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# Association of white matter microstructural integrity with cognition and dementia

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ABSTRACT

Late-life measures of white matter (WM) microstructural integrity may predict cognitive status, cognitive decline, and incident mild cognitive impairment (MCI) or dementia. We considered participants of the Atherosclerosis Risk in Communities study who underwent cognitive assessment and neuroimaging in 2011–2013 and were followed through 2016–2017 (n = 1775 for analyses of prevalent MCI and dementia, baseline cognitive performance, and longitudinal cognitive change and n = 889 for analyses of incident MCI, dementia, or death). Cross-sectionally, both overall WM fractional anisotropy and overall WM mean diffusivity were strongly associated with baseline cognitive performance and risk of prevalent MCI or dementia. Longitudinally, greater overall WM mean diffusivity was associated with accelerated cognitive decline, as well as incident MCI, incident dementia, and mortality, but WM fractional anisotropy was not robustly associated with cognitive change or incident cognitive impairment. Both cross-sectional and longitudinal associations were attenuated after additionally adjusting for likely downstream pathologic changes. Increased WM mean diffusivity may provide an early indication of dementia pathogenesis.



## 1. Introduction

Diffusion tensor imaging (DTI) quantifies the microstructural integrity of white matter (WM) (Alexander et al., 2007). Commonly used DTI measures include fractional anisotropy (FA) and mean diffusivity (MD). FA measures the directional constraint of water diffusion, and MD measures the average rate of diffusion in any direction. As WM is generally anisotropic (i.e., the direction of diffusion is highly constrained), lower WM FA and higher WM MD are generally thought to reflect worse WM microstructural integrity.

DTI-based measures of WM microstructural integrity appear to provide an assessment of pathologic changes that precede and predict the development of white matter hyperintensities (WMHs) and WM loss(Ly et al., 2014; Maillard et al., 2011, 2013, 2014; Salat et al., 2005). Given this link and the recognized association of WMH and WM loss with cognition (Ikram et al., 2010; Prins and Scheltens, 2015; Stout et al., 1996), DTI-based measures of WM microstructural integrity may provide an early indication of future cognitive decline, cognitive impairment, and dementia. Despite heterogeneity in the specific findings across studies (Stebbins and Murphy, 2009), substantial cross-sectional evidence suggests a link between DTI-based measures and current cognitive status, (Bagepally et al., 2012; Charlton et al., 2006; Chua et al., 2008; Fellgiebel et al., 2004; Huang and Auchus, 2007; Huang et al., 2007; Kantarci et al., 2011, 2014; Medina et al., 2006; Naggara et al., 2006; Oishi et al., 2011; Sala et al., 2015; Stebbins and Murphy, 2009; Tuladhar

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et al., 2015; Ukmar et al., 2008; van Norden et al., 2012; Vernooij et al., 2009). However, few studies have considered whether WM microstructural integrity is associated with future cognition. Thus, the purpose of this study is to examine both the cross-sectional and longitudinal associations of late-life measures of WM microstructural integrity with cognition and dementia, using data from the Atherosclerosis Risk in Communities Study (ARIC).

## 2. Materials and methods

### 2.1. Study sample

The ARIC study is a longitudinal cohort study that recruited 15,792 persons in 1987–1989 (visit 1) aged 45–65 years from 4 U.S. communities: Forsyth County, NC; Washington County, MD; Minneapolis suburbs, MN; and Jackson, MS. At the fifth full-cohort study visit in 2011–2013 (ARIC Visit 5), the ARIC cohort added dementia ascertainment and an expanded cognitive test battery to the study protocol. In addition, a stratified random sample (stratified on cognitive status, prior substudy participation, age, and study site) of approximately 2000 ARIC participants were recruited into a brain MRI substudy as part of the ARIC Neurocognitive Study (ARIC-NCS). All living ARIC participants were subsequently invited to visit 6 in 2016–2017, which included dementia ascertainment and repeat administration of the expanded cognitive test battery from visit 5.

Our study sample includes all participants who completed the visit 5 ARIC-NCS MRI (n = 1951), excluding nonblack and nonwhite participants (n = 6) and black participants from MD or MN (n = 9) as the small numbers made meaningful adjustment for race/ethnicity including these participants untenable, persons disallowing use of genetic data (n = 11), and persons with documented stroke (n = 67), history of brain tumor, surgery or radiation to the head (n = 14), lacking valid DTI data (n = 8), missing data on primary covariates, or visit 5 cognitive data (n = 61). Thus, 1775 persons met our eligibility criteria for inclusion in our primary analyses of WM microstructural integrity with baseline cognitive status (normal, mild cognitive impairment (MCI), or dementia) as well as analyses of WM microstructural integrity and cognition, including associations with baseline cognition and cognitive change (Fig. 1). Primary analyses of the association between WM microstructural integrity and of incident cognitive impairment or mortality were additionally restricted to those who were cognitively normal at visit 5 and who we could categorize as having dementia, having MCI, cognitively normal, or deceased at the time of visit 6 in 2016–2017 (n = 889, Fig. 1).

### 2.2. Standard protocol approvals

The institutional review boards of all participating institutions approved this study, and participants provided written informed consent before participation.

### 2.3. Neuroimaging

Participants of the MRI substudy at visit 5/ARIC-NCS completed 3T brain MRI, including sagittal T1-weighted MPRAGE, axial T2 FLAIR, and axial DTI pulse sequences. Imaging and image analysis followed identical protocols across sites. The ARIC MRI Reading Center (Mayo Clinic, Rochester, MN) conducted all image analysis.

They used in-house algorithms to quantify WMH and estimated intracranial volume (Jack et al., 2014; Raz et al., 2013), which was used to normalize other volumetric measures as a covariate in our statistical analyses, and used FreeSurfer (version 5.1) to measure total brain volume and gray matter (GM) volumes including hippocampal volume and used an in-house atlas of lobar and deep WM regions, derived from the STAND400 template (Vemuri et al., 2008), intersected with GM and WM segmentation from the T1 and FLAIR scans, to define regions of interest (ROIs) for measuring WM FA and WM MD.

