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FUNCTIONAL AND COGNITIVE CRITERIA PRODUCE DIFFERENT RATES OF MCI AND CONVERSION TO DEMENTIA

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Abstract

Objective—To compare rates of Mild Cognitive Impairment (MCI) and rates of progression to dementia, using different MCI diagnostic systems

Methods—MCI was investigated at baseline in 3063 community-dwelling non-demented elderly in the Ginkgo Evaluation of Memory (GEM) study who were evaluated every six months to identify presence of dementia. Overall MCI frequency was determined using (1) Clinical Dementia Rating (CDR) score of 0.5 and (2) neuropsychological (NP) criteria, defined by impairment on standard cognitive tests.

Results—40.2% of participants met CDR MCI criteria and 28.2% met NP MCI criteria (amnestic-MCI=16.6%). 15.7% were classified as MCI by both criteria and 47.4% as Normal by both. Discordant diagnoses were observed in 24.5% who met NP Normal/CDR MCI; and 12.4% who met NP MCI/CDR Normal. Factors associated with CDR MCI among NP Normal included, lower education, lower NP scores, more IADL impairment, greater symptoms of depression and subjective health problems. Individuals meeting NP MCI/CDR normal were significantly more likely to develop dementia over the median follow up of 6.1 years than those meeting NP Normal/CDR MCI.

Conclusions—Different criteria produce different MCI rates and different conversion rates to dementia. Although a higher percentage of MCI was identified by CDR than NP, a higher percentage of NP MCI progressed to dementia. These findings suggest that the CDR is sensitive to subtle changes in cognition not identified by NP algorithm but is also sensitive to demographic and clinical factors probably leading to a greater number of false positives. These results suggest that identifying all individuals with CDR scores of 0.5 as Alzheimer's disease is not advisable.

Keywords

Clinical Dementia Rating Scale; Neuropsychological tests

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INTRODUCTION

Mild Cognitive Impairment (MCI) describes a state between normal aging and dementia.[1] The identification of individuals with MCI that leads to Alzheimer's disease (AD) has become increasingly important as new therapies have become available. Current diagnostic criteria for MCI highlight the need for evidence of cognitive decline which has been documented using either direct performance-based measures or clinical interview-based measures, or in some case, both approaches. Petersen's original criteria[1,2] used neuropsychological test performance, as a direct performance-based measure of cognitive functioning, and operationalized MCI as a score more than 1.5 standard deviations below that of age-appropriate norms on a measure of episodic memory with performance within the normal range on non-memory tests. Using a similar approach, the International Working Group on MCI [3] has recently adapted Petersen's criteria to take into account differing presenting patterns of cognitive test performance and allowing the possibility of either memory or nonmemory impairment and focal (i.e. single cognitive domain) or multiple impaired domains. Interview-based assessments have also been used to identify MCI. The Clinical Dementia Rating (CDR) is a highly validated clinically-based interview that stages cognitive and functional decline across the spectrum of AD and a Global CDR score of 0.5 is often used to indicate the presence of MCI.[4-6]

The goal of this study was to compare two different approaches to the classification of MCI within the same cohort in order to (1) investigate the factors associated with baseline classification using one method over another and (2) compare the rates of progression to dementia using the two systems. We hypothesized that a significantly higher percentage of individuals would meet CDR criteria for MCI than cognitive criteria. Furthermore, we hypothesized that individuals diagnosed with MCI by CDR criteria would have more complaints of everyday memory loss and a greater number of health related disorders compared to individuals identified as MCI by cognitive criteria. In contrast, individuals meeting cognitive criteria for MCI would be older and less educated and therefore more likely than those with CDR MCI, to develop dementia over time.

