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Revised Criteria for Mild Cognitive Impairment May Compromise the Diagnosis of Alzheimer Disease Dementia

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Abstract

Objective—To evaluate the potential impact of revised criteria for mild cognitive impairment (MCI), developed by a Workgroup sponsored by the National Institute on Aging and the Alzheimer’s Association, on the diagnosis of very mild and mild Alzheimer disease (AD) dementia.

Design—Retrospective review of ratings of functional impairment across diagnostic categories. Participants: The functional ratings of individuals (N = 17,535) with normal cognition, MCI, or AD dementia who were evaluated at Alzheimer’s Disease Centers and submitted to the National Alzheimer’s Coordinating Center were assessed in accordance with the definition of “functional independence” allowed by the revised criteria.

Methods—Pairwise demographic differences between the 3 diagnostic groups were tested using t-tests for continuous variables and chi-square for categorical variables.

Results—Almost all (99.8%) of individuals currently diagnosed with very mild AD dementia and the large majority (92.7%) of those diagnosed with mild AD dementia could be reclassified as MCI with the revised criteria, based on their level of impairment in the Clinical Dementia Rating domains for performance of instrumental activities of daily living in the community and at home. Large percentages of these AD dementia individuals also meet the revised “functional independence” criterion for MCI as measured by the Functional Assessment Questionnaire.

Conclusions—The categorical distinction between MCI and milder stages of Alzheimer dementia has been compromised by the revised criteria. The resulting diagnostic overlap supports the premise that “MCI due to AD” represents the earliest symptomatic stage of AD.

Keywords

Dementia Diagnosis; Alzheimer disease; MCI

Mild cognitive impairment (MCI) aims to identify cognitive decline in its earliest stages. It is a popular concept: the National Institute on Aging (NIA) in 2004 noted MCI as a top discovery of the Alzheimer’s Disease Centers (ADCs) program,¹ and in 2010 over 1220 publications listed “MCI” in the title, abstract, or keywords (Elsevier SciVerse Scopus). Given its importance, the NIA and the Alzheimer’s Association convened a Workgroup to update criteria for MCI. The revised criteria recently were published,² as were revised criteria for Alzheimer disease (AD) dementia³ and for the preclinical stage of AD.⁴ A key criterion for MCI is the absence of dementia.² The revised criteria for AD dementia, which are comparable to widely used criteria for dementia of the Alzheimer type (DAT),⁵ stipulate

that impairment must be present in two or more cognitive domains and must interfere with the ability to function in usual activities. The original diagnosis of MCI^{6,7} was limited to individuals with cognitive impairment in a single domain (memory), thus distinguishing MCI from dementia, but more recently its differentiation from dementia has come to rest solely on the preservation of functional activities.^{8,9} The revised criteria for MCI², however, allow considerable latitude as to what represents functional independence and thus blur the categorical distinction between MCI and dementia.

Initially proposed as a predictor of progressive cognitive decline in older adults,¹⁰ MCI later was defined as an amnesic syndrome that denoted a transitional stage between aging and dementia (particularly dementia caused by AD).^{6,7} With experience, however, came the realization that individuals classified as MCI frequently were impaired in cognitive domains other than memory.^{11,12} Criteria for MCI thus were broadened to include both non-amnesic presentations and the involvement of multiple cognitive domains but continued to require “essentially normal” functional activities.^{8,9} The recently published revised criteria for MCI require: 1) change in cognition recognized by the affected individual or observers; 2) objective impairment in one or more cognitive domains; 3) independence in functional activities; and 4) absence of dementia.² Although on the surface these revised criteria conform to earlier definitions,^{8,9} the revised criteria operationalize “independence in functional activities” more expansively than before. For example, “mild problems” in performing daily activities such as shopping, paying bills, and cooking are permissible, as is dependency on aids or assistance to complete such activities.² This interpretation of “independence in functional activities” thus has the potential to characterize as MCI some individuals who now are diagnosed with very mild and mild AD dementia.

To assess this potential, the functional ratings of participants enrolled at federally-funded Alzheimer’s Disease Centers (ADCs) with clinical and cognitive data maintained by the National Alzheimer’s Coordinating Center (NACC; U01 AG016976; W. Kukull, Principal Investigator) were evaluated. The degree of functional impairment as assessed by two ratings of activities of daily living, the Functional Activities Questionnaire (FAQ)¹³ and the Clinical Dementia Rating (CDR),¹⁴ was determined for NACC participants with MCI and for participants with very mild and mild AD dementia (all diagnoses were made prior to the publication of the revised criteria for MCI). These functional ratings then were interpreted in accordance with the definition in the revised criteria for MCI of “independence in functional activities” to examine their potential to change current diagnoses.

