAMI group, and thus may also include many who do not decline to dementia. Additionally, stability over time was generally poor, with approximately one third of the group converting back to cognitively

normal status. Thus, the AACD group may contain a large number of individuals who also meet AAMI criteria and have been misclassified as possible preclinical dementia subjects. The stability results were in contrast to a previous study (Ritchie et al., 2001), which found that 58% of the AACD group remained stable. Different psychometric measures were used to determine group status, which may account for the discrepancy. Previous studies of the specificity and sensitivity of AACD have shown either excellent sensitivity and moderate specificity (Ritchie et al., 2001), or the opposite pattern (Busse et al., 2003a). In the current study, both sensitivity and specificity were generally good, with ranges between 65-75%. CIND performed similarly to AACD in overlap and stability analyses, despite differences between the two constructs in exclusion criteria and neuropsychological cutoffs (1.5 SD vs. 1 SD below the norm). It was also a significant predictor of later dementia and AD. In summary, although AACD and CIND did not have significantly better stability than the AAMI constructs, they do appear to have better validity in the prediction of later dementia and AD.

The emphasis in the current study was on the three constructs which are purported to be predictive of later AD (aMCI, fMCI, and MA). Although they share a theoretical basis, empirically there were some important differences that were highlighted by the current study results. First, aMCI continues to perform poorly in epidemiological studies, both in terms of stability and prediction of later dementia. Specifically, 60% of the aMCI group converted back to cognitively normal at the follow-up evaluation, and although rates of conversion were similar to other constructs, it did not emerge as a statistically significant predictor of later dementia or AD. In contrast, sensitivity and specificity of the demographically-controlled construct indicated reasonable values indistinct from the other constructs. Results

point to ongoing discrepancies between memory clinic samples and population-based samples. Second, although the kappa statistics indicated very poor overlap among the constructs, descriptive evaluation revealed that aMCI was completely subsumed by MA, and that the discrepancy between MA and fMCI was related to the operationalization of functional impairment. Additionally, both MA and fMCI were significant predictors of AD and dementia, and MA was statistically superior over other significant constructs in predicting dementia, although not AD. In sum, it appears that consideration of mild functional decline in population-based studies may enhance predictive models of later dementia. Additionally, the current study provides additional data that the construct of aMCI is overly restrictive and not practically useful.

A general issue highlighted by the current study concerns the definition of functional impairment, as well as the time point at which the individuals crosses the threshold to dementia. Related to this issue is the appropriate criteria used to determine if an individual has dementia, which, in its most recent iteration, includes memory impairment, cognitive impairment in one additional domain, as well as functional impairment (APA, 1994). As such, many individuals who are presently classified as "multiple-domain MCI" could also simply have very mild dementia (Morris et al., 2001), in that they evidence deficits in memory and one additional cognitive domain, and have evidence of functional decline. Additionally, functional impairment appeared much more stable than cognitive impairment over the three year period in the current study, which may be construed as further evidence that those with MCI are further along a trajectory of decline and do, in fact, have dementia. Recent studies have explored whether those who are functionally impaired are concurrently cognitively impaired (e.g., Tuokko et al., 2005), and the answer is generally positive. Several

recent studies have also shown that in individuals with cognitive impairment, the rates of functional impairment are much higher than in the general population (Artero, Touchon, & Ritchie, 2001; Ng, Niti, Chiam, & Kua, 2006). Although the prevailing belief is that cognitive impairment precedes functional impairment, and there are many studies that support this supposition (Ebly et al., 1995; Ritchie et al., 2001), at least one study has shown that functional impairment at baseline can also predict cognitive impairment five years later (Tuokko et al., 2005). Thus, the temporal relationship between the two remains relatively unexplored and far from conclusive. Focus on early functional impairment could lead to new theoretical and practical approaches to both behavioral and pharmacological interventions for delay or prevention of later dementia.

Limitations and future directions

Caveats to interpreting the present data include concerns related to sample composition and length of follow-up. First, the study sample was primarily Caucasian, highly educated, and physically healthy. These results may thus not generalize to other ethnically-diverse samples that include individuals in a broader range of socioeconomic levels, since neuropsychological norms in most epidemiological study samples (the current study being no exception) do not take into account cultural effects on these tests (Manly et al., 2005). Second, the screening process used was designed to detect dementia, not MCI, and the psychometric measures included may therefore lack the sensitivity to detect the mild cognitive and functional changes that accompany this transitional state. Therefore, there may be cognitively impaired individuals who should have been included in the sample who were not. In support of this notion, those who dropped out of the study or died had lower baseline 3MS scores and higher rates of the APOE _4 allele, both risk factors for later dementia,

suggesting that the dropout group may have included many cases of preclinical dementia. Arguing against this idea, however, is the evidence that rates of progression to dementia in the non-cognitively impaired subjects were low and consistent with national averages. Third, the follow-up period was fairly brief. It will be useful to confirm findings with Wave 3 data (6 years post-baseline). In particular, with respect to the stability analyses, it will be interesting to determine to what extent those who converted back to cognitively normal after being classified as preclinical dementia remain intact or show additional cognitive or functional decline.

Continued emphasis on assessing subtle changes in functional abilities is clearly warranted, both in light of recent studies demonstrating its predictive power for later dementia (Pérès et al., 2006) and the current study's findings of enhanced predictive utility and stability over time in constructs relying on functional decline. There is little research regarding which IADL abilities tend to decline first and how these may or may not co-occur with cognitive impairments, although at least one small, study that included volunteers has started to explore these issues (Royall et al., 2005). Moreover, there may be sub-domains within the concept of IADLs that could be clinically and practically useful. For example, recent work has shown that IADLs can be split into tasks that require a greater physical effort, such as grocery shopping, from those that require more complex cognitive skills, such as managing money (Ng et al., 2006). Future studies should determine whether sub-domains of IADLs enhance sensitivity of early preclinical dementia detection, and/or prediction of later dementia.

An additional future direction for the MCI literature would be to systematically implement a combination of sensitive functional and cognitive measures of function, as both

these domains seem to independently predict variance associated with a dementia outcome, but with an additive effect (Tschanz et al., 2000). Additionally, our results confirm the utility of using a supplementary algorithmic approach to MCI categorization in general population studies, which may provide an additional source of confirmatory data, rather than relying solely on consensus-based diagnosis.

In summary, the present results provide a systematic and comprehensive exploration of seven commonly used definitions of preclinical dementia. The current results confirm that not all definitions are equal in their utility in population-based studies. Specifically, preclinical dementia constructs that focused on decline in functional abilities (MA, fMCI) or multiple cognitive domains (AACD, CIND) were associated with later development of dementia. Moreover, MA, with its emphasis on memory and/or functional impairment, was superior to the other three constructs in the prediction of dementia. In terms of practical application, using sensitive measures of functional impairment or change appears to produce the most accurate determination of whether an individual progresses to later dementia. Future studies should seek to determine which IADL activities decline first, as well as their neuropsychological and neuroanatomical correlates, ideally in a population-based sample.