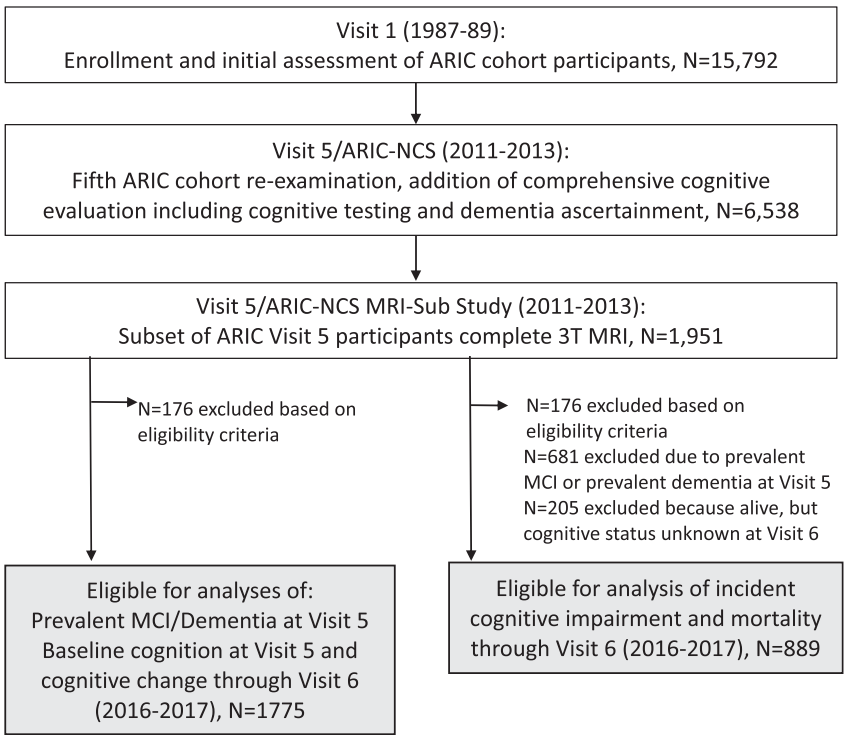


**Fig. 1.** ARIC data collection and analytical sample derivation. Abbreviation: ARIC, Atherosclerosis Risk in Communities; NCS, Neurocognitive Study; MCI, mild cognitive impairment.

The DTI scans had 1 diffusion unweighted volume (b = 0) followed by 64 volumes with diffusion weighting (b) = 1000 s/mm$^2$ in distinct directions evenly distributed over the whole sphere. The voxel size was 2.7 mm isotropic. Head motion and eddy current distortion were corrected using FSL's eddy_correct, and each subject's DTI scan was then deformably registered to their T1-weighted image using BrainSuite (Bhushan et al., 2015), which also corrects for susceptibility distortion and fits diffusion tensors to the data using a weighted least squares algorithm. The lobar and deep WM atlas was deformably registered to each subject's T1-weighted image using ANTS (Avants et al., 2014).

We averaged left and right WM FA and WM MD measures to calculate WM FA and WM MD in 6 ROIs (frontal lobe, temporal lobe, occipital lobe, parietal lobe, anterior corpus callosum, and posterior corpus callosum); we then took a weighted average of these 6 regions, with weights proportional to the number of voxels in each WM ROI, to calculate measures of overall WM FA and overall WM MD. Additional details of the neuroimaging protocol and image analysis are available elsewhere (Power et al., 2016, 2017).

### 2.4. Assessment of cognitive decline

All ARIC participants were asked to complete a cognitive battery of 11 neuropsychological tests at visits 5 and 6. Prior examination of the factor structure (Gross et al., 2015; Rawlings et al., 2016) indicates these tests broadly assess cognition in 3 domains: (1) memory, (2) language and verbal fluency, and (3) sustained attention/processing speed. Tests contributing to the memory domain include the Delayed Word Recall Test, Logical Memory Test, and a test of incidental learning. Tests contributing to the language and verbal fluency domain include the animal naming test, the Boston Naming Test, and a word fluency test. Tests contributing to the sustained attention and processing speed domain include the Trail Making Test, Parts A and B (TMT), the Digit-Symbol Substitution Test, and Digit Span Backwards Test. The overall cognitive function domain incorporated all tests used in the 3 subdomains, as well as the item-level data from the Mini–Mental State Examination (MMSE); note that information from the MMSE did not contribute to any of the domain-specific factor scores, as derived in the following.

Before computing factor scores to quantify domain-specific and overall cognitive function, we calculated standardized Z scores scaled to visit 5 by subtracting the visit 5 test mean from each participant's test score and dividing by the visit 5 test standard deviation (SD) for those tests with approximately Gaussian distributions (Logical Memory Test, animal naming test, Boston Naming Test, word fluency test, TMTA time, TMTB time, and Digit-Symbol Substitution Test). Both visit 5 and visit 6 scores were standardized to visit 5 to examine cognitive decline. TMTA and TMTB times were both skewed and were natural-log-transformed before standardizing. TMTB times additionally displayed a "spike" at the maximum time of TMTB = 240 seconds, which we handled with censored distribution methods as described in the following. Other tests were considered to be categorical variables (Delayed Word Recall Test, incidental learning, TMTA errors, TMTB errors, Digit Span Backwards Test) or binary (MMSE item-level responses). Missing test scores for participants who were unable to complete a test because of difficulty were assigned to the minimum observed test score, similar to previous ARIC work.

Factor analysis examines covariation among sets of observed variables to estimate a smaller number of underling latent variables. Generalized Structural Equation Model (GSEM) methods include factor analysis as a special case and allow expanded distributions, latent linkages, and other extensions. We fit GSEMs to sets of the ARIC cognitive instruments to construct measures of latent overall cognitive function and the a priori specified cognitive subdomains. Cognitive subdomain GSEMs and an overall cognitive function GSEM were fit separately using full maximum likelihood estimation methods, allowing inclusion of all participants who had at least one test score. We assumed Gaussian distributions where scores were approximately normally distributed and assumed probit or ordered probit distributions for binary and categorical scores, respectively.

GSEMs for cognitive scores were fit using only the visit 5 data. Parameters from the visit 5 GSEMs were then applied to the visit 6 data such that latent cognitive scores at visit 6 were scaled to visit 5, enabling examination of cognitive decline in further longitudinal models. This technique is similar conceptually to longitudinal analyses that use standardized z-scores across time, where the baseline mean and SD are used to standardize across all visits instead of the visit-specific means and SDs; this allows tracking of changes over time.