METHODS

Data were obtained from participants entered into the NACC between September, 2005, and May 20, 2011, who were diagnosed by ADC clinicians as being cognitively normal, having MCI, or having probable AD; standard criteria were used to diagnose MCI^{8,9} and probable AD.¹⁵ Diagnoses were made by a single clinician or by consensus conference. A uniform assessment battery to characterize individuals with MCI and probable AD in comparison with cognitively normal aging was developed by a Clinical Task Force of the ADCs and implemented at each ADC in September, 2005. This Uniform Data Set (UDS)^{16,17} defines the standard clinical and cognitive observations that are collected longitudinally on ADC participants; the UDS data are submitted to NACC. Incorporated into the UDS is the FAQ, a measure of the participant’s functional impairment as rated by an informant. The FAQ rates the participant’s current ability to perform 10 instrumental activities of daily living: 1) household finances; 2) assembling financial and tax documents; 3) shopping; 4) hobbies; 5) simple kitchen functions, such as heating water; 6) preparing a meal; 7) monitoring current events; 8) comprehending televised programs or a book; 9) monitoring family occasions or personal medications; and 10) transportation (e.g., driving). Performance in each of the 10

activities is rated along a 4-point scale, from no difficulty in performance (0), to difficulty but still performing “by self” (1), to performing with assistance (2), to dependent (3). Only those activities that the participant previously performed are rated and, in the UDS, reflect impairment due only to cognitive loss. A conservative operationalization of the functional “independence” permitted by the revised criteria for MCI is considered here to include FAQ scores of 0 or 1 for each rated activity. As the revised criteria for MCI allow activities to be performed with assistance, also considered here is a more liberal interpretation where FAQ ratings of 0, 1, and 2 could be compatible with this definition of functional “independence”.

The UDS also includes the CDR. Using both informant report and an examination of the participant, an experienced clinician rates the presence or absence of cognitive and functional loss and, when present, rates severity in each of 6 domains: Memory, Orientation, Judgment and Problem Solving, and function in Community Affairs (CA), Home & Hobbies (HH), and Personal Care. The clinician synthesizes all relevant information, including that obtained with the FAQ, in rating instrumental activities of daily living in the community (CA) and at home (HH). Only impairment caused by cognitive loss is rated on a 5-point scale as none (0), very mild (0.5), mild (1), moderate (2), or severe (3). An algorithm combines the individual ratings in each of the 6 domains to derive a global CDR score, where CDR 0 indicates cognitive normality and CDR 0.5, 1, 2, and 3 indicate questionable/very mild, mild, moderate, and severe dementia.¹⁴ The CDR has demonstrated reliability in multicenter studies.^{18,19} Qualitative descriptions for different levels of impairment serve as anchor points to guide ratings of function in the CA and HH domains, or “boxes”, and are shown in Table 1. For both the CA and HH boxes, “slight” impairment is rated as 0.5. Mild impairment at the 1 level for CA translates to pretense of independent function (may engage in activities and appear “normal”, although does not function without assistance) and to independence in HH for simpler activities but not more complex ones. Impairment at the CDR 0.5 level for either CA and HH conservatively is consistent with revised MCI criteria for functional “independence”, and impairment at the CDR 1 level for CA and HH also could be interpreted more liberally as compatible with the “mild problems” in shopping, paying bills, and meal preparation and the need for assistance allowed by the revised criteria.

Analyses

Data were analyzed from the first UDS assessment for NACC participants with non-missing data on age, gender, race, education, CA and HH box scores, and who had non-missing data on one or more of the FAQ items. Participants in the cognitively normal group were required to be CDR 0. Eligibility criteria for the MCI group included all subtypes (Amnesic MCI – memory impairment only; Amnesic MCI – memory impairment plus impairment in one or more other domains; Non-amnesic MCI – single domain; and Non-amnesic MCI – multiple domains),^{8,9} global CDR=0.5, and the clinician’s indication that the participant did not have dementia at that assessment. Data from participants younger than 50 years of age at the index assessment and individuals with Down syndrome were excluded from analyses. For persons who met eligibility criteria at more than one assessment (e.g., a cognitively normal participant who later developed AD dementia), data from the first assessment meeting eligibility criteria were used in the analyses.

