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Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the Framingham Offspring Study

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Abstract

INTRODUCTION—We examined associations between magnetic resonance imaging (MRI) markers of cerebrovascular disease and neurodegeneration with mild cognitive impairment (MCI) diagnosis at baseline and conversion from normal cognition to MCI at follow-up.

METHODS—Framingham Offspring participants underwent brain MRI and neuropsychological assessment at baseline (n=1,049) and follow-up (n=561). Participants were classified at baseline and at follow-up as cognitively normal or MCI using sensitive neuropsychological criteria. White matter hyperintensity (WMH) volume, covert brain infarcts, hippocampal volume, and total cerebral brain volume were quantified.

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RESULTS—Baseline measures of WMH and hippocampal volume were associated with MCI status cross-sectionally and also with conversion from normal cognition to MCI at 6.5-year follow-up. Annualized change rates in total cerebral brain volume and hippocampal volume were associated with conversion from normal cognition to MCI to follow-up.

DISCUSSION—Baseline WMH and hippocampal volume are markers that are both associated with conversion from normal cognition to MCI, highlighting the role of both vascular lesions and neurodegeneration in MCI.

Keywords

Mild cognitive impairment; MCI; MRI; Volumetric MRI; White matter hyperintensity; Hippocampal volume

INTRODUCTION

Mild cognitive impairment (MCI) was conceived to represent a transitional state between normal aging and Alzheimer's disease (AD).[1] MCI—even the amnestic subtype—has been shown to be pathologically heterogeneous and often involve co-existing cerebrovascular and neurodegenerative pathologies.[2] In addition to established involvement of medial temporal neurodegeneration in MCI,[3] mounting evidence suggests that cerebrovascular changes associated with small-vessel disease play an important role in risk and clinical expression of MCI and AD.[4–7] Small vessel cerebrovascular disease, as reflected by white matter hyperintensities (WMH) (i.e., areas of increased signal on T2-weighted magnetic resonance imaging [MRI]), and reduced hippocampal volume have both been associated with decreased cognitive functioning in MCI[8,9] and with faster rates of cognitive decline in MCI.[5] Less is known about how MRI biomarkers of neurodegeneration and cerebrovascular disease are associated with later conversion from normal cognition to MCI, particularly in community-based cohorts.

There is no consensus on one set of diagnostic criteria for MCI, leading to varying definitional schemes and prevalence rates.[10] Many studies have relied on one impaired score (e.g., delayed free recall on story memory) to define impairment; however, reliance on a single neuropsychological test as a marker of impairment is problematic given that a single impaired score within a cognitive battery is common in neurologically normal adults.[11] Research has emerged suggesting that actuarial neuropsychological criteria utilizing comprehensive neuropsychological protocols to assess a wide range of cognitive abilities beyond memory improves diagnostic rigor.[12] Our previous work using actuarial criteria to diagnosis MCI suggest that two impaired scores, defined as <1 SD below normative expectations, within a cognitive domain[10] bolsters associations between MCI status and biomarkers while decreasing false positive errors compared with more conventional approaches.[12]

In the current study, we examined associations of MRI markers of cerebrovascular disease (WMH volume, covert brain infarcts) and neurodegeneration (hippocampal volume, total cerebral volume) with MCI diagnosis using actuarial neuropsychological criteria in the Framingham Offspring Cohort. In addition, we examined the extent to which baseline MRI

markers are associated with conversion to MCI and the degree to which change in MRI markers from baseline to follow-up is associated with conversion to MCI. Given the well-established involvement of medial temporal lobe structures in MCI and AD, we expected that hippocampal volume would be associated with MCI status. Considering growing evidence of the role of small-vessel cerebrovascular disease in MCI and AD[5,13], we additionally hypothesized that WMH volume would also be associated with conversion to MCI.