### 2.5. Assessment of incident MCI and dementia and vital status

At visit 5, all participants with prior MRI, suspected cognitive impairment (defined by poor cognitive test scores or evidence of substantial cognitive decline from a prior visit), and a random sample of those presumed to be cognitively normal were invited to in-person clinical assessment and informant interview. Diagnoses of cognitively normal, MCI, and dementia were assigned algorithmically based on cognitive tests scores at visit 5 (MMSE and 10 additional tests), change in cognitive test scores from earlier assessments on 3 consistently administered cognitive tests (Digit Symbol Substitution, Delayed Word Recall, and Word Fluency Tests), clinical dementia rating interview scores, and functional activities questionnaire scores. Algorithmic diagnoses were reviewed and confirmed or revised by expert adjudicators (Knopman et al., 2016). Participants who attended visit 6 were classified as having normal cognition, MCI, or dementia at the time of the study visit according to a similar protocol based on data collected at the in-person study visit. Primary analyses only consider cognitive status based on adjudicated diagnoses referencing data from these in-person study visits. Vital status at the time of visit 6 was assessed through follow-up calls and supplemented through cross-reference with the national death index.

As we were concerned that those who did not attend visit 6 may not do so because of their dementia status, which could lead to bias, we conducted secondary analyses where visit 6 nonparticipants who were known to be alive were classified as demented if they were suspected of having dementia based on cohort surveillance efforts (include telephone-based cognitive screening, informant interview, interview with informants when poor function was suspected, and review of hospitalization discharge codes).

### 2.6. Other covariates

We defined age at each study visit using self-reported date of birth and visit date. We ascertained education (<high school, high school or vocational school, and >high school), smoking status at the time of visit 5 (current, former, or never), sex, and race by self-report. Information on race and study site was combined to create a site-race variable (Washington County/white, Minneapolis/white, Forsyth County/white, Forsyth County/black, Jackson/black). We calculated body mass index as the mass in kg at visit 5 divided by the square of height in meters. We considered diabetes status in midlife (at visit 1) and hypertension status in late life (at visit 5), given previously described time-dependent relationships between these risk factors with both DTI measures and cognition (Power et al., 2017; Qiu et al., 2005). Participants were classified as diabetic if they had self-reported diagnosis by a physician, ≥126 mg/dL fasting glucose, ≥200 mg/dL nonfasting glucose, or diabetes

medication use. Participants were classified as hypertensive if they had measured systolic blood pressure ≥140 mm Hg, measured diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use. We determined presence or absence of an apolipoprotein (APOE) ε4 allele via genotyping for use as a covariate, given evidence of accelerated cognitive change in APOE ε4 carriers (Caselli et al., 2004, 2007; Cosentino et al., 2008; Nilsson et al., 2006) and the potential for a link between APOE ε4 and WM microstructural integrity (Heise et al., 2011; Kanchibhotla et al., 2013; Nyberg and Salami, 2014; Westlye et al., 2012).

### 2.7. Statistical methods

We standardized WM FA and WM MD measures by subtracting the sample mean and dividing by the sample SD. We report associations with a 1SD unit worsening in WM FA (1 SD decrease) or WM MD (1 SD increase).

We used linear mixed models with random intercepts and Huber–White robust variance estimates to assess associations of visit 5 WM microstructural integrity measures with overall and domain-specific cognitive status at visit 5 and cognitive decline from visit 5 to visit 6. We used multinomial logistic regression models to examine associations of WM microstructural integrity with MCI and dementia at visit 5 and with incident MCI, dementia and death outcomes at visit 6 among those with normal cognition at visit 5.

Primary adjustors for all models included age, sex, education, APOE e4 carrier status, and site-race. We included both main effects and interactions with time for all covariates in our linear mixed models. All models were weighted to account for the stratified random sampling approach used to select ARIC participants for visit 5 MRI.

Primary analysis models considered overall WM MD and WM FA. In secondary analyses, we considered (1) associations with ROI-specific WM MD and WM FA, (2) models additionally adjusted for WMH and estimated intracranial volumes, (3) models additionally adjusted for WMH, hippocampal, total brain, and estimated intracranial volumes. For models of cognitive change, we also considered whether the association differed based on baseline cognitive status (cognitively normal vs. MCI or dementia at visit 5). For models of incident MCI, dementia, and death, we also conducted analyses using an expanded sample including visit 6 nonparticipants who remained alive and who were suspected of having dementia through surveillance efforts as having incident dementia at visit 6. Analyses exploring ROI-specific effects were designed to look for regional effects. Analyses adjusting for additional brain features were designed to explore whether the associations were potentially mediated by markers of pathology thought to follow changes to WM microstructural integrity. Analyses using the expanded sample of dementia cases identified via surveillance were designed to address potential issues related to loss-to-follow-up.

We also ran sensitivity analyses incorporating additional adjustments for comorbidities (hypertension, smoking, BMI, and midlife diabetes), omitting weighting for selection into the MRI subsample, and implementing inverse probability weighting to account for missingness due to loss to follow-up for analyses considering incident outcomes or cognitive change. For analyses of global cognitive change only, we also tried an average z-score, a longitudinal GSEM approach, as well as alternate summary scores consisting of subsets of the potential components. All analyses were completed with STATA, Version 14 (StataCorp. 2015. College Station, TX: StataCorp LP).

### 2.8. Data availability

ARIC makes individual-level data available to qualified research investigators who collaborate with an ARIC investigator, use publicly available date accessed through the website https://biolincc.nhlbi.nih.gov/studies/aric, or successfully propose ancillary studies. ARIC's data sharing policies are provided on the https://www2.cscc.unc.edu/aric/node/10303 website.

## 3. Results

On average, participants in our primary analytical sample were 76 years old at the baseline (visit 5), 40% were male, and 28% were black. Participant characteristics were generally similar in the sample used for analyses of incident cognitive impairment or mortality. Average follow-up time for both samples was 4.9 years. Additional participant characteristics are provided in Table 1. Correlations between cognitive factor scores at visit 5 and change in cognitive factor scores from visit 5 to visit 6 are available in Supplemental Tables S1 and S2.