Participants were assigned to one of six groups based on their global CDR and diagnosis: CDR 0, CDR 0.5/MCI, CDR 0.5/AD, CDR 1/AD, CDR 2/AD, and CDR 3/AD. Two levels of FAQ ratings and CDR box scores for CA and HH that meet the revised criteria’s operationalized functional “independence” for a diagnosis of MCI were examined: 1) conservative, with FAQ ratings of 0 or 1 and CDR box scores of 0 or 0.5, and 2) liberal, with FAQ ratings of 0, 1, or 2 and CDR box scores of 0, 0.5, and 1. The number and percent

of participants at each CA and HH box score level and each FAQ item was reported for each group.

Pairwise demographic differences between the CDR 0, CDR 0.5/MCI, and CDR 0.5/AD groups were tested (t-tests for continuous variables, chi-square for categorical variables). Logistic regression using bias correction was employed to test differences across the CDR 0, CDR 0.5/MCI, and CDR 0.5/AD groups in the likelihood of functional impairment while adjusting for the effects of age, sex, education, race, and apolipoprotein E genotype. The CDR 0.5/MCI group was used as the reference category in these analyses.

RESULTS

There were 17,535 individuals from 33 ADCs entered into the NACC database who met eligibility criteria, including a diagnosis of normal cognition ($n = 6,379$), MCI ($n = 4,947$), or probable AD ($n = 6,209$). The mean age of the total sample was 74.6y (standard deviation [SD] 9.5y; range 50–110y) with a mean educational attainment of 14.7y (SD 3.5y). Fifty-nine percent were women, 79.8% were white, and 14.9% were African American. Of the 9,557 individuals for whom their apolipoprotein E allele status was known, 3,994 (41.7%) were carriers of at least one $\epsilon 4$ allele.

Table 2 shows the demographic characteristics of the sample as a function of CDR stage and diagnosis at time of entry into the NACC database, with statistical tests of differences between the groups of greatest interest (CDR 0 vs CDR 0.5/MCI and CDR 0.5/AD versus CDR 0.5/MCI). The CDR 0.5/MCI and the CDR 0.5/AD groups statistically were similar with regard to age and sex. For each of the remaining demographic variables, there were significant differences between CDR 0, CDR 0.5/MCI and CDR 0.5/AD groups. Regardless of how functional impairment was operationalized, the CDR 0 group was less likely, and the CDR 0.5/AD group more likely, than the CDR 0.5/MCI group to be functionally impaired. As expected, given the large sample sizes, all differences were statistically significant (see Supplementary Table).

Table 3 shows the severity of functional impairment of the NACC sample. More than two thirds (68.3%) of CDR 0.5/MCI individuals were performing normally in community activities (CA box score = 0) versus only 23.9% of CDR 0.5/AD individuals; for CDR 1/AD individuals, only 0.2% were performing normally. Very similar percentages were found for normal performance of home activities (HH box score = 0) for these three diagnostic groups. By virtue of a score of 3 (“does with assistance”) on any of the four FAQ items (assembling tax records; writing checks; preparing a balanced meal; shopping) that are equivalent to the “mild problems in paying bills, preparing a meal, or shopping” of the revised criteria for MCI,² 41.8% of CDR 0.5/AD individuals are impaired versus 79.4% of CDR 1/AD individuals ($p < .0001$). When either a score of “2” or “3” for these FAQ items is considered, 73.8% of CDR 0.5/AD individuals versus 94.7% of CDR 1/AD individuals are impaired ($p < .0001$).

Box scores of 0, 0.5, or 1 in CA and in HH (i.e., normal, slight, and mild impairment) are allowable under the liberal operationalization of “functional independence” described by the revised criteria for MCI. The data in Table 3 indicate that 99.8% of all individuals currently diagnosed as CDR 0.5/AD and 92.7% of all individuals currently diagnosed as CDR 1/AD could be reclassified as MCI with the revised criteria, as these individuals have box scores of 0, 0.5, or 1 for CA and HH (Figure 1). Limiting the operationalization of “functional independence” to box scores of 0 and 0.5 still results in 90.1% (for CA) and 84.5% (for HH) of currently diagnosed CDR 0.5/AD individuals potentially meeting revised criteria for

MCI, although the percent of currently diagnosed CDR 1/AD that could be reclassified as MCI is notably reduced (Figure 2).

