Mild Cognitive Impairment Due to Alzheimer Disease in the Community

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Objective: The newly proposed National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for mild cognitive impairment (MCI) due to Alzheimer disease (AD) suggest a combination of clinical features and biomarker measures, but their performance in the community is not known.
Methods: The Mayo Clinic Study of Aging (MCSA) is a population-based longitudinal study of nondemented subjects in Olmsted County, Minnesota. A sample of 154 MCI subjects from the MCSA was compared to a sample of 58 amnestic MCI subjects from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) to assess the applicability of the criteria in both settings and to assess their outcomes.
Results: Fourteen percent of MCSA and 16% of ADNI-1 of subjects were biomarker negative. In addition, 14% of MCSA and 12% of ADNI-1 subjects had evidence for amyloid deposition only, whereas 43% of MCSA and 55% of ADNI-1 subjects had evidence for amyloid deposition plus neurodegeneration (magnetic resonance imaging atrophy, fluorodeoxyglucose positron emission tomography hypometabolism, or both). However, a considerable number of subjects had biomarkers inconsistent with the proposed AD model; for example, 29% of MCSA subjects and 17% of ADNI-1 subjects had evidence for neurodegeneration without amyloid deposition. These subjects may not be on an AD pathway. Neurodegeneration appears to be a key factor in predicting progression relative to amyloid deposition alone.
Interpretation: The NIA-AA criteria apply to most MCI subjects in both the community and clinical trials settings; however, a sizeable proportion of subjects had conflicting biomarkers, which may be very important and need to be explored.

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Mild cognitive impairment (MCI) represents a state between the cognitive changes of aging and early dementia.[1,2] Although MCI as a general construct need not be progressive nor be the earliest stage of Alzheimer disease (AD), it has been most often studied in this context and is commonly referred to as the earliest clinical manifestation of AD pathophysiology.[3]

The National Institute on Aging and the Alzheimer's Association recently published research criteria for MCI due to AD that incorporated the use of biomarkers to assess the likelihood that the MCI syndrome is due to the underlying pathophysiology of AD.[3] At present, although only the clinical diagnosis of MCI has been recommended for use by practitioners, a growing body of evidence strongly suggests that the clinical diagnosis of MCI plus the use of imaging and fluid biomarkers will enhance the likelihood of predicting which subjects are likely to progress to AD dementia.[4–11] The new MCI due to AD criteria are currently untested, and, in particular, their performance in the general community is

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unknown. The distribution of these biomarkers in a clinically diagnosed group of MCI subjects who have been derived from a random sample of nondemented subjects would be particularly informative with respect to the utility of the biomarkers in general clinical practice and potentially for US Food and Drug Administration regulatory purposes.

The present study assesses the distribution of imaging biomarkers in an MCI cohort drawn from the Mayo Clinic Study of Aging (MCSA), which is a population-based sample of nondemented subjects in Olmsted County, Minnesota.[12] A comparison of biomarker distributions between the MCSA and the Alzheimer's Disease Neuroimaging Initiative (ADNI) is also reported.

Subjects and Methods

This biomarker study was part of the MCSA, a population-based study of residents in Olmsted County, Minnesota, aged 70 to 89 years at the time of enrollment. The overall study design has been published elsewhere.[12]

Briefly, all Olmsted County residents who were aged 70 to 89 years on October 1, 2004, were identified using the Rochester Epidemiology Project medical records linkage system.[13–15] We randomly selected 5,233 of them for recruitment, subjects with a pre-existing diagnosis of dementia were identified by screening the medical records in the system, and the clinical information was reviewed in detail by a neurologist (D.S.K.). Subjects who had been diagnosed with dementia were not invited to participate in this study, and consequently a total of 4,398 subjects were considered eligible for participation in the active evaluation.

