MRI and MRS predictors of mild cognitive impairment in a population-based sample

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ABSTRACT

Objective: To investigate MRI and proton magnetic resonance spectroscopy (MRS) predictors of mild cognitive impairment (MCI) in cognitively normal older adults.

Methods: Subjects were cognitively normal older adults (n = 1,156) who participated in the population-based Mayo Clinic Study of Aging MRI/MRS study from August 2005 to December 2010 and had at least one annual clinical follow-up. Single-voxel MRS was performed from the posterior cingulate gyri, and hippocampal volumes and white matter hyperintensity volumes were quantified using automated methods. Brain infarcts were assessed on MRI. Cox proportional hazards regression, with age as the time scale, was used to assess the effect of MRI and MRS markers on the risk of progression from cognitively normal to MCI. Linear mixed-effects models were used to assess the effect of MRI and MRS markers on cognitive decline.

Results: After a median follow-up of 2.8 years, 214 participants had progressed to MCI or dementia (estimated incidence rate = 6.1% per year; 95% confidence interval = 5.3%–7.0%). In univariable modeling, hippocampal volume, white matter hyperintensity volume, and *N*-acetylaspartate/*myo*-inositol were significant predictors of MCI in cognitively normal older adults. In multivariable modeling, only decreased hippocampal volume and *N*-acetylaspartate/*myo*-inositol were independent predictors of MCI. These MRI/MRS predictors of MCI as well as infarcts were associated with cognitive decline ($p < 0.05$).

Conclusion: Quantitative MRI and MRS markers predict progression to MCI and cognitive decline in cognitively normal older adults. MRS may contribute to the assessment of preclinical dementia pathologies by capturing neurodegenerative changes that are not detected by hippocampal volumetry. *Neurology*® 2013;81:126–133

GLOSSARY

AD = Alzheimer disease; **Cr** = creatine; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; **FDG** = ^{18}F-fluorodeoxyglucose; **FLAIR** = fluid-attenuated inversion recovery; **¹H-MRS** = proton magnetic resonance spectroscopy; **HR** = hazard ratio; **IQR** = interquartile range; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **mI** = *myo*-inositol; **MRS** = magnetic resonance spectroscopy; **NAA** = *N*-acetylaspartate; **TIV** = total intracranial volume; **WM** = white matter; **WMH** = white matter hyperintensity.

Magnetic resonance markers of preclinical dementia–related pathologies are needed for identifying individuals who may benefit from preventive interventions.[1] The most common dementia-related pathologies observed in cognitively normal older adults are Alzheimer disease (AD) and vascular disease.[2–4] MRI and proton magnetic resonance spectroscopic (¹H-MRS) findings typically associated with early neurodegenerative pathology of AD include hippocampal atrophy on structural MRI as well as elevated glial metabolite *myo*-inositol (mI) and decreased neuronal metabolite *N*-acetylaspartate (NAA) on MRS.[5,6] MRI findings associated with vascular disease include brain infarcts and white matter hyperintensities (WMH) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI. Brain infarcts and WMH are associated with cognitive decline and dementia in older adults without dementia,[7–11] and may increase the risk of mild cognitive impairment (MCI) along with the MRI and MRS abnormalities associated with preclinical AD. Hippocampal volumes and MRS abnormalities were complementary in differentiating MCI from

cognitively normal subjects and in predicting memory performance in cohorts of elderly persons without dementia.[12–14] We previously demonstrated that patients with MCI who have both hippocampal atrophy and MRS metabolite abnormalities have an increased risk of incident dementia compared with those who have only one of the imaging abnormalities (i.e., hippocampal atrophy or MRS abnormalities).[15]

We hypothesized that MRI and MRS studies performed during a single magnetic resonance examination may provide complementary information about the risk of MCI. Our objective was to determine the AD-associated and vascular disease–associated MRI and MRS predictors of MCI and cognitive decline in cognitively normal older adults from a population-based sample.