METHODS

Participants

The Framingham Heart Study (FHS) is a community-based, prospective study initiated in 1948 to identify cardiovascular disease risk factors. Participants in the current study were members of the Offspring Cohort, which includes biological children of the original FHS cohort and offspring spouses (n=5,124) who have undergone health examinations approximately every 4 years since 1971. The present analysis is based on the 3,539 participants who attended the 7th Offspring examination. As part of an ancillary study, participants were invited to undergo neuropsychological assessment and brain MRI (1999–2005). 2,551 participants who attended the 7th examination also underwent neuropsychological assessment. As MCI prevalence is low in younger adults, we restricted our sample to the 1,422 participants aged ≥60 years at the time of neuropsychological testing. Of these, 1,215 participants also completed a MRI scan contemporaneously with the 7th examination cycle. We excluded participants with prevalent dementia (n=14), prevalent stroke (n=28), or incomplete neuropsychological data (n=111), resulting in a final sample size of 1,049 for cross-sectional analysis (supplementary figure 1).

For longitudinal analysis, we included the 813 participants from the cross-sectional analysis who were free of MCI at baseline. Of these, 665 participants underwent a repeat neuropsychological test contemporaneously (within 1 year before and 5 years after) with the 8th Framingham Offspring examination cycle (2005–2008). We excluded participants due to prevalent dementia (n=14), stroke (n=13), and other neurological conditions (n=9) at follow-up neuropsychological testing, and incomplete neuropsychological data (n=68), resulting in a final sample size of 561 participants for longitudinal analysis (supplementary figure 2).

The protocol was approved by the Institutional Review Board of Boston University Medical Center. All participants provided written informed consent.

Neuropsychological Assessment

Standardized neuropsychological tests were administered at baseline and follow-up. Based on the administered battery, there were three cognitive domains in which there were at least two tests in that domain, which is necessary for MCI classification as described below and as previously published in this sample.[14] *Memory* was assessed with Wechsler Memory Scale (WMS) Logical Memory delayed recall and recognition and Visual Reproduction delayed recall and recognition. *Executive Functioning/Attention/Processing Speed* was measured by Trail Making Tests A and B. *Language* was assessed with the Boston Naming

Test and Similarities from the Wechsler Adult Intelligence Scale. Neuropsychological tests scores were regressed onto age and education within gender. Residuals from these regressions were standardized to have a mean of zero and a standard deviation of one using z-score transformations.

MCI Classification

Participants were classified as normal or MCI according to comprehensive neuropsychological criteria that operationalizes impairment as performance falling greater than one standard deviation below normative expectations on at least two measures within a cognitive domain.[10] Participants were classified as *Amnestic* MCI when memory was impaired and *Non-Amnestic* MCI when non-memory domain(s) was impaired.

Neuroimaging

MRI methods have been described in detail.[15–17] Briefly, participants were imaged on a 1 or 1.5 Tesla Siemens Magnetom MRI scanner (see supplementary methods online). Three-dimensional T1 and double echo proton density and T2 coronal images were acquired in 4-mm contiguous slices. Images were analyzed with semi-automated segmentation methods that have been previously described.[16] Manual tracing was performed to determine total intracranial volumes. Hippocampal and cerebral volumes were determined using automated procedures described below.

Hippocampal volume was computed using a standard atlas based diffeomorphic approach[18] with label refinement modifications. Harmonized hippocampal masks developed through the European Alzheimer's Disease Consortium (EADC) and Alzheimer's Disease Neuroimaging Initiative (ADNI) Working Group on the Harmonized Protocol for Manual Hippocampal Segmentation were used with the following procedures: 1) pre-processing with extraction of intracranial cavity, non-uniformity correction, and tissue classification;[19] 2) atlas registration of EADC-ADNI hippocampal masks;[20] 3) atlas fusion utilizing Multi-Atlas Label Fusion;[21] and 4) intensity-based label refinement.