With the exception of no evidence to support an association between WM FA and memory, both WM FA and WM MD were strongly associated with baseline cognitive performance overall and with each domain (Table 2). Generally, these associations weakened, but remained statistically significant after adjustment for WHM and/or brain volumes.

To the contrary, there was little evidence to support an association between WM FA and the subsequent rate of overall or domain-specific cognitive change or between WM MD and domain-specific cognitive change (Table 2). However, despite no clear association with domain-specific change, worse WM MD was associated with faster overall cognitive decline. For context, the excess annual decline per 1SD increase in WM MD we observed (−0.013, 95% CI: −0.021, −0.005; *p*-value: 0.002, Table 2), is approximately 77% of the excess annual overall rate of cognitive decline we observe when comparing APOE e4 carriers to non-carriers in this model (excess annual decline in APOE e4 carriers −0.017, 95% CI: −0.028, −0.005). Sensitivity analyses suggest the presence of the effect for the summary measure but not the domain-specific measures is driven by the additional information inherent in the overall measure relative to the individual measures (Supplemental Table S2) which was not wholly dependent on any single global cognitive measure definition (Supplemental Table S3). Adjustment for WMH volumes attenuated these estimates slightly (Table 2); nonetheless, the association between greater WM MD and overall cognitive decline persisted (excess annual decline per 1SD increase in WM MD −0.010, 95% CI: −0.019, −0.001). Simultaneous adjustment for WMH, hippocampal, and total brain volumes further attenuated this association (excess annual decline per 1SD increase in WM MD −0.007, 95% CI: −0.017, 0.002). Findings were generally consistent across additional sensitivity analyses (data not shown) and analyses considering ROI-specific WM MD or WM FA (data not shown, Fig. 2). There was no evidence to support a difference in the association with cognitive change by whether the participant was cognitively normal or diagnosed with MCI/dementia at the baseline (all *p*-values for interaction >0.35).

WM FA and WM MD were strongly associated with prevalent cognitive status, although these associations were attenuated, and most became nonsignificant after adjustment for WMH, hippocampal, and total brain volumes (Table 3).

When examining associations with incident outcomes, there was little evidence to support an association between WM FA and incident MCI or mortality in those who were cognitively normal at the baseline (Table 4). While WM FA appeared associated with incident dementia in our primary analysis, this association was not robust to sensitivity analyses (data not shown). By contrast, we observed strong associations of higher WM MD with incident MCI, dementia, and mortality (Table 4). These associations were slightly attenuated after adjustment for WMH

**Table 1**
Characteristics of eligible ARIC participants at ARIC visit 5/ARIC-NCS unless otherwise noted

| Characteristic | Primary analysis sample (N = 1775) | Sample for analysis of incident cognitive impairment or mortality (N = 889) |
|---|---|---|
| | No. (%) or mean(SD) | No. (%) or mean(SD) |
| Age | 76.3 (5.3) | 75.6 (5.2) |
| Male | 704 (40%) | 332 (37%) |
| APOE e4 | 522 (29%) | 236 (27%) |
| Education | | |
| <High school | 252 (14%) | 116 (13%) |
| High school | 725 (41%) | 333 (37%) |
| >High school | 798 (45%) | 440 (49%) |
| Site race | | |
| Washington County whites | 468 (26%) | 226 (25%) |
| Minneapolis whites | 387 (22%) | 175 (20%) |
| Jackson blacks | 468 (26%) | 275 (31%) |
| Forsyth County blacks | 32 (2%) | 18 (2%) |
| Forsyth County whites | 420 (24%) | 195 (22%) |
| Total intracranial ($cm^3$) | 1381.1 (155.8) | 1372.01 (144.97) |
| White matter hyperintensities ($cm^3$) | 17.2 (16.9) | 15.4 (16.3) |
| Hippocampal volume ($cm^3$) | 6.9 (1.0) | 7.1 (0.9) |
| Total brain volume ($cm^3$) | 1013.0 (107.4) | 1019.5 (104.4) |
| Cognitive Status at visit 5 | | |
| Normal | 1081 (61.0%) | 889 (100%) |
| MCI | 598 (33.8%) | 0 (0%) |
| Dementia | 92 (5.2%) | 0 (0%) |
| Cognitive/Vital Status at visit 6 | | |
| Normal | 849 (47.8%) | 662 (74.5%) |
| MCI | 210 (11.8%) | 116 (13.1%) |
| Dementia | 100 (5.6%) | 25 (2.8%) |
| Dead | 227 (12.8%) | 86 (9.7%) |
| Lost to follow-up | 389 (21.9%) | N/A |
| Fractional anisotropy, by region (unitless) | | |
| Frontal | 0.28 (0.02) | 0.28 (0.02) |
| Temporal | 0.28 (0.02) | 0.28 (0.02) |
| Parietal | 0.30 (0.02) | 0.30 (0.02) |
| Occipital | 0.22 (0.02) | 0.22 (0.02) |
| Anterior corpus callosum | 0.42 (0.06) | 0.43 (0.06) |
| Posterior corpus callosum | 0.57 (0.06) | 0.58 (0.06) |
| Overall | 0.28 (0.02) | 0.28 (0.02) |
| Mean diffusivity, by region ($10^{-4}$ $mm^2/s$) | | |
| Frontal | 8.60 (0.54) | 8.52 (0.51) |
| Temporal | 8.88 (0.59) | 8.76 (0.55) |
| Parietal | 8.79 (0.61) | 8.70 (0.57) |
| Occipital | 8.74 (0.63) | 8.67 (0.60) |
| Anterior corpus callosum | 11.62 (1.12) | 11.42 (1.09) |
| Posterior corpus callosum | 11.20 (1.03) | 11.05 (0.99) |
| Overall | 8.78 (0.55) | 8.68 (0.51) |
| Cognitive Domain Factor Scores at visit 5 | | |
| Overall | −0.06 (0.76) | 0.27 (0.65) |
| Memory | −0.05 (0.62) | 0.22 (0.55) |
| Language and verbal | −0.00 (0.12) | 0.03 (0.11) |
| Sustained attention and processing speed | −0.03 (0.33) | 0.08 (0.31) |
| Cognitive Domain Factor Scores at visit 6 | | |
| Overall | −0.10 (0.82) | 0.12 (0.72) |
| Memory | −0.01 (0.64) | 0.15 (0.59) |
| Language and verbal | −0.01 (0.12) | 0.01 (0.12) |
| Sustained attention and processing speed | −0.07 (0.35) | −0.01 (0.34) |