METHODS Subjects. Subjects of this study were cognitively normal older adults (n = 1,156) who participated in the Mayo Clinic Study of Aging (MCSA) MRI/MRS study from August 2005 to December 2010 and had at least one clinical follow-up evaluation until October 2012. The MCSA is a prospective, population-based study of older adults without dementia in Olmsted County, Minnesota. Individuals participating in the MCSA undergo clinical evaluations and a battery of neuropsychological tests approximately every 15 months as previously described.[16] The operational definition of MCI was based on clinical judgment through a history from the patient and from an informant (for the majority of patients) without reference to MRI using the following published criteria: cognitive complaint, cognitive function not normal for age, decline in cognition, essentially normal functional activities, and not demented.[17] Diagnosis of dementia was based on the *DSM-III-R* criteria.[18] Diagnosis was determined by a consensus committee including the neurologist, neuropsychologist, and the nurse who evaluated each participant shielded from prior diagnosis.

Inclusion criterion for the present analyses was normal cognitive function at first MRI/MRS examination, which was judged according to the published criteria from normative data.[17] Subjects who had a contraindication for MRI such as a pacemaker, or who were unable to participate in imaging studies because of severe illness, were excluded. Subjects were not excluded because of neurologic, psychiatric, or systemic illnesses to preserve the representativeness of the study sample as much as possible.

Neuropsychological testing. Memory was evaluated by free-recall retention scores computed after a 30-minute delay for the Wechsler Memory Scale–Revised Logical Memory and Visual Reproduction subtests and the Rey Auditory Verbal Learning Test. Language tests measured naming to confrontation (i.e., the Boston Naming Test) and category fluency (i.e., naming animals, fruits, and vegetables). The attention/executive measures included the Trail Making Test part B and the Wechsler Adult Intelligence Scale–Revised Digit Symbol subtest. Visual-spatial processing was examined using the Wechsler Adult Intelligence Scale–Revised Picture Completion and Block Design subtests. All tests were administered by experienced psychometrists and supervised by a clinical neuropsychologist (R.J.I.). All raw neuropsychological test scores were scaled such that they had a mean of 0.0

and a standard deviation of 1.0 among all MCSA full participants.[17] We obtained individual domain scores by averaging and scaling the tests within each domain. A global cognitive function standard score was derived by averaging and scaling the 4 standardized cognitive domain scores.

MRI and ¹H-MRS. All subjects underwent MRI and MRS examinations at 3-tesla using an 8-channel phased array coil (GE Healthcare, Waukesha, WI). A 3-dimensional, high-resolution magnetization-prepared rapid-acquisition gradient echo[19] was performed for hippocampal volume measurements. Hippocampal volume was measured with FreeSurfer software (version 4.5.0)[20] and was divided by subject's total intracranial volume (TIV) and multiplied by 100 to reflect the percent of TIV occupied by the hippocampus. A FLAIR sequence with repetition time/inversion time/echo time = 11,000/2,250/147 milliseconds, 256 × 192 matrix, 24-cm field of view, and 3-mm interleaved images of the whole head was performed to quantify WMH volume and for the assessment of brain infarcts. Brain infarcts were assessed by a trained image analyst (G.M.P.) and secondarily confirmed by a radiologist (K.K.) blinded to all clinical information. Subcortical infarcts included infarcts in the white matter (WM), deep gray matter nuclei, cerebellum, and brainstem not involving the hemispheric cortices. Cortical infarcts were ≥1 cm in largest diameter. Intra-rater reliability of this assessment is excellent (proportion in agreement 0.98 for cortical and 0.94 for subcortical infarcts).[13]

WMH on FLAIR images were segmented using an automated slice-based seed initialization and region-growing method as previously described.[21] WMH volumes were divided by the total WM volume in order to adjust for the differences in "WM-at-risk" across subjects and denoted by WMH/WM.

¹H-MRS was performed using a point-resolved spectroscopic sequence with repetition time/echo time = 2,000/30 milliseconds and an 8-cm³ (2 × 2 × 2 cm) voxel, prescribed on a midsagittal slice, including right and left posterior cingulate gyri and inferior precunei.[22] Metabolite intensities were quantified by referencing to an internal standard creatine (Cr).

Standard protocol approvals, registrations, and patient consents. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Board, and informed consent for participation was obtained from every subject.

