

Longitudinal Changes in White Matter Disease and Cognition in the First Year of the Alzheimer Disease Neuroimaging Initiative

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Objective: To evaluate relationships between magnetic resonance imaging (MRI)-based measures of white matter hyperintensities (WMHs), measured at baseline and longitudinally, and 1-year cognitive decline using a large convenience sample in a clinical trial design with a relatively mild profile of cardiovascular risk factors.

Design: Convenience sample in a clinical trial design.

Subjects: A total of 804 participants in the Alzheimer Disease Neuroimaging Initiative who received MRI scans, cognitive testing, and clinical evaluations at baseline, 6-month follow-up, and 12-month follow-up visits. For each scan, WMHs were detected automatically on coregistered sets of T1, proton density, and T2 MRI images using a validated method. Mixed-effects regression models evaluated relationships between risk factors for WMHs, WMH volume, and change in outcome measures including Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and Clinical Dementia Rating Scale sum of boxes scores. Covariates in these models included race, sex, years

of education, age, apolipoprotein E genotype, baseline clinical diagnosis (cognitively normal, mild cognitive impairment, or Alzheimer disease), cardiovascular risk score, and MRI-based hippocampal and brain volumes.

Results: Higher baseline WMH volume was associated with greater subsequent 1-year increase in ADAS-Cog and decrease in MMSE scores. Greater WMH volume at follow-up was associated with greater ADAS-Cog and lower MMSE scores at follow-up. Higher baseline age and cardiovascular risk score and more impaired baseline clinical diagnosis were associated with higher baseline WMH volume.

Conclusions: White matter hyperintensity volume predicts 1-year cognitive decline in a relatively healthy convenience sample that was similar to clinical trial samples, and therefore should be considered as a covariate of interest at baseline and longitudinally in future AD treatment trials.

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A complete listing of ADNI investigators is available at <http://adni.loni.ucla.edu>.

AREAS OF ABNORMALLY HIGH signal in cerebral white matter on T2-weighted magnetic resonance images (MRI) are commonly found in elderly individuals. A large body of research suggests that these white matter hyperintensities (WMHs) may represent nonspecific markers of axonal injury, which accrues over the lifespan, and is exacerbated by cerebrovascular disease and late-life neurodegenerative diseases such as Alzheimer disease (AD).¹⁻⁴ Several cross-sectional studies have suggested that WMHs are associated with decreased cognitive performance in elderly persons and therefore may constitute a clinically useful marker of cognitive aging⁴⁻⁷ and clinically relevant cognitive decline.^{8,9} Therefore, there is need to understand the time course of WMH accrual in relation to cognitive decline, both

to understand the degree to which WMH changes precede, coincide with, or follow cognitive changes, and to understand whether risk factors may influence longitudinal changes in WMH, with possible cognitive consequences.

While a small number of epidemiological studies have measured longitudinal trajectories in WMH and cognition, they have generally focused on long-term changes that accumulate over several years. These studies suggest that the rate of WMH accrual may be higher in those with increased cardiovascular risks, may accelerate with advancing age, and may be associated with increased rate of cognitive decline.¹⁰⁻¹⁴ These studies typically include a long observation period with several years between evaluations. The long follow-up period is advantageous for robust measurement of longitudinal change but the infrequent fol-

Table 1. Demographic Characteristics

Characteristic	Total, Mean (SD)	Diagnosis at Baseline, Mean (SD)		
		Cognitively Normal	MCI	AD
Sample, No.	804	224	391	189
Measurements per subject, No.	2.7 (0.57)	2.8 (0.52)	2.7 (0.57)	2.6 (0.63)
Baseline age, y	76 (6.9)	76 (4.8)	75 (7.5)	76 (7.5)
CV risk	1.7 (1)	1.6 (1)	1.7 (1.1)	1.7 (1)
Education, y	16 (3.1)	16 (2.9)	16 (3.1)	15 (3.1)
Male, No. (%)	446 (59)	112 (52)	240 (65)	94 (53)
Race				
White	709	198	346	165
Other	95	26	45	24
APOE genotype, 2-2/2-3/2-4/3-3/3-4/4-4	2/52/18/354/290/88	2/31/3/132/51/5	0/16/11/164/153/47	0/5/4/58/86/36
MMSE baseline score	27 (2.7)	29 (1)	27 (1.8)	23 (2.1)
MMSE score change rate per y	-0.93 (3.1)	0.0029 (1.3)	-0.75 (2.8)	-2.4 (4.4)
ADAS-Cog baseline score	19 (9.2)	9.5 (4.3)	19 (6.3)	29 (7.7)
ADAS-Cog score change rate per y	1.8 (6.2)	-0.4 (3.9)	1.5 (5.8)	5.2 (7.5)
CDR sum at baseline	1.8 (1.8)	0.03 (0.12)	1.6 (0.89)	4.3 (1.7)
CDR sum change rate per y	0.7 (1.5)	0.12 (0.61)	0.66 (1.4)	1.5 (2.2)
WMH at baseline, cm ³	0.72 (1.4)	0.51 (1.1)	0.66 (1.2)	1.1 (2)
WMH change rate per y	0.2 (1.2)	0.082 (0.92)	0.24 (1.2)	0.24 (1.5)