MATERIALS AND METHODS

Volunteers aged 75 years or older were recruited from 4 communities in the United States: Hagerstown, Maryland; Pittsburgh, Pennsylvania; Sacramento, California; Winston-Salem and Greensboro, North Carolina. The study was approved by the Institutional Review Boards of each of the participating sites and was conducted in accordance with the Helsinki Declaration (http://www.wma.net/e/policy/17-c_e/html). A variety of recruitment methods were used.[7] The vast majority of participants were recruited via mass mailings based on voter registration lists, commercially purchased mailing lists and university lists. Less than 8% of participants responded to media advertisements. The recruitment procedures for the GEM Study have been described elsewhere.[8] Persons meeting any of the following criteria were excluded: 1) currently taking the anti-coagulant warfarin (Coumadin); 2) taking cholinesterase inhibitors for cognitive problems or dementia; 3) unwilling to discontinue taking over-thecounter *G. biloba* for the duration of the study; 4) currently treated with tricyclic antidepressants, antipsychotics or other medications with significant psychotropic effects; 5) daily use of >400 IU vitamin E; 6) history of bleeding disorders; 7) hospitalization for depression within the last year or Electroconvulsive Therapy within last 10 years; 8) history of Parkinson's disease or taking anti-Parkinson's medications; 9) abnormal thyroid tests, serum creatinine > 2.0 mg/dL, or liver function tests > 2X upper limit of normal at baseline; 10) baseline vitamin B12 levels ≥ 210 pg/mL; 11) hematocrit < 30%; 12) platelet count < 100,000 K/cm; 13) disease-related life expectancy < 5 years; 14) known allergy to *G. biloba*.

All participants were required to identify a proxy willing to be interviewed every 6 months at each study visit. At baseline and every 6 months participants completed a broad range of assessment scales/questionnaires that have been described previously [9] including self-reports of medical history and medications, ratings of health problems, mobility, instrumental activities of daily living (IADL) [10], the Telephone Interview for Cognitive Status[11], the Modified Mini Mental State examination (3MSE)[12], the Alzheimer's Disease Assessment Scale (ADAS-Cog) [13] and the Center for Epidemiological Studies Depression (CES-D) scale [14] and the CDR [4-6], completed by the participant and his/her informant. Persons with prevalent dementia (meeting DSM-IV criteria for dementia [15], a 3MSE score of less than 80, or a score the Clinical Dementia Rating scale [5] (CDR) > 0.5 were excluded from participation. The remaining individuals completed the baseline comprehensive neuropsychological test battery (described below). Those individuals scoring within the range of dementia on this battery were also excluded from the study. Cut-off scores for each test were determined based on data from cognitively normal subjects taking part in the Cardiovascular Health Study (CHS) [7,9,16,17]. Sixty-four participants who passed the 3MSE and CDR criteria were subsequently excluded based on their neuropsychological test scores (mean age 79.8 years, mean education 13.8 years).

The screening visit also included blood drawn for laboratory screening as well as DNA storage for subsequent apolipoprotein E (ApoE) genotyping. DNA was extracted with a Puregene Kit (QUIAGEN; Valencia, CA) and ApoE genotyping was performed utilizing the TaqMan genotyping assays (Applied Biosystems; Foster City, CA) by Dr. M. Ilyas Kamboh, University of Pittsburgh. Of note, 16 participants refused phlebotomy consent, 425 samples had insufficient volume for DNA extraction and 174 did not have sufficient blood drawn for other reasons, resulting in a subset of 2454 of total baseline participants with ApoE data available.

A total of 3,072 participants were recruited into the GEM study. Three participants were subsequently excluded because of protocol violations not detected at baseline. An additional six subjects were excluded from these analyses: 4 had missing CDR data and two had a CDR score of 1.0 indicating dementia. The final *N* was 3,063.

Neuropsychological test battery and NP criteria for MCI

The remaining participants completed the comprehensive neuropsychological battery, which included tests within five cognitive domains (see Table 1) and two tests to estimate premorbid intellectual functioning, the National Adult Reading Test - American Version;[18] and Raven's Coloured Progressive Matrices.[19] Tenth percentile cut-off scores were located on each neuropsychological test based on normative data from the Cardiovascular Health Study (CHS) [20] for 2 age (< 80 vs. ≥ 80 years) and 3 education (≤ 12; 13-16; > 16 years) subgroups reported previously.[7,9] A tenth percentile cut-off is close to the commonly used cut-off of 1.5 SD below the normative mean (corresponding to approximately the 7^{th} percentile on a theoretically normal curve). We used this somewhat higher, more sensitive, cut-off because this cohort had already been screened for dementia.[9] In addition, many of the cognitive test scores were not normally distributed and percentile rank cut-offs are therefore more appropriate.[21] Also, tenth percentile cut-offs have been used in other MCI studies.[22-24] The number of subjects with missing neuropsychological measures in this healthy cohort screened for dementia was very low: only 9 participants (0.4 %) were missing 2 - 4 measures for physical reasons (sensory or motor impairment).