Table 1. Core articles used to define preclinical dementia constructs

Construct	*Core articles*
Age Associated Memory Impairment (original; AAMIO)	Crook et al. (1986)
Age Associated Memory Impairment (revised; AAMI)	Blackford & LaRue (1989)
Age Associated Cognitive Decline (AACD)	Levy (1994)
Cognitive Impairment No Dementia (CIND)	Graham et al., (1997); Tuokko, Frerichs, & Kristjansson (2001)
Amnestic Mild Cognitive Impairment (Petersen; aMCI)	Petersen, Smith, Waring, Ivnik, Tangalos & Kokmen (1999); Petersen et al., (2001); Petersen et al., (1995)
Functional Mild Cognitive Impairment (Morris; fMCI)	Morris, et al., (2001)
Mild Ambiguous (MA)	Breitner et al., (1995)

Table 2a. Operationalized criteria for preclinical dementia constructs: AAMIO (age-associated memory impairment, original criteria)

Age-Associated Memory Impairment (original criteria): Crook et al. (1986)		
Criterion	**Variables used**	**How operationalized**
Decrease in day-to-day memory functioning**	DQ, IQCODE	Caregiver report of at least one of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of at least 3.0 on the IQCODE
Decreased memory**	BVRT, Logical Memory II	A score >1 SD below young norms on at least one test
No neurological or vascular condition that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, Toxic exposure, head injury, mental retardation, ALS, NPH, other neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, acute hypoxic episode w/LOC, myotonic dystrophy, multiple sclerosis, B12 deficiency, seizure disorder, encephalopathy, brain tumor, TIA, neurotoxin exposure, neurosyphilis, HIV
No medical problems that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Current dx of: medical condition thought to be contributory to cognitive impairment, HTN, CHF, MI, schizophrenia, COPD, pulmonary CA, GI CA, renal CA, prostate CA, breast CA, IDDM, hypothyroidism, folate deficiency, anemia, leukemia, lymphoma
No concurrent psychological disorders	Consensus diagnosis or, if not available, case staffing diagnosis; patient and/or informant depression interview	Any hx of: drug or alcohol dependence Current dx of: depression, anxiety disorder, psychotic disorder, other neuropsychiatric disorder
Intact intellect** *(supportive)*	Shipley-Hartford Vocabulary Test	Score of at least –0.33 SD (equivalent to Scaled Score of 9 on WAIS Vocabulary)
Gradual onset** *(supportive)*	DQ	No evidence of sudden onset of symptoms
MMSE in normal range** *(supportive)*	MMSE	Score ≥24
AAMIO Unimpaired		
No change in day-to-day memory functioning	DQ, IQCODE	Caregiver report of none of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of less than 3.0 on the IQCODE
Intact memory	BVRT, Logical Memory II	A score higher than 1 SD below young norms on all tests

Note. **denotes criteria necessary for "AAMIO-meets inclusion criteria only" designation.

Table 2b. Operationalized criteria for preclinical dementia constructs: AAMI (age-associated memory impairment, revised criteria)

Age-Associated Memory Impairment, revised: Blackford & LaRue, 1989		
Criterion	**Variables used**	**How operationalized**
Age 50-79**	Date of birth	Age calculated for date of neuropsychological assessment
Decrease in day-to-day memory functioning**	DQ, IQCODE	Caregiver report of at least one of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of at least 3.0 on the IQCODE
Decreased memory**	BVRT, Logical Memory II	A score >1 SD below young norms on at least one test
No neurological or vascular condition that could affect memory or cognition	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, mental retardation, ALS, NPH, other neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, myotonic dystrophy, multiple sclerosis, seizure disorder, encephalopathy, malignant brain tumor, TBI, neurosyphilis, HIV
No medical problems that could impact memory	Consensus diagnosis or, if not available, case staffing diagnosis	Current dx of: medical condition thought to be contributory to cognitive impairment, CHF, schizophrenia, COPD, pulmonary CA, GI CA, renal CA, prostate CA, breast CA, anemia, leukemia, lymphoma
No concurrent psychological disorders	Consensus diagnosis or, if not available, case staffing diagnosis; patient and/or informant depression interview	Any hx of: drug or alcohol dependence Current dx of: depression, anxiety disorder, psychotic disorder, other neuropsychiatric disorder
Intact intellect** *(supportive)*	Shipley-Hartford Vocabulary Test	Score between –0.67 SD to +2.0 SD (equivalent to WAIS VIQ/PIQ 90-130)
AAMI Unimpaired		
No change in day-to-day memory functioning	DQ, IQCODE	Caregiver report of none of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of less than 3.0 on the IQCODE
Intact memory	BVRT, Logical Memory II	A score above 1 SD below young norms on all tests

Note. **denotes criteria necessary for "AAMI-meets inclusion criteria only" designation.

Table 2c. Operationalized criteria for preclinical dementia constructs: AACD (age-associated cognitive decline)

Age-Associated Cognitive Decline: Levy (1994)		
Criterion	**Variables used**	**How operationalized**
Self or caregiver report of cognitive decline**	DQ, IQCODE	Caregiver report of at least one of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of at least 3.0 on the IQCODE
Difficulty in at least one of the following areas: memory and learning, attention and concentration, thinking, language, or visuospatial functioning**	*Memory and learning*: BVRT, Logical Memory II, Word List Delayed Recall *Attention and concentration*: Trails A *Thinking*: Trails B, SDMT *Language*: Animal Fluency, COWA, Boston Naming Test *Visuospatial functioning*: Constructional Praxis	A score >1 SD below norms on at least one test
No neurological or medical condition that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, mental retardation, ALS, NPH, other medical or neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, myotonic dystrophy, multiple sclerosis, malignant brain tumor, schizophrenia, neurosyphilis, HIV, encephalopathy, acute hypoxic episode w/LOC, TBI
No psychological disorders	Consensus diagnosis or, if not available, case staffing diagnosis; patient and/or informant depression interview	Any hx of: depression, bipolar disorder, anxiety disorder, psychotic disorder or other neuropsychiatric disorder Current dx of: alcohol or drug dependence
Gradual onset** *(supportive)*	DQ	No evidence of sudden onset of symptoms
Duration of at least 6 months** *(supportive)*	DQ	Duration of at least 6 months between onset of symptoms and date of neuropsychological testing
AACD Unimpaired		
No report of cognitive decline	DQ, IQCODE	Caregiver report of none of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score less than 3.0 on the IQCODE
Intact cognitive functioning	*Memory and learning*: BVRT, Logical Memory II, Word List Delayed Recall *Attention and concentration*: Trails A *Thinking*: Trails B, SDMT *Language*: Animal Fluency, COWA, Boston Naming Test *Visuospatial functioning*: Constructional Praxis	All scores better than 1 SD below norms

Note. **denotes criteria necessary for "AACD-meets inclusion criteria only" designation.