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; CDR, Clinical Dementia Rating Scale sum of boxes; CV, cardiovascular; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities.

low-up limits inferences that can be drawn about relationships between short-term changes in cognition and WMH that may occur over several months. An understanding of these short-term changes may be especially important in clinical trials that assess the effect of treatments on late-life cognitive function and typically include an observation period of several months; WMH burden may influence cognitive endpoints and thus may be an important covariate to consider when assessing efficacy. In addition, measures of WMH change may be especially important in trials of therapies aimed at modifying the evolution of the WMHs themselves.

The goals of this study were to assess the significance of WMH as a predictor of cognitive change and the strength of association between longitudinally measured WMH and longitudinally measured cognition by measuring cognitive performance and WMH burden in a group of 804 individuals in a convenience sample that had a clinical trial design. Most participants were measured at 3 time points over the course of 1 year. The individuals were enrolled in the Alzheimer Disease Neuroimaging Initiative (ADNI) study, which was designed to mimic the salient characteristics of large-scale AD treatment trials, in particular, the precise measurement of short-term longitudinal change.

METHODS

SUBJECTS

Data were obtained from ADNI (www.loni.ucla.edu/ADNI), a 5-year study with a primary goal of testing whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Subjects were recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to

recruit 800 adults aged 55 to 90 including approximately 200 cognitively normal older individuals to be followed up for 3 years, 400 people with MCI to be followed up for 3 years, and 200 people with early AD to be followed up for 2 years.

This study includes data from 804 ADNI subjects who completed cognitive evaluations and MRI scans at their baseline visit; most subjects additionally completed cognitive evaluations and MRI scans at 6-month and 1-year follow-up visits. Summary data are shown in **Table 1**.

CLINICAL DIAGNOSIS AND COGNITIVE EVALUATION

The clinical assessment and cognitive testing of ADNI subjects followed a standardized protocol that was described previously.¹⁵ At each evaluation, participants underwent a standardized clinical evaluation and cognitive tests including the Mini-Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). Inclusion criteria for the cognitively normal group included MMSE scores between 24 and 30, a Clinical Dementia Rating Scale (CDR) sum of boxes score of 0, and no evidence of major depression, MCI, or dementia. Participants were included in the MCI group if they had a subjective memory concerns, objective memory loss measured by education-adjusted Wechsler Memory Scale–Revised Logical Memory II scores, a CDR sum of 0.5, absence of significant impairment in other cognitive domains, preserved activities of daily living, and absence of dementia. Participants with AD met the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association criteria for probable AD and had an MMSE score between 18 and 26 and a CDR sum of 0.5 to 1.0. Exclusion criteria included history of structural brain lesions or head trauma, significant neurological disease other than incipient Alzheimer disease, use of psychotropic medications that could affect memory, and a Hachinski Ischemic Scale score of 4 or greater. Findings on MRI that served as exclusionary criteria included major hemispheric infarction or structural abnormalities that severely distort brain anatomy such as tumor or prior resective surgery.

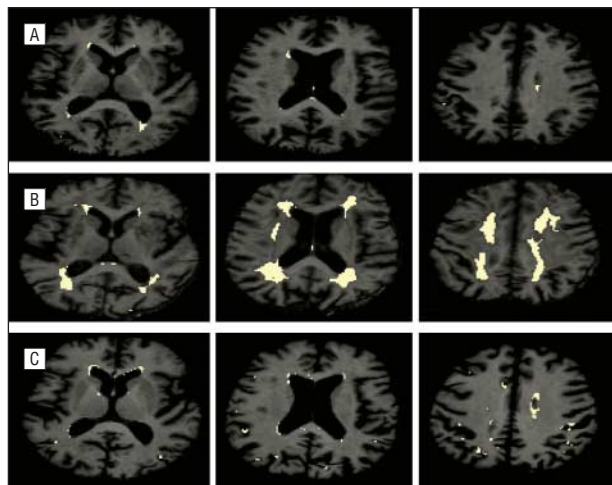


Figure 1. Example white matter hyperintensity (WMH) detection results for 3 individuals whose WMH distributions are representative of the broader sample. Detected WMHs are overlaid in white on slices of T1-weighted images. Each row shows a set of 3 slices for a given individual. Each column shows detection at an analogous slice across all 3 individuals. The 3 individuals differ in their WMH distribution: they possess very mild periventricular capping (A), pronounced periventricular caps and confluent WMHs (B), and punctate WMHs scattered throughout the brain (C).

