# Global clinical dementia rating of 0.5 in MCI masks variability related to level of function

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## ABSTRACT

**Objective:** To evaluate whether ratings on Clinical Dementia Rating (CDR) items related to instrumental activities of daily living (IADL) are associated with cognitive or brain morphometric characteristics of participants with mild cognitive impairment (MCI) and global CDR scores of 0.5.

**Methods:** Baseline cognitive and morphometric data were analyzed for 283 individuals with MCI who were divided into 2 groups (impaired and intact) based on their scores on the 3 CDR categories assessing IADL. Rates of progression to Alzheimer disease (AD) over 2 years were also compared in the 2 groups.

**Results:** The impaired IADL MCI group showed a more widespread pattern of gray matter loss involving frontal and parietal regions, worse episodic memory and executive functions, and a higher percentage of individuals progressing to AD than the relatively intact IADL MCI group.

**Conclusions:** The results demonstrate the importance of considering functional information captured by the CDR when evaluating individuals with MCI, even though it is not given equal weight in the assignment of the global CDR score. Worse impairment on IADL items was associated with greater involvement of brain regions beyond the mesial temporal lobe. The conventional practice of relying on the global CDR score as currently computed underutilizes valuable IADL information available in the scale, and may delay identification of an important subset of individuals with MCI who are at higher risk of clinical decline. *Neurology*® 2011;76:652–659

## GLOSSARY

**ACC** = anterior cingulate cortex; **AD** = Alzheimer disease; **ADL** = activities of daily living; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BNT** = Boston Naming Test; **CDR** = Clinical Dementia Rating; **FAQ** = Functional Activity Questionnaire; **HC** = healthy control; **IADL** = instrumental activities of daily living; **LM II** = Logical Memory II; **MANOVA** = multivariate analysis of variance; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PCC** = posterior cingulate cortex; **RAVLT** = Rey Auditory Verbal Learning Test; **ROI** = region of interest; **SB** = sum of boxes; **WAIS-R** = Wechsler Adult Intelligence Scale–Revised.

Mild cognitive impairment (MCI) is an established risk state for the development of Alzheimer disease (AD).[1] The requirement that functional activities remain essentially intact was originally considered central for differentiating MCI from mild dementia. However, recent studies have shown that subtle changes in the ability to perform instrumental activities of daily living (IADL) occur in MCI.[2-6]

The designation of MCI is often supported by a global rating of 0.5 on the Clinical Dementia Rating (CDR)[7] scale. The most heavily weighted component of the global CDR score is memory function; nonmemory components, including the 3 IADL categories, receive less weighting. Consequently, 2 individuals with MCI receiving the same global CDR score can noticeably differ in IADL performance. This lack of richness in characterizing IADL changes might prevent identification of meaningful clinical differences in individuals with MCI. To address this possibility, we compared baseline brain morphometry, cognition, and 2-year clinical outcome in subgroups of MCI partici-

Supplemental data at www.neurology.org

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Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available online.

pants who had global CDR scores of 0.5 but who differed with regard to IADL items. We predicted that, relative to individuals with intact IADL, those with relatively impaired IADL would show 1) a more widespread pattern of cortical atrophy involving frontal regions in addition to the expected medial temporal lobe involvement, 2) poorer cognitive performance, especially on tests of executive function, and 3) a higher rate of progression to probable AD.

**METHODS** Raw data used in the current study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public–private partnership. ADNI's goal is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

**Standard protocol approvals, registrations, and patient consents.** This study was approved by an ethical standards committee on human experimentation at each institution. Written informed consent was obtained from all participants or authorized representatives participating in the study.

**Participants.** ADNI eligibility criteria are described at http://www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx. Briefly, participants were 55–90 years old, nondepressed, with a modified Hachinski score of 4 or less, and a study partner able to provide an independent evaluation of functioning. Individuals with a history of significant neurologic or psychiatric disease, substance abuse, or metal in their body other than dental fillings were excluded.