Statistical analysis. We used Cox proportional hazards regression models to evaluate associations between MRI/MRS predictors and the hazard of progression from cognitively normal to MCI or dementia. As the distribution of WMH/WM was skewed, this measure was transformed to the natural logarithm scale for analysis. Because age is strongly associated with the risk of MCI, it was used as the time scale in these regression models when evaluating these relationships. Study participants were considered to be at risk of progression from normal cognition to MCI only for those ages at which they were under observation, through the application of the "period at risk" formulation of the Cox model. The initial age was taken to be the age at the baseline magnetic resonance visit. The censoring age for subjects who did not convert to MCI or dementia was the age when the subjects were last evaluated and found to be normal. The age at incident MCI was taken to be the age at the midpoint between the study visit when MCI was diagnosed and the prior visit when the participant was last classified as having normal cognition.

Quantitative imaging measures were entered into proportional hazards models as continuous variables, modeled as restricted cubic splines with knots at the 10th, 50th, and 90th percentiles. We report hazard ratios (HR_{IQR}) and corresponding 95% confidence intervals for hypothetical subjects whose imaging measures differ by

the interquartile range (IQR) of the imaging measure. These HRs compare the "unfavorable" with the "favorable" quartiles, depending on whether larger values of the imaging measure are associated with decreased (e.g., hippocampal volume) or increased (e.g., WMH/WM) hazards of incident MCI. Our use of HR_{IQR} is motivated by the desire to avoid strong functional assumptions for the predictors, and to facilitate comparisons across predictors. In addition to HRs, we illustrate the associations of interest by presenting Kaplan-Meier survival curves for groups defined by quartiles of the imaging features.

We performed an extensive number of sensitivity analyses to evaluate the validity of our conclusions. In particular, a) we tested the proportional hazards assumption required by the Cox models; b) we evaluated the sensitivity of our HR estimates to possible participation bias using inverse probability weighting based on associations between baseline features and participation in imaging studies; and c) we evaluated the sensitivity of our HR estimates to possible nonrandom censoring (possibly due to competing risks) using inverse probability weighting based on associations between baseline features and continued participation in the MCSA, where participation was defined conservatively as being no more than 3 months past due for a regularly scheduled follow-up visit or death.

In addition to the time-to-event analyses, we used restricted maximum likelihood linear mixed-effects models, which incorporated random subject-specific slopes and intercepts, to model longitudinal trends in a standardized composite "global z" cognitive score over time. Our models treated time from baseline magnetic resonance as the time scale and included terms for baseline age and baseline imaging measures, both modeled with restricted cubic splines as in our Cox models. Through the use of interaction terms, our models allowed a participant's baseline cognitive score and his or her rate of cognitive change to be associated with both baseline age and baseline imaging markers. We performed a likelihood ratio test to compare the fit of the full model with one omitting the imaging measure to assess whether the imaging measure was associated with global z in general. We summarize the association between the imaging measures and global z by reporting differences at baseline and differences in rate of change for the unfavorable vs favorable quartiles, fixing age at 79 years, its mean/median. All longitudinal and survival models included sex and education as adjustment variables.

RESULTS Baseline characteristics of the MCSA participants who had at least one clinical follow-up visit are listed in table 1. Demographic characteristics of cognitively normal subjects who underwent MRI/MRS were comparable to those of MCSA participants who did not undergo magnetic resonance examinations. However, MRI/MRS study participants had 1-year-longer median education and performed slightly better on cognitive tests than the nonparticipants, suggesting a minor nonparticipation bias. After a median (range) of progression-free follow-up of 2.8 (0.9–6.6) years, 234 participants were diagnosed with incident MCI and 9 participants were diagnosed with dementia. Because there were so few progressors to dementia, the results described for MCI include the 9 participants with incident dementia. The estimated incidence rate of progression to MCI was 6.1% per year (95% confidence interval = 5.3%–7.0%). The rate of progression to MCI was strongly associated with age (relative risk ratio for age 85 vs 75 years = 2.1; 95% confidence interval = 1.7–2.8). These rates are comparable to those reported in the entire MCSA.[23] The flow chart in figure 1 demonstrates the follow-up and outcomes in the MRI/MRS study participants and nonparticipants.