Clinical Evaluations

Each participant received an evaluation by a study coordinator, who collected information regarding medical history, family history, and medications. The study coordinator also interviewed a study partner about the individual and completed a modified Clinical Dementia Rating.[16] The second part of the examination was conducted by a physician who performed a medical history review, mental status examination, and neurological examination. The third component consisted of a neuropsychological evaluation in which 9 tests were performed, comprising 4 cognitive domains. Three tests were used for memory and 2 for the other domains. Memory was tested by the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II (delayed recall), WMS-R Visual Reproductions II (delayed recall), and Auditory Verbal Learning Test (delayed recall).[17,18] Attention–executive function was tested by the Trail Making Test Part B and Digit Symbol Substitution from the Wechsler Adult Intelligent Scale-Revised (WAIS-R).[19,20] Language was tested by the Boston Naming Test and category fluency scores.[21] Visuospatial skills were tested by the Block Design and Picture Completion tests from the WAIS-R.[20] The raw scores from each test were transformed into age-adjusted scores using independent normative data from Mayo's Older American Normative Studies.[22,23]

Diagnostic Categories

For the purposes of this study, performance of an individual in a particular cognitive domain was measured by comparing the person's domain score to the score in normal subjects from the normative work in the same but independent population.[22] Subjects with scores of approximately 1.0 standard deviation (SD) or greater below the age-specific mean in the general population were considered for possible cognitive impairment. However, it is important to note that no algorithm was used to derive the diagnosis of MCI; rather, a panel including the study coordinator, neuropsychologist, and a physician who had examined the subject discussed each component of the examination and assigned a diagnosis of MCI according to published criteria.[24] The criteria used for MCI included the following: (1) cognitive concern by the subject, informant, or clinician; (2) impairment in 1 or more of 4 cognitive domains from the neuropsychological test battery; (3) essentially normal functional activities as derived from the Clinical Dementia Rating (CDR) and the Functional Activities Questionnaire; and (4) absence of dementia (per Diagnostic and Statistical Manual of Mental Disorders, 4th edition).[25] Subjects who were diagnosed with MCI were further classified as having amnestic MCI (aMCI) if the memory domain was impaired or nonamnestic MCI (naMCI) if there was no impairment in memory.[24] In follow-up evaluations in the MCSA, approximately 15 months after the previous assessment, the investigators were blinded to the previous diagnostic classification of the subjects.

ADNI Comparison Group

Individuals from the ADNI-1 who had aMCI and 1.5T magnetic resonance imaging (MRI), fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), and ^{11}C Pittsburgh compound B (PiB) PET scans at the time of the aMCI diagnosis were selected as a comparison sample to determine the correspondences between population-based and clinical trial samples of subjects. The ADNI-1 subjects all had aMCI and had to have a memory impairment at approximately 1.5 SD below an education-adjusted norm for Logical Memory II, and their CDR had to be 0.5.[16,17]

Imaging Methods

For both Mayo (3T) and ADNI (1.5T) subjects, MRI was performed with a 3-dimensional magnetization prepared rapid acquisition gradient echo sequence.[26] Images were corrected for distortion due to gradient nonlinearity and for bias field.[27] Our primary MRI measure was hippocampal volume measured with FreeSurfer software (version 4.5.0).[28] Each subject's raw hippocampal volume was adjusted by his/her total intracranial volume,[29] measured using an in-house algorithm, to form an adjusted hippocampal volume (HVa). We calculated HVa as the residual from a linear regression of hippocampal volume (y) versus total intracranial volume (x).

At Mayo, PET images were acquired using a GE (Milwaukee, WI) Discovery RX PET/CT scanner. A computed tomographic image is obtained for attenuation correction. The PiB PET scan consisting of four 5-minute dynamic frames was

acquired 40 to 60 minutes after injection.[30,31] ^{18}F-FDG PET images were obtained 1 hour after the PiB scan. Subjects were injected with ^{18}F-FDG and imaged after 30 to 38 minutes, for an 8-minute image acquisition consisting of four 2-minute dynamic frames. PET acquisition protocols for ADNI were similar to those at Mayo, but scanner models varied, as ADNI is a multisite study.

Quantitative image analysis for both PiB and FDG was done using our in-house fully automated image processing pipeline.[32] A global cortical PiB PET retention ratio (standardized uptake value ratio [SUVR]) was obtained by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus values for each subject and dividing this by the median uptake over voxels in the cerebellar gray matter regions of interest (ROIs) of the atlas.[32] FDG PET scans were analyzed in a similar manner. We used angular gyrus, posterior cingulate, and inferior temporal cortical ROIs to denote an "AD-signature meta ROI," as described in Landau et al,[33] normalized to pons and vermis uptake. Imaging data for MCSA and ADNI subjects was analyzed at Mayo; thus, analytic methods were identical for Mayo and ADNI subjects.