Healthy control (HC) participants had Mini-Mental State Examination (MMSE) scores of 24–30, normal activities of daily living (ADL) as assessed with the Functional Activity Questionnaire (FAQ, clinical judgment without suggested cutoff), a global CDR score of 0, and normal memory function, as indicated by education-adjusted scores on the modified Wechsler Memory Scale Logical Memory II (LM II, story A only) (i.e., a score >8 for individuals with ≥16 years of education; >4 for individuals with 8–15 years of education; and >2 for individuals with 0–7 years of education). MCI participants had a subjective memory complaint, objective memory loss as indicated by education-adjusted scores on the LM II (score ≤8 for individuals with ≥16 years of education; ≤4 for individuals with 8–15 years of education; and ≤2 for individuals with 0–7 years of education), a global CDR score of 0.5 and a score ≥0.5 on the memory box of the CDR, essentially preserved ADL primarily assessed by the FAQ, and an absence of dementia.[1]

This study included individuals classified as HC or MCI within ADNI with baseline MRI scans that passed local quality inspection. We excluded 7 HC who converted to MCI at any follow-up visit to minimize the possibility of misclassification of HC participants at baseline. The present study thus consisted of 202 HC and 283 MCI participants. MCI participants were divided into 2 subgroups (intact IADL and impaired IADL) based on their scores on the 3 CDR categories assessing IADL (i.e., judgment and problem solving, community affairs, home and hobbies). Specifically, the intact IADL group (n = 179) consisted of individuals with a rating of 0 on all 3 IADL categories or a rating of 0.5 on 1 of the 3 categories; the impaired IADL group (n = 104) consisted of individuals with a rating of 0.5 on 2 or more of the 3 IADL categories or a rating of 1 on any 1 of the categories. The 2 MCI groups did not differ in age ($t_{281} = 1.79$, $p = 0.07$), level of education ($t_{281} = 0.15$, $p = 0.88$), sex distribution ($\chi^2_{(1)} = 0.65$, $p = 0.42$), history of hypertension ($\chi^2_{(1)} = 0.67$, $p = 0.41$), use of hypertension medications ($\chi^2_{(1)} = 0.08$, $p = 0.78$), or scores on the Geriatric Depression Scale ($t_{281} = -1.67$, $p = 0.10$). The impaired IADL group demonstrated higher FAQ scores ($t_{281} = -7.95$, $p < 0.001$) and a higher frequency of *APOE* ϵ4 carriers relative to the intact IADL group ($\chi^2_{(1)} = 3.95$, $p = 0.04$; table 1). Two-year follow-up clinical outcome data (i.e., reversion to normal cognitive status, stable MCI, or progression to probable AD) were available for 233 of the MCI participants. The determination of progression to probable AD was based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria (see appendix e-2 on the *Neurology*® Web site at www.neurology.org for operational criteria).

**Neuropsychological assessment.** All participants were administered a cognitive battery as previously described.[8,9] Measures included MMSE,[10] Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Span and Digit Symbol subtests, Boston Naming Test (BNT),[11] animal fluency, Rey Auditory Verbal Learning Test (RAVLT),[12] the LM II,[13] and the Trail Making Test.[14]

**Magnetic resonance scanning and brain morphometry.** Dual 3-dimensional T1-weighted volumes were downloaded from the public ADNI database (http://www.loni.ucla.edu/ADNI/Data/index.shtml). All image processing and analyses occurred at the Multimodal Imaging Laboratory, University of California, San Diego. Images were corrected for gradient nonlinearities[15] and intensity nonuniformity.[16] The 2 images were aligned, averaged to improve signal-to-noise ratio, and resampled to isotropic 1-mm voxels. Methods based on FreeSurfer software were used to obtain cortical gray matter volume and thickness measures in distinct regions of interest (ROIs).[17-22]

To limit the number of statistical comparisons, analyses only included regions assumed to be involved in early AD pathology,[23] such as bilateral hippocampal formation (volumetric measures) and regions of temporal, frontal, parietal, and cingulate cortex (thickness measures) (see ROIs listed in table e-1). The caudal and rostral anterior cingulate regions were combined as anterior cingulate cortex (ACC); the isthmus and posterior cingulate regions were combined as posterior cingulate cortex (PCC).