Table 2d. Operationalized criteria for preclinical dementia constructs: CIND (cognitive impairment, no dementia)

Cognitive Impairment, No Dementia: Graham et al. (1997)		
Criterion	**Variables used**	**How operationalized**
Self or caregiver report of cognitive decline	DQ, IQCODE	Caregiver report of at least one of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of at least 3.0 on the IQCODE
Difficulty in at least one of the following areas: memory and learning, executive functioning, language, or visuospatial functioning	*Memory and learning*: BVRT, Logical Memory II, Word List Delayed Recall *Executive functioning*: Trails A, Trails B, SDMT *Language*: Animal Fluency, COWA, Boston Naming Test *Visuospatial functioning*: Constructional Praxis	A score >1.5 SD below norms on at least one test

Table 2e. Operationalized criteria for preclinical dementia constructs: fMCI (functional mild cognitive impairment)

Functional Mild Cognitive Impairment (fMCI): Morris et al. (2001)		
Criterion	**Variables used**	**How operationalized**
Impairment in IADLs**	DSRS	Sum >11 on IADL and ADL items (11 items)
No neurological or medical condition that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, mental retardation, ALS, NPH, other medical or neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, myotonic dystrophy, multiple sclerosis, malignant brain tumor, schizophrenia, neurosyphilis, HIV, encephalopathy, acute hypoxic episode w/LOC, TBI
No psychological disorders (excluding depression)	Consensus diagnosis, or, if not available, case staffing diagnosis	Any hx of: anxiety, psychotic, or other neuropsychiatric disorder; alcohol or other drug dependence
No currently symptomatic depression	Consensus diagnosis, or, if not available, case staffing diagnosis; patient and/or informant depression interview, NPI	If diagnosis of depression is present, sum of 9 depression symptoms must be ≤5 on either informant or patient interview. If missing interview data, NPI depression question regarding current depressive symptoms must be negative.
CDR score** *(supportive)*	CDR	=0.5
fMCI Unimpaired		
Intact IADLs	DSRS	Sum ≤11 on IADL and ADL items (11 items)
CDR score** *(supportive)*	CDR	=0

Note. **denotes criteria necessary for "fMCI-meets inclusion criteria only" designation.

Table 2f. Operationalized criteria for preclinical dementia constructs: aMCI (amnestic mild cognitive impairment)

Amnestic Mild Cognitive Impairment (aMCI): Petersen et al. (1995; 1999; 2001)		
Criterion	**Variables used**	**How operationalized**
Self or caregiver report of cognitive decline**	DQ, IQCODE	Caregiver report of at least one of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of at least 3.0 on the IQCODE
Normal IADLs**	DSRS	Sum <=11 on IADL items only
Abnormal memory for age**	BVRT, Logical Memory II, Word List Delayed Recall	A score >1.5 SD below norms on at least one test
No neurological or medical condition that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, mental retardation, ALS, NPH, other medical or neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, myotonic dystrophy, multiple sclerosis, malignant brain tumor, schizophrenia, neurosyphilis, HIV, encephalopathy, acute hypoxic episode w/LOC, TBI
No psychological disorders (excluding depression)	Consensus diagnosis, or, if not available, case staffing diagnosis	Any hx of: anxiety, psychotic, or other neuropsychiatric disorder; alcohol or other drug dependence
No currently symptomatic depression	Consensus diagnosis, or, if not available, case staffing diagnosis; patient and/or informant depression interview, NPI	If diagnosis of depression is present, sum of 9 depression symptoms must be ≤5 on either informant or patient interview. If missing interview data, NPI depression question regarding current depressive symptoms must be negative.
MMSE in normal range** *(supportive)*	MMSE	≥24
Normal general cognitive functioning- VIQ/PIQ within 0.5 SD of age norms** *(supportive)*	Shipley Hartford Vocabulary Test	Score between –0.5SD to +0.5SD
CDR=0.5** *(supportive)*	CDR	Score =0.5
aMCI Unimpaired		
No report of cognitive decline	DQ, IQCODE	Caregiver report of none of the following: decreased memory for day to day happenings, names, faces, or impaired ability to remember a short list of items AND/OR a score of less than 3.0 on the IQCODE
Intact memory	BVRT, Logical Memory II, Word List Delayed Recall	A score better than 1.5 SD below norms on all tests
CDR=0** *(supportive)*	CDR	Score =0

Note. **denotes criteria necessary for "aMCI-meets inclusion criteria only" designation.

Table 2g. Operationalized criteria for preclinical dementia constructs: MA (mild ambiguous/prodromal AD)

Mild Ambiguous: Breitner et al. (1995)		
Criterion	**Variables used**	**How operationalized**
Impairment in either or both of the following areas: memory, IADLs**	*Memory*: BVRT, Logical Memory II, Word List Delayed Recall *IADLs*: DSRS	For memory, a score >1.5 SD below norms on at least one test For IADLs, score >11 on IADL items only
No neurological or medical condition that could produce cognitive deterioration	Consensus diagnosis or, if not available, case staffing diagnosis	Any hx of: stroke, incidental or definite vascular changes, Parkinson's, Huntington's, PSP, mental retardation, ALS, NPH, other medical or neurological diagnosis thought to contribute to cognitive impairment, Binswanger's disease, cerebritis, cerebral palsy, myotonic dystrophy, multiple sclerosis, malignant brain tumor, schizophrenia, neurosyphilis, HIV, encephalopathy, acute hypoxic episode w/LOC, TBI
No psychological disorders (excluding depression)	Consensus diagnosis, or, if not available, case staffing diagnosis	Any hx of: anxiety, psychotic, or other neuropsychiatric disorder; alcohol or other drug dependence
No currently symptomatic depression	Consensus diagnosis, or, if not available, case staffing diagnosis; patient and/or informant depression interview, NPI	If diagnosis of depression is present, sum of 9 depression symptoms must be <=5 on either informant or patient interview. If missing interview data, NPI depression question regarding current depressive symptoms must be negative.
Gradual onset** *(supportive)*	DQ	No evidence of sudden onset of symptoms
MA Unimpaired		
Intact memory and IADLs	*Memory*: BVRT, Logical Memory II, Word List Delayed Recall *IADLs*: DSRS	For memory, scores better than 1.5 SD below norms For IADLs, score ≤11 on IADL items only

Note. **denotes criteria necessary for "MA-meets inclusion criteria only" designation.