Statistical Methods for Developing Imaging Biomarker and Cognitive Testing Cut Points

Although all biomarkers and cognitive tests are continuous measures, the new criteria for MCI due to AD require the classification of every biomarker and cognitive test as either normal or abnormal.[3] Thus, cut points must be created in these continuous distributions. The ideal method for selecting biomarker cut points would be to use autopsy diagnoses as the standard for comparison.[34–37] Because we do not have autopsy cohorts with antemortem 3T MRI, PiB PET, and FDG PET, we created cut points such that a majority of clinically defined AD dementia patients would be deemed abnormal. Cut points were based on estimated percentiles. For biomarkers where higher values are worse (PiB PET), the cut point was the 10th percentile of AD distribution (corresponding to 90% sensitivity).[38] For biomarkers where lower values are worse (FDG PET, HVa), the cut point was the 90th percentile of the AD distribution. In this way, approximately 90% of ADs were considered abnormal. Although we did not have cerebrospinal fluid available in our subjects, we had amyloid (PiB PET) and neurodegenerative (FDG PET and MRI) biomarkers in all subjects, and were therefore able to stage all subjects in accordance with the new MCI due to AD criteria.[3] We had 2 measures in the neurodegenerative biomarker category (FDG PET and MRI), and we considered a subject positive for evidence of neurodegeneration if 1 or both measures fell below the cut point.

Variables were described as median (interquartile range [IQR]) or count (percentage). Differences between the MCSA aMCI and ADNI-1 subjects and between the MCSA aMCI and naMCI subjects were tested with Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical data. Differences across the 4 biomarker groups were tested with Kruskal–Wallis tests for continuous variables and χ^2 tests for categorical data. We computed multinomial 95% confidence intervals for the percentages in each of the 4 biomarker groups within the ADNI-1 and aMCI MCSA subjects. The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

Results

For this study, 154 subjects met the clinical criteria for any type of MCI in the MCSA and had received an MRI, FDG PET, and PiB PET scans at the time of the MCI diagnosis. Of these, 126 (82%) were aMCI subjects and 28 (18%) were naMCI subjects. In the ADNI-1, 58 subjects met the clinical criteria for aMCI and received MRI, FDG PET, and PiB PET scans. The demographic, clinical, and imaging characteristics of the aMCI MCSA subjects and ADNI-1 subjects are shown in Table 1.

The ADNI subjects were younger and more highly educated than the MCSA aMCI subjects. The MCSA aMCI subjects on average were more mild in the state of their disease process, with a median CDR sum of boxes (SB) of 1.0 (IQR = 0.5–1.5), whereas the ADNI subjects were more impaired, by design, with a CDR SB of 1.5 (IQR = 1.0–2.4).

The subjects were classified into 1 of 4 groups based on their amyloid status and the presence or absence of neurodegenerative features as measured by FDG PET or MRI hippocampal volume. Cut points for normal and abnormal were used as described above.[38] Table 1 and the Figure show the similar distribution of subjects into the 4 biomarker groups for the MCSA aMCI and ADNI-1 subjects. In the MCSA, among those aMCI subjects with amyloid and neurodegeneration, 13 (24%) had abnormal HVa alone, 10 (19%) had abnormal FDG alone, and 31 (57%) had both abnormal HVa and FDG, and in the ADNI-1 subjects, 7 (22%) had abnormal HVa, 8 (25%) had abnormal FDG, and 17 (53%) had both. Among those with neurodegeneration but no evidence of amyloid deposition, 9 (25%) had abnormal HVa, 16 (44%) had abnormal FDG, and 11 (31%) had both abnormal HVa and FDG in the MCSA aMCI subjects and in the ADNI-1 subjects, 1 (10%) had abnormal HVa, 5 (50%) had abnormal FDG, and 4 (40%) had both.