**Statistical analysis.** Group comparisons were performed with separate independent sample *t* tests or $\chi^2$ tests for demographic, cognitive, and clinical outcome variables. Cognitive test scores for MCI participants were converted to *z* scores based upon the mean and SD of the HC group (means and standard deviations of the raw test scores for MCI and HC groups are shown in table e-2). Because the impaired IADL group had more *APOE* ϵ4 carriers than the intact group, analyses of cognitive variables were also performed with separate one-way analyses of covariance, controlling for *APOE* genotype. Although some of the distribu-

**Table 1** Demographic, clinical, and cognitive characteristics of the 2 MCI groups

| | Intact IADL, mean (SD) (n = 179) | Impaired IADL, mean (SD) (n = 104) | *p* Value | Cohen *d* |
|---|---|---|---|---|
| Age, y | 75.69 (6.97) | 74.12 (7.27) | 0.07 | — |
| Education, y | 15.93 (2.92) | 15.88 (2.85) | 0.88 | — |
| % Men | 65 | 61 | 0.42 | — |
| % *APOE* ε4+ | 48 | 62 | 0.04* | — |
| % Hypertension history | 50 | 55 | 0.41 | — |
| % On hypertension meds | 72 | 75 | 0.78 | — |
| Geriatric Depression Scale | 1.47 (1.33) | 1.76 (1.45) | 0.10 | — |
| Functional Assessment Questionnaire | 1.98 (2.82) | 5.83 (5.33) | <0.001* | — |
| CDR sum of boxes | 0.96 (0.40) | 2.10 (0.58) | <0.001* | — |
| MMSE (raw score) | 27.25 (1.76) | 27.34 (1.58) | 0.69 | 0.05 |
| Language (*z* score) | | | | |
| Boston Naming Test | −0.83 (1.60) | −0.97 (1.75) | 0.48 | 0.08 |
| Category fluency | −0.58 (0.85) | −0.73 (0.86) | 0.17 | 0.18 |
| Executive function/attention/ processing (*z* score) | | | | |
| Digit Span forward | −0.19 (1.02) | −0.36 (1.01) | 0.18 | 0.17 |
| Trail Making Test A[a] | −0.31 (1.25) | −0.56 (1.84) | 0.18 | 0.16 |
| Digit symbol | −0.59 (0.99) | −0.82 (1.08) | 0.07 | 0.22 |
| Digit Span backward | −0.39 (0.96) | −0.61 (0.94) | 0.06 | 0.23 |
| Trail Making Test B[a] | −0.61 (1.44) | −1.02 (1.76) | 0.03* | 0.25 |
| Learning and memory (*z* score) | | | | |
| Logical memory | | | | |
| Immediate recall | −1.78 (0.86) | −1.90 (0.88) | 0.28 | 0.14 |
| Delayed recall | −2.50 (0.75) | −2.54 (0.75) | 0.57 | 0.05 |
| RAVLT | | | | |
| Trial 1–5 total | −1.21 (1.07) | −1.41 (0.87) | 0.10 | 0.21 |
| Short-delay recall | −1.10 (0.99) | −1.38 (0.84) | 0.02* | 0.30 |
| Long-delay recall | −1.07 (0.96) | −1.33 (0.82) | 0.02* | 0.29 |
| Recognition discriminability | −1.24 (1.39) | −1.84 (1.72) | 0.001* | 0.38 |