Table 3. Number (% of sample) who meet criteria for preclinical dementia constructs at baseline examination.

Constructs N=661	AAMIO	AAMI	AACD	CIND	aMCI	fMCI	MA
Meets full criteria	21 (3.2)	21 (3.2)	118 (17.9)	249 (37.7)	10 (1.5)	324 (49.0)	209 (31.6)
Meets inclusion criteria only	61 (9.2)	25 (3.8)	145 (21.9)	N/A	2 (0.3)	116 (17.5)	103 (15.6)
Cognitively normal	380 (57.5)	366 (55.4)	364 (55.1)	381 (57.6)	489 (74.0)	162 (24.5)	321 (48.6)
Unable to classify	199 (30.1)	249 (37.7)	34 (5.1)	31 (4.7)	160 (24.2)	59 (8.9)	28 (4.2)

Table 4. Number (% of sample) who meet criteria for preclinical dementia constructs at follow-up examination.

N=661	AAMIO	AAMI	AACD	CIND	aMCI	fMCI	MA
Meets full criteria	14 (2.1)	17 (2.6)	88 (13.3)	98 (14.8)	6 (0.9)	240 (36.3)	133 (20.1)
Meets inclusion criteria only	29 (4.4)	8 (1.2)	0 (0.0)	N/A	2 (0.3)	31 (4.7)	24 (3.6)
Cognitively normal	250 (37.8)	245 (37.1)	247 (37.4)	282 (42.7)	328 (49.6)	100 (15.1)	217 (32.8)
Unable to classify	98 (14.8)	121 (18.3)	56 (8.5)	11 (1.7)	55 (8.3)	20 (3.0)	17 (2.6)
Alzheimer's disease	45 (6.8)						
Dementia (includes AD)	68 (10.3)						
Deceased	86 (13.0)						
Refused further examination	116 (17.5)						

Table 5. Number (% of subset of sample) who meet criteria for preclinical dementia constructs at follow-up examination.

n=459	AAMIO	AAMI	AACD	CIND	aMCI	fMCI	MA
Meets full criteria	14 (3.1)	17 (3.7)	88 (19.2)	98 (21.4)	6 (1.3)	240 (52.3)	133 (29.0)
Meets inclusion criteria only	29 (6.3)	8 (1.7)	0 (0.0)	N/A	2 (0.4)	31 (6.8)	24 (5.2)
Cognitively normal	250 (52.5)	245 (51.4)	247 (51.9)	282 (59.5)	328 (69.5)	100 (19.8)	217 (45.3)
Unable to classify	98 (21.4)	121 (26.4)	56 (12.2)	11 (2.4)	55 (12.0)	20 (4.4)	17 (3.7)
Alzheimer's disease	45 (9.8)						
Dementia (includes AD)	68 (14.8)						

Note. Excluded those who refused examination or were deceased.

Table 6. Demographic characteristics and mean (SD) neuropsychological test scores of subjects with preclinical dementia constructs at baseline evaluation

Characteristics	AAMIO n=21	AAMI n=21	AACD n=118	CIND n=249	aMCI n=10	fMCI n=324	MA n=209	Full sample N=661
Mean age (SD)	79.7 (5.9)	**73.2* (3.3)**	81.6 (8.2)	82.2* (7.6)	77.0 (9.4)	81.4* (7.6)	81.9* (8.3)	80.6 (7.6)
% female	61.9	47.6	49.2	57.4*	30.0	50.9	53.1	54.9
Mean years of education (SD)	13.8 (3.5)	14.0 (3.1)	13.2 (3.0)	12.8* (2.8)	11.7* (1.8)	13.3 (3.0)	12.8* (2.9)	13.3 (2.9)
% APOE e4	57.2	76.2*	57.6	55.0	60.0	54.6	52.2	52.6
Shipley-Hartford Vocabulary Test	**33.5* (3.0)**	**33.8* (3.0)**	29.4 (5.3)	27.6* (5.6)	**32.4* (1.9)**	29.7 (5.4)	28.8* (5.2)	29.5 (5.5)
MMSE	**28.0* (1.7)**	28.9* (1.2)	26.7 (2.7)	25.8* (2.8)	**28.1 (1.9)**	27.1 (2.6)	26.4* (2.7)	27.0 (2.7)
Semantic Fluency	16.7 (3.6)	18.4* (3.8)	**15.8 (4.5)**	**14.1* (4.5)**	16.1 (5.9)	16.2 (4.8)	15.3* (4.6)	16.1 (4.9)
Boston Naming Test (15-item)	14.1* (0.9)	14.2* (0.9)	**13.3 (1.7)**	**12.8* (1.9)**	13.8 (1.9)	13.4 (1.8)	13.2 (1.9)	13.4 (1.8)
Constructional Praxis	10.2* (1.0)	10.5* (1.0)	**9.7 (1.3)**	**9.4* (1.4)**	10.1 (0.9)	9.8 (1.3)	9.5* (1.4)	9.7 (1.2)
Delayed Word Recall	5.4 (2.1)	6.0 (1.7)	**4.9* (2.2)**	**4.2* (2.0)**	**3.7* (1.6)**	5.3 (2.3)	**4.1* (2.1)**	5.4 (2.3)
Trails A	56.6 (29.5)	48.1* (14.4)	**61.0 (32.7)**	**70.2* (39.4)**	62.0 (55.1)	58.1 (29.6)	61.8 (32.3)	58.7 (35.4)
Trails B	118.0* (47.9)	117.2* (56.3)	**160.1 (77.0)**	**193.7* (90.0)**	120.2* (38.2)	159.9 (82.2)	171.5* (84.6)	155.9 (79.8)
Benton Visual Retention Test- # correct	**4.9 (1.2)**	**5.9* (1.2)**	**4.6 (1.9)**	**3.8* (1.7)**	**5.2 (1.3)**	4.7 (2.0)	**3.9* (2.0)**	4.7 (2.0)
Benton Visual Retention Test- # errors	**9.0 (2.6)**	**7.2* (1.9)**	**9.7 (4.0)**	**11.5* (3.9)**	**9.0 (2.8)**	9.6 (4.2)	**11.2* (4.4)**	9.6 (4.3)
Controlled Oral Word Association	36.7* (8.6)	37.4* (8.4)	**30.9 (10.8)**	**27.0* (10.7)**	25.6 (9.0)	31.2 (10.6)	28.5* (10.1)	30.8 (11.0)
Symbol-Digit Modality Test	29.9 (8.4)	35.4* (7.2)	**28.2 (9.1)**	**25.4* (9.1)**	31.7 (8.8)	29.5 (9.6)	27.0* (9.7)	29.8 (9.8)
WMS-III Logical Memory II	**14.8 (6.6)**	**16.7 (6.8)**	**13.3* (7.4)**	**10.7* (7.0)**	**12.4 (7.6)**	14.6 (8.0)	**11.5* (7.4)**	14.7 (8.0)

Note. Text in bold indicates that characteristic was used in construct definition.
*$p<.05$ in comparison to mean of full sample less those in construct group.