Proportional hazards models for each of the MRI/MRS variables indicate that lower hippocampal volume/TIV, %WMH, NAA/Cr, mI/Cr, and NAA/mI were predictors of the risk of progression to MCI using age as the time scale and adjusting for sex and education, and choline/Cr showed a similar trend. By contrast, neither subcortical infarcts nor cortical infarcts were significantly associated with the risk of MCI in univariate modeling adjusted for sex and education (figure 2A).

Although decreased NAA/Cr and NAA/mI and elevated mI/Cr ratios were associated with the risk of MCI, we only included NAA/mI ratio in multivariable modeling and excluded NAA/Cr and mI/Cr because of the colinearity with NAA/mI. Proportional hazards multivariable modeling showed independent effects of hippocampal volume/TIV and NAA/mI ratios as

Table 1	Demographic characteristics and MRI/MRS findings among MCSA subjects with at least one follow-up visit	
Characteristic[a]	MRI/MRS study participants	MRI/MRS study nonparticipants
No. of subjects	1,156	749
Female sex, n (%)	562 (49)	378 (50)
Age, y	79 (74, 83)[a]	80 (75, 84)
Education, y	14 (12, 16)[a]	13 (12, 16)
APOE ε4 carrier, n (%)	290 (25)	186 (25)
Short Test of Mental Status score	35 (33, 36)[a]	34 (32, 36)
CDR Sum of Boxes score	0 (0, 0)[a]	0 (0, 0)
Cognitive domain scores		
Global	0.5 (−0.1, 1.1)[a]	0.2 (−0.5, 0.8)
Memory	0.6 (−0.1, 1.2)[a]	0.2 (−0.5, 0.8)
Attention	0.5 (−0.1, 1.0)[a]	0.2 (−0.4, 0.7)
Visual spatial	0.4 (−0.2, 1.0)[a]	0.0 (−0.6, 0.7)
%Hippocampal volume/TIV	0.49 (0.45, 0.53)	
%WMH	0.019 (0.012, 0.033)	
NAA/Cr	1.67 (1.59, 1.75)	
mI/Cr	0.51 (0.47, 0.55)	
Cho/Cr	0.64 (0.60, 0.68)	
NAA/mI	3.20 (2.96, 3.62)	
Subcortical infarcts, n (%)	229 (20)	
Cortical infarcts, n (%)	72 (6)	
Any infarct, n (%)	269 (23)	

Abbreviations: CDR = Clinical Dementia Rating; Cho = choline; Cr = creatine; MCSA = Mayo Clinic Study of Aging; mI = myo-inositol; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; TIV = total intracranial volume; WMH = white matter hyperintensity. Unless otherwise noted, values shown are median (interquartile range).
[a] $p < 0.001$ on Wilcoxon rank sum tests.
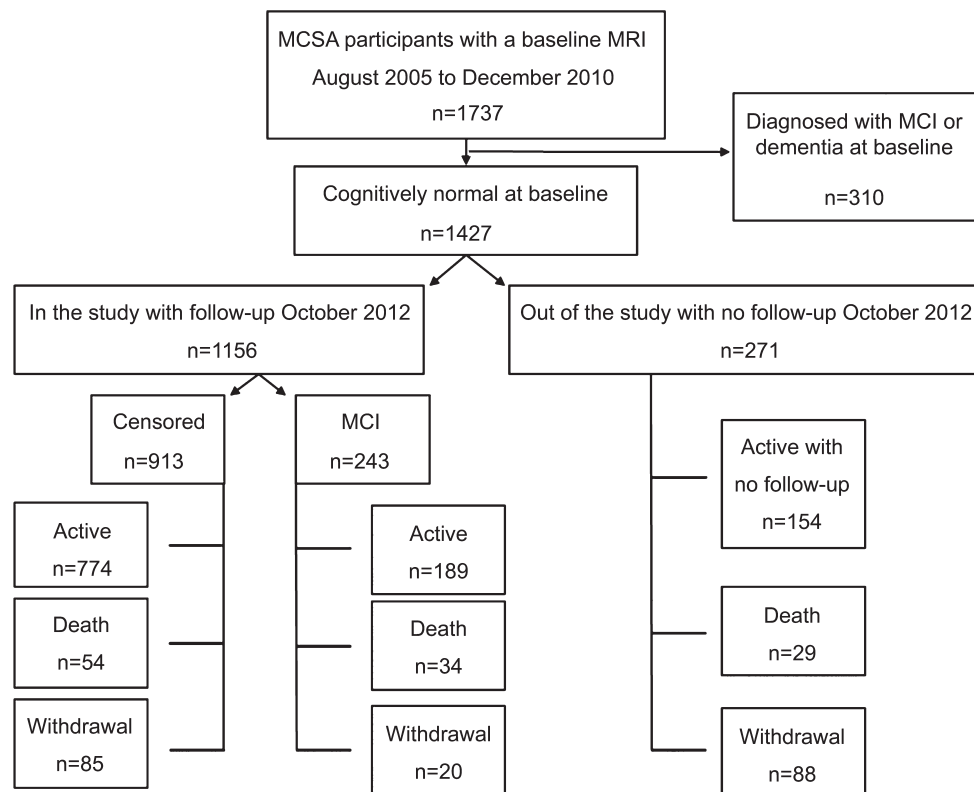
We followed 1,156 subjects and observed 243 events (21%). Of the remaining 913 "nonevents," 657 of 1,156 (57%) were censored in that by October 2012 they were not known to be dead and not more than 3 months overdue for their next scheduled follow-up visit. The remaining 256 of 1,156 (22%) were considered dropouts in that they died before follow-up (70/1,156, 6%) or were more than 3 months overdue for their visit (186/1,156, 16%). MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging.