Data from FAQ items (Table 3) are consistent with the findings from the CA and HH box scores. Because “mild problems” in performing finances, cooking, and shopping or the need for assistance to perform these activities are allowed by the revised criteria for MCI, scores for the 4 corresponding FAQ items (assembling tax records, writing checks, preparing meals, shopping) of 0 (normal), 1 (does by self with difficulty), and 2 (does with assistance) are found for between 71.5% (assembling tax records) and 94.6% (shopping) of currently diagnosed CDR 0.5/AD individuals and for between 31.2% (assembling tax records) to 71.7% (shopping) of currently diagnosed CDR 1/AD individuals (Figure 3). These individuals thus could meet the revised criteria for MCI. Limiting FAQ scores to 0 and 1 shows that between 43.4% (assembling tax records) and 80.4% (shopping) of currently diagnosed CDR 0.5/AD individuals and between 11.1% (assembling tax records) and 38.7% (preparing meals) of currently diagnosed CDR 1/AD individuals could be reclassified as MCI (Figure 4).

DISCUSSION

The differentiation between MCI and AD dementia in its earliest symptomatic stages has been based primarily on whether the cognitive impairment interferes with the conduct of activities of daily living. Clinicians for ADC participants currently submitted to NACC appear to follow this distinction, as two-thirds or more of individuals diagnosed with MCI are rated with no impairment in performance of activities in the community and at home, whereas over 75% of CDR 0.5/AD individuals have at least slight impairment in these activities. However, revised criteria for MCI² now obscure this distinction by permitting mild difficulties in functional activities to be part of the MCI spectrum. As a result, the large majority of individuals currently diagnosed with milder stages of AD dementia now could be reclassified as MCI with the revised criteria. The elimination of the functional boundary between MCI and AD dementia means that their distinction will be based solely on the individual judgment of clinicians, resulting in nonstandard and ultimately arbitrary diagnostic approaches to MCI. This recalibration of MCI moves its focus away from the earliest stages of cognitive decline, confounds clinical trials of individuals with MCI where progression to AD dementia is an outcome, and complicates diagnostic decisions and research comparisons with legacy data.

The diagnostic overlap of MCI and AD dementia suggests ambiguity in the MCI concept,^{20,21} as also may be reflected by the continuing evolution of its criteria. The original criteria specified impairment in memory only with the preservation of other cognitive abilities and intact functional performance,^{6,7} distinguishing it from AD dementia where deficits in multiple cognitive domains and interference with functional activities are required. A multicenter clinical trial of donepezil and vitamin E in 769 individuals classified as MCI using the original criteria found, however, that very mild impairments often were present in cognitive domains other than memory.¹¹ Criteria for MCI subsequently were modified to allow both impairment in cognitive domains other than memory and impairments in multiple domains, thus erasing one of the original distinguishing features of MCI and leaving only the “essentially normal” performance of functional activities in MCI as the difference between MCI and the milder stages of AD dementia.^{8,9}

Standardizing the degree of functional impairment that is associated with dementia rather than MCI has been problematic,⁸ in part because the determination of impairment is dependent on how carefully performance of usual activities is interrogated by the clinician. It nonetheless has become apparent that many individuals characterized as MCI are

functionally impaired.^{22,23} Ninety-six individuals with MCI in one study showed a wide range of impairment in everyday function as compared with 105 cognitively normal older adults,²⁴ and another study of 285 individuals with MCI found that 34.3% were restricted in their ability to perform at least 2 of 4 activities (using a telephone; handle transportation; responsibility for medications; handle finances), compared with only 5.4% of cognitively older healthy persons.²⁵ Even using criteria for MCI that require “essentially normal” activities for daily living, as is specified for the Alzheimer’s Disease Neuroimaging Initiative that examines the progression of MCI to very mild AD dementia, 104 (37%) of 283 MCI individuals were rated as functionally impaired with 0.5 ratings for both CA and HH on the CDR or a rating of 1 for either box.²⁶

It is not surprising that their criteria essentially are indistinguishable if MCI and AD dementia are produced by the same underlying disease process. In many (but not all) instances the underlying process for MCI is AD, a brain disorder that is characterized by continuous deterioration of synaptic and neuronal integrity.^{27–29} The concept of an AD continuum has been noted from many perspectives, including epidemiological,³⁰ neuropsychological,^{31,32} structural and metabolic imaging,³³ and pathophysiological.³⁴ The initial stages of the continuum, representing a preclinical stage of AD,⁴ are marked by no or only minimal synaptic and neuronal deterioration^{35–37} and correspondingly symptoms are absent (at least as detected by currently available methods). As the disease process progresses over time and neurodegeneration increases, the symptomatic stage of AD gradually develops.³⁸ The symptomatic stage may be subdivided by the degree of cognitive and functional impairment, ranging from minimal to severe. (Table 4)