To segment WMH from other brain tissues, the first and second echo images from T2 sequences were summed and a log-normal distribution was fitted to the summed data (after removal of CSF and correction of image intensity non-uniformities).[22] A segmentation threshold for WMH of 3.5 SD in voxel intensity greater than the mean of the fitted distribution of brain parenchyma was applied.[17] Brain infarcts were defined as areas of abnormal signal intensity in a vascular distribution; 3mm or larger in size; with a CSF density on the subtraction image (proton density minus T2 image); and for lesions in the basal ganglia, distinct separation from the circle of Willis vessels.[16,23]

Statistical Analyses

Descriptive statistics were calculated using means and SDs, medians and interquartile ranges, and frequency counts and percent. Continuous MRI measures were standardized to a mean of zero and a SD of one to facilitate comparisons between measures. Natural log transformation was used to improve distribution normality of WMH volume. MRI variables were examined as both continuous and ordinal variables. Ordinal variables were examined

given the possibility of nonlinear relationships between MRI variables and cognitive status/cognitive outcome. For total cerebral brain volume and hippocampal volume, those in the bottom quartile (with the smallest total cerebral brain volume and the smallest hippocampal volume, respectively) were compared with those from the top three quartiles. For WMH volume, those in the top quartile (with the greatest WMH volume) were compared with those from the three bottom quartiles. Covert brain infarcts were categorized as present or absent. Annualized change in MRI brain measures was calculated as the difference between the raw MRI volumes from baseline to follow-up, divided by the follow-up period in years.

Logistic regression models examined associations between MRI brain measures and presence of MCI at baseline and follow-up. Logistic regression was used rather than survival analysis given there were two time points for the MRI and neuropsychological data. Our primary models were adjusted for age at MRI, years between MRI and neuropsychological testing, education group (<high school degree, high school degree, some college, ≥college degree), APOE ε4 status (carrier versus noncarrier), vascular risk factors (systolic blood pressure, hypertension treatment, diabetes, current smoking, history of cardiovascular disease and history of atrial fibrillation), and all other MRI variables. All models that examined annualized change in MRI measures adjusted for the same variables as the logistic regression analyses for baseline MRI variables described above and additionally adjusted for baseline MRI measures. We additionally constructed models adjusted for demographics only and adjusted for demographics, APOE ε4 status, and vascular risk factors (presented in the online supplement). Overall, results from these models were similar to results from fully adjusted models presented in our primary analysis. In addition, analyses were conducted assessing whether there was an interaction between WMH volume and hippocampal volume on presence of MCI or conversion from normal cognition to MCI. Secondary analyses were performed restricting the MCI group to only those with amnestic MCI. In addition, brain MRI were acquired using different MRI machine types that included differences in field strength (i.e., 1 Tesla and 1.5 Tesla) and analyses were performed to assess the potential confounding effects of these differences on MRI quantification. All analyses were performed with Statistical Analyses System software version 9.4 (SAS Institute, Cary, NC). A p-value of <0.05 was considered statistically significant.

RESULTS

Participant characteristics

Participant characteristics are presented in Table 1. At baseline, 22.5% of participants were classified as MCI (17.4% amnestic MCI, 5.1% non-amnestic MCI). Longitudinal analyses, which included those participants who were free of MCI at baseline, demonstrated that at follow-up (average 6.5 years after baseline) 13.5% of participants had new onset MCI (9.8% amnestic MCI, 3.7% non-amnestic MCI).

Cross-sectional associations of MRI markers with MCI

Table 2 presents cross-sectional associations between each MRI brain measure and MCI status at baseline adjusting for demographic variables, APOE ε4 status, vascular risk factors, and all other MRI measures. Being in the top quartile for WMH volume was associated with

48% higher odds of MCI at baseline (OR=1.48, 95% CI:1.03–2.12, p-value=0.03). When the MCI group was restricted to those with amnestic MCI, the odds ratio remained similar to that observed for any MCI but the statistical significance was attenuated (p-value=0.05). When WMH volume was examined as a continuous variable, there were trends toward greater WMH volume being associated with higher odds of MCI (p-values ranged from 0.09 to 0.12).

Being in the bottom quartile of hippocampal volume was associated with 58% higher odds of MCI (OR=1.58, 95% CI:1.12–2.24, p-value=0.01) and 80% higher odds of MCI when the MCI group was restricted to those with amnestic MCI (OR=1.80, 95% CI:1.23–2.64, p-value=0.002). Similarly, when examined continuously, lower hippocampal volume was significantly associated with higher odds of MCI. Neither total cerebral brain volume (continuously or as quartiles) nor presence of covert brain infarcts were associated with the presence of MCI at baseline. There was no interaction between WMH volume and hippocampal volume on presence of MCI at baseline (p=0.99).