Table 2 shows the demographics, clinical characteristics, and imaging features of the 4 biomarker classification groups in the subgroup of MCSA subjects with aMCI. The percentage of apolipoprotein E4 (ApoE4) carriers correlated with the presence of amyloid as expected ($p < 0.001$).

Of the 126 aMCI subjects in the MCSA, 96 had a follow-up at 15 months, and 49 of the 58 ADNI-1 subjects had a follow-up at approximately 12 months (Table 3). For the aMCI MCSA subjects during the 15-month period, 14 (15%) progressed to dementia (12 of 14 aMCI subjects

TABLE 1. Characteristics of All Amnestic Mild Cognitive Impairment Participants with Magnetic Resonance Imaging and Positron Emission Tomography from the MCSA and ADNI-1

Characteristic	MCSA, n = 126	ADNI-1, n = 58	*p*
Age, yr, median (IQR)	82 (78, 86)	75 (71, 81)	<0.001
Male gender, No. [%]	84 [67]	37 [64]	0.70
Education, yr, median (IQR)	13 (12, 16)	16 (14, 18)	<0.001
ApoE4 positive, No. [%]	49 [40]	32 [55]	0.05
MMSE, median (IQR)	26 (24, 27)	27 (26, 29)	<0.001
CDR-SB, median (IQR)	1.0 (0.5, 1.5)	1.5 (1.0, 2.4)	<0.001
PiB ratio, median (IQR)	1.66 (1.36, 2.22)	1.90 (1.39, 2.28)	0.39
PiB> 1.50, No. [%]	72 [57]	39 [67]	0.19
FDG ratio, median (IQR)	1.29 (1.18, 1.42)	1.27 (1.17, 1.37)	0.32
FDG < 1.31, No. [%]	68 [54]	34 [59]	0.56
Adjusted hippocampal volume, median (IQR)	−0.71 (−1.29, −0.29)	−0.70 (−1.42, 0.03)	0.34
HVa < 0.70, No. [%]	64 [51]	29 [50]	0.92
Biomarker group, No. [%]			0.32
All biomarkers negative	18 [14]	9 [16]	
Amyloid positive only	18 [14]	7 [12]	
Amyloid positive + neurodegeneration	54 [43]	32 [55]	
Neurodegeneration only	36 [29]	10 [17]	
Follow-up diagnosis, No. [%][a]			0.006
CN	25 [26]	3 [6]	
MCI	57 [59]	32 [65]	
Dementia	14 [15]	14 [29]	
Annual change in MMSE			
No.	93	48	
Median (IQR)	0.00 (−1.58, 0.74)	−0.82 (−2.93, 0.97)	0.38
Annual change in CDR-SB			
No.	96	48	
Median (IQR)	0.38 (0.00, 1.23)	0.50 (0.00, 1.00)	0.53

[a]Follow-up data were obtained at the 15-month visit in the MCSA and the 12-month visit in the ADNI.
ADNI = Alzheimer's Disease Neuroimaging Initiative; ApoE4 = apolipoprotein E4; CDR = Clinical Dementia Rating; CN = cognitively normal; FDG = fluorodeoxyglucose; HVa = adjusted hippocampal volume; IQR = interquartile range; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; MMSE = Mini-Mental State Examination; PiB = ^{11}C Pittsburgh compound B; SB = sum of boxes.

progressed clinically to dementia due to AD), 57 (59%) maintained MCI status, and 25 (26%) were designated as cognitively normal. For the ADNI-1 subjects, 14 (29%) had progressed to dementia (all 14 to clinical dementia due to AD), 32 (65%) maintained MCI status, and 3 (6%) were designated as cognitively normal. In both MCSA and ADNI-1 aMCI groups, the highest proportion of subjects who progressed to dementia was found in the amyloid plus neurodegeneration group and the neurodegeneration only group. In neither MCSA nor ADNI-1 did progression to dementia occur in subjects who were in the amyloid only biomarker group.

Table 4 shows the comparisons of the aMCI and naMCI subjects in the MCSA. The PiB ratios were higher ($p = 0.048$), and HVa values were smaller ($p < 0.001$) in the aMCI subjects compared to the naMCI subjects, with a greater proportion of the aMCI subjects having abnormal HVa values ($p = 0.013$).