We applied a neuropsychological (NP) algorithm to classify each individual as Normal (NP Normal) or MCI (NP MCI). In order to meet NP criteria for MCI, at least two of the cognitive tests had to fall at or below the 10^{th} percentile of the normative data. A minimum of two out of ten impaired tests was chosen to minimize MCI cases that “revert to normal” on follow-up primarily because of measurement error, regression to the mean, etc.[9] Using these criteria

individuals with a single score falling below the 10th percentile for age and education were classified as normal based on the assumption that this represents normal variability. We also identified individuals with the major clinical subtypes of MCI: amnestic and nonamnestic. Individuals with impaired performance on one or more memory tests were classified as NP amnestic MCI (NP a-MCI). Individuals with both impaired tests in non-memory domains were identified as NP nonamnestic MCI (NP na-MCI).

Clinical Dementia Rating Scale and CDR criteria for MCI

All GEMS interviewers completed a standardized training program for administration and scoring for the CDR including use of videotapes.[25] In addition, interviewers participated in annual reliability training including observation of GEMS interviews conducted by a study author (LOD). Based on information obtained from both the subject and informant, CDR ratings are given for six domains: memory, orientation, home and hobbies, judgment and problem solving, community affairs and personal care. Each CDR subscale can be rated on a scale of 0-3 where 0 indicates no impairment and 3 indicates the need for maximal assistance. A global CDR score is calculated using an algorithm that takes into account each subscale score, with an additional weighting for the memory section. The overall possible range of Global CDR scores is 0 (indicating a normal healthy individual with no cognitive or functional deficits), 0.5 (a normal healthy individual but with questionable cognitive and/or functional abilities indicating MCI), 1 (mild dementia), 2 (moderate dementia) and 3 (severe dementia). Subjects in this study obtained Global CDR scores of either 0 or 0.5. A score of 0.5 is used to denote mild cognitive and functional impairment consistent with MCI (CDR MCI) and a Global CDR score of 0 indicates no functional deficits (CDR Normal).

MCI subgroups

Using the above criteria, four subgroups were identified:

Group 1: participants classified as Normal by both NP and CDR criteria (i.e. *congruent*: Normal/Normal)

Group 2: participants classified as Normal by NP but MCI by CDR (i.e. *incongruent*: NP Normal/CDR MCI)

Group 3: participants classified as MCI by NP but Normal by CDR (i.e. *incongruent*: NP MCI/CDR Normal)

Group 4: participants classified as MCI by both NP and CDR criteria (i.e. *congruent*: MCI/MCI)

Dementia criteria

The GEM study began in September 2000 and assessed subjects every six months until April 2008. The median follow-up period for 6.1 years and the primary end point was a diagnosis of dementia by DSM-IV criteria.[15] This was determined by an expert panel of clinicians using an adjudication process validated on a similar population [16] and described previously [17] that involved a comprehensive review of all available clinical and cognitive assessments over multiple years. Neuropsychological criteria for dementia end-point were operationalized as follows:

1. Incident abnormal scores on 5 or more cognitive tests, and at least 1 abnormal score was on a memory test.
2. Incident abnormal scores on 4 tests, at least 1 on a memory test, and the participant failed to complete 1 or more of the other tests.

3. Incident abnormality on 2 or more cognitive domains (impaired scores on both tests of that domain) and 1 domain was memory.

Statistical Analyses

To determine differences among diagnostic sub-groups on demographic, clinical and cognitive variables, omnibus ANOVAs were performed for continuous variables and chi-square tests for categorical variables. Student-Neuman-Keuls procedure for continuous variables and modified Keppel Bonferroni adjustment for categorical variables were used to determine post-hoc pair-wise differences among subgroups to control for Type I error. To account for differences between study sites in frequency of MCI groups (see below) we included site as a covariate in the ANOVAS for continuous variables and performed a series of multinomial logistic regressions (predicting MCI sub-group) including site as a covariate for categorical variables.

RESULTS

The mean age of the overall cohort was 78.5 (SD 3.3) and the mean education level was 14.3 (SD 3.0) years. The proportion of women was 46.2% and the proportion of individuals reporting themselves as white was 95.5% (see DeKosky et al. [7] for full description of the GEMS cohort).

Comparison of overall MCI rates using CDR and NP criteria

Table 2 shows the frequency of MCI for the two different diagnostic methods. The overall frequency of MCI using CDR criteria was 40.2% (n=1232) and using NP criteria was 28.1% (n = 861). 47.4% of participants (n=1451) were identified as “normal” and 15.7% (n=480) as MCI by both CDR and NP criteria for an overall agreement of 63%. However, 24.5% of participants (n=751) met NP criteria for Normal but were classified as MCI by CDR criteria and 12.4% (n=381) met NP criteria for MCI but were classified as Normal by CDR.