A summary measure of cardiovascular risk on a scale from 0 to 5 was constructed for each individual by starting with 0 and adding 1 point for self-reported history of each of the following: hypertension, stroke, smoking, diabetes mellitus, and cardiovascular disease.

To reduce skew in the distributions of cognitive outcome measures, we transformed MMSE and CDR sum by taking the square root. The transformed measures and ADAS-Cog were converted to *z* scores prior to analysis.

IMAGE ACQUISITION METHODS

Acquisition of 1.5-T MRI data at each performance site followed a previously described standardized protocol that was rigorously validated across sites.¹⁶ The protocol included a high-resolution, T1-weighted sagittal volumetric magnetization prepared rapid gradient echo sequence and axial proton density (PD)/T2-weighted fast spin echo sequence. The ADNI MRI core optimized the acquisition parameters of these sequences for each make and model of scanner included in the study. Before being allowed to scan ADNI participants, all performance sites were required to pass a strict scanner validation test, including magnetization prepared rapid-gradient echo scans of human subjects and a spherical fluid-filled phantom. Additionally, each scan of ADNI participants included a scan of the phantom, which was required to pass strict validation tests. All vetted raw scan data were transferred to the University of California, Davis, Imaging of Dementia and Aging Laboratory (IDeA Laboratory) for analysis.

IMAGE ANALYSIS METHODS

White matter hyperintensities were detected on coregistered T1-, T2-, and PD-weighted images using an automated method described previously.¹⁷ Briefly, for each fast-spin echo scan, the PD and T2 images were linearly combined to form a “pseudo-T1,” which was rigidly aligned to the T1 scan from the same session. Nonbrain tissues were removed from the T1 scan, which was then nonlinearly warped to a minimum deformation template.^{18,19} Corresponding PD and T2 images were stripped of nonbrain tissues and moved to the space of the minimum de-

formation template based on the T1 alignment and warping parameters. Magnetic resonance imaging bias fields were estimated during minimum deformation template warp estimation for the T1 image and using an iterative statistical method for the PD and T2 images.²⁰ White matter hyperintensities were detected in minimum deformation template space at each voxel based on corresponding PD, T1, and T2 intensities there, the prior probability of WMH there, and the conditional probability of WMH there based on the presence of WMH at neighboring voxels. The resulting map of WMH voxels across the brain is summarized by an estimate of total WMH volume. White matter hyperintensity volumes estimated with this method agreed strongly with WMH volumes estimated from fluid-attenuated inversion recovery MRI in a large, diverse elderly sample.¹⁷ Example WMH detection results on 3 ADNI scans covering mild, confluent, and punctate WMH distributions are shown in **Figure 1**. To account for skew in the distribution of WMH volumes, we took the log of the WMH volume and converted it to a *z* score prior to analysis.

STATISTICAL ANALYSIS: MIXED EFFECTS REGRESSION

We used mixed-effects repeated-measures regression models to assess relationships between WMH, longitudinal change in cognitive measures, and risk factors for WMH and cognitive decline.²¹ This included 3 sets of models. First, to assess whether known risk factors for WMH accrual affected baseline WMH volume and WMH change, we modeled longitudinal change in WMH volume with baseline cardiovascular risk factors as predictors. Second, to assess the viability of baseline WMH volume as a risk factor for subsequent 1-year cognitive decline, we modeled changes in cognitive measures with baseline WMH and other baseline risk factors as predictors. Third, to determine whether cross-sectional relationships between baseline WMH volume and baseline cognitive function were also evident at follow-up visits, we modeled longitudinal measurements of the cognitive measures as a function of WMH volume measured at the same time point, along with other predictors. This analysis did not formally assess the association between change in cognition and change in WMH; instead, it determined whether cognition at a given time point was associated with WMH at the same time point. In each case, we modeled the mean trajectory of an outcome measure—WMH volume in the first model and cognitive measures in the other two—over time. These mean trajectories were modeled as linear trends, with the predicted initial level (intercept) and the rate of change (slope) allowed to vary with a set of predictors (fixed effects). In addition, our model allowed for people to have systematic differences, not accounted for by predictors, in the starting level of outcome measures (random effects).²² The WMH and cognitive trajectories did not include substantial enough interindividual variability in slopes to allow us to estimate a random effect parameter for slope in the models. Models were fitted using *nlme* in R 3.1.²³

We used a sequential model-building approach. We began with reference models of each outcome as a simple function of time; the reference models for cognitive change additionally included WMH as a covariate. We then added individual predictors to the reference model and used likelihood ratio tests to determine whether doing so added significant explanatory power. For any predictor whose likelihood ratio test was significant ($P < .05$), we used *F* tests to evaluate the fixed effects of the predictor on baseline and change rate. Any fixed effect whose *F* test passed a liberal significance threshold ($P < .25$) was entered into a final model to evaluate the independent fixed effects of all relevant predictors simultaneously.