For virtually all persons with AD, MCI represents the earliest clinically detectable stage of symptomatic AD. Imparting binary distinctions on the cognitive continuum of AD by designating one side as “MCI” and the other as “dementia” inherently is difficult and has been made more challenging because experts cannot agree on the operationalization of MCI.³⁹ It has proven equally difficult to provide operational criteria that distinguish MCI from normal cognitive aging. Although the increased variability of cognitive performance with age⁴⁰ complicates this distinction, another factor is the reliance on cognitive performance measured at a single point in time to determine “impairment”. This approach, based on present level of performance, cannot capture the salient cognitive feature of AD, which is decline from that individual’s previously attained abilities. Intraindividual decline (i.e., the temporal loss of cognitive abilities) must be obtained with serial cognitive measurements or by a history of change from previously attained levels as reported by an observant informant.⁴¹ (Self-reported memory complaints rarely predict either impairment^{42,43} or future dementia,^{44–46} although some investigators find that subjective memory complaints in highly educated older adults may do so.⁴⁷)

The operational cutpoint for MCI frequently has been a neuropsychological test score in a relevant domain, most often memory, that is 1.5 or more SDs below age-corrected means,^{48–51} but occasionally a score that is only 1 SD or more below normative values is used,⁵² as are other algorithms.^{53,54} Differing cutpoints produce different classifications of MCI and contribute to variable outcomes.⁵⁵ Furthermore, the effects of preclinical AD artificially lower cognitive performances in putatively “normal” samples and produce cutoffs that are too lenient to identify initial change from truly healthy cognitive aging, thus resulting in an ascertainment bias where “impairment” is detected only after notable cognitive decline has occurred.^{56,57} Variable cutoff scores used to characterize MCI, ascertainment bias caused by preclinical AD, and problems of misclassification when using a measurement at a single time point to identify a process of intraindividual decline all introduce heterogeneity to MCI.^{49,58–62} Just as there are non-AD causes of dementia, there are non-AD causes of MCI.⁶³ The use of informant report to capture the intraindividual

cognitive and functional decline that is the hallmark of symptomatic AD both minimizes this heterogeneity and enables the accurate identification of the subset of MCI that is caused by AD.^{23,64–67} The clinical diagnosis of symptomatic AD with this method, even in individuals who meet MCI criteria, is supported by autopsy confirmation of AD neuropathology at rates (92%) comparable to those found for AD dementia.⁶⁸

The revised criteria for MCI laudably recommend an etiologic diagnosis, “MCI due to AD”, when the clinical judgment is that AD is responsible for the cognitive dysfunction. The Workgroup also suggests that diagnostic confidence for AD could be enhanced by utilizing biomarkers for amyloid-beta deposition and neuronal injury.² Some clinicians, however, are reluctant to diagnose symptomatic AD in this situation, presumably because of uncertainty as to whether “MCI due to AD” will progress to AD dementia and because the diagnosis of AD is perceived as stigmatizing. As noted above, an informant-based diagnostic method to capture intraindividual decline accurately identifies individuals in the MCI stage who have underlying AD and who longitudinally progress in dementia severity.⁶⁷ Clinicians using other diagnostic approaches may increasingly use AD biomarkers to improve diagnostic certainty. An early etiologic diagnosis is advocated for other devastating neurodegenerative diseases such as amyotrophic lateral sclerosis^{69,70} without resorting to terms such as “minimal motor impairment” and thus allow patients and families to initiate planning to cope with the illness and enable therapeutic interventions early in the disease course. An analogous approach should be implemented for AD.

Some studies report that between 30%–60% of physicians do not disclose the diagnosis of dementia, much less “MCI due to AD”, to their patients,^{71–73} although over 94% of the same physicians disclosed a diagnosis of terminal cancer.⁷¹ Factors cited against disclosing a dementia diagnosis included concern about provoking psychological distress in patients and families.^{74,75} Although individuals given a diagnosis of dementia can experience catastrophic reactions, including suicide,⁷⁶ the actual risk of suicide is very small and in one study of community living individuals with dementia was estimated to be less than 0.1%.⁷⁷ Patients and families have consistently indicated that receiving a diagnosis of dementia is very important to them to indicate that the cognitive symptoms have an identifiable cause and to plan for the future.^{78,79} A study of individuals who qualify for a MCI classification showed that depressive symptoms and measures of stress after disclosure of the diagnosis of AD dementia did not worsen from pre-diagnosis levels and indeed often improved for both the affected individuals and their family members.⁸⁰