Abbreviations: CDR = Clinical Dementia Rating; IADL = instrumental activities of daily living; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test.
[a] For ease of interpretation, scores on the Trail Making Test were inverted so negative scores represent poorer performance, consistent with other tests.
* Statistically significant results.

tions of scores on cognitive tests were skewed, we did not transform the data since the sample size was sufficiently robust to enable appropriate use of the *t* statistic.[24]

Differences in morphometric variables among HC, intact IADL MCI, and impaired IADL MCI groups were assessed with multivariate analyses of variance (MANOVAs) followed by univariate analyses of variance with Bonferroni adjustments for Type I error ($\alpha = 0.001$) (table e-1). Pairwise comparisons were conducted through separate independent sample *t* tests ($\alpha = 0.05$). Effects of age and gender were regressed from all thickness and volumetric measures and standardized residual values (i.e., *z* scores) were used for analyses. Hippocampal volumes were also corrected for differences in head size by regressing the estimated total cranial vault volume.[25] Results controlling for *APOE* status are only reported if they differed from noncontrolled analyses. Effect sizes were calculated with Cohen *d* for significant group differences on cognitive and morphometric measures. All analyses were conducted in SPSS (version 17.0).

**RESULTS** **Neuropsychological differences.** Performance did not differ between MCI groups on MMSE, Digit Span forward and backward, Trail Making Test Part A, Digit Symbol, LM immediate and delayed recall, RAVLT Trials 1–5 total learning score, animal fluency, or BNT. However, the impaired IADL group demonstrated poorer performance than the intact IADL group on the Trail Making Test Part B ($t_{281} = -2.13$, $p = 0.03$), RAVLT short ($t_{281} = 2.45$, $p = 0.02$) and long ($t_{281} = 2.39$, $p = 0.02$) delayed recall, and RAVLT recognition discriminability ($t_{281} = 3.22$, $p = 0.001$) (table 1).

**Table 2** Standardized residual values (i.e., *z* scores and corresponding standardized errors relative to healthy control individuals) of regions that differed between the 2 MCI groups

| | Intact IADL, mean (SD) | Impaired IADL, mean (SD) | *p* Value | Cohen *d* |
|---|---|---|---|---|
| Right lateral orbitofrontal | 0.46 (0.07) | −0.24 (0.10) | 0.02 | 0.28 |
| Left medial orbitofrontal | −0.01 (0.07) | −0.29 (0.09) | 0.02 | 0.28 |
| Right parahippocampus | −0.01 (0.07) | −0.34 (0.09) | 0.007 | 0.33 |
| Right supramarginal | −0.02 (0.07) | −0.27 (0.09) | 0.03 | 0.27 |

Abbreviations: IADL = instrumental activities of daily living; MCI = mild cognitive impairment.

When *APOE* status was included as a covariate, the same pattern of findings was observed except that Digit Symbol, which was marginally significant before, now reached significance ($F_{1,271} = 4.73$, $p = 0.03$).

**Regional differences in morphometry.** The overall MANOVA for group effects on all ROIs was significant (Wilks lambda = 0.64, $F_{72,896} = 3.06$, $p < 0.001$, partial $\eta^2 = 0.19$). Follow-up univariate analyses comparing the MCI groups to the HC group showed that both MCI groups had smaller than normal hippocampal volumes bilaterally and thinner than normal cortex in frontal (i.e., bilateral caudal and rostral middle frontal, superior frontal, and right lateral orbitofrontal areas), temporal (i.e., bilateral entorhinal cortex, parahippocampal, superior, middle, and inferior temporal, and temporal pole areas), and parietal (i.e., bilateral inferior parietal lobule and left supramarginal) regions, as well as in the bilateral PCC. Moreover, the impaired IADL group—but not the intact IADL group—showed cortical thinning in bilateral medial orbitofrontal, pars orbitalis, and right supramarginal regions. Information on magnetic resonance morphometric measures for the 3 groups in all ROIs are presented in table e-1.