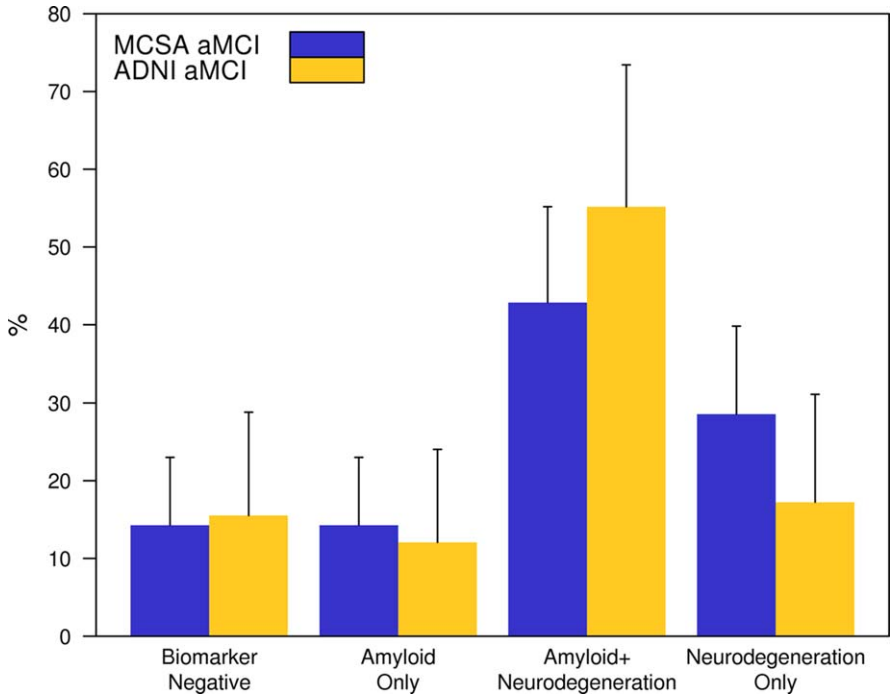

FIGURE 1: Frequency of positive biomarkers in the Mayo Clinic Study of Aging (MCSA) and Alzheimer's Disease Neuroimaging Initiative (ADNI). aMCI = amnestic mild cognitive impairment. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

Discussion

Our investigation of biomarkers in the MCSA MCI group is the first population-based study to assess the recently published MCI criteria with respect to the distribution of imaging biomarkers in MCI. The distribution of biomarker abnormalities was similar between the MCSA aMCI subjects and ADNI-1, although the ADNI-1 subjects were selected to be more impaired at baseline as evidenced by the CDR scores. Although the number of subjects who progressed in both cohorts was small, the trends were very similar.

The neurodegeneration-positive but amyloid-negative group provides conflicting information for the model of the temporal progression of biomarkers in AD proposed by Jack et al, but may be very important.[44] The model suggests that by the time of symptomatic impairment with MCI, both amyloid and neurodegeneration should be present.[39–41] Although not statistically significant, this group had the highest rate of progression to dementia in the MCSA and was second highest in the ADNI cohort, raising questions regarding the salience of amyloid. Neurodegeneration may be more important at predicting progression than amyloid, and other work by Landau et al and Hiester et al has suggested that neurodegenerative features such as hypometabolism on FDG PET and hippocampal atrophy are key in predicting progression.[5,39] This group of subjects with MCI is similar to the "suspected non-AD pathway" (sNAP) subjects who were cognitively normal in the MCSA and could be designated as MCI-sNAP.[38]

Subjects with an aMCI subtype may have AD biomarkers present more frequently than subjects with an naMCI subtype, as suggested by greater amyloid burden and more hippocampal atrophy. Although the most common clinical phenotype for AD pathophysiology is an amnestic presentation, certainly nonamnestic clinical profiles can occur, and this study highlights the expected heterogeneity of the MCI construct in the community. It is also possible that naMCI subjects may represent prodromal stages of non-AD dementias.[40–43] The ADNI subjects are uniquely selected and may not represent community MCI subjects (younger, more ApoE4 carriers, higher Mini-Mental State Examination, and higher CDR sum of boxes), but do simulate clinical trial populations. Both groups provide complementary data on the criteria.