The pathobiologically-based “next step” now is to transition from the syndromic label of “MCI” to its etiologic diagnosis when the responsible disorder is believed to be AD.⁸¹ This “next step” circumvents the difficulty in attempting to dichotomize MCI and AD dementia and more appropriately reflects the continuum of AD. However, “MCI” still could be used to characterize individuals who may be in the early symptomatic stages of a non-AD dementing disorder, where there is less experience in accurately determining etiology than exists for “MCI due to AD”, or when potentially reversible disorders such as cognitive dysfunction associated with medications are suspected. Similar recommendations have been proposed by the International Working Group for New Research Criteria for the Diagnosis of AD. This Working Group proposes that “MCI” be reclassified as “prodromal AD” when this diagnosis is supported by clinical phenotype and biomarker profile,⁸² and suggests that the use of “MCI” be limited to individuals without a diagnosable illness.

The revised criteria² accept that MCI can be associated with impaired functional activities, such that the distinction of MCI from dementia now simply is a matter of an individual clinician’s threshold for what represents one condition versus the other. The diagnostic overlap for MCI with milder cases of AD dementia is considerable and suggests that any

distinction is artificial and arbitrary. Already, many individuals with MCI are treated with pharmacological agents approved for symptomatic AD, indicating that clinicians often do not distinguish the two conditions when faced with issues of medical management.^{83,84} It now is time to advance AD patient care and research by accepting that “MCI due to AD” is more appropriately recognized as the earliest symptomatic stage of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Percent of AD dementia participants in NACC who would be considered “independent” in functional activities by revised MCI criteria where “independent” includes CDR box scores of 0, 0.5, and 1. These individuals could thus be reclassified as MCI.

Figure 2. Percent of AD dementia participants in NACC who would be considered “independent in functional activities” by revised MCI criteria where “independent” includes CDR box scores of 0 and 0.5. These individuals could thus be reclassified as MCI.

Figure 3. Percent of AD dementia participants in NACC who would be considered “independent in functional activities” by revised MCI criteria where “independent” includes “does with assistance” (FAQ = 0, 1, 2). These individuals could thus be reclassified as MCI.

Figure 4. Percent of AD dementia participants in NACC who would be considered “independent in functional activities” by revised MCI criteria where “independent” includes “does by self with difficulty” (FAQ = 0, 1). These individuals could thus be reclassified as MCI.

Table 1

Anchor Points For Clinical Dementia Rating Levels in Functional Domains

	0	0.5	1
Community Affairs	Independent function at usual level	Slight impairment in these activities	Although may still be engaged in activities, unable to function independently; appears normal to casual inspection
Home and Hobbies	Home, hobbies, and intellectual interests well-maintained	Home, hobbies, and intellectual interests slightly impaired	Mild impairment; more difficult chores and hobbies abandoned
FAQ [*] Equivalency	Normal	Has difficulty but does by self	Requires assistance

^{*} FAQ = Functional Assessment Questionnaire

Table 2

Demographics.

	CDR 0 (N=6379)		CDR 0.5/MCI (N=4947)		CDR 0.5/AD (N=1684)		CDR 1/AD (N=2836)		CDR 2/AD (N=1127)		CDR 3/AD (N=562)		P-values for Differences Between the Groups			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	CDR 0 vs. 0.5/AD	CDR 0 vs. 0.5/AD	CDR 0.5/AD vs. 0.5/AD	CDR 0.5/AD vs. 0.5/AD
Age, y	71.9	9.3	75.6	9.2	75.5	8.9	76.4	9.2	78.0	9.4	77.9	9.8	<.0001	<.0001	.7142	<.0001
Educ, y	15.5	3.0	14.8	3.5	14.5	3.4	14.1	3.8	13.0	4.2	13.2	4.2	<.0001	<.0001	.0026	<.0001
Women, %	4282	67.1%	2543	51.4%	892	53.0%	1614	56.9%	715	63.4%	337	60.0%	<.0001	<.0001	.2672	<.0001
Race, %													<.0001	<.0001	<.0001	<.0001
White	5019	78.7%	3972	80.3%	1434	85.2%	2284	80.5%	835	74.1%	442	78.7%				
African American	1126	17.7%	659	13.3%	183	10.9%	371	13.1%	203	18.0%	74	13.2%				
Other	234	3.7%	316	6.4%	67	4.0%	181	6.4%	89	7.9%	46	8.2%				
Mini Mental State Examination score	28.9	1.5	27.0	2.5	23.9	3.7	20.5	4.6	14.2	5.5	5.4	5.4	<.0001	<.0001	<.0001	<.0001
CDR Sum of Boxes	0.02	0.1	1.4	0.9	2.9	1.0	5.9	1.4	11.3	1.6	17.2	1.1	<.0001	<.0001	<.0001	<.0001
APOE genotype													<.0001	<.0001	<.0001	<.0001
e3, e3	2214/3817	58.0%	1290/2680	48.1%	297/852	34.9%	469/1341	35.0%	214/571	37.5%	100/296	33.8%				
e3, e4	894/3817	23.4%	854/2680	31.9%	366/852	43.0%	563/1341	42.0%	252/571	44.1%	151/296	51.0%				
e3, e2	498/3817	13.1%	265/2680	9.9%	52/852	6.1%	90/1341	6.7%	20/571	3.5%	7/296	2.4%				
e4, e4	94/3817	2.5%	177/2680	6.6%	102/852	12.0%	182/1341	13.6%	67/571	11.7%	34/296	11.5%				
e4, e2	89/3817	2.3%	82/2680	3.1%	32/852	3.8%	36/1341	2.7%	15/571	2.6%	4/296	1.4%				
e2, e2	28/3817	0.7%	12/2680	0.5%	3/852	0.4%	1/1341	0.1%	3/571	0.5%	0/296	0.0%				
Dx by consensus conference, %	4517	70.8%	4122	83.3%	1196	71.0%	2218	78.2%	816	72.4%	432	76.9%				