The majority of individuals classified by CDR criteria as MCI were impaired on the CDR memory subscale (n=1180; 95.9%; overall frequency = 38.5%) Only 4.1% (n=52) of the CDR 0.5 participants were impaired on non-memory CDR subscales and met criteria for CDR na-MCI (overall frequency = 1.7%). The overall frequency of NP a-MCI subtype was 16.6 % (n= 508) and na-MCI subtype was 11.5% (n = 353).

We also examined differences across the four GEM sites in the overall frequency of MCI. The proportion of MCI cases by CDR was higher at Wake Forest University (WFU) (60.7%) than at the other clinical centers (ranging from 27.5% to 42.7%; X^2= 218.8 p < .001). With regard to NP criteria, the UC-Davis site had the lowest proportion of MCI cases (22.6%) compared to comparable frequencies at the other 3 sites (28.6% - 31.6%; X^2 = 21.12, p < .001).

Descriptive Statistics

Table 3 summarizes descriptive statistics for demographic and clinical variables for the four diagnostic subgroups. Overall differences between the four subgroups were significant on all demographic variables and most clinical variables.

Post hoc analyses showed that individuals diagnosed as MCI by both systems (Subgroup 4) were older, had poorer scores on mental status tests and tests of premorbid IQ, endorsed more symptoms of depression and more health problems, had greater IADL impairment and poorer mobility than individuals diagnosed as Normal by both systems (Subgroup 1). There was no difference in the reported number of medications across all groups. Of note, there was a statistical trend toward higher ApoE4 allele proportion in Subgroup 4 compared to Subgroup 1 (p = .08). When site was included as a covariate in the multinomial regression analyses the

only difference was that the gender distribution was no longer significantly different among MCI subgroups. All other results were unchanged.

Neuropsychological test performance

Table 4 summarizes the neuropsychological test scores for the four diagnostic subgroups. After adjusting for age, education, race and depression score, the majority of cognitive test scores remained significantly worse across subgroups with individuals in subgroup 1 (congruent Normal/Normal) performing better on all NP tests (except Digits forwards and Rey copy and recall) than individuals in subgroup 2 (incongruent NP Normal/CDR MCI) who performed better on all tests than individuals in subgroup 3 (incongruent NP MCI/CDR Normal); who performed better on all NP tests (except Digits forwards and Rey copy) than individuals in subgroup 4 (congruent MCI/MCI).

Factors that influence a diagnosis of MCI by CDR among individuals with normal cognition by NP criteria (comparison groups 1 and 2)

Significant differences in individuals meeting NP criteria for normal cognition who received a CDR classification of MCI included fewer years of education, poorer scores on mental status tests and tests of premorbid IQ, more depressive symptoms, more reported health problems, and more IADL impairment than individuals who received a CDR classification of Normal. Additionally, individuals with CDR diagnosis of MCI had significantly poorer NP test scores (except digits forwards, Rey copy and recall) than individuals classified as CDR Normal, even though both groups met NP criteria for Normal.

Factors that influence a diagnosis of MCI by NP among individuals diagnosed as Normal by CDR (comparison groups 1 and 3)

Significant differences in individuals meeting NP classification of MCI (and CDR Normal) included more years of education, poorer scores on mental status tests and tests of premorbid IQ, and more reported IADL difficulty than individuals who received a NP classification of Normal. However, there were no differences between these groups in reported symptoms of depression or health problems.

Factors that influence a diagnosis of Normal by CDR among individuals classified as MCI by NP criteria (comparison groups 3 and 4)

Individuals classified as MCI by NP performance and Normal by CDR were younger, had significantly more years of education, higher scores on mental status tests and tests of premorbid IQ, less depressive symptoms, less IADL impairment and better mobility than individuals who were diagnosed as MCI by CDR. These individuals also had significantly better scores on all NP tests (except digits forwards and Rey copy), even though they met NP criteria for MCI.