the only independent predictors of MCI risk using age as the time scale (figure 2B). The joint effects of the 2 independent magnetic resonance predictors are demonstrated with survival curves comparing 3 groups as defined by the quartiles in figure 3.

MRI/MRS variables that were found to be associated with the risk of MCI were also associated with decline in global cognitive function (z scores) in linear mixed-effects models (table 2). Hippocampal volume/TIV, %WMH, NAA/Cr, mI/Cr, and NAA/mI at baseline were predictors of cognitive decline. In addition, we found an association between the presence of any infarct (cortical or subcortical) and cognitive decline.

Overall, we found no evidence of participation bias and competing risk influence on our findings. Although table 1 indicates statistically significant differences between imaging participants and nonparticipants, our HRs changed little when we performed inverse probability testing. When performing inverse probability of censoring weighting, we found that older ages and lower levels of education were associated with increased odds of withdrawing from the study, and to some extent, lower cognitive performance was associated with increased odds of withdrawing. However, our HRs did not differ

in the model that inversely weighted participants by their probability of withdrawing from the study.

DISCUSSION In a population-based sample of cognitively normal older adults, MRI and MRS markers of neurodegeneration and WMH were significant predictors of progression to MCI and cognitive decline. Among these markers, only hippocampal atrophy on MRI and low NAA/mI on MRS independently predicted increased risk of MCI in multivariable modeling. Although infarcts were associated with greater decline in global cognitive function, they did not increase the risk of MCI during the median follow-up period of 2.8 years.

Single-voxel MRS is a molecular imaging modality providing an array of information on neuronal integrity, glial activity, and membrane turnover from a region of interest during a 6-minute scan. We chose to study the posterior cingulate gyrus voxel because of greater metabolite measurement reliability and higher sensitivity to early AD pathology compared with other regions of the brain, including the hippocampus.[24] We found that low levels of the neuronal integrity marker NAA and high levels of the glial metabolite mI increased the

Univariable models   **Multivariable model**

	HR (95% CI)		HR (95% CI)
Hippocampal volume / TIV	2.0 (1.6, 2.5)		1.8 (1.4, 2.2)
WMH / WM	1.4 (1.1, 1.7)		1.2 (1.0, 1.5)
NAA / Cr	1.4 (1.2, 1.6)		
mI / Cr	1.3 (1.1, 1.5)		
Cho / Cr	1.2 (1.0, 1.3)		1.0 (0.8, 1.1)
NAA / mI	1.5 (1.2, 1.7)		1.4 (1.1, 1.7)
Subcortical infarcts	1.1 (0.8, 1.5)		
Cortical infarcts	1.2 (0.7, 2.0)		
Any infarcts	1.1 (0.8, 1.4)		0.9 (0.7, 1.2)