Key: APOE, apolipoprotein; ARIC, Atherosclerosis Risk in Communities; AD, Alzheimer's disease; APOE e4, apolipoprotein E e4 allele; NCS, Neurocognitive Study; MCI, mild cognitive impairment.

volumes (Table 4) and were further attenuated after additionally adjusting for WMHs, hippocampal and total brain volume (OR per 1 SD increase in WM MD for incident dementia: 1.82, 95% CI: 0.95, 3.49, for incident MCI: 1.30, 95% CI: 0.87, 1.94, for death: 1.63, 95% CI: 0.97, 2.73). Results were similar when we included additional dementia cases identified via surveillance (Table 4) and across additional sensitivity analyses (data not shown). Analyses of ROI-specific WM FA and MD were generally consistent with our primary analyses (Fig. 3 and Fig. 4), although it is notable that the association between WM MD and incident MCI, dementia, and death was generally strongest for WM MD in the frontal, temporal, and parietal lobes (Fig. 4).

## 4. Discussion

Our study found that the cross-sectional and longitudinal associations between WM microstructural integrity and cognitive outcomes differ. Although both WM FA and WM MD were strongly associated with the baseline cognitive performance and prevalent cognitive status (i.e., normal, MCI, dementia), associations of WM FA and WM MD with cognitive change or incident MCI, dementia, or death were mixed. While we did not find strong evidence of associations between WM FA and cognitive change or incident outcomes, our study found strong, consistent associations between higher overall WM MD and subsequent late-life cognitive decline,

**Table 2**
Primary and sensitivity analyses for the association quantifying difference in the annual rate of cognitive change per 1SD unit decrease (worsening) in overall WM FA or 1SD unit increase (worsening) in overall WM MD

| Analysis | WM FA[a] | | | | WM MD[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline difference[b] beta (95% CI) | *p*-value | Excess annual rate of change[b] beta (95% CI) | *p*-value | Baseline difference[b] beta (95% CI) | *p*-value | Excess annual rate of change[b] beta (95% CI) | *p*-value |
| Primary analyses | | | | | | | | |
| Overall | −0.081 (−0.114,−0.049) | <0.001 | −0.004 (−0.010,0.002) | 0.23 | −0.173 (−0.213,−0.133) | <0.001 | −0.013 (−0.021,−0.005) | 0.002 |
| Memory | −0.005 (−0.035,0.025) | 0.75 | −0.003 (−0.011,0.004) | 0.36 | −0.055 (−0.090,−0.020) | 0.002 | −0.007 (−0.016,0.002) | 0.13 |
| Language | −0.017 (−0.022,−0.011) | <0.001 | −0.000 (−0.001,0.001) | 0.69 | −0.023 (−0.029,−0.017) | <0.001 | −0.001 (−0.002,0.000) | 0.25 |
| Attention/processing Speed | −0.046 (−0.059,−0.033) | <0.001 | 0.000 (−0.003,0.003) | 0.85 | −0.082 (−0.097,−0.067) | <0.001 | −0.003 (−0.007,0.000) | 0.09 |
| Additional adjustment for WMH and intracranial volume | | | | | | | | |
| Overall | −0.053 (−0.090,−0.016) | 0.005 | −0.001 (−0.009,0.006) | 0.70 | −0.177 (−0.224,−0.131) | <0.001 | −0.010 (−0.019,−0.001) | 0.03 |
| Memory | 0.015 (−0.023,0.052) | 0.44 | −0.002 (−0.011,0.006) | 0.61 | −0.059 (−0.102,−0.017) | 0.007 | −0.005 (−0.015,0.006) | 0.39 |
| Language | −0.014 (−0.020,−0.007) | <0.001 | −0.000 (−0.001,0.001) | 0.71 | −0.022 (−0.030,−0.015) | <0.001 | −0.001 (−0.002,0.000) | 0.22 |
| Attention/processing Speed | −0.042 (−0.058,−0.026) | <0.001 | 0.002 (−0.002,0.006) | 0.28 | −0.089 (−0.107,−0.071) | <0.001 | −0.002 (−0.006,0.003) | 0.46 |
| Additional adjustment for WMH, intracranial, hippocampal, and total brain volume | | | | | | | | |
| Overall | −0.045 (−0.081,−0.010) | 0.01 | −0.001 (−0.008,0.006) | 0.70 | −0.116 (−0.164,−0.068) | <0.001 | −0.007 (−0.017,0.002) | 0.13 |
| Memory | 0.014 (−0.023,0.050) | 0.46 | −0.003 (−0.011,0.006) | 0.53 | −0.026 (−0.072,0.019) | 0.26 | −0.004 (−0.015,0.007) | 0.51 |
| Language | −0.012 (−0.018,−0.005) | <0.001 | −0.000 (−0.001,0.001) | 0.83 | −0.014 (−0.023,−0.006) | 0.001 | −0.001 (−0.002,0.001) | 0.37 |
| Attention/processing Speed | −0.036 (−0.052,−0.021) | <0.001 | 0.002 (−0.002,0.006) | 0.29 | −0.064 (−0.085,−0.044) | <0.001 | −0.000 (−0.005,0.004) | 0.87 |

Key: APOE, apolipoprotein; WM FA, white matter fractional anisotropy; WM MD, white matter mean diffusivity; SD, standard deviation; WMH, white matter hyperintensity.
[a] Lower FA and higher MD are indicative of worse brain microstructural integrity.
[b] Adjusted for age, sex, education, race-center, and APOE e4 carrier status and additional variables as noted (main effects and interactions with time) and weighted to account for the stratified random sampling approach to select participants for visit 5 MRI unless otherwise specified.