Participant/Informant characteristics

We examined the baseline characteristics of the participant/informant relationship because of the potential impact this may have had on CDR ratings. 59.6% of informants reported living with the participants. Of those informants who did not live with a participant, 78% reported visiting with the participant at least once a week and 88.8% reported phone or e-mail contact with participants at least once a week. There were no differences in the proportions of CDR ratings between informants who reported living with the participant and those who did not. Among those who live with the participant, 60.1% of participants were rated as CDR 0 and 39.9% as CDR 0.5, and among those who did not live with the participant, 59.9% were rated as CDR 0 and 40.1% were rated as CDR 0.5. Similar proportions of CDR ratings were observed among informants not living with the participant who reported visiting with the participant

more than once a week (62.2% CDR 0; 37.7% CDR 0.5) and those who reported visiting once a week or less (57.8% CDR 0; 42.2% CDR 0.5).

Rates of death, drop out and progression to dementia

The GEM study began in September 2000 and assessed subjects every six months until April 2008, median follow-up was 6.1 years. During this time 194 participants were either lost to follow-up or withdrew consent. There were no differences between the participants who declined to continue the study and the 2,874 who remained in the study by age, gender, minority race, baseline disease categories (e.g. myocardial infarction, stroke, heart failure, and cancer) or smoking status. However, a difference in MCI status at baseline was found with 22.6% of drop-outs lost to follow-up compared to 15.2% of those who completed the study (p=.01). Individuals who met both MCI criteria were more likely to drop out than in the other three subgroups. There were 383 deaths from any cause and no differences in rates of death across subgroups.

Cognitive status was known for 93.6% of all participants at study end point. 522 participants were diagnosed with dementia during the follow-up period. There were significant differences across the four subgroups in rates of dementia. The lowest rates were observed in individuals meeting both CDR and NP criteria for Normal (subgroup 1 = 7.4%) and the highest rates were observed in individuals who met both CDR and NP criteria for MCI (subgroup 4 = 41.5%). 17.2% of individuals with CDR MCI/NP Normal (subgroup 2); and 22.8% of individuals with CDR Normal/NP MCI (subgroup 3) developed dementia. Taking study site into account as a covariate in multinomial regression did not alter the pattern of results.

DISCUSSION

The goals of this paper were to compare baseline rates of MCI and rates of progression to dementia over six years, using different MCI diagnostic systems. 40.2% of individuals were identified as MCI using a CDR score of 0.5 and 28.2% using NP criteria (amnestic and nonamnestic combined). There was agreement between the two diagnostic methods in over 63% of cases, 47.4% were classified as Normal by both criteria (NP Normal/CDR Normal) and 15.7% were classified as MCI by both criteria (NP MCI/CDR MCI). There were no significant differences between the four subgroups (congruent and incongruent) in the number of medications reported and the number of deaths but there were a higher number of drop-outs in the group meeting both sets of MCI criteria. The percentage of ApoE4 carriers also did not differ between subgroups and is similar to that reported in other community studies (CHS, 24.1%) [33] although lower than observed in some clinical samples [34]. Not surprisingly, individuals diagnosed as MCI by both methods were older, sicker, and more functionally and cognitively impaired.

Our overall rate of amnestic MCI (16.6%) as determined by neuropsychological algorithm is comparable with other studies, although comparison is difficult because different criteria were used. [20,35,36] However, our rate of MCI using CDR criteria (40.2%) is higher than other studies, for example, Meguro and colleagues [37] who reported an overall frequency of CDR 0.5 of 30.2%. The main purpose of this study, however, was not to compare rates of MCI in the GEM study to other population studies but rather to compare the rates of MCI using the two approaches within the same cohort. We found that the two diagnostic methods were largely concordant for the identification of Normal individuals but there was lower agreement for the identification of MCI and, furthermore, there were a surprisingly high number of individuals who either had normal test performance but CDR scores of 0.5 or impaired test performance and CDR scores were 0. Similar rates of MCI were reported in patients attending a memory clinic [38] using a Global Deterioration Scale [39] score of 2 or 3 as the measure of subjective cognitive complaints and a NP definition of a-MCI.

Our results suggest that individuals with normal cognition but CDR-measured deficits are more likely to have lower education; endorse a higher number of health, and report symptoms of depression (but not meet formal criteria for a diagnosis of depression) than those without CDR-measured deficits. Depression is common in preclinical AD and can be an early sign of a neurodegenerative disorder [38,40]. Our results also suggest that the CDR is sensitive to very subtle differences in cognition. Thus, among individuals who were classified as Normal by the NP algorithm, the CDR classified, on average, those with higher test scores as CDR Normal and those with poorer scores as CDR MCI and, similarly, among individuals classified as MCI by the neuropsychological algorithm, the CDR classified those with higher test scores as CDR Normal those with lower scores as CDR MCI.