It has been suggested that the amyloid levels increase to a maximum level and then plateau as one progresses along the putative continuum for AD pathophysiology proposed by Jack and colleagues.[44] Our data partially support this model but also recognize some inconsistencies concerning the model, because the neurodegenerative only group was prevalent and tended to progress to dementia. These findings are more consistent with the revised model proposed recently by Jack et al,

TABLE 2. Characteristics of All Mayo Clinic Study of Aging Amnestic Mild Cognitive Impairment Subjects by Biomarker Group

Characteristic	Biomarker Negative, n = 18	Amyloid Only, n = 18	Amyloid + Neurodegeneration, n = 54	Neurodegeneration Only, n = 36	*p*
Age, yr median (IQR)	80 (76, 84)	79 (77, 83)	84 (80, 87)	82 (78, 85)	0.15
Male gender, No. [%]	14 [78]	10 [56]	32 [59]	28 [78]	0.15
Education, yr, median (IQR)	12 (12, 14)	12 (12, 16)	14 (12, 16)	13 (12, 16)	0.50
ApoE4 positive, No. [%]	2 [12]	9 [50]	34 [63]	4 [11]	<0.001
MMSE, median (IQR)	27 (25, 27)	24 (24, 27)	26 (24, 27)	25 (24, 27)	0.22
CDR-SB, median (IQR)	0.5 (0.0, 1.0)	1.0 (0.5, 1.5)	1.0 (0.5, 2.4)	0.5 (0.0, 1.0)	0.003
PiB ratio, median (IQR)	1.36 (1.34, 1.39)	1.97 (1.85, 2.13)	2.23 (1.80, 2.50)	1.35 (1.28, 1.40)	—
FDG ratio, median (IQR)	1.46 (1.41, 1.53)	1.45 (1.39, 1.54)	1.22 (1.14, 1.30)	1.26 (1.18, 1.31)	—
Adjusted hippocampal volume, median (IQR)	−0.21 (−0.55, 0.34)	−0.18 (−0.48, 0.01)	−1.04 (−1.70, −0.81)	−0.87 (−1.18, −0.52)	—
Diagnosis at follow-up, No. [%]					0.005
CN	6 [50]	5 [36]	2 [5]	12 [36]	
MCI	5 [42]	9 [64]	29 [78]	14 [42]	
Dementia	1 [8]	0 [0]	6 [16]	7 [21]	
Annual change in MMSE					
No.	12	14	35	32	
Median (IQR)	0.00 (−0.82, 0.84)	0.00 (−0.70, 0.83)	−0.80 (−2.34, 0.00)	0.00 (−1.58, 0.77)	0.042
Annual change in CDR-SB					
No.	11	13	39	33	
Median (IQR)	0.00 (−0.36, 0.00)	0.35 (−0.38, 0.42)	0.39 (0.00, 1.50)	0.40 (0.00, 1.55)	0.15

ApoE4 = apolipoprotein E4; CDR = Clinical Dementia Rating; CN = cognitively normal; FDG = fluorodeoxyglucose; IQR = interquartile range; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PiB = ^{11}C Pittsburgh compound B; SB = sum of boxes.

TABLE 3. Characteristics of All Alzheimer's Disease Neuroimaging Initiative Amnestic Mild Cognitive Impairment Subjects by Biomarker Group