The models considered race, sex, years of education, baseline age, apolipoprotein E genotype, baseline clinical diagnosis (cognitively normal, MCI, or AD), and baseline cardiovascular risk as possible predictors. These predictors were selected because they have been implicated repeatedly in the literature as risk factors for cognitive decline, and with the exception of apolipoprotein E, they are all readily available from data items that would be routinely collected during clinical evaluation. Apolipoprotein E was included because it is a common covariate, exclusion criterion, or stratification variable in AD clinical trials. Because sex was never a significant predictor in any model, we omitted it from the results. Because the ADNI was intentionally designed to approximately represent 3 strata of AD neuropathological burden across the 3 diagnostic categories, baseline clinical diagnosis was an important categorical indicator of overall AD-related neurodegeneration, giving us an approximate means to assess whether relationships between WMH and the cognitive measures may be independent of, or additional to, cognitive changes caused by AD-associated neurodegeneration.

Additional models added baseline hippocampal and brain volumes, the 2 most firmly established MRI markers of AD-associated neurodegeneration, as model covariates to more carefully address whether the relationships between WMHs and cognition may have been purely secondary to a primary relationship between AD-associated neurodegeneration and cognition. Because all 3 MRI measures are strongly correlated with clinical diagnosis, we removed clinical diagnosis from models in which trend-level, but nonsignificant, relationships were indicated between the MRI measures and cognitive measures. Baseline hippocampal and brain volumes were calculated using a modified version of the FreeSurfer automated software that was optimized by ADNI investigators for application to the aging brain.²⁴

RESULTS

DEMOGRAPHICS

A summary of the subject characteristics is shown in Table 1. The 3 baseline diagnostic groups were similar across numerous demographic variables. Predictably, the groups varied substantially in cognitive and functional baseline and change. Specifically, on average, individuals who had AD at baseline had poorer baseline cognitive performance and faster mean declines in performance compared with those who had MCI at baseline. Individuals who had MCI at baseline, in turn, had poorer baseline performance and steeper declines than individuals who were cognitively normal at baseline. Variability in cognitive baselines and rates of change were lowest in those who were cognitively normal at baseline, higher in those who had MCI at baseline, and higher still in those who had AD at baseline. In addition, the MCI and AD groups exhibited higher mean WMH volumes and greater 1-year increases in WMH volumes compared with persons who were cognitively normal at baseline. Variability in baseline WMH was similar among those who were cognitively normal at baseline and those with baseline MCI but it was higher among those with AD at baseline. Variability in rate of WMH change was lowest among those who were cognitively normal at baseline, higher among those who had MCI at baseline, and higher still among those who had AD at baseline.

BASELINE PREDICTORS OF LONGITUDINAL WMH CHANGE

Baseline age, cardiovascular risk score, and clinical diagnosis were strongly associated with baseline WMH volume (all $P < .003$). Each year of advancing age was associated with a 0.04-SD increase in baseline WMH; baseline diagnoses of MCI and AD were associated with 0.22- and 0.47-SD increases in baseline WMH. Each additional cardiovascular risk was associated with a 0.1-SD increase in baseline WMH. No associations between the various predictors and subsequent WMH change were statistically significant in the mixed effects model. Table 1 lists rates of WMH change across baseline diagnostic groups.

BASELINE WMH AS A PREDICTOR OF LONGITUDINAL COGNITION

Higher baseline WMH volume was strongly associated with lower baseline performance in tests of global cognition and function (ADAS-Cog and CDR sum; **Table 2**). Specifically, a 1-SD increase in baseline WMH was associated with higher baseline ADAS-Cog and CDR sum scores of 0.056 and 0.06, respectively. In addition, higher baseline WMH volume was associated with greater subsequent 1-year decreases in global cognition as measured by MMSE and ADAS-Cog (**Table 3**). Specifically, each 1-SD increase in baseline WMH was associated with an additional 0.096-SD decrease per year in MMSE and an additional 0.034-SD increase per year in ADAS-Cog. **Figure 2** and **Figure 3** plot the MMSE and ADAS-Cog measurements for 90 randomly selected participants, including 30 each among those who were cognitively normal at baseline, those who had MCI at baseline, and those who had AD at baseline. Also shown are the trajectories in those measurements that were predicted by the fitted mixed-effects model based solely on predictors measured at baseline. These Figures demonstrate the expected differences between groups: qualitatively, cognitively normal individuals appear to have better baseline performance and reduced rates of change compared with those with AD, and baseline and rate of change was intermediate among MCI (note the differences in scaling of the y-axis between cognitively normal individuals and those with MCI and AD). Additionally, the Figures suggest that the mixed effects models provided adequate fits to the cognitive trajectories, especially among MCI and AD groups. We note, however, that many of the cognitively normal individuals had highly nonlinear cognitive trajectories that were poorly approximated by our linear models. These nonlinearities may be due to the measurement characteristics of the cognitive instruments.