In this study the majority of individuals with MCI did not progress to dementia over the follow-up period. This finding is consistent with other studies of community-dwelling elderly [41] [42] and also clinic populations [38]. The rates of dementia identified by different MCI diagnostic criteria are also consistent with other studies which show that a slightly higher percentage of individuals convert to dementia using cognitive test scores as a predictor than using functional criteria [38]. Reported conversion rates based on a CDR 0.5 definition of MCI vary across studies [6,43] and may be related to the broad range of functional disability that falls within the CDR 0.5 category. For example, a CDR 0.5 sum of box score of 2.0 or higher has been shown to accurately predict 50% or higher conversion rate to AD over 3 years compared to a 10% conversion rate for individuals with a CDR 0.5 sum of box score of 1.0 [43]. The specific clinical subtype of CDR 0.5, as determined by clinical impression, has also been shown to predict conversion rates to dementia with 60.5% of individuals classified as “CDR 0.5 Dementia of the Alzheimer's Type” (DAT) and 35.7% of individuals classified as “CDR 0.5 Incipient DAT” progressing to dementia over 5 years [6]. Our findings show significantly higher rates of conversion to dementia (41.5%) when individuals meet both MCI criteria compared to individuals who meet both Normal criteria (7.5%). Significant differences were also observed in the two incongruent groups. Although the rates are similar, a higher percentage of those classified as NP MCI/CDR Normal progressed to dementia (22.8%) than those classified as CDR MCI/NP Normal (17.2%), suggesting that poor performance on neuropsychological tests is a slightly better indicator of future progression to dementia than functional impairment.

Several factors may contribute to our findings. First, these data were gathered as part of a clinical trial and it is possible that *G. biloba* had an effect on the progression to dementia in one group over another. However, we have previously reported that *G. biloba* was not effective in lowering either the overall incidence rate of dementia or AD incidence in normal elderly or persons with MCI; nor was there any effect of *G. biloba* on mortality, stroke or myocardial infarction [17] and as a randomized trial it is unlikely there was a disproportionate effect of *G. biloba*.

Second, different findings may occur across studies if the CDR is administered differently. GEM study interviewers completed standardized training procedures and were certified by one of the co-authors (LOD) who has had more than ten year's experience as a CDR trainer. We also considered the possibility that community informants are not as reliable as informants in clinical settings but the majority of GEM informants lived with the participant and of those informants who did not, most reported visiting at least once a week. Furthermore, we found little difference in CDR classification based on informant characteristics suggesting that information obtained from GEM informants was reliable. There is also the possibility of circularity in our diagnosis of MCI and dementia, both of which used performance on the neuropsychological battery. However, the dementia diagnosis was not limited to the neuropsychological battery but involved a comprehensive review of clinical assessments across multiple years and included performance on screening tests (3MSE and the ADAS-Cog)

not used in the MCI or dementia algorithm. Finally, although the participants in this study were drawn from the community they are a unique hybrid of a representative community sample but with a clinical trial selection bias. This sample may not be typical of the referral population seen in most clinical trials but also is not an epidemiological community cohort and this may also contribute to our findings. However, having said this, the critical finding in this study is not the overall rates of MCI compared to other studies, but the comparison of the two classification methods within the same cohort. Nevertheless, the sample may include large numbers of so-called, “worried well” who have more subjective complaints of memory loss, depression and poor health and this may contribute to higher rates of CDR 0.5.

Finally, proponents of the CDR have suggested that, when followed longitudinally, the majority of individuals with CDR 0.5 progress to AD and, based on this finding, they suggest that a CDR of 0.5 more correctly represents early mild AD rather than MCI.[6,44] The implications of this suggestion are potentially enormous, especially considering that more than 40% of individuals in this study received a CDR of 0.5 at baseline. Our findings confirm that the CDR picks up subtle cognitive loss but also suggests that the CDR is sensitive to subtle psychiatric and clinical factors and that these also influence the likelihood that an individual will be classified as MCI by the CDR. In one of the few studies addressing this issue, the Helsinki Aging Study[44] administered the CDR as part of a dementia work-up for 900 individuals between the ages of 75 and 80 living in the city of Helsinki. The CDR was completed by community physicians who, contrary to standard guidelines, were instructed to record CDR deficits related to any reason, not only cognition. Thirty-two individuals scored 1.0 on the CDR, indicating the presence of dementia, but in a follow-up neurological evaluation were assessed by a neurologist as not suffering from dementia. As in our study, discordant diagnoses were associated with the presence of psychiatric symptoms (37%), especially depression (28%), and medical disorders (47%).