Characteristic	Biomarker Negative, n = 9	Amyloid Only, n = 7	Amyloid + Neurodegeneration, n = 32	Neurodegeneration Only, n = 10	*p*
Age, yr, median (IQR)	72 (64, 77)	75 (74, 80)	75 (71, 81)	77 (73, 83)	0.45
Male gender, No. [%]	6 [67]	5 [71]	19 [59]	7 [70]	0.89
Education, yr, median (IQR)	18 (16, 18)	16 (14, 16)	16 (14, 18)	16 (16, 18)	0.61
ApoE4 positive, No. [%]	1 [11]	6 [86]	21 [66]	4 [40]	0.007
MMSE, median (IQR)	28 (27, 29)	28 (28, 30)	27 (26, 28)	28 (26, 29)	0.07
CDR-SB, median (IQR)	1.5 (1.0, 2.0)	1.0 (1.0, 1.5)	2.0 (1.4, 2.6)	1.0 (0.6, 1.9)	0.23
PiB ratio, median (IQR)	1.32 (1.24, 1.39)	1.78 (1.67, 2.29)	2.24 (2.09, 2.34)	1.30 (1.28, 1.36)	—
FDG ratio, median (IQR)	1.43 (1.36, 1.60)	1.41 (1.39, 1.45)	1.23 (1.16, 1.29)	1.16 (1.05, 1.26)	—
Adjusted hippocampal volume, median (IQR)	0.56 (0.13, 1.29)	0.03 (−0.29, 0.70)	−0.96 (−1.59, −0.71)	−0.85 (−1.63, 0.02)	—
Diagnosis at follow-up, No. [%]					0.19
CN	0 [0]	1 [17]	2 [8]	0 [0]	
MCI	8 [89]	5 [83]	13 [50]	6 [75]	
Dementia	1 [11]	0 [0]	11 [42]	2 [25]	
Annual change in MMSE					
No.	9	6	25	8	
Median (IQR)	0.00 (0.00, 1.05)	0.43 (−1.44, 0.96)	−1.00 (−3.00, 0.00)	−2.41 (−3.19, 0.24)	0.44
Annual change in CDR-SB					
No.	9	6	25	8	
Median (IQR)	0.50 (0.00, 0.52)	−0.49 (−0.77, 0.25)	0.50 (0.40, 1.45)	0.49 (−0.12, 0.68)	0.17

ApoE4 = apolipoprotein E4; CDR = Clinical Dementia Rating; FDG = fluorodeoxyglucose; IQR = interquartile range; MMSE = Mini-Mental State Examination; PiB = ^{11}C Pittsburgh compound B; SB = sum of boxes.

TABLE 4. Characteristics of All Mayo Clinic Study of Aging MCI Subjects by aMCI and naMCI

Characteristic	aMCI, n = 126	naMCI, n = 28	*p*
Age, yr, median (IQR)	82 (78, 86)	84 (78, 87)	0.66
Male gender, No. [%]	84 [67]	19 [68]	0.90
Education, yr, median (IQR)	13 (12, 16)	12 (12, 14)	0.13
ApoE4 positive, No. [%]	49 [40]	6 [22]	0.09
MMSE, median (IQR)	26 (24, 27)	26 (24, 27)	0.30
CDR-SB, median (IQR)	1.0 (0.5, 1.5)	0.8 (0.0, 1.5)	0.61
PiB ratio, median (IQR)	1.66 (1.36, 2.22)	1.36 (1.32, 1.82)	0.048
PiB > 1.50, No. [%]	72 [57]	11 [39]	0.09
FDG ratio, median (IQR)	1.29 (1.18, 1.42)	1.29 (1.19, 1.36)	0.72
FDG < 1.31, No. [%]	68 [54]	15 [54]	0.97
Adjusted hippocampal volume, median (IQR)	−0.71 (−1.29, −0.29)	−0.22 (−0.60, 0.18)	<0.001
HVa < 0.70, No. [%]	64 [51]	7 [25]	0.013
Biomarker group, No. [%]			0.28
All biomarkers negative	18 [14]	7 [25]	
Amyloid positive only	18 [14]	4 [14]	
Amyloid positive + neurodegeneration	54 [43]	7 [25]	
Neurodegeneration only	36 [29]	10 [36]	
Diagnosis at follow-up, No. [%]			0.79
CN	25 [26]	6 [27]	
MCI	57 [59]	14 [64]	
Dementia	14 [15]	2 [9]	
Annual change in MMSE			
No.	93	22	
Median (IQR)	0.00 (−1.58, 0.74)	−0.38 (−1.94, 0.00)	0.46
Annual change in CDR-SB			
No.	96	22	
Median (IQR)	0.38 (0.00, 1.23)	0.00 (−1.01, 0.40)	0.016

aMCI = amnestic mild cognitive impairment; ApoE4 = apolipoprotein E4; CDR = Clinical Dementia Rating; CN = cognitively normal; FDG = fluorodeoxyglucose; HVa = adjusted hippocampal volume; IQR = interquartile range; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; naMCI = nonamnestic mild cognitive impairment; PiB = ^{11}C Pittsburgh compound B; SB = sum of boxes.