The relationships between WMH and cognition were not substantially modified when hippocampal and brain volumes were added to the models. In particular, baseline WMH ($P < .001$) and hippocampal volumes ($P = .01$) independently predicted longitudinal change in MMSE score in a model including baseline clinical diagnosis. All MRI variables had weak trend-level associations with change in ADAS-Cog score in a model that included base-

Table 2. Association of Baseline WMH With Baseline Cognition^a

Variable	MMSE		ADAS-Cog		CDR Sum	
	β	P Value	β	P Value	β	P Value
Baseline WMH	0.056	.02	0.06	<.001
Race
Education, y	0.021	.004
Baseline age, y
APOE	0.078	.04
CV risk
Baseline diagnosis
MCI	-0.531	<.001	0.831	<.001	1.321	<.001
AD	-1.487		1.757		2.244	

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; CV, cardiovascular; CDR Sum, Clinical Dementia Rating Scale sum of boxes; MCI, mild cognitive impairment; ellipses, fixed effects that were not statistically significant; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities.

^aSummary of the mixed effects models of cognitive change using baseline WMH volume and other predictors as fixed effects. Entries show the regression coefficient for the listed fixed effect followed by the associated P value for an F test on the marginal sum of squares. The fixed effect for baseline diagnosis had normal cognition as the reference group; the fixed effect for race had not white as the reference group. Regression coefficients represent the number of standard deviations' difference in the cognitive baseline that were associated with a 1-unit change in a predictor measured at baseline. Baseline WMH was log-transformed and converted to a z score prior to analysis.

Table 3. Association of Baseline WMH With Change in Cognition^a

Variable	MMSE		ADAS-Cog		CDR Sum	
	β	P Value	β	P Value	β	P Value
Baseline WMH	-0.096	<.001	0.034	.05
Race
Education	0.013	.01
Baseline age	0.008	.02	0.005	.02
APOE
CV Risk	0.033	.01
Baseline diagnosis	...	<.001	...	<.001	...	<.001
MCI	-0.147		0.137		0.109	
AD	-0.648		0.444		0.251	

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; CV, cardiovascular; CDR Sum, Clinical Dementia Rating Scale sum of boxes; MCI, mild cognitive impairment; ellipses, fixed effects that were not statistically significant; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities.

^aSummary of the mixed effects models of cognitive change using baseline WMH volume and other predictors as fixed effects. Entries show the regression coefficient for the listed fixed effect followed by the associated P value for an F test on the marginal sum of squares. The fixed effect for baseline diagnosis had normal cognition as the reference group; the fixed effect for race had not white as the reference group. Regression coefficients represent the number of standard deviations of change in the cognitive outcome per year that were associated with a 1-unit change in a predictor measured at baseline. Baseline WMH was log-transformed and converted to a z score prior to analysis.

line clinical diagnosis but when clinical diagnosis was removed, hippocampal ($P < .001$) and WMH volumes ($P = .03$) independently predicted ADAS-Cog score change.

RELATIONSHIP BETWEEN TIME-VARYING COGNITION AND TIME-VARYING WMH

Higher WMH volume was associated with lower global cognitive function at baseline and follow-up as measured by MMSE and ADAS-Cog scores (**Table 4**). Specifically, each standard deviation increase in WMH at a given time point was associated with an additional 0.1-SD lower MMSE score at that time point and 0.036-SD higher ADAS-Cog score at that time point. These relationships were not substantially modified by the inclusion of brain and hippocampal volumes. At baseline and follow-up, WMH volume ($P < .001$) and hippocampal volume ($P = .005$) were independently associated with lower

MMSE score, and higher brain volume showed a trend toward association with lower MMSE score ($P = .07$). Time-varying MRI variables were weakly associated with time-varying measurement of ADAS-Cog score in a model that included clinical diagnosis, and when clinical diagnosis was removed from the model, higher WMH volume ($P = .03$) and lower hippocampal volume ($P < .001$) at baseline and follow-up were both independently associated with higher ADAS-Cog score.