Longitudinal associations of baseline MRI markers with conversion to MCI at follow-up

Table 3 shows the association between baseline MRI and conversion from normal cognition to MCI at follow-up adjusting for demographic variables, APOE ε4 status, vascular risk factors, and all other MRI measures. Higher WMH volume (being in the top quartile) at baseline was associated with higher odds of conversion to MCI (OR=2.04, 95% CI:1.09–3.79, p-value=0.03). When the MCI group was restricted to those with amnestic MCI, findings were no longer statistically significant. When examined as a continuous variable, baseline WMH volume was not associated with conversion to MCI at follow-up. Being in the bottom quartile of hippocampal volume was associated with higher odds of MCI (OR=2.13, 95% CI:1.14–3.96, p-value=0.02) and findings remained similar then the MCI group was restricted to those with amnestic MCI only (OR=2.60, 95% CI:1.29–5.23, p-value=0.007). Similarly, when examined continuously, lower hippocampal volume was significantly associated with higher odds of MCI. Results remained similar when the MCI group was restricted to those individuals with amnestic MCI. Total cerebral brain volume (either continuously or as quartiles) and presence of brain infarcts were not associated with conversion from normal cognition to MCI at follow-up. There was no significant interaction between WMH volume and hippocampal volume on conversion to MCI at follow-up (p=0.06).

Longitudinal associations of change in MRI markers between baseline and follow-up with conversion to MCI at follow-up

Table 4 presents longitudinal associations between annualized change in MRI brain measures between baseline and follow-up and conversion to MCI adjusting for age at MRI, years between baseline MRI and follow-up neuropsychological testing, education group, APOE ε4 status, vascular risk, baseline MRI measures, and all other MRI measures. Change in total cerebral brain volume, both continuously and as quartiles, was significantly associated with conversion from normal cognition to MCI although findings were attenuated when the MCI group was restricted to those with amnestic MCI. Change in continuous hippocampal volume was associated with conversion to MCI when the MCI group was

restricted to those with amnestic MCI (OR=0.68, 95% CI:0.48–0.96, p-value=0.03). There were no significant associations between conversion from normal cognition to MCI and annualized change in hippocampal volume as quartiles or WMH volumes (continuously or as quartiles). The interaction between change in WMH volume and hippocampal volume on conversion to MCI at follow-up was not significant (p=0.88).

Analyses to Examine Potential Bias across MRI Scanners and Field Strengths

Brain MRI were acquired using different MRI machine types that included differences in field strength (1 Tesla versus 1.5 Tesla). To assess the potential confounding effects of these differences on MRI quantification, MRI machine, operating system and field strength were added to age and gender estimates as predictors of the quantitative MRI measures included in this study for all Framingham subjects studied during the period of observation of this study. Adjusting for the multiple comparisons across regions, no significant effects of MRI machine, operating system or field strength was found.

DISCUSSION

We found that baseline WMH and hippocampal volume were associated with presence of MCI at baseline and associated with conversion from normal cognition to MCI at follow-up. Annualized change from baseline to follow-up in total cerebral brain and hippocampal volumes, but not WMH volume, was associated with conversion to MCI. This pattern of findings raises the possibility that both cerebrovascular and neurodegenerative changes play prominent roles prior to the development of frank cognitive impairment whereas neurodegeneration may continue to play a larger role more proximal to conversion to MCI. This pattern of findings is consistent with models and data indicating that cerebrovascular changes, including WMH, play an important early role in individuals at risk for dementia[5,24] as well as neuropathological data suggesting that AD-related neurodegeneration initially occurs in MTL structures and progresses to more global involvement over time.[3] Future studies with additional time points are necessary to more fully examine this possibility.