Hazard ratio and 95% CI   Hazard ratio and 95% CI
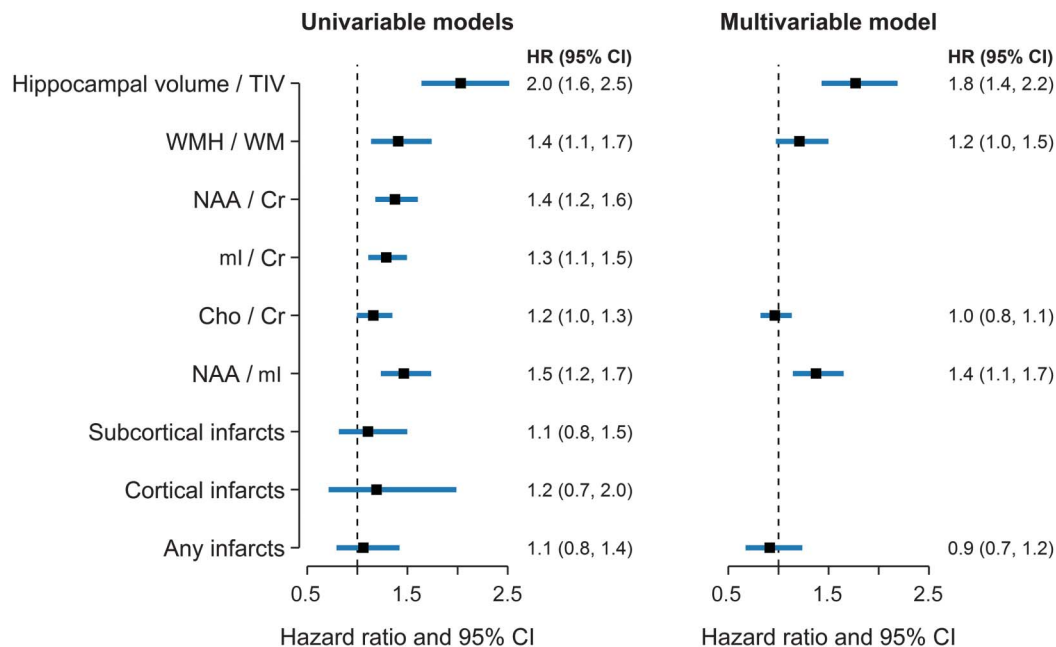
Hazard ratios for continuous predictors represent an interquartile difference (HR$_{IQR}$, described in the Methods section) to aid interpretation and facilitate comparisons across variables. Cho = choline; CI = confidence interval; Cr = creatine; mI = *myo*-inositol; NAA = *N*-acetylaspartate; TIV = total intracranial volume; WM = white matter; WMH = white matter hyperintensity volume.