COMMENT

The key finding of this study is that, in a model that controlled for baseline age, apolipoprotein E genotype, clinical diagnosis, cardiovascular risks, and other relevant covariates, WMH volume at baseline was significantly associated with greater subsequent declines in global cog-

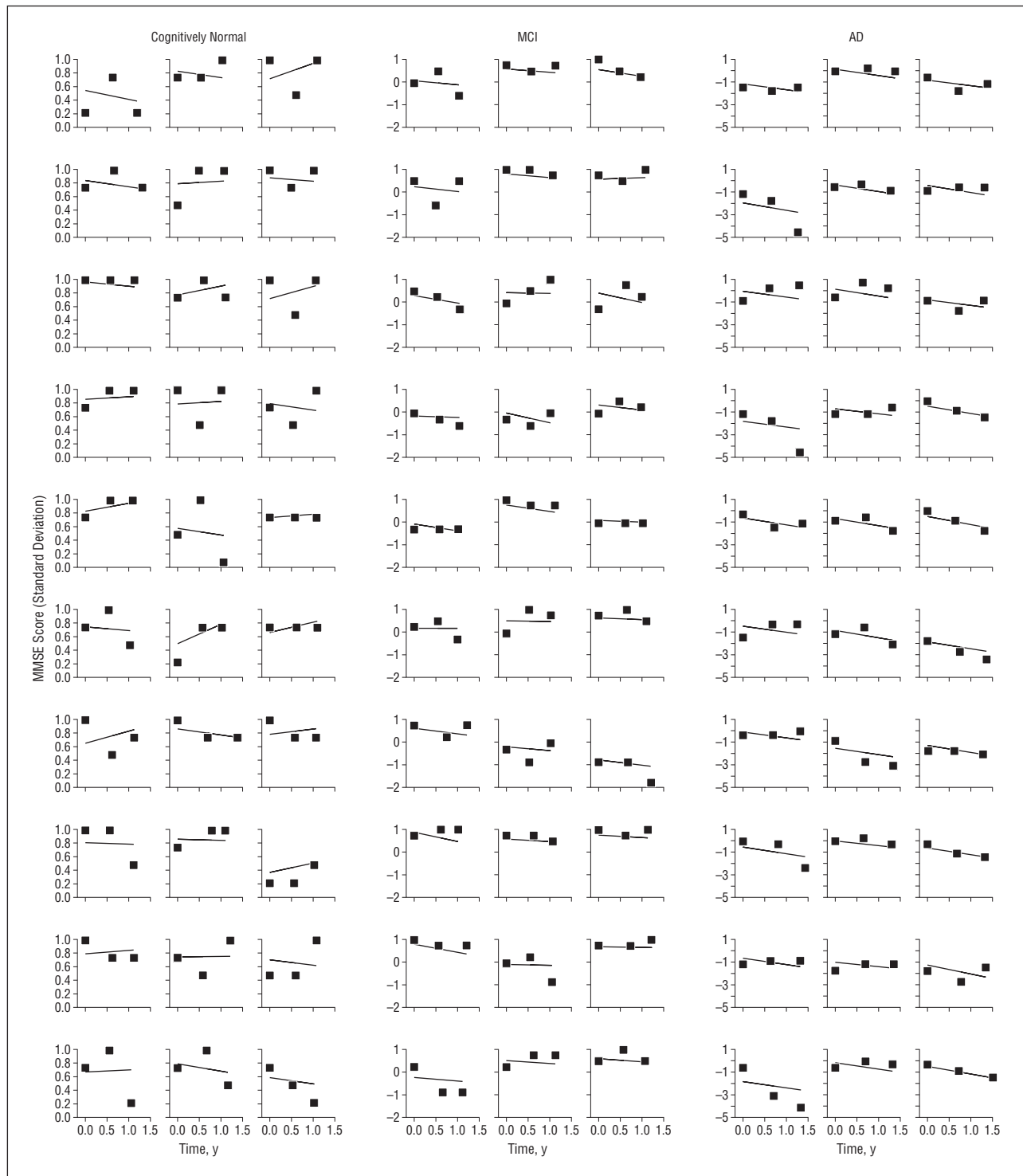


Figure 2. Mini-Mental State Examination (MMSE) trajectories by baseline diagnostic group. Longitudinal measurements of MMSE in 90 randomly selected subjects from the Alzheimer’s Disease Neuroimaging Initiative, including 30 each from groups that were cognitively normal at baseline (cognitively normal), had mild cognitive impairment (MCI) at baseline, and had Alzheimer disease (AD) at baseline, are shown as dots. Trajectories in these measurements predicted by the mixed effects statistical models are shown as lines. The models used factors measured at baseline to predict the baseline and slope of the trajectory. Note that the y-axes for the 3 subplots are scaled differently to account for broad differences in MMSE trajectory across groups.