Although we found that baseline WMH volume was associated with baseline MCI status and conversion from normal cognition to MCI at follow-up, we did not find associations between increased WMH volume over time and higher odds of conversion to MCI. This contrasts with other studies which have found that increased progression of WMH volume is associated with conversion to MCI.[25,26] Compared to the current study, participants in these previous studies were older at baseline (mean age in 80s versus 60s), the follow-up period was longer, and baseline WMH volume was higher. Differences in cohort characteristics and study design may explain discrepancies in findings. Nonetheless, findings from these previous studies and the current study provide support for the notion that WMH volume may be useful in determining those at risk for later cognitive impairment and may inform treatment strategies that would be useful prior to dementia onset.

In the current study, the effect of WMH was somewhat reduced when treating this variable continuously rather than categorically suggesting the presence of a nonlinear relationship whereby increased risk of MCI was particularly evident when comparing those in the highest quartile of WMH volume compared to all other participants. This observation is

consistent with other studies, including previous research from the FHS, indicating that extensive WMH volume in particular may relate to decreased cognitive functioning.[27] In addition, for cross-sectional and longitudinal models the effect of WMH was attenuated when the analyses where restricted to amnestic MCI whereas hippocampal volume was significantly associated with MCI status in the whole sample as well as when the MCI sample was restricted to amnestic MCI. This pattern of findings may relate to reduced power. Amnestic and non-amnestic MCI have been linked to different underlying etiologies although it should be noted that amnestic MCI is not specific to a pre-AD condition and vascular disease has been associated with memory impairment. Findings related to WMH have been mixed with some studies demonstrating that non-amnestic MCI subgroups have greater WMH volume relative to MCI subgroups characterized by memory deficits[6] whereas other studies have found that amnestic MCI subgroups show greater WMH burden relative to non-amnestic MCI.[28] Other studies have provided evidence for a threshold effect whereby small-vessel cerebrovascular disease may induce specific patterns of cognitive impairment.[7] Given the small number of participants characterized as non-amnestic MCI, we did not conduct separate analyses for this subtype.

Although MCI is associated with greater vascular risk burden[29] and small-vessel cerebrovascular disease,[6,30] prevailing models of AD pathogenesis[31] and proposed research biomarkers of MCI[32] do not yet formally integrate either MRI evidence of cerebrovascular disease or cerebrovascular risk factors in their models or conceptualizations. Although there are no widely accepted criteria for determining biomarker positivity for cerebrovascular disease, there is a need to develop such methodologies. A metric has recently been proposed to identify participants with cerebrovascular imaging abnormalities based on a combination of infarcts and WMH burden in the context of absence or presence of amyloid elevation.[33] Further research is needed to clarify the link between small-vessel cerebrovascular disease and MCI, particularly in light of evidence that vascular changes may precede neuronal dysfunction and may initiate and exacerbate neurodegeneration.[24,34] Our work has shown that small-vessel cerebrovascular disease increases AD risk,[13] relates to heterogeneity among MCI phenotypic subgroups,[6,28] predicts disease course in prodromal dementia,[5] and is more reliably associated with markers of neurodegeneration than are measures of Aβ.[35] Whether or not WMH represents a pathogenic factor of AD per se, it is clear that small-vessel cerebrovascular disease is an important component of the clinical expression of the disease, which has implications not only for models of AD pathophysiology and diagnostic criteria but also for treatment.[13] Given that traditional vascular risk factors are known risk factors for the development of WMH pathology, aggressive efforts to prevent and manage these risk factors may reduce risk for MCI and AD.

We excluded individuals with clinical stroke, suggesting that even subclinical cerebrovascular changes play an important role in the expression and evolution of MCI. The notion is in line with our previous work showing that, in a sample of autopsy-confirmed AD patients, the presence of mild cerebrovascular changes was associated with less severe AD pathology yet there were no differences in severity of cognitive impairment between the AD patients with and without evidence of cerebrovascular disease.[36] These findings raise the possibility that cerebrovascular pathology contributes to overall severity of cognitive

impairment, even in patients with autopsy-confirmed AD and relatively mild cerebrovascular disease.[36]

The lack of consensus for defining MCI may contribute to uncertainty regarding the optimal biomarkers for prodromal AD. Our previous work showing that actuarial clinical diagnostic decision-making using a full range of neuropsychological test measures provides more nuanced MCI distinctions and leads to tighter associations with respect to biomarkers related to cognitive impairment as well as progression to dementia.[37] In the current study, we applied rigorous actuarial MCI criteria and MCI conversion was associated with MRI markers of small vessel cerebrovascular disease, providing further support for the involvement of WMH in MCI.