suggesting that there may be other pathways for progression.[45] The amyloid-positive only aMCI group in the MCSA had a median SUVR of 1.97, and the amyloid-positive plus neurodegenerative biomarker group had an SUVR of 2.23 ($p = 0.06$), and a similar trend was observed in the ADNI-1 subjects (1.78 vs 2.24, $p = 0.30$), supporting the concept of a progression from amyloid positivity to amyloid plus neurodegeneration. However, as discussed above, this may not be the only path to progression.

Forty-three percent of the MCSA aMCI subjects had evidence for the presence of amyloid and neurodegeneration, whereas another 43% had no evidence of amyloid at the time of aMCI. Only 33% of ADNI-1 subjects were amyloid negative.[46] The high percentage of MCI subjects who are amyloid positive implies that aMCI typically leads to dementia due to AD. However, the fact that not all aMCI are amyloid positive indicates that this is not always the case and argues for the use of biomarkers to stratify subjects at the MCI stage of the cognitive disorders spectrum,

especially for clinical trials. Although the distributions were similar, more of the ADNI subjects had imaging evidence for the AD signature (amyloid plus neurodegeneration) than MCSA subjects, but the neurodegeneration alone was more prevalent in the MCSA subjects. This was probably a result of the requirement in ADNI-1 that MCI subjects have impaired memory and be more advanced, whereas in the MCSA, all MCI subjects were enrolled, again underscoring the importance of studying these biomarkers in the community.

In summary, this study suggests that the proposed addition of biomarkers to the clinical diagnosis of MCI is largely valid. The frequency of conflicting biomarkers, however, suggests the necessity of following these subjects. The final validation of the use of biomarkers will come from longitudinal studies, but the initial categorization of subjects with clinical MCI and a variety of biomarkers appears to be appropriate. When evaluating cognitively normal individuals, there are also many subjects who appear to be outside of the AD pathophysiological pathway (when defined to require biomarker evidence of amyloid deposition), as has been demonstrated by us previously, and now a corresponding group of subjects with MCI here designated as MCI-sNAP is also recognized.[38,47] Subjects evaluated in a population-based study such as the MCSA are, by definition, more heterogeneous than those seen in AD or dementia clinics, and consequently this factor needs to be considered when planning for clinical trials. However, given that these compounds will be used by typical community patients, these data are important.

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Potential Conflicts of Interest

R.C.P.: board membership, Alzheimer's Association Board; consultancy, Pfizer, Janssen Alzheimer Immunotherapy, Elan Pharmaceuticals, GE Healthcare; speaking fees, Novartis; royalties, Oxford University Press. P.A.: consultancy, Elan, Wyeth, Eisai, Bristol-Myers Squibb, Eli Lilly, NeuroPhage, Merck, Roche, Amgen, Abbott, Pfizer, Novartis, Bayer, Astellas, Dainippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, Medivation, Theravance, Cardeus, Anavex; grants/grants pending, Baxter, Pfizer, Lilly, NIH. B.F.B.: board membership, Tau Consortium; grants/grants pending, NIH, Cephalon, Allon Pharmaceuticals, Mangurian Foundation, Alzheimer's Association, GE Healthcare; royalties, *Behavioral Neurology of Dementia*; paid educational presentations, American Academy of Neurology. D.S.K.: consultancy, Tau-Rx Pharmaceuticals, Allon Pharmaceuticals, Lilly Pharmaceuticals; grants/grants pending, Janssen, Baxter. M.M.: consultancy, Eli Lilly; grants/-grants pending, NIH. M.W.: consultancy, stock/stock options, Synarc, Elan. C.R.J.: consultancy, Janssen, Bristol-Myers Squibb, General Electric, Johnson & Johnson; grants/grants pending, NIH, Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation; involved in clinical trials sponsored by Allon and Baxter.

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