Table 7. Unweighted kappa statistics for preclinical dementia constructs: full criteria, inclusion criteria only, cognitively normal, and unable to classify.

N=661	AAMI	AAMIO	AACD	CIND	fMCI	aMCI
AAMIO	**.80**	----				
AACD	**.41**	**.41**	----			
CIND	.27	.25	**.43**	----		
fMCI	.13	.11	.27	.14	----	
aMCI	**.50**	**.46**	.26	.26	.08	----
MA	.11	.12	.33	.24	.34	.23

Note. Bold indicates good or excellent agreement

Table 8. Kappas for "Impaired" versus "Cognitively Normal" (n in parens) at baseline examination.

	AAMI	AAMIO	AACD	CIND	fMCI	aMCI
AAMIO	**.96** (404)	----				
AACD	**.66** (405)	**.67** (455)	----			
CIND	**.49** (388)	**.50** (435)	**.87** (597)	----		
fMCI	.08 (380)	.13 (423)	.28 (571)	.26 (573)	----	
aMCI	.32 (392)	.24 (422)	.11 (482)	.19 (472)	.01 (468)	----
MA	.00 (399)	.07 (450)	.33 (611)	**.41** (603)	.19 (588)	.09 (483)

Note. Bold indicates good or excellent agreement

Table 9. Wave 2 outcome for those meeting full criteria for constructs at baseline examination.

	Wave 2 Status							
	Meets full criteria	Meets inclusion criteria only	Cog Normal	Dementia	Alzheimer's Disease	Deceased	Refused	Unable to classify
AAMIO *n=21*	5 (23.8%)	3 (14.3%)	8 (38.1%)	1 (4.8%)	1 (4.8%)	0	2 (9.5%)	2 (9.5%)
AAMI *n=21*	5 (23.8%)	0	11 (52.4%)	0	0	0	3 (14.3%)	2 (9.5%)
AACD *n=118*	21 (17.8%)	0	41 (34.7%)	14 (11.9%)	12 (10.2%)	12 (10.2%)	17 (14.4%)	13 (11.0%)
CIND *n=249*	45 (18.1%)	N/A	70 (28.1%)	46 (18.5%)	34 (13.7%)	39 (15.7%)	45 (18.1%)	4 (1.6%)
aMCI *n=10*	0	0	6 (60.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)
fMCI *n=324*	149 (46.0%)	10 (3.1%)	29 (9.0%)	31 (9.6%)	25 (7.7%)	39 (12.0%)	56 (17.3%)	10 (3.1%)
MA *n=209*	57 (27.3%)	13 (6.2%)	40 (19.1%)	29 (13.9%)	24 (11.5%)	32 (15.3%)	32 (15.3%)	6 (2.9%)

Note. Dementia totals include AD cases.

Table 10. Wave 2 outcome for those impaired (full criteria or inclusion criteria only) and cognitively normal at baseline examination.

		Status at Follow up examination						
		Impaired	Cog Normal	Dementia	Alzheimer's Disease	Deceased	Refused	Unable to classify
AAMIO	*Impaired N=82*	18 (21.9%)	25 (30.5%)	10 (12.2%)	9 (11.0%)	6 (7.3%)	10 (12.2%)	13 (15.9%)
	Cognitively Normal N=380	22 (5.7%)	172 (45.3%)	20 (5.3%)	9 (2.4%)	46 (12.1%)	72 (18.9%)	48 (12.6%)
AAMI	*Impaired N=46*	12 (26.1%)	19 (41.3%)	4 (8.7%)	3 (6.5%)	1 (2.2%)	5 (10.9%)	5 (10.9%)
	Cognitively Normal N=366	11 (3.0%)	165 (45.1%)	18 (5.0%)	9 (2.5%)	44 (12.0%)	69 (18.9%)	59 (16.1%)
AACD	*Impaired N=263*	34 (12.9%)	76 (28.9%)	46 (17.5%)	33 (12.5%)	34 (12.9%)	44 (16.7%)	29 (11.0%)
	Cognitively Normal N=364	48 (13.2%)	166 (45.6%)	17 (4.7%)	9 (2.5%)	42 (11.5%)	66 (18.1%)	25 (6.9%)
CIND	*Impaired N=249*	45 (18.1%)	70 (28.1%)	46 (18.5%)	34 (13.7%)	39 (15.7%)	45 (18.1%)	4 (1.6%)
	Cognitively Normal N=381	48 (12.6%)	201 (52.8%)	21 (5.5%)	11 (2.9%)	41 (10.8%)	63 (16.5%)	7 (1.8%)
aMCI	*Impaired N=12*	1 (8.3%)	6 (50.0%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	1 (8.3%)
	Cognitively Normal N=489	4 (0.8%)	285 (58.3%)	21 (4.3%)	12 (2.5%)	53 (10.8%)	88 (18.0%)	38 (7.8%)
fMCI	*Impaired N=440*	197 (44.8%)	35 (8.0%)	55 (12.5%)	37 (8.4%)	60 (13.6%)	82 (18.6%)	11 (2.5%)
	Cognitively Normal N=162	60 (37.0%)	58 (35.8%)	4 (2.5%)	3 (1.9%)	15 (9.3%)	19 (11.7%)	6 (3.7%)
MA	*Impaired N=312*	89 (28.5%)	49 (15.7%)	57 (18.3%)	38 (12.2%)	52 (16.7%)	57 (18.3%)	8 (2.6%)
	Cognitively Normal N=321	63 (19.7%)	164 (51.1%)	7 (2.2%)	5 (1.6%)	27 (8.4%)	54 (16.8%)	6 (1.9%)

Table 11. Outcome and predictive utility of preclinical dementia algorithms for prediction of dementia.