Strengths of the current study include the large, well-characterized, community-based sample; prospective study design; and ongoing follow-up for several years. The present findings extend previous FHS results showing associations of WMH volume with decreased cognitive performance[27] and incident MCI[38] by incorporating rigorous actuarial neuropsychological criteria for MCI, excluding those with history of clinical stroke or dementia, examining longitudinal change in MRI volume, and including MRI markers of neurodegeneration (i.e., hippocampal volume). We found that baseline measures of both WMH volume and hippocampal volume contributed to new onset MCI.

There are limitations to the present findings. We assessed two MRI markers of cerebrovascular changes and neurodegeneration each and did not examine additional markers that may relate to MCI (e.g., microinfarcts, tau, cortical thickness). A recent multimodal study suggested that the influence of WMH volume on cognition may be mediated by clinically covert processes, such as microinfarcts.[39] In addition, hippocampal volume has been associated with non-neurodegenerative pathologies including subcortical cerebrovascular disease.[40] Future research integrating additional markers of neurodegeneration such as AD-related patterns of cortical thickness may be more specific to neurodegeneration than hippocampal volume alone. Notably, participants included in the longitudinal study sample were younger, had completed more education, and had lower vascular risk burden than those who were not included in the longitudinal sample and who were also free of MCI at baseline (Table s1). Despite heterogeneity in cognitive characterization, our sample was generally well-educated, medically healthy, and had relatively low WMH burden, which may have attenuated our ability to detect group differences. The magnitude of effects of our findings may have differed in a sample with greater vascular risk, use of a T2-weighted fluid attenuated inversion recovery (FLAIR) to quantify WMH, and a more heterogeneous group of MCI participants that did not include predominantly amnestic MCI. For instance, we found trends toward associations between the presence of covert brain infarcts and MCI at baseline as well as conversion from normal cognition to MCI at follow-up. These associations may have been statistically significant in a cohort with greater burden of cerebrovascular disease.

Despite these limitations, in the search for reliable biomarkers of MCI and dementia risk, in addition to assessment of medial temporal lobe volume and neurodegeneration, consideration of WMH may prove useful. The combination of white matter markers with

additional biomarkers (e.g., CSF amyloid, hippocampal volume) as well as consideration of MCI clinical subtypes (e.g., amnestic, non-amnestic) may more completely inform the AD and cerebrovascular contributions to the dementia prodrome. In summary, our results show that small-vessel cerebrovascular disease increases risk for MCI, a known risk factor for subsequent transition to dementia. Our findings suggest that hippocampal atrophy and WMHs are useful biomarkers associated with conversion to MCI. Our findings extend earlier results highlighting the association between WMH and risk of AD to conversion from normal cognition to MCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant characteristics