In conclusion, using different MCI criteria, we identified different rates of MCI at baseline and different rates of progression to dementia over time. CDR ratings of MCI were influenced by a number of demographic, cognitive and clinical factors some of which may be more relevant to the identification of MCI within community cohorts than in memory clinics where patients present with existing memory complaints. Slightly more individuals meeting NP MCI criteria progressed to dementia over the follow-up than individuals identified as MCI by the CDR. These results suggest that identifying all individuals with CDR scores of 0.5 as AD is not advisable.

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Appendix

APPENDIX

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Abbreviations

GEM, Ginkgo Evaluation of Memory study; CHS, Cardiovascular Health Study; MCI, Mild Cognitive Impairment; a-MCI, amnestic MCI; na-MCI, nonamnestic MCI; CDR, Clinical Dementia Rating scale; 3MSE, Modified Mini Mental State Examination; CVLT, California Verbal Learning Test; R-O figure, Rey-Osterrieth Complex Figure; Ravens CPM, Ravens Coloured Progressive Matrices.

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Table 1

Cognitive test variables and domains included in MCI case identification

Domain	Test variable
Estimated premorbid IQ	AMNART[26]
	Ravens CPM[27]
Memory - verbal	California Verbal Learning Test (CVLT) - long delayed free recall[28]
- visual	24-point modified Rey Osterrieth figure (R-O figure) - delayed recall[29]
Construction	24-point modified Rey Osterrieth figure (R-O figure) - copy condition[29]
	24-point modified WAIS-R Block Design[7]
Language	30-item Boston Naming Test[30]
	Animal fluency[31]
Attention/Psychomotor Speed	WAIS-R Digit Span forward - total score[26]
	Trail Making Test A - time in sec.[27]
Executive Functions	Trail Making Test B - time in sec.[27]
	Stroop color/ word test - interference condition, number of colors named[32]

Table 2

Number (%) of participants classified as Normal or MCI (amnestic + nonamnestic) by Neuropsychological (NP) and CDR criteria

	CDR criteria		
NP Criteria	**CDR Normal Global score = 0 (*n*=1832; 58.8%)**	**CDR MCI Global score = 0.5 (*n*=1231; 40.2%)**	**TOTAL**
NP Normal (*n*=2202; 71.9%)	1451 (47.4%)	751 (24.5%)	2202 (71.9%)
NP MCI (*n*=861; 28.1%)	381 (12.4%)	480 (15.7%)	861 (28.1%)
TOTAL	1832 (59.8%)	1231 (40.2%)	3063 (100%)

Table 3

Demographic, clinical and health variables (mean +/- SD, or n / %) by subgroup

	NP Normal/ CDR Normal (*n* = 1451) Subgroup 1	**NP Normal/ CDR MCI (*n* = 751) Subgroup 2**	**NP MCI/ CDR Normal (*n* = 381) Subgroup 3**	**NP MCI/ CDR MCI (*n* = 480) Subgroup 4**	**ANOVA F or Chi-square**
Demographic variables					
Age	78.0 (2.9)[a]	78.7 (3.4)[b]	78.7 (3.5)[c]	79.6 (3.7)[d]	31.62***
Education (years)	14.5 (2.8)[a]	13.8 (2.8)[b]	15.0 (3.1)[c]	14.2 (3.3)[a]	19.72***
Gender (% female)	690 (47.6%)[a]	317 (42.2%)[b]	172 (45.1%)[a,b]	237 (49.4%)[a]	Chi-square = 7.99*
Mental Status Tests					
ADAS	5.6 (2.1)[a]	6.7 (2.6)[b]	7.1 (2.7)[c]	8.4 (3.2)[d]	159.73***
3MSE	95.0 (3.8)[a]	93.1 (4.4)[b]	92.2 (4.4)[c]	89.7 (5.4)[b]	189.28***
Premorbid Functioning					
AMNART IQ	118.3 (7.8)[a]	115.7 (8.1)[b]	116.1 (8.7)[b]	113.7 (9.2)c	41.29***
Ravens CPM	29.7 (4.1)[a]	28.9 (4.0)[b]	26.5 (4.9)[c]	25.7 (4.9)[d]	129.29***
Clinical/health variables					
ApoE 4 allele (% carriers)†	237 (20.0%)	133 (22.3%)	64 (21.3%)	88 (24.2%)	Chi square = 3.39
CESD depression scale	3.2 (3.1)[a]	3.9 (3.7)[b]	3.4 (3.4)[a]	4.6 (4.1)c	24.13***
Sum endorsed health problems (out of 24)	1.8 (1.6)[a]	2.1 (1.8)[b]	1.9 (1.8)[a,b]	2.1 (1.8)[b]	7.31***
Difficulty with IADLs (% yes)	383 (26.4%)[a]	239 (31.8%)[b]	119 (31.3%)[b]	177 (36.9%)[b]	Chi square = 21.29***
# medications (Rx and OTC)	7.1 (3.9)	7.5 (4.2)	7.0 (3.8)	7.2 (3.9)	0.54
Mobility: Difficulty walking half mile ‡ (% yes)	277 (19.2%)[a]	167 (22.4%)[a]	85 (22.7%)[a]	143 (30.2%)[b]	Chi square = 24.09***
Outcomes					
Deaths	177 (12.2%)	104 (13.8%)	43 (12.3%)	59 (12.3%)	Chi-square = 1.90
Dropouts	77 (5.3%)[a]	47 (6.3%)[a,b]	26 (6.8%)a,[b]	44 (9.2%)[b]	Chi-square = 9.28*
Dementia	107 (7.4%)[a]	129 (17.2%)[b]	87 (22.8%)[c]	199 (41.5%)[d]	Chi-square = 307.40***