	Baseline Status	Number (%) converted to dementia	Odds Ratio	95% Confidence Interval	*P* value
AAMI-original	*Full criteria (N=21)*	1 (4.8%)	0.7	0.09-5.49	.723
	Impaired (N=82)	10 (12.2%)	1.8	0.8-4.3	.173
	Cognitively Normal (N=380)	20 (5.3%)			
AAMI-revised	*Full criteria (N=21)*	0	n/a	n/a	n/a
	Impaired (N=46)	4 (8.7%)	2.2	0.6-7.9	.233
	Cognitively Normal (N=366)	18 (5.0%)			
AACD	*Full criteria (N=118)*	14 (11.9%)	2.3	1.05-4.94	.038
	Impaired (N=263)	46 (17.5%)	4.2	2.3-7.8	.000
	Cognitively Normal (N=364)	17 (4.7%)			
CIND	*Full criteria (N=249)*	46 (18.5%)	4.1	2.31-7.41	.000
	Cognitively Normal (N=381)	21 (5.5%)			
aMCI	*Full criteria (N=10)*	1 (10.0%)	3.2	0.36-28.94	.293
	Impaired (N=12)	1 (8.3%)	2.3	0.2-21.6	.538
	Cognitively Normal (N=489)	21 (4.3%)			
fMCI	*Full criteria (N=324)*	31 (9.6%)	3.9	1.31-11.39	.014
	Impaired (N=440)	55 (12.5%)	5.7	2.0-16.2	.001
	Cognitively Normal (N=162)	4 (2.5%)			
MA	*Full criteria (N=209)*	29 (13.9%)	8.4	3.48-20.17	.000
	Impaired (N=312)	57 (18.3%)	13.4	5.8-30.8	.000
	Cognitively Normal (N=321)	7 (2.2%)			

Note. Baseline N's reflect number of participants meeting full criteria at baseline for each construct and are non-mutually exclusive. Cognitively normal N's varied for each construct because status was determined using construct-specific definitions for normal cognition. Impaired group includes those meeting full criteria and those meeting inclusion criteria only (e.g., generally with an exclusionary medical condition). Remaining participants include those unable to be classified.

Table 12. Outcome and predictive utility of preclinical dementia algorithms for prediction of Alzheimer's disease.

	Baseline Status	Number (%) converted to Alzheimer's	Odds Ratio	95% Confidence Interval	*P* value
AAMI-original	*Full criteria (N=21)*	1 (4.8%)	1.5	0.2-12.5	.730
	Impaired (N=82)	9 (11.0%)	3.8	1.4-10.4	.010
	CognitivelyNormal (N=380)	9 (2.4%)			
AAMI-revised	*Full criteria (N=21)*	0	n/a	n/a	n/a
	Impaired (N=46)	3 (6.5%)	3.9	0.8-19.3	.095
	Cognitively Normal (N=366)	9 (2.5%)			
AACD	*Full criteria (N=118)*	12 (10.2%)	3.8	1.5-9.6	.005
	Impaired (N=263)	33 (12.5%)	5.8	2.6-12.7	.000
	Cognitively Normal (N=364)	9 (2.5%)			
CIND	*Full criteria (N=249)*	34 (13.7%)	5.7	2.7-12.0	.000
	Cognitively Normal (N=381)	11 (2.9%)			
aMCI	*Full criteria (N=10)*	1 (10.0%)	7.9	0.8-74.2	.072
	Impaired (N=12)	1 (8.3%)	5.1	0.5-51.9	.167
	Cognitively Normal (N=489)	12 (2.5%)			
fMCI	*Full criteria (N=324)*	25 (7.7%)	4.4	1.3-15.4	.019
	Impaired (N=440)	37 (8.4%)	5.3	1.6-17.8	.008
	Cognitively Normal (N=162)	3 (1.9%)			
MA	*Full criteria (N=209)*	24 (11.5%)	9.9	3.6-27.2	.000
	Impaired (N=312)	38 (12.2%)	11.7	4.4-31.0	.000
	Cognitively Normal (N=321)	5 (1.6%)			

Note. Baseline N's reflect number of participants meeting full criteria at baseline for each construct and are non-mutually exclusive. Cognitively normal N's varied for each construct because status was determined using construct-specific definitions for normal cognition. Impaired group includes those meeting full criteria and those meeting inclusion criteria only (e.g., generally with an exclusionary medical condition). Remaining participants include those unable to be classified.

Table 13. Relative predictive power of preclinical dementia constructs to predict dementia after controlling for age, education, gender and APOE status.

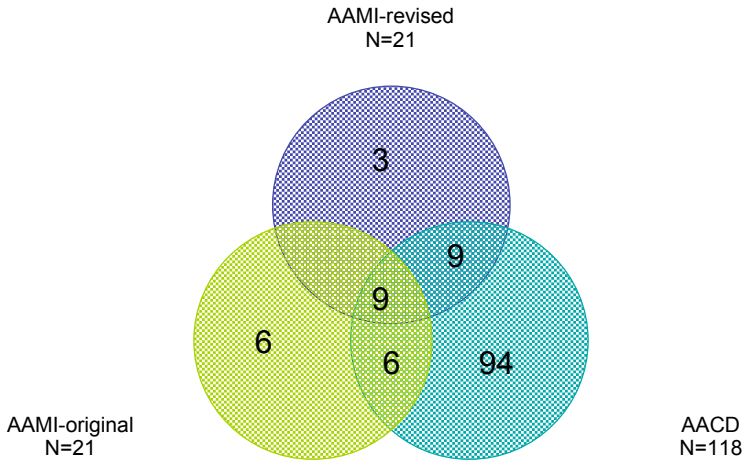
		Sensitivity, %	Specificity, %	AUC	SE	Asymptotic significance	95% CI
AAMI-original	*Full criteria (N=21)*	69.7	69.8	.753	.033	.000	.689-.817
	Impaired (N=82)	65.5	63.8	.705	.048	.000	.611-.798
AAMI-revised	*Full criteria (N=21)*	72.7	68.3	.754	.031	.000	.693-.814
	Impaired (N=46)	68.2	60.4	.694	.053	.002	.590-.798
AACD	*Full criteria (N=118)*	66.7	72.4	.771	.031	.000	.710-.832
	Impaired (N=263)	68.9	68.3	.754	.032	.000	.691-.817
CIND	*Full criteria (N=249)*	69.7	68.8	.755	.032	.000	.693-.817
aMCI	*Full criteria (N=10)*	68.2	85.7	.830	.030	.000	.770-.889
	Impaired (N=12)	72.2	62.5	.716	.053	.001	.613-.819
fMCI	*Full criteria (N=324)*	74.2	67.3	.762	.029	.000	.705-.820
	Impaired (N=440)	77.6	57.3	.723	.032	.000	.659-.787
MA	*Full criteria (N=209)*	73.7	80.3	.843	.024	.000	.797-.889
	Impaired (N=312)	82.3	68.3	.830	.025	.000	.782-.878

Table 14. Relative predictive power of preclinical dementia constructs to predict AD after controlling for age, education, gender and APOE status.