Table 3

Functional performance for each group as reflected in Community Affairs box score, Home and Hobbies box score, and Functional Assessment Questionnaire (FAQ) items.

	CDR 0 (N=6379)		CDR 0.5/MCI (N=4947)		CDR 0.5/AD (N=1684)		CDR 1/AD (N=2836)		CDR 2/AD (N=1127)		CDR 3/AD (N=562)	
	N	%	N	%	N	%	N	%	N	%	N	%
Community Affairs Box Score												
0	6358	99.7	3377	68.3	403	23.9	6	0.2	0	0.0	0	0.0
0.5	21	0.3	1490	30.1	1115	66.2	310	10.9	0	0.0	0	0.0
1	0	0.0	78	1.6	164	9.7	2315	81.6	112	9.9	0	0.0
2	0	0.00	2	0.04	2	0.11	205	7.2	1015	90.1	562	100.0
Home and Hobbies Box Score												
0	6365	99.8	3312	67.0	406	24.1	28	1.0	0	0.0	0	0.0
0.5	14	0.2	1503	30.4	1017	60.4	269	9.5	3	0.3	0	0.0
1	0	0.0	127	2.6	254	15.1	2172	76.6	70	6.2	1	0.2
2	0	0.0	5	0.1	7	0.4	367	12.9	1054	93.5	561	99.8
FAQ items endorsed with "Normal"												
Writing checks...	6051/6197	97.6	2911/1540	65.4	363/1414	25.7	140/2515	5.6	5/1041	0.5	2/549	0.4
Assembling tax records...	5869/6052	97.0	2567/4152	61.8	291/1271	22.9	99/2350	4.2	4/1007	1.4	2/533	0.4
Shopping alone...	6213/6321	98.3	3740/4814	77.7	779/1621	48.1	332/2745	12.1	11/1102	1.0	1/558	0.2
Playing a game of skill...	5997/6054	99.1	3596/4329	83.1	767/1400	54.8	532/2415	22.0	50/1011	5.0	5/548	0.9
Heating water...	6270/6347	98.8	4354/4866	89.5	1292/1641	78.7	1281/2729	46.9	121/1091	11.1	7/560	1.3
Preparing a balanced meal	6011/6095	98.6	3450/4276	80.7	732/1337	54.8	410/2389	17.2	20/1043	1.9	2/556	0.4
Keeping track of current events	6285/6361	98.8	3672/4901	74.9	755/1662	45.4	427/2794	15.3	32/1108	2.9	2/560	0.4
Paying attention to and understanding a TV program...	6303/6371	98.9	3983/4923	80.9	899/1673	53.7	745/2822	26.4	93/1115	8.3	5/560	0.9
Remembering appointments...	6088/6366	95.6	2522/4918	51.3	336/1678	20.0	114/2821	4.0	6/1115	0.5	2/561	0.4
Traveling out of the neighborhood...	6182/6350	97.4	3242/4886	66.4	548/1657	33.1	201/2795	7.2	8/1109	0.7	1/560	0.18
FAQ items endorsed with "Normal" or "Has difficulty but does by self"												
Writing checks...	6148/6197	99.2	3742/4451	84.1	749/1414	53.0	405/2110	16.1	20/1021	1.9	3/549	0.6
Assembling tax records...	5981/6052	98.8	3299/853	79.5	551/1271	43.4	261/2350	11.1	12/995	1.2	2/533	0.4
Shopping alone...	6266/6321	99.1	4415/4814	91.7	1303/1621	80.4	887/2745	32.3	53/1102	4.8	4/558	0.7
Playing a game of skill...	6043/6054	99.8	4173/4329	96.4	1206/1400	86.1	1368/2415	56.7	176/1011	17.4	16/553	2.9