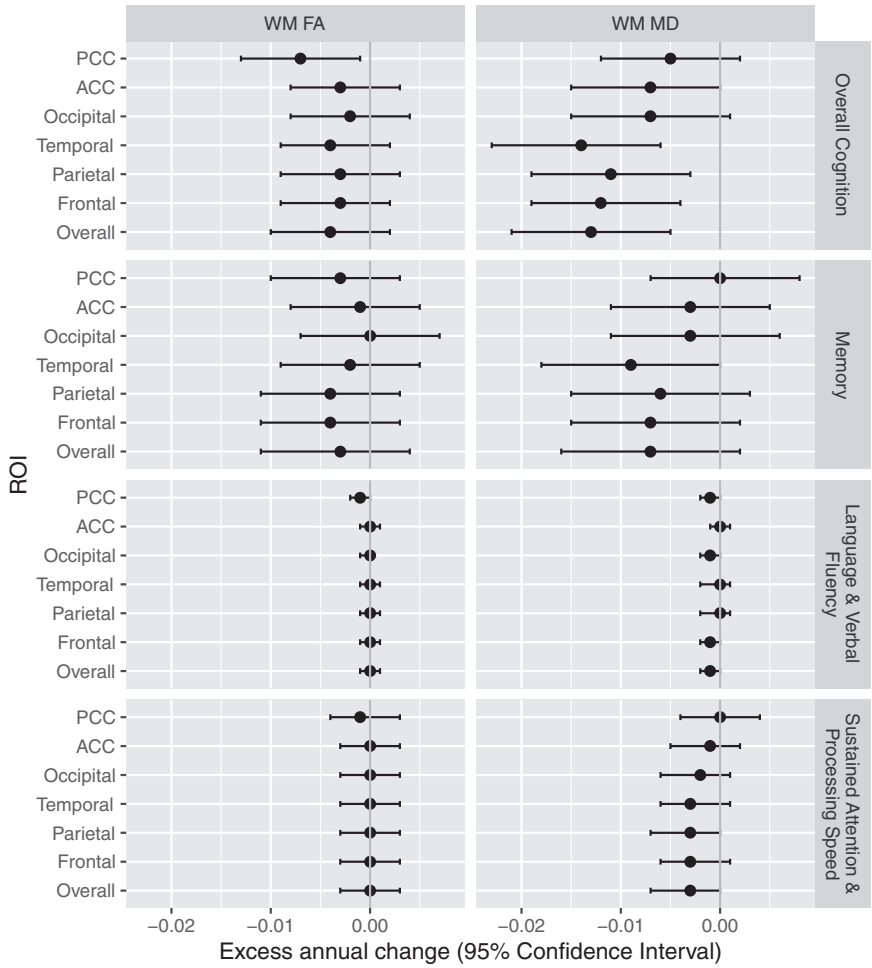


**Fig. 2.** Difference in the annual cognitive change per 1SD unit worsening in ROI-specific WM FA or WM MD. Lower FA and higher MD are indicative of worse brain microstructural integrity. All models are adjusted for age, sex, education, race-center, and APOE e4 carrier status (main effects and interactions with time) and weighted to account for the stratified random sampling approach to select participants for visit 5 MRI. Abbreviation: APOE, apolipoprotein; WM, white matter; FA, fractional anisotropy; MD, mean diffusivity; SD, standard deviation; ROI, region of interest.

**Table 3**
Association quantifying change in odds of prevalent MCI or dementia at Visit 5 per 1SD unit decrease (worsening) in overall WM FA or increase (worsening) in WM MD

| Analysis | WM FA[a] | | WM MD[a] | |
|---|---|---|---|---|
| | OR[b] (95% CI) | *p*-value | OR[b] (95% CI) | *p*-value |
| Primary Analyses | | | | |
| MCI | 1.16 (1.03,1.30) | 0.01 | 1.37 (1.18,1.59) | <0.001 |
| Dementia | 1.47 (1.17,1.86) | 0.001 | 2.79 (2.16,3.59) | <0.001 |
| Additional adjustment for WMH and intracranial volume | | | | |
| MCI | 1.05 (0.91,1.22) | 0.48 | 1.29 (1.08,1.53) | 0.005 |
| Dementia | 1.40 (1.03,1.89) | 0.03 | 3.17 (2.37,4.24) | <0.001 |
| Additional adjustment for WMH, intracranial, hippocampal, and total brain volume | | | | |
| MCI | 1.05 (0.90,1.22) | 0.56 | 1.13 (0.93,1.37) | 0.21 |
| Dementia | 1.34 (0.96,1.86) | 0.08 | 2.00 (1.41,2.83) | <0.001 |

Key: APOE, apolipoprotein; MCI, mild cognitive impairment; WM FA, white matter fractional anisotropy; WM MD, white matter mean diffusivity; WMH, white matter hyperintensity.
[a] Lower FA and higher MD are indicative of worse brain microstructural integrity.
[b] Adjusted for age, sex, education, race-center, and APOE e4 carrier status and weighted to account for the stratified random sampling approach to select participants for visit 5 MRI.

incident dementia, and mortality over a period of approximately 5 years. Results linking WM MD to global cognitive decline were stronger than those considering domain-specific cognitive decline, reflecting the additional information captured by the global measure, and associations between WM MD and dementia appear strongest when considering WM MD in the frontal, temporal, and parietal lobes, consistent with the demonstrated importance of these regions in cognitive function commonly affected by dementia, particularly executive function and memory. All observed associations were attenuated after simultaneous adjustment for WMH, hippocampal, and total brain volumes, which are thought to be downstream pathologic changes.

Consistent with our findings, most cross-sectional studies suggest an association between WM microstructural integrity and cognitive function. However, there remains heterogeneity in the specific findings. Several, but not all, studies report that age-related differences in processing speed or other aspects of cognitive performance are partially mediated by WM microstructural integrity(Burgmans et al., 2011; Charlton et al., 2008; Madden et al., 2004, 2017, 2009, 2012; O'Sullivan et al., 2001; Salami et al., 2012). In a sample of older adults, FA and MD were associated with perceptual speed, but other cognitive domains (Laukka et al., 2013). In the Rotterdam Study, lower WM FA and higher WM MD were associated with decreased cognitive test performance (Vernooij et al., 2009) and greater risk of mortality (Sedaghat et al., 2016). In the Mayo Clinic Study of Aging, specific cognitive domain functions are associated with distinct patterns of cortical and WM diffusivity in elderly with no dementia (Kantarci et al., 2011), and these changes were in-part explained by GM neurodegeneration but not β-amyloid (Kantarci et al., 2014). Similar associations between DTI-based measures and performance on tests of cognition and reaction time were frequently observed in other samples (Charlton et al., 2006; Sala et al., 2015; Tuladhar et al., 2015; Ukmar et al., 2008; van Norden et al., 2012). Finally, in related cross-sectional work, persons with a diagnosis of Alzheimer's disease or MCI frequently exhibit worse regional WM microstructural integrity compared with cognitively intact controls, despite some heterogeneity within sets of analyses considering specific regions (Bagepally et al., 2012; Chua et al., 2008; Fellgiebel et al., 2004; Huang and Auchus, 2007; Huang et al., 2007; Medina et al., 2006; Naggara et al., 2006; Oishi et al., 2011; Stebbins and Murphy, 2009; Ukmar et al., 2008).