Figure 3 Survival curves based on tertile groups for hippocampal volume/TIV and NAA/mI
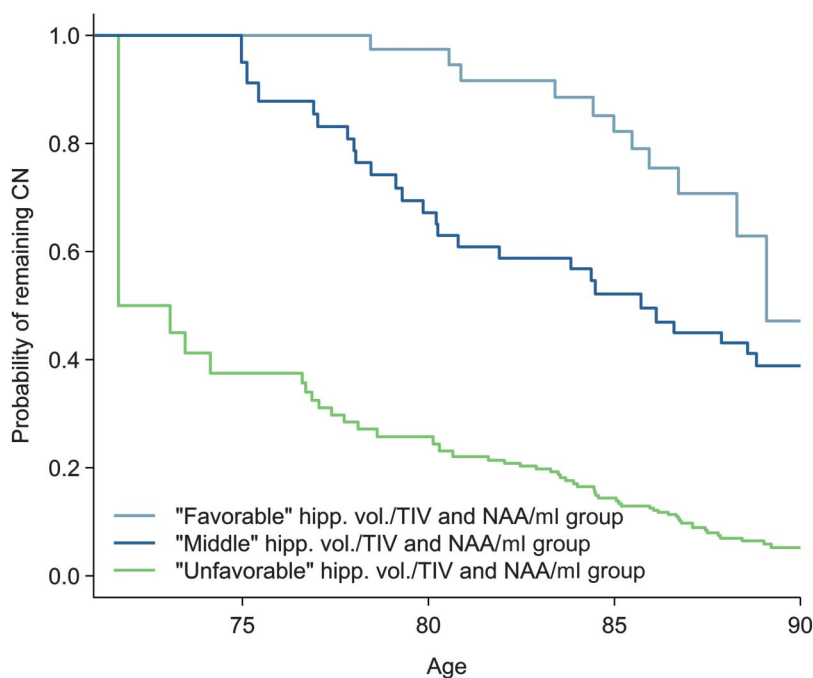
Curves illustrate the estimated probability of remaining cognitively normal (CN), assuming normal cognition at age 70 years. The light blue line corresponds to subjects in the favorable or higher hippocampal volume/TIV and NAA/mI. The dark blue line corresponds to subjects in the middle hippocampal volume/TIV and NAA/mI. The light green line corresponds to subjects in the unfavorable or low hippocampal volume/TIV and NAA/mI. hipp. vol. = hippocampal volume; mI = *myo*-inositol; NAA = *N*-acetylaspartate; TIV = total intracranial volume.

risk for MCI. We combined NAA and mI as NAA/mI ratio because previously among all MRS measures, low antemortem NAA/mI was the strongest predictor of intermediate- and high-likelihood AD at autopsy,[6] and showed the greatest decline in patients with AD compared with the cognitively normal controls.[25] For these reasons and to avoid multicollinearity, only NAA/mI ratio was included in the multivariable modeling to detect independent predictors of MCI risk.

Hippocampal atrophy on MRI is a sensitive marker for the neurodegenerative pathology associated with AD.[5] Hippocampal atrophy is included as one of the imaging markers of neurodegeneration in the National Institute on Aging–Alzheimer's Association criteria for preclinical AD.[26] We recently operationalized these criteria in the MCSA cognitively normal participants.[27,28] An exception, however, is patients with the hippocampal-sparing subtype of AD, which was identified in up to 11% of a pathologically confirmed AD cohort.[29] As expected, patients with the hippocampal-sparing subtype of AD have relatively preserved hippocampal volumes on MRI.[30] However, there is evidence from patients with posterior cortical atrophy that the posterior cingulate gyrus NAA/mI is decreased in these individuals with AD pathology and normal hippocampal volumes.[31] Thus, MRS may have added value in detecting the preclinical neurodegenerative involvement in cases of atypical AD pathology. Current study participants with

	Univariable model		Multivariable model	
	Baseline difference[b]	Rate difference[c]	Baseline difference[b]	Rate difference[c]
Hippocampal volume/TIV[d]	−0.19 ± 0.05	−0.04 ± 0.01	−0.14 ± 0.05	−0.03 ± 0.01
WMH/WM[d]	−0.11 ± 0.05	−0.03 ± 0.01	−0.04 ± 0.05	−0.02 ± 0.01
NAA/Cr[d]	−0.04 ± 0.04	−0.02 ± 0.01	—	—
Cho/Cr[e]	−0.11 ± 0.04	0.00 ± 0.01	−0.11 ± 0.04	0.00 ± 0.01
mI/Cr	−0.11 ± 0.04	0.00 ± 0.01	—	—
NAA/mI[d]	−0.14 ± 0.05	−0.01 ± 0.01	−0.09 ± 0.05	−0.01 ± 0.01
Cortical infarct	−0.09 ± 0.14	−0.05 ± 0.04	—	—
Subcortical infarct[f]	−0.16 ± 0.08	−0.03 ± 0.02	—	—
Any infarct[e]	−0.16 ± 0.08	−0.04 ± 0.02	−0.09 ± 0.05	−0.01 ± 0.01