ADAS = Alzheimer's Disease Assessment Scale; 3MSE = Modified Mini Mental State Examination; AMNART = National Adult Reading Test - American Version; Raven CPM = Raven's Coloured Progressive Matrices. CESD = Center for Epidemiological Studies Depression Scale.

Notes. Means or proportions within a given row with different superscripts are statistically different by Student-Neuman-Keuls procedure or modified Keppel-Bonferonni correction, respectively. Site included as covariates in omnibus ANOVAs

*** p<.001

* p<.05

† Reduced sample with ApoE genotyping, total n = 2445 (see Methods)

‡ Self-report

Table 4

Neuropsychological variables (mean +/- SD) by subgroup

	NP Normal/ CDR Normal (*n* = 1451) Subgroup 1	**NP Normal/CDR MCI (*n* = 751) Subgroup 2**	**NP MCI/CDR Normal (*n* = 381) Subgroup 3**	**NP MCI/ CDR MCI (*n* = 480) Subgroup 4**	**ANOVA F**
Episodic memory					
CVLT long-delay recall	9.9 (2.8)[a]	8.8 (2.9)[b]	7.9 (3.2)[c]	6.3 (2.9)[d]	173.79***
R-O delayed recall	17.3 (4.0)[a]	16.9 (4.0)[a]	13.2 (5.2)[b]	11.9 (5.2)[c]	234.65***
Attention/perceptual speed					
Digit span forward	6.3 (1.3)[a]	6.1 (1.3)[a]	5.9 (1.3)[b]	5.8 (1.3)[b]	14.83***
Trails A (sec)	39.5 (11.8)[a]	42.6 (12.1)[b]	50.0 (18.5)[c]	54.8 (24.3)[d]	113.06**
Visuospatial construction					
R-O copy (24 points)	22.6 (1.7)[a]	22.7 (1.6)[a]	20.6 (3.0)[b]	20.6 (3.2)[b]	176.00**
Block design (24 pts)	13.2 (3.8)[a]	12.1 (3.8)[b]	9.7 (4.6)[c]	8.7 (4.3)	168.91***
Language					
30-point BNT	27.4 (2.2)[a]	27.0 (2.5)[b]	25.6 (3.4)[c]	24.5 (3.9)[d]	134.11***
Category fluency	17.1 (4.2)[a]	16.3 (3.9)[b]	14.2 (4.2)[c]	13.0 (3.6)[d]	133.49***
Executive functions					
Trails B (sec)	95.0 (33.0)[a]	111.1 (40.3)[b]	127.9 (49.6)[c]	148.7 (55.1)[d]	192.70***
Stroop interference	83.2 (19.9)[a]	76.9 (19.5)[b]	66.1 (23.1)[c]	59.8 (22.0)[d]	151.20***

Note: Overall Fs reported for ANCOVAS with age, education, race and CES-D score included as covariates. Means within a given row with different superscripts are statistically different at $p < .05$ by Student-Neuman-Keuls procedure

*** $p < .001$