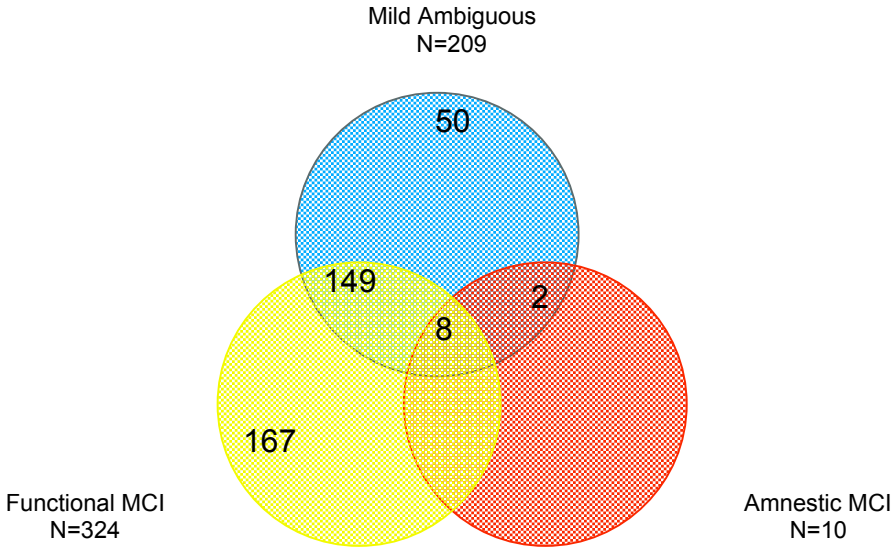
		Sensitivity, %	Specificity, %	AUC	SE	Asymptotic significance	95% CI
AAMI-original	*Full criteria (N=21)*	71.1	73.3	.797	.036	.000	.727-.867
	Impaired (N=82)	72.2	71.2	.757	.058	.000	.643-.871
AAMI-revised	*Full criteria (N=21)*	73.3	72.1	.801	.034	.000	.733-.868
	Impaired (N=46)	66.7	62.9	.712	.073	.013	.569-.854
AACD	*Full criteria (N=118)*	75.6	72.8	.800	.037	.000	.728-.871
	Impaired (N=263)	69.0	72.5	.793	.038	.000	.718-.868
CIND	*Full criteria (N=249)*	68.9	72.8	.802	.036	.000	.731-.873
aMCI	*Full criteria (N=10)*	71.1	82.3	.846	.035	.000	.777-.915
	Impaired (N=12)	61.5	64.7	.716	.072	.008	.576-.857
fMCI	*Full criteria (N=324)*	68.9	66.0	.757	.038	.000	.683-.830
	Impaired (N=440)	70.0	65.3	.759	.040	.000	.681-.836
MA	*Full criteria (N=209)*	82.2	72.1	.828	.033	.000	.763-.893
	Impaired (N=312)	79.1	72.1	.831	.033	.000	.765-.896

Figure 1. Overlap among select preclinical dementia constructs

a. Overlap among AAMI-original, AAMI-revised, and AACD



b. Overlap among aMCI, fMCI, and MA



c. Overlap among MA, AACD, and CIND

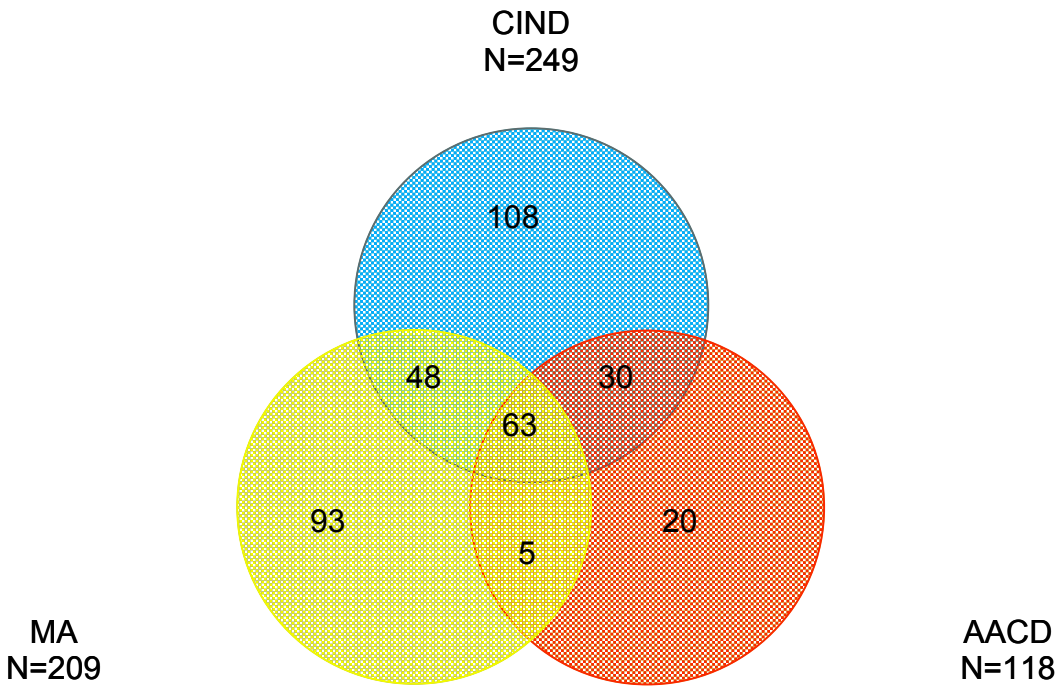


Figure 2a. Comparison of significant predictor AUC curves in the prediction of dementia (full criteria)

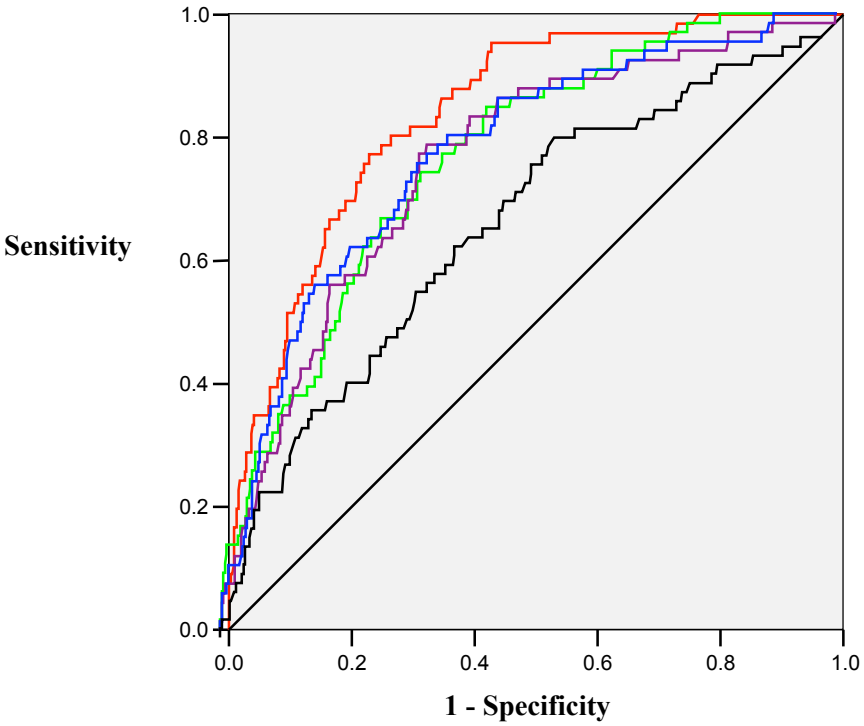


Figure 2b. Comparison of significant predictor AUC curves in the prediction of dementia (impaired)