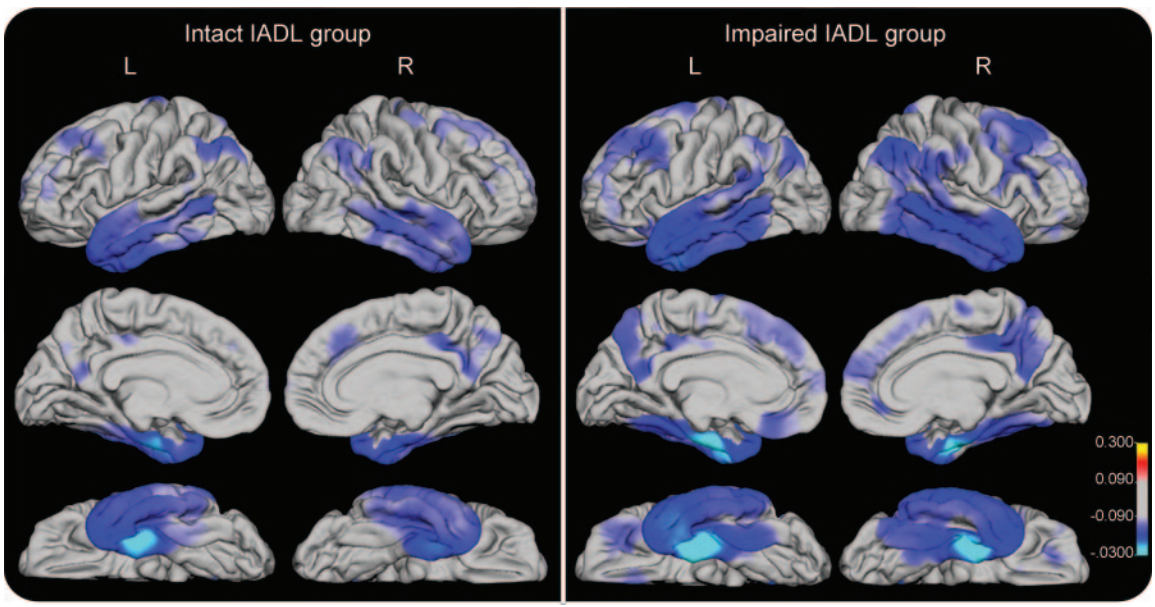
The 2 MCI groups showed comparable hippocampal volumes and similar cortical thickness in entorhinal, lateral temporal, dorsolateral prefrontal, and cingulate ROIs bilaterally. However, the impaired IADL group had reduced cortical thickness in left medial orbitofrontal ($t_{281} = 2.29$, $p = 0.02$), right lateral orbitofrontal ($t_{281} = 2.32$, $p = 0.02$), right parahippocampus ($t_{281} = 2.71$, $p = 0.007$), and right supramarginal regions ($t_{281} = 2.25$, $p = 0.03$) compared to the intact IADL group (table 2 and figure).

**Longitudinal progression rates.** Two-year rate of progression to AD was higher in the impaired IADL group (46%; 41/89 participants) than in the intact group (31%; 45/144 participants; $\chi^2_{(1,\ n\ =\ 233)} = 5.19$, $p = 0.02$).

MCI participants with or without clinical outcome data did not differ in age, education level, gender distribution, *APOE* ϵ4 status, or MMSE scores (all *p* values >0.05; table 3).

**DISCUSSION** When MCI participants with global CDR scores of 0.5, CDR memory ratings of 0.5, and impaired performance on the LM II were divided into groups with relatively intact or impaired ratings on the CDR IADL components, those with impaired IADL ratings exhibited poorer cognitive test perfor-

**Figure** Reconstructed cortical surface maps for the 2 mild cognitive impairment (MCI) groups relative to the healthy control (HC) group




Reconstructed cortical surface maps representing the average mean difference in thickness (mm, $p < 0.001$) for the 2 MCI groups, relative to the HC group, after controlling for the effects of age and gender. Blue and cyan indicate thinning. IADL = instrumental activities of daily living.