Abbreviations: Cho = choline; Cr = creatine; mI = *myo*-inositol; NAA = *N*-acetylaspartate; TIV = total intracranial volume; WM = white matter; WMH = WM hyperintensity.
[a] Values shown represent an estimate ± standard error for the difference in baseline cognition or rate of cognitive decline comparing subjects with an "unfavorable" vs "favorable" imaging value assuming age set at 79 years, the mean/median.
[b] Difference at baseline in mean global z scores for a subject with unfavorable vs favorable quartiles, or present vs absent infarctions. Negative values indicate lower mean z scores among those at the unfavorable level.
[c] Defined as the difference in annual change in mean global z scores for a subject with unfavorable vs favorable quartiles, or present vs absent infarctions. Negative values indicate greater declines in mean z scores among those at the unfavorable level.
[d] $p < 0.01$, [e] $p < 0.05$, [f] $p < 0.10$, likelihood ratio test of overall association between imaging measure and global z.

preserved hippocampal volumes but low NAA/mI ratios who progressed to MCI may have atypical AD, a non-AD degenerative pathology, or cerebrovascular pathology.

In this population-based sample of cognitively normal older adults, MRI markers of small-vessel disease, such as WMH and infarcts, were modestly associated with cognitive decline or MCI. WMH was associated with the risk of MCI, and infarcts were associated with decline in cognitive function, although the decline in cognitive function in those with infarcts was not sufficient to increase the risk of MCI during the median follow-up time of 2.8 years. Findings on WMH and infarcts in the current study are consistent with the findings from community-based cohorts of similar size[7,11,32,33] and other cohorts of cognitively normal elderly persons or those without dementia.[8–10] Interestingly, in multivariable modeling including hippocampal volumes and MRS metabolites, WMH did not independently increase the risk of MCI. NAA levels are decreased in vascular dementia, even in cortical regions remote from the infarction.[34–36] With the additional information gained from elevated glial metabolite mI, it is possible that NAA/mI ratio on MRS has a higher sensitivity in detecting cellular and molecular changes associated with small-vessel disease than WMH load. This hypothesis needs to be tested in an autopsy-confirmed sample.

Contrary to findings in WMH, we did not find an association between infarcts and the risk of MCI. One explanation is that people with infarcts that affect cognition are often diagnosed with MCI immediately after the infarction and therefore are not included in the current study on cognitively normal participants. Higher prevalence of stroke in MCI compared with cognitively normal participants in the MCSA further supports this hypothesis.[37] It also is possible that the risk of cognitive decline or MCI in cognitively normal participants with infarcts will increase with longer follow-up and subsequent infarcts affecting cognition, as demonstrated previously.[7,38] Another reason, however, may be nonparticipation bias. Although all MCSA participants were offered MRI/MRS examinations, only 61% of the sample with a follow-up visit participated in the MRI/MRS study. The remaining 39% were either not willing to participate or could not participate in imaging studies because of medical reasons such as having a pacemaker or poor general health (e.g., participants with poststroke disabilities). However, participation-weighted analysis indicated that participation bias did not change our findings.

Using a standard vendor-provided acquisition protocol and software for the analysis of the MRS data, we demonstrated that MRS can contribute to the assessment of preclinical dementia–related abnormalities by capturing neurodegenerative changes not reflected by hippocampal atrophy. MRS metabolite abnormalities in the posterior cingulate gyrus are not currently included among the MRI and ^{18}F-fluorodeoxyglucose (FDG)-PET markers of neurodegeneration in preclinical staging of AD. However, in the current study, we demonstrate that both hippocampal atrophy and

reduced NAA/mI can be valuable markers of early neurodegeneration and that together these quantitative magnetic resonance markers may improve the detection of preclinical dementia–related pathology. Although we have not used MRS in our operationalization of the National Institute on Aging–Alzheimer's Association preclinical AD criteria,[27,28] MRS should be included in future investigations. If MRS and FDG-PET, for example, had substantial overlap, a magnetic resonance examination alone might suffice for assessment of risk. A better understanding of the pathologic basis of MRS metabolite abnormalities in aging and dementia would further increase the impact of MRS as a biomarker in neurodegenerative diseases.

AUTHOR CONTRIBUTIONS

STUDY FUNDING

DISCLOSURE

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