In comparison, relatively few studies have assessed the longitudinal relationship between WM microstructural integrity and cognition in older adults, and the results are mixed. In a small sample of 77 persons over age 81 years selected from the Swedish National

**Table 4**
Association quantifying change in odds of incident MCI or dementia among persons who were cognitively normal at visit 5 per 1SD unit decrease (worsening) in overall WM FA or increase (worsening) in WM MD

| Analysis | WM FA[a] | | WM MD[a] | |
|---|---|---|---|---|
| | OR[b] (95% CI) | *p*-value | OR[b] (95% CI) | *p*-value |
| Primary analyses | | | | |
| MCI | 1.16 (0.86, 1.55) | 0.34 | 1.54 (1.09, 2.18) | 0.02 |
| Dementia | 1.87 (1.17, 3.01) | 0.009 | 2.51 (1.62, 3.88) | <0.001 |
| Death | 1.12 (0.76, 1.65) | 0.57 | 1.89 (1.26, 2.85) | 0.002 |
| Additional adjustment for WMH and intracranial volume | | | | |
| MCI | 1.09 (0.80, 1.50) | 0.59 | 1.48 (1.01, 2.18) | 0.04 |
| Dementia | 1.66 (0.86, 3.18) | 0.13 | 2.22 (1.35, 3.68) | 0.002 |
| Death | 0.90 (0.55, 1.46) | 0.66 | 1.76 (1.10, 2.83) | 0.02 |
| Additional adjustment for WMH, intracranial, hippocampal, and total brain volume | | | | |
| MCI | 1.07 (0.77, 1.48) | 0.71 | 1.30 (0.87, 1.94) | 0.20 |
| Dementia | 1.42 (0.76, 2.67) | 0.27 | 1.82 (0.95, 3.49) | 0.07 |
| Death | 0.86 (0.52, 1.42) | 0.55 | 1.63 (0.97, 2.73) | 0.06 |
| Secondary analyses, including additional dementia cases identified by cohort surveillance | | | | |
| MCI | 1.16 (0.87, 1.55) | 0.32 | 1.55 (1.09, 2.20) | 0.01 |
| Dementia | 1.40 (0.94, 2.09) | 0.10 | 2.17 (1.49, 3.17) | <0.001 |
| Death | 1.11 (0.76, 1.62) | 0.59 | 1.89 (1.26, 2.83) | 0.002 |

Key: APOE, apolipoprotein; MCI, mild cognitive impairment; WM FA, white matter fractional anisotropy; WM MD, white matter mean diffusivity.
[a] Lower FA and higher MD are indicative of worse brain microstructural integrity.
[b] Adjusted for age, sex, education, race-center, and APOE e4 carrier status and weighted to account for the stratified random sampling approach to select participants for visit 5 MRI.

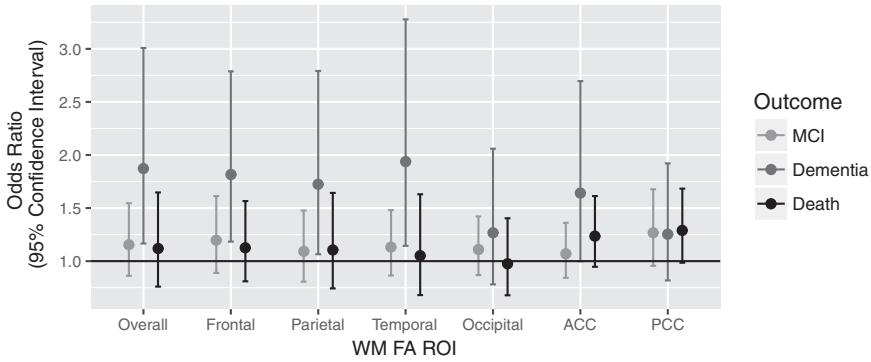


**Fig. 3.** OR (95% CI) for incident MCI or dementia per 1SD unit worsening in ROI-specific WM FA. Adjusted association quantifying change in odds of incident MCI or dementia were quantified among persons who were cognitively normal at Visit 5. All analyses were adjusted for age, sex, education, race-center, and APOE e4 carrier status. Lower WM FA reflects worse WM FA. Abbreviations: APOE, apolipoprotein; ACC, anterior corpus callosum; FA, fractional anisotropy; MCI, mild cognitive impairment; SD, standard deviation; PCC, posterior corpus callosum; ROI, region of interest; WM MD, white matter mean diffusivity.