	Cross-Sectional Study Sample[a] (N=1049)	Longitudinal Study Sample[b] (N=561)
Continuous characteristics, mean (SD)		
Age at baseline MRI (years)	68.6 (5.7)	67.8 (5.4)
Systolic blood pressure (mm Hg)	131 (19)	129 (18)
Continuous characteristics, median (25^{th}, 75^{th} percentile)		
Days between baseline MRI and baseline neuropsychological assessment	0.0 (0.0, 0.0)	—
Years between baseline MRI and follow-up neuropsychological assessment	—	6.5 (6.0, 6.9)
Days between follow-up MRI and follow-up neuropsychological assessment	—	0.0 (0.0, 0.0)
Years between baseline MRI and follow-up MRI	—	6.5 (5.9, 6.9)
Categorical characteristics, n (%)		
Women	556 (53.0)	306 (54.6)
Education Group		
<High school degree	43 (4.1)	15 (2.7)
High school degree	336 (32.0)	173 (30.8)
Some college	322 (30.7)	171 (30.5)
≥College degree	348 (33.2)	202 (36.0)
APOE ε4 allele	225 (21.9)	120 (21.8)
Diabetes	144 (14.0)	57 (10.3)
Current smoker	84 (8.0)	32 (5.7)
Hypertension treatment	422 (40.2)	199 (35.5)
History of cardiovascular disease	152 (14.5)	65 (11.6)
History of atrial fibrillation	52 (5.0)	19 (3.4)
Any MCI diagnosis at baseline	236 (22.5)	0 (0.00)
Amnestic MCI	183 (17.4)	0 (0.00)
Non-Amnestic MCI	53 (5.1)	0 (0.00)
Any MCI diagnosis at follow-up	—	72 (12.8)
Amnestic MCI	—	52 (72.2)
Non-Amnestic MCI	—	20 (27.8)
MRI measures at baseline, median (25^{th} percentile, 75^{th} percentile)		
Total cranial volume (cm^3)	1239 (1148, 1332)	1239 (1151, 1337)
Total cerebral brain volume (%)	78.3 (76.2, 80.4)	78.7 (76.8, 80.6)
White matter hyperintensities volume (%)	0.067 (0.036, 0.13)	0.060 (0.035, 0.11)
Hippocampal volume (%)	0.53 (0.49, 0.56)	0.53 (0.50, 0.56)
Covert brain infarct (present), n (%)	133 (12.7)	61 (10.9)
Annualized change in MRI measures between baseline and follow-up, median (25^{th} percentile, 75^{th} percentile)		

	Cross-Sectional Study Sample[a] (N=1049)	**Longitudinal Study Sample[b] (N=561)**
Total cerebral brain volume (cm^3/year)	—	−7.02 (−9.53, −4.24)
White matter hyperintensities volume (cm^3/year)	—	0.15 (0.052, 0.33)
Hippocampal volume (cm^3/year)	—	−0.010 (−0.035, 0.013)

[a] Cross-sectional analysis includes participants who have MRI and neuropsychological data at baseline.

[b] Longitudinal analysis includes participants who were free of MCI at baseline and had neuropsychological data available at follow-up.

Note that MRI variables expressed as percent are normalized by total intracranial volume to correct for head size.

Table 2

Cross-sectional association between baseline MRI brain measures and presence of MCI (N=1049)

Baseline MRI Measure	Classification	MCI Outcome (versus no MCI)			
		Any MCI (N=236)		Amnestic MCI (N=183)	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Total cerebral brain volume (%)	Continuous (Per SD increment)[a]	1.04 (0.86–1.26)	0.68	1.13 (0.92–1.40)	0.24
	Q1 vs Q234	1.07 (0.73–1.59)	0.72	0.83 (0.53–1.30)	0.41
Ln white matter hyperintensities volume (%)	Continuous (Per SD increment)[a]	1.14 (0.97–1.35)	0.12	1.17 (0.97–1.42)	0.09
	Q4 vs Q123	**1.48 (1.03–2.12)**	**0.03**	1.49 (0.99–2.23)	0.05
Hippocampal volume (%)	Continuous (Per SD increment)[a]	**0.79 (0.67–0.94)**	**0.007**	**0.72 (0.60–0.86)**	**0.0005**
	Q1 vs Q234	**1.58 (1.12–2.24)**	**0.01**	**1.80 (1.23–2.64)**	**0.002**
Covert brain infarct	Present vs Absent	1.46 (0.95–2.23)	0.08	1.55 (0.97–2.47)	0.06

All models are adjusted for age at MRI, sex, days between baseline MRI and baseline neuropsychological assessment, education group (<high school degree, high school degree, some college, ≥college degree), APOE ε4 status (carrier versus noncarrier) vascular risk factors (systolic blood pressure, hypertension treatment, diabetes, smoking, history of cardiovascular disease, history of atrial fibrillation), and all of the other MRI measures (continuous) listed in the table.

[a]Standard deviation increment calculated using the entire sample.