**Table 3** Demographic and global cognitive characteristics of individuals with or without clinical outcome data (i.e., progression to Alzheimer disease) for the 2 MCI groups

| | Intact IADL | | | Impaired IADL | | |
|---|---|---|---|---|---|---|
| Clinical outcome data | Yes (n = 144) | No (n = 35) | Statistical comparison | Yes (n = 89) | No (n = 15) | Statistical comparison |
| Age | 76.00 (6.83) | 74.39 (7.48) | $t_{177} = 1.22, p = 0.22$ | 73.97 (7.32) | 75.03 (7.12) | $t_{102} = -0.52, p = 0.60$ |
| Education | 16.01 (2.78) | 15.57 (3.46) | $t_{177} = 0.80, p = 0.42$ | 15.92 (2.83) | 15.60 (3.04) | $t_{102} = 0.40, p = 0.69$ |
| % Men | 63 | 74 | $\chi^2_{(1)} = 1.53, p = 0.22$ | 62 | 53 | $\chi^2_{(1)} = 0.39, p = 0.58$ |
| MMSE | 27.31 (1.74) | 27.00 (1.86) | $t_{177} = 0.94, p = 0.35$ | 27.34 (1.50) | 27.33 (2.06) | $t_{102} = 0.01, p = 0.99$ |
| % *APOE* ϵ4+ | 49 | 46 | $\chi^2_{(1)} = 0.14, p = 0.71$ | 60 | 64 | $\chi^2_{(1)} = 0.07, p = 0.79$ |

Abbreviations: IADL = instrumental activities of daily living; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.

mance, more widespread gray matter thinning in frontal and parietal lobe brain regions, and a higher rate of progression to probable AD over a 2-year follow-up period. Group differences in cognitive test performance were apparent on tests of executive function (i.e., TMT-B and Digit Symbol test) and episodic memory (i.e., RAVLT). Differences on episodic memory measures were somewhat unexpected since all participants had CDR memory ratings of 0.5 and groups did not differ in degree of atrophy in mesial temporal lobe structures implicated in memory (i.e., hippocampus and entorhinal cortices), or on performance on the LM II. Although the RAVLT, an unstructured list-learning task, may simply be a more sensitive measure of episodic memory than the LM II, a structured story-memory task, it is possible that the worse performance of the IADL-impaired group on the RAVLT is related to their greater deficit in executive functions. Although memory for complex narrative such as that required by the LM II is impaired in patients with frontal lobe lesions,[26] the RAVLT may place greater demands on executive abilities for organizing the unstructured word-list material during encoding or for strategic search during retrieval.[27] We previously found that MCI participants with impaired executive function performed more poorly on the RAVLT, but not on the LM II, than did MCI participants without executive dysfunction, and that thinning in frontal areas contributed to RAVLT performance beyond the well-known contribution of medial temporal structures.[27] These subtle distinctions between memory measures are not likely to be made within the CDR because memory ability is assessed as an overall rating based on the subjective judgment of an informant and does not take into account various cognitive processes underlying objective memory performance.

Morphometric analyses showed that the impaired IADL group had greater and more widespread atrophy than the intact IADL group in left medial orbitofrontal, right lateral orbitofrontal, right supramarginal, and right parahippocampal cortex. The bilateral involvement of the orbitofrontal cortex is consistent with a recent study that highlighted the role of ventromedial prefrontal regions in carrying out complex cognitive and emotional tasks encountered in everyday life.[28] Greater cortical thinning in frontal regions in the impaired IADL group than in the intact group is consistent with their poorer performance on measures of executive function. The finding that cortical thickness was thinner in the right supramarginal and parahippocampal areas in the impaired IADL group than in the intact group is consistent with recent results that suggest brain atrophy spreads from medial temporal lobe structures to parietal and frontal cortical regions as severity of MCI increases,[29] and with the typical distribution of AD neuropathology early in the disease process.[30]