Study of Aging and Care in Kungsholmen (SNAC-K, mean(SD): MMSE 28.6 (1.4)), of whom 40 had a repeat MRI, change in FA and MD in the corticospinal tract was associated with change in perceptual speed but not other domains of cognitive function, over 2 years of follow-up (Lovden et al., 2014). This study did not consider the influence of other neuroimaging parameters on their analyses. In participants of the Lothian Birth Cohort 1936, worse baseline FA did not predict subsequent cognitive decline, but change in FA from approximately age 73 to 76 years was correlated with change in general cognition in analyses accounting for potential confounding by age and sex (Ritchie et al., 2015). In a sample of 265 cognitively normal individuals from the Harvard Aging Brain Study, lower global FA, but not tract-specific FA, predicted accelerated decline in processing speed and episodic memory in analyses adjusted for demographics (Rabin et al., 2019). The RunDMC study considered a sample of older nondemented adults with cerebral small vessel disease, defined as the presence of lacunes or WMH. Reports from RunDMC conclude no association between WM FA or WM MD in normal appearing WM and subsequent cognitive decline. However, before Bonferroni correction for multiple testing, worse WM microstructural integrity was associated with greater decline on tests of verbal memory and fluency at standard cutoffs for statistical significance (van Uden et al., 2015). In related work in RunDMC, WM microstructural integrity was not associated with incident dementia after adjusting for WMH volumes, WM volumes, and hippocampal volumes (van Uden et al., 2016). To the contrary, in the LADIS study, which enrolled older adults with mild or no IADL disability and evidence of WMH on MRI (mean (SD) MMSE score 27 (2.3)), MD was associated with accelerated decline in processing speed, executive function, and memory; these associations persisted after adjustment for WMH volumes, lacunes, and brain atrophy (Jokinen et al., 2013). Similarly, in the GENIE study, which enrolled healthy individuals without known neurological conditions from a local physician practice, change in WM microstructural integrity was correlated with change in working memory after adjusting for age and WMH volumes (Charlton et al., 2010). Differences in the severity of existing brain pathologies, baseline cognitive status, or other sample characteristics may contribute to the observed heterogeneity across studies. However, our analysis suggests differences across studies are partially attributable to differences in adjustment for other MRI indicators of brain pathology. As changes to WM microstructural integrity appear to precede WM hyperintensities (WMH), which themselves are thought to precede loss of brain volume (Appelman et al., 2009; Ly et al., 2014; Maillard et al., 2011, 2013, 2014; Salat et al., 2005), we may expect that estimates of the impact of WM microstructural integrity on late-life cognition be attenuated when we adjust for these proposed markers of intermediaries on the causal pathway.

Strengths of this study include the relatively large number of well-characterized participants originally recruited from the community with MRI, longitudinal follow-up, and in-person dementia ascertainment. In addition, given the community-based nature of the original enrollment, we expect our results to be broadly generalizable. However, this study also has limitations. Although the association between WM MD and late-life cognitive change may not be homogenous, our study was not large enough to justify consideration of effect modification. We focused on regional summaries of WM FA and WM MD, as this allowed us to cover the entire WM, which may be important because vascular lesions in the WM

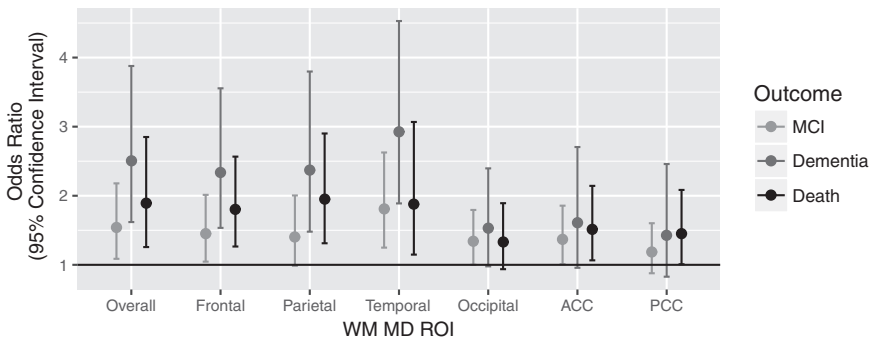


**Fig. 4.** OR (95% CI) for incident MCI or dementia per 1SD unit worsening in ROI-specific WM MD. Adjusted association quantifying change in odds of incident MCI or dementia was quantified among persons who were cognitively normal at visit 5. All analyses were adjusted for age, sex, education, race-center, and APOE e4 carrier status. Higher WM MD reflects worsening WM MD. Abbreviations: APOE, apolipoprotein; ACC, anterior corpus callosum; MCI, mild cognitive impairment; PCC, posterior corpus callosum; ROI, region of interest; WM MD, white matter mean diffusivity.

tend to involve vascular watershed zones that may not follow specific tracts. Measures based on tractography or analyses using voxelwise comparisons would better identify how the health of specific WM tracts relates to cognition. While we did not find robust associations between WM FA and either cognitive change or incident cognitive impairment, this may be related to the fact that FA can be influenced by crossing-fibers more than MD, limiting the power of FA to detect WM degeneration (Jeurissen et al., 2013). Similarly, we quantify WM FA and WM MD in total WM, rather than normal appearing WM. This choice allowed us to adjust for WMH in our sensitivity analyses, demonstrating that associations with WM MD or WM FA were not driven by correlation between these measures and WMH burden (Svard et al., 2017). We did not include alternate measures such as axial or radial diffusivity in our imaging analysis protocol given concerns about interpretability (Wheeler-Kingshott and Cercignani, 2009), limiting synthesis with other investigations using such methods. In addition, using track-based approaches may be a better approach to explore tract-specific integrity. Finally, bias is always a potential issue in observational studies. However, our sensitivity analyses addressing residual confounding and potential selection bias were consistent with our primary analyses. Moreover, we anticipate only nondifferential measurement error, which may account for our negative findings but is unlikely to account for our positive findings.

## 5. Conclusions

DTI-based measures of WM microstructural integrity have been shown to precede and predict the development of WMHs and WM loss (Ly et al., 2014; Maillard et al., 2011, 2013, 2014; Salat et al., 2005). Thus, the findings of our study suggest that WM microstructural integrity, as measured by WM MD, may be a useful early indicator of pathologic changes that lead to future cognitive decline and incident dementia. Future work will need to better understand how WM MD contributes to declining cognition, as our work suggests this relationship may be mediated by accumulation of other brain pathologies.

## Disclosure

Drs Coresh, Griswold, Huang, Mosley, Power, Reid, Sharrett, and Wu, and Ms Su have nothing to declare. Dr Clifford R. Jack Jr consults for Lily and serves on an independent data monitoring board for Roche, but he received no personal compensation from any commercial entity. He received research support from the NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. Dr David Knopman serves on a Data Safety Monitoring Board for the DIAN study; is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California; and received research support from the NIH. Kejal Kantarci serves on the Data Safety Monitoring Board for Takeda Global Research and Development Center, Inc; received research support from Avid Radiopharmaceuticals and Eli Lilly, and received funding from the NIH and Alzheimer's Drug Discovery Foundation. Dr Rebecca G. Gottesman is an associate editor for Neurology.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.08.021.

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