Note that MRI variables expressed as percent are normalized by total intracranial volume to correct for head size.

Statistically significant findings ($p < 0.05$) appear in bold font.

Table 3

Association between baseline MRI brain measures and presence of MCI at follow-up (N=561).

Baseline MRI Measure	Classification	MCI Outcome (versus no MCI)			
		Any MCI (N=72)		Amnestic MCI (N=52)	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Total cerebral brain volume (%)	Continuous (Per SD increment)[a]	1.20 (0.85–1.70)	0.31	1.24 (0.83–1.87)	0.30
	Q1 vs Q234	1.16 (0.60–2.26)	0.66	1.15 (0.53–2.51)	0.73
Ln white matter hyperintensities volume (%)	Continuous (Per SD increment) [a]	1.20 (0.89–1.61)	0.23	1.14 (0.81–1.61)	0.46
	Q4 vs Q123	**2.04 (1.09–3.79)**	**0.03**	1.73 (0.83–3.63)	0.14
Hippocampal volume (%)	Continuous (Per SD increment)[a]	**0.62 (0.46–0.85)**	**0.003**	**0.58 (0.41–0.83)**	**0.003**
	Q1 vs Q234	**2.13 (1.14–3.96)**	**0.02**	**2.60 (1.29–5.23)**	**0.007**
Covert brain infarct	Present vs Absent	0.39 (0.14–1.08)	0.07	0.24 (0.05–1.06)	0.06

Models are adjusted for age at MRI, sex, years between MRI and neuropsychological assessment, education group (<high school degree, high school degree, some college, ≥college degree), APOE ε4 status (carrier versus noncarrier), vascular risk factors (systolic blood pressure, hypertension treatment, diabetes, smoking, history of cardiovascular disease, history of atrial fibrillation), and all other MRI measures (continuous) listed in the table.

[a]Standard deviation increment calculated using the entire sample.

Note that MRI variables expressed as percent are normalized by total intracranial volume to correct for head size.

Statistically significant findings ($p < 0.05$) appear in bold font.

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2019 January 01.

Table 4

Association between annualized change in MRI brain measures between baseline and follow-up and presence of MCI at follow-up (N=491).

Annualized change in MRI Measure between Baseline and Follow-up	Classification	MCI Outcome (versus no MCI)			
		Any MCI (N=56)		Amnestic MCI (N=42)	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Total cerebral brain volume (cm^3/year)	Continuous (Per SD increment)[a]	**0.64 (0.46–0.88)**	**0.007**	0.73 (0.52–1.03)	0.07
	Q1 vs Q234	**3.03 (1.50–6.10)**	**0.002**	**2.69 (1.20–5.99)**	**0.02**
Ln white matter hyperintensities volume (cm^3/year)	Continuous (Per SD increment)[a]	0.94 (0.69–1.27)	0.69	0.92 (0.67–1.28)	0.63
	Q4 vs Q123	1.33 (0.67–2.65)	0.42	1.17 (0.54–2.53)	0.70
Hippocampal volume (cm^3/year)	Continuous (Per SD increment)[a]	0.77 (0.56–1.04)	0.09	**0.68 (0.48–0.96)**	**0.03**
	Q1 vs Q234	1.31 (0.66–2.60)	0.44	1.64 (0.77–3.49)	0.20

Models are adjusted for age at MRI, sex, years between baseline MRI and follow-up neuropsychological assessment, education group (<high school degree, high school degree, some college, ≥college degree), APOE ε4 status (carrier versus noncarrier), vascular risk factors (systolic blood pressure, hypertension treatment, diabetes, smoking, history of cardiovascular disease, history of atrial fibrillation), baseline brain MRI volume, and the other MRI measures (continuous) listed in the table.

[a]Standard deviation increment calculated using the entire sample

Note: Annualized change in MRI brain measures was calculated as the difference between the raw MRI volumes from baseline to follow-up, divided by the follow-up period (in years). Individuals with MCI at baseline are excluded from the analysis. In addition, 70 participants from the longitudinal study sample did not complete a follow-up MRI and thus were not included in the analysis of annualized change in MRI measures.