nition over 1 year, as measured by MMSE and ADAS-Cog scores. These associations were independent of relationships between key MRI markers of AD and cognition. The finding is significant because it suggests that, even in a sample that was intentionally designed to mimic a clinical trial, with frequent evaluations, short-

term follow-up, and a relatively mild profile of cardiovascular risk, white matter disease may be an important predictor of subsequent short-term global cognitive change. In treatment trials in particular, WMH burden may be an especially important covariate to consider when assessing the effect of treatments on longitudinal

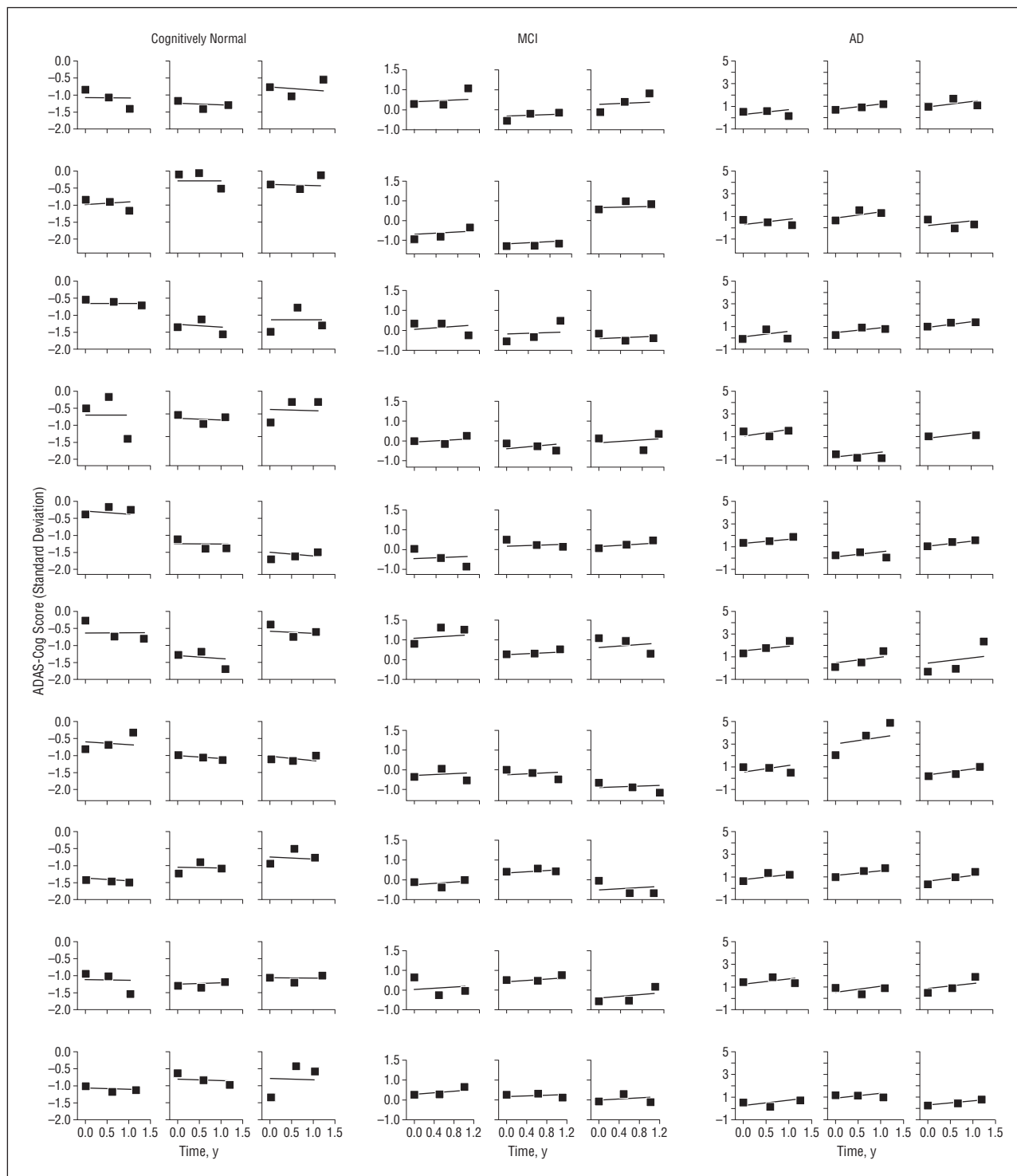


Figure 3. Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) trajectories by baseline diagnostic group. Longitudinal measurements of ADAS-Cog in 90 randomly selected subjects from the Alzheimer’s Disease Neuroimaging Initiative including 30 each from groups that were cognitively normal at baseline (cognitively normal), had mild cognitive impairment (MCI) at baseline, and had Alzheimer disease (AD) at baseline, are shown as dots. Trajectories in these measurements predicted by the mixed effects statistical models are shown as lines. The models used factors measured at baseline to predict the baseline and slope of the trajectory. Note that the y-axes for the 3 subplots are scaled differently to account for broad differences in ADAS-Cog trajectory across groups.