	CDR 0 (N=6379)		CDR 0.5/MCI (N=4947)		CDR 0.5/AD (N=1684)		CDR 1/AD (N=2836)		CDR 2/AD (N=1127)		CDR 3/AD (N=562)	
	N	%	N	%	N	%	N	%	N	%	N	%
Heating water...	6335/6347	99.8	4747/4866	97.6	1549/1641	94.4	2007/2729	73.5	286/1091	26.2	12/560	2.1
Preparing a balanced meal	6065/6095	99.5	3962/4276	92.7	1047/1337	78.3	924/2389	38.7	69/1043	6.6	4/556	0.7
Keeping track of current events	6353/6361	99.9	4713/4901	96.2	1363/1662	82.0	1316/2794	47.1	142/1108	12.8	7/560	1.3
Paying attention to and understanding a TV program...	6364/6371	99.9	4799/4923	97.5	1482/1673	88.6	1879/2822	66.6	346/1115	31.0	23/560	4.1
Remembering appointments...	6339/6366	99.6	4218/4918	85.8	975/1678	58.1	612/2821	21.7	46/1121	4.1	5/561	0.9
Traveling out of the neighborhood...	6277/6350	98.9	4251/4886	87.0	1052/1657	63.5	652/2795	23.3	37/1109	3.3	2/560	0.36
FAQ items rated as "Normal", "Has difficulty but does by self", or "Requires assistance"												
Writing checks...	6181/6197	99.7	4194/4451	94.2	1123/1414	79.4	1039/2515	41.3	97/1041	9.3	4/549	0.7
Assembling tax records...	6033/6052	99.7	3814/4152	91.9	909/1271	71.5	732/2350	31.2	53/1007	5.3	4/529	0.8
Shopping alone...	6302/6321	99.7	4714/4814	97.9	1533/1621	94.6	1967/2745	71.7	275/1102	25.0	17/558	3.1
Playing a game of skill...	6047/6054	99.9	4283/4329	98.9	1349/1400	96.4	1999/2415	82.8	435/1011	43.0	37/553	6.7
Heating water...	6341/6347	99.9	4829/4866	99.2	1611/1641	98.2	2409/2729	88.3	495/1091	45.4	33/560	5.9
Preparing a balanced meal	6086/6095	99.9	4171/4276	97.5	1239/1337	92.7	1625/2389	68.0	231/1043	22.2	13/556	2.3
Keeping track of current events	6357/6361	99.9	4876/4901	99.5	1617/1662	97.3	2257/2794	80.8	441/1108	39.8	36/560	6.4
Paying attention to and understanding a TV program...	6366/6371	99.9	4907/4923	99.7	1645/1673	98.3	2613/2822	92.6	740/1115	66.4	78/560	13.9
Remembering appointments...	6361/6366	99.9	4813/4918	97.9	1541/1678	91.8	1812/2821	64.2	249/1121	22.2	24/561	4.3
Traveling out of the neighborhood...	6318/6350	99.5	4609/4886	94.3	1395/1657	84.2	1376/2795	49.2	117/1109	10.6	6/560	1.1

Table 4**A Nonconformist's View of Alzheimer Disease**

<ul style="list-style-type: none">• The term “Alzheimer disease” (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, and represents a continuous process of synaptic and neuronal deterioration
<ul style="list-style-type: none">• AD has two major stages<ul style="list-style-type: none">– Preclinical (presymptomatic; asymptomatic), which is undetectable by current clinical methods– Symptomatic (clinical)
<ul style="list-style-type: none">• Symptomatic AD is defined by intraindividual cognitive decline that results in interference with daily function and progresses in degree from subtle to severe. Based on symptom severity, symptomatic AD can be subclassified:<ul style="list-style-type: none">– Incipient (prodromal), replacing “mild cognitive impairment”– Dementia