Consistent with previous studies,[2,3,5] MCI participants with impaired IADL were more likely than those with intact IADL to progress to a clinical diagnosis of probable AD within the next 2 years. The 2 MCI subgroups may thus represent points along an MCI-to-AD continuum with the impaired IADL group having progressed farther toward AD than the intact IADL group. The higher scores on the FAQ in the impaired than the intact IADL group is consistent with this. It could be argued that the presence of deficits in 2 or more areas of cognition (episodic memory and executive function), coupled with impaired IADL, would support a diagnosis of mild dementia rather than MCI. However, the conventional practice of relying on summary screening measures and rating scales such as the MMSE, LM, and CDR to differentiate MCI from AD suffers from a certain granularity[31] and fails to capture the subtle but significant cognitive and functional changes in early dementia. Alternative approaches that incorporate more comprehensive neuropsychologically based methods for the diagnosis of MCI and AD have recently shown advantage in improving the stability and reliability of a diagnosis that predicts clinical decline.[32-35]

Global CDR score is one of the most commonly used measures for identifying and staging MCI or AD dementia. There are, however, a number of problems that have been pointed out[36-39] with regard to the established methods for computing a global CDR. These include inconsistency in ratings across features (e.g., rating of memory vs other cognitive features or function) and a lack of precision in detecting or scaling levels of impairment within a particular CDR category (e.g., 0.5) or with progression. Indeed, in the present study we found that, despite comparable global CDR scores, MCI groups that differed in IADL CDR subratings had meaningful differences in baseline cognitive performance, brain morphometry, and rate of progression to AD. This suggests that the global CDR score is not sensitive enough to distinguish levels of severity or predict progression within MCI cohorts. The present findings support studies that propose alternative algorithms[38,39] to overcome this lack of sensitivity. One such algorithm is the CDR sum of boxes (SB), which has been used in several recent studies to increase the ability to discriminate MCI from very early AD and track disease progression.[36,39,40] Though conceptually different from the CDR-SB, our results coincide with studies that show higher CDR-SB scores predict higher rates of progression to AD.[36,39]

A limitation of the current study is that 2-year clinical outcome data were available for only 82% of individuals with MCI at the time we conducted this study. However, MCI participants with clinical outcome data did not significantly differ from those without outcome data on any baseline demographic or global cognitive characteristic, making it unlikely that selective attrition biased the results. Another limitation inherent to the CDR is that changes in IADL abilities are based solely on an informant's report and may be subject to reporter bias. Objective assessment of functional abilities such as subject-performed tasks might provide better discrimination between MCI subgroups and have greater predictive ability. Additionally, histopathologic verification of disease is lacking; some MCI participants may have disorders other than or in addition to AD, which might explain, in part, some of the differences observed between the 2 MCI groups. Finally, diagnosticians had access to all CDR data when making a determination of conversion to dementia, and thus could conceivably have used baseline CDR IADLs when making the diagnosis of dementia at follow-up. However, since the same inclusion/exclusion criteria (i.e., global CDR of 0.5 and CDR memory of 0.5) were applied to all MCI participants at baseline, it is more likely that the determination of functional impairment of sufficient severity to interfere with daily life was based on follow-up FAQ and global CDR scores.

The present findings demonstrate that the readily available informant-based information on IADL incorporated in a baseline administration of the CDR is useful for identifying subgroups of individuals with MCI who have more widespread neurodegeneration and are more likely to progress to probable AD.

## AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Yu-Ling Chang.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## DISCLOSURE

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## Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.[1-3]

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**Classification scheme requirements for therapeutic questions**

**Class I.** A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

**Class II.** A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

**Class III.** All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

**Class IV.** Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

**AAN classification of recommendations**

**A =** Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

**B =** Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

**C =** Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

**U =** Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.