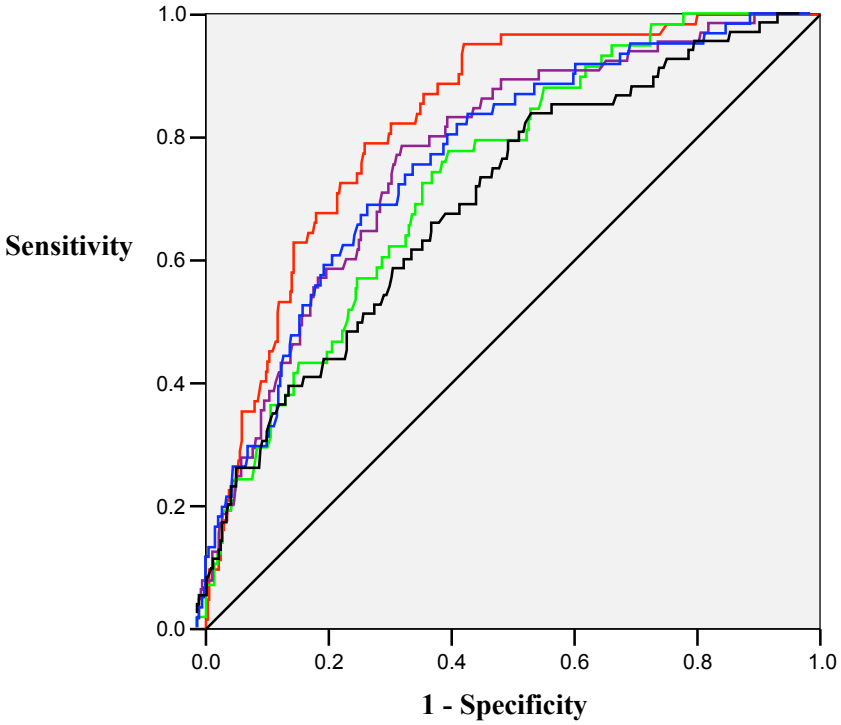


Figure 3a. Comparison of significant predictor AUC curves in the prediction of AD (full criteria)

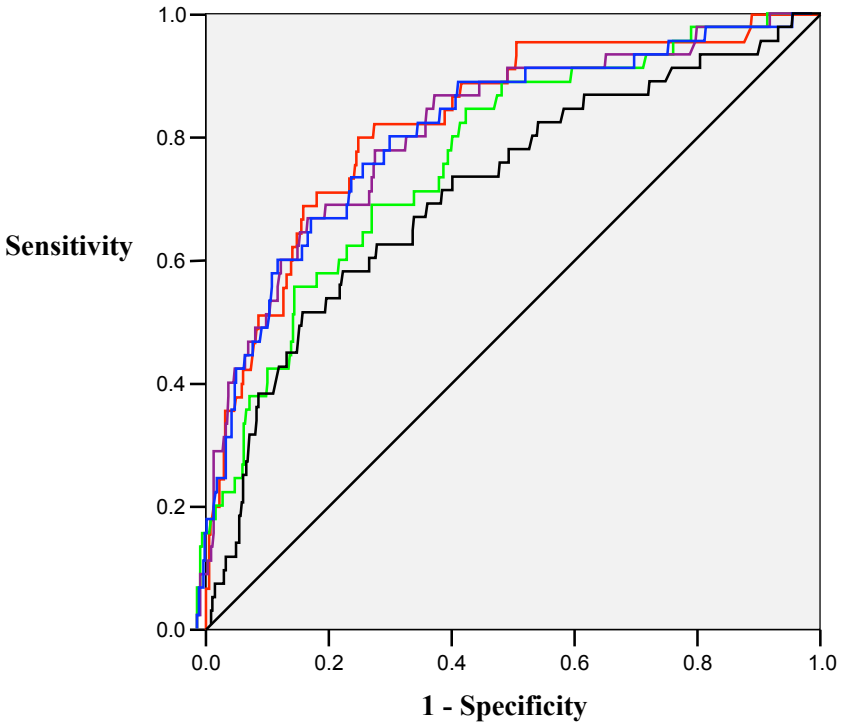
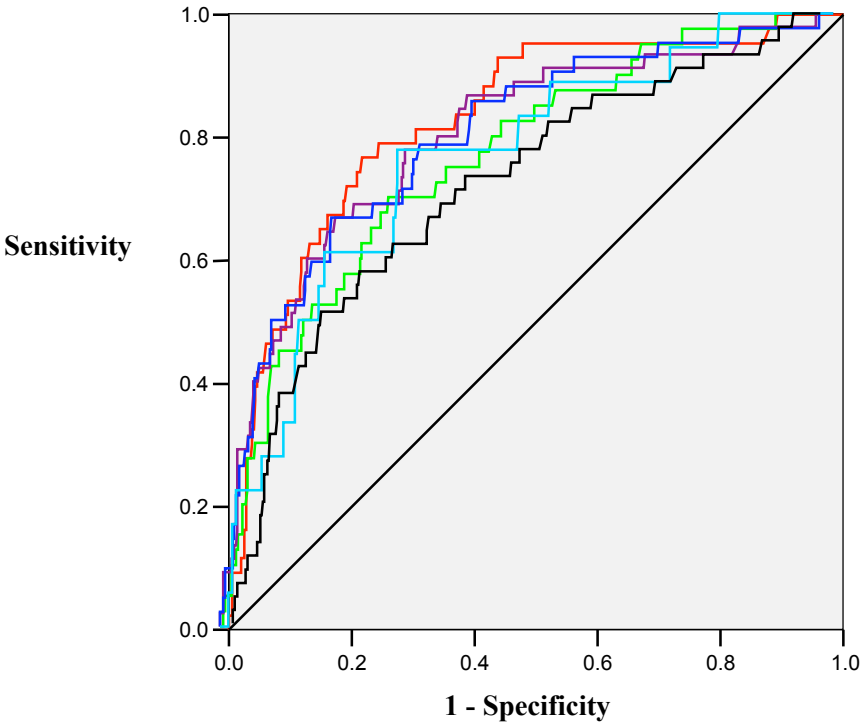


Figure 3b. Comparison of significant predictor AUC curves in the prediction of AD (impaired)



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