change in cognitive endpoints. While the associations between WMH and ADAS-Cog score may have been only marginally significant and the magnitude of WMH-associated cognitive change may be clinically small, we emphasize that the sensitivity of our measurements of WMH and cognitive change were limited by

the measurement properties of the cognitive instruments, short duration of follow-up, and high cardiovascular health of the participants. Therefore, we speculate that the true magnitude of WMH-associated cognitive changes may be even higher in this sample and in the broader population.

Table 4. Association Between Longitudinal WMH and Longitudinal Cognition^a

Variable	MMSE		ADAS-Cog		CDR Sum	
	β	<i>P</i> Value	β	<i>P</i> Value	β	<i>P</i> Value
WMH	-0.1	<.001	0.036	.05
Race
Education	0.012	.02
Baseline age	0.008	.03
<i>APOE</i>
CV risk	0.036	.005
Baseline diagnosis		<.001		<.001		<.001
MCI	-0.139		0.131		0.103	
AD	-0.634		0.435		0.242	

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; CV, cardiovascular; CDR Sum, Clinical Dementia Rating Scale sum of boxes; MCI, mild cognitive impairment; ellipses, fixed effects that were not entered into the final multivariate model because they failed significance tests earlier in the model-building process; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities.

^aSummary of the mixed effects models of longitudinal cognition using time-varying WMH volume and other covariates as fixed effects. Entries show the regression coefficient for the listed fixed effect, followed by the associated *P* value for an *F* test on the marginal sum of squares. The fixed effect for baseline diagnosis had normal cognition as the reference group; the effects of being MCI and AD are shown along with the *P* value for an omnibus *F* test. The WMH value was log-transformed and converted to a *z* score prior to analysis.

Additional findings agree strongly with prior epidemiological reports. In particular, greater WMH at baseline and follow-up were associated with decreased global cognition at baseline and follow-up¹⁴; higher baseline WMH was associated with lower baseline cognitive performance⁵⁻⁷; and higher baseline age, higher baseline cardiovascular risk score, and more impaired baseline clinical diagnosis were associated with higher baseline WMH.^{10,12} Each of these convergent findings strengthen the impression that, while the ADNI was designed to mimic a clinical trial in which participants presumably possessed relatively low levels of WMH, the sample appears similar in many ways to community-based samples in terms of determinants of WMH and its importance in influencing cognitive trajectories. Moreover, because WMH burden may influence cognitive outcomes, these findings support the notion that WMH burden may be an important covariate to consider when assessing treatment effects in the broader community where key factors associated with WMHs, including cardiovascular risks and clinically silent cerebrovascular disease, may be much more common.

The key strength of this study is data collection that follows AD clinical trial conventions: specifically, frequent, short-term evaluation of a large pool of highly educated, physically healthy elderly participants. Key prior studies generally included larger epidemiological cohorts evaluated every several years over a long follow-up interval.¹⁰⁻¹⁴ These have complementary strengths, including a longer interval to robustly measure longer-term longitudinal change over and greater generalizability to the broader population; however, in many studies the long interevaluation interval precluded acquisition of a sufficient number of measurements required for accurate characterization of change. The long follow-up intervals also precluded detection of cognitive or brain changes that often occur between evaluations. Because ADNI evaluated individuals every 6 months, we were able to extend prior findings to a clinical trial setting by showing that longitudinal relationships between risk factors, white matter disease, and cognition are detectable over

the short follow-up interval that is a fact of life in clinical trials.

The key limitation of the study was our use of traditional cognitive measures whose measurement properties inhibit our ability to robustly detect fine-grained changes in domain-specific cognitive function across a broad ability range. This type of instrument is used nearly universally in AD treatment trials and epidemiological studies but they nonetheless exhibit significant ceiling or floor effects and have measurement properties that decrease sensitivity to mild cognitive changes.²⁵ Composite measures developed using modern psychometric methods such as Rasch analysis or item response theory may provide higher-fidelity estimates of cognitive change.

This study is part of a broad effort to predict changes in late-life cognition and function using baseline information from imaging, biological samples, cognitive tests, and other sources. The role of this study is to suggest that MRI-based measures of WMH may have value as predictors of cognitive changes in this setting. Future study should build on these findings by assessing the predictive power of more anatomically-specific measures of WMH burden, which may be differentially associated with future cognitive decline in specific domains.¹

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