**ARIC Manuscript Proposal # 3075**

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| **PC Reviewed: 11/14/17** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Association between white matter microstructural integrity and cognitive decline, MCI, and incident dementia

**b. Abbreviated Title (Length 26 characters)**: DTI and later cognition

**2. Writing Group**:

Writing group members (alphabetical):
Aozhou Wu, MHS; Clifford R. Jack, MD; Dan Su, David S. Knopman, MD; Joe Coresh, MD; Juebin Huang, MD, PhD; Kejal Kentarci, MD, MS; Melinda C Power, ScD (first author); Mike Griswold, PhD; Rebecca G. Gottesman, MD; A. Richey Sharrett, MD, DrPH; Thomas Mosley, PhD; others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.
__MP_____**[please confirm with your initials electronically or in writing]**


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**3. Timeline**:

Analyses will be completed within 1 year of receipt of final Visit 6 outcome data.

**4. Rationale**:

Diffusion tensor imaging (DTI) quantifies the microstructural integrity of white matter.[1] Commonly used DTI measures include fractional anistotrophy (FA) and mean diffusivity (MD). FA measures directional constraint of water diffusion, and MD measures the average rate of diffusion in any direction. As white matter (WM) is generally anisotrophic (i.e. the direction of water diffusion is highly constrained), lower WM FA and higher WM MD are thought to reflect worse white matter tract integrity, at least in regions lacking white matter tract crossings. DTI complements other neuroimaging measures, namely measures of white matter hyperintensities (WMH) or WM volumes, as DTI-based measures appear to provide an assessment of pathologic changes that precede and predict the development of WMH or WM loss,[2-4,5-7] and these, in turn, appear related to cognition.[8-14]

We previously demonstrated that hypertension and elevated midlife glucose were associated with reduced white matter microstructural integrity, and that this association was independent of the degree of white matter hyperintensities (WMH) in the brain.[15] Others have demonstrated that it is possible to quantify changes in WM microstructural integrity over follow-up periods of two years or less.[16-19] Thus, DTI-based measures may be useful in clinical trials intervening on vascular risk factors as a risk stratification tool, identifying persons at risk of subsequent risk of WMH or WM loss, or as a tool used to demonstrate that interventions successfully target preservation of WM microstructural integrity. However, it remains unclear whether DTI measures would be useful as a surrogate endpoint in clinical trials. Given the hypothesized link between WM microstructural integrity and WMH or WM loss, and their relationship with cognition, DTI-based measures likely provide an early indication of later cognitive decline, cognitive impairment, and dementia diagnosis. While substantial cross-sectional evidence links DTI-based measures to cognition, fewer studies have considered associations with cognitive change, and strong evidence linking DTI-based measures to the clinical outcomes of MCI or dementia is lacking.

Multiple cross-sectional studies suggest a relationship between worse WM microstructural integrity assessed using DTI and APOE E4 status, cognition, or dementia. Compared to non-carriers, APOE E4 carriers exhibited worse regional WM microstructural integrity in most[20-26] but not all[27] studies, and APOE E4 carriers also appear to have decreased interconnectivity of structural brain networks quantified from DTI neuroimaging.[28] Several studies report that age-related differences in cognitive performance or processing speed are partially mediated by white matter microstructural integrity.[29-35] In the Rotterdam Study, lower WM FA and higher WM MD were associated with cognitive test performance[36] and greater mortality risk of subsequent mortality.[37] Similar associations between DTI-based measures and performance on tests of cognition and reaction time were frequently observed in other samples.[38-43] Finally, in cross-sectional work, persons with a diagnosis of Alzheimer's disease (AD) or mild cognitive impairment (MCI) frequently exhibit worse regional WM microstructural integrity compared to cognitively intact controls.[20, 41, 44-51]

In comparison, relatively few studies have assessed the relationship between WM microstructural integrity and subsequent cognitive change or incident dementia, and the results are mixed. In addition, many of these studies are small and may not adequately adjust for

potential confounders. For example, the RunDMC study considered a sample of older non-demented adults with cerebral small vessel disease, defined as the presence of lacunes or WMH. Reports from this study conclude no association between WM FA or WM MD in normal appearing white matter and subsequent cognitive decline after correcting for multiple testing using a conservative Bonferroni correction. However, prior to correction, worse white matter microstructural integrity did appear associated with greater decline on tests of verbal memory and fluency at standard cut-offs for statistical significance.[52] In related work in the Run DMC study, WM microstructural integrity was not associated with incident dementia after considering WMH volumes, WM volumes, and hippocampal volumes.[53] To the contrary, in the LADIS study, MD was associated with accelerated decline in processing speed, executive function, and memory; moreover, these associations persisted after adjustment for WMH volumes, lacunes, and a measure of brain atrophy.[54] Similarly, in the GENIE study, change in white matter microstructural integrity was correlated with change in working memory after adjusting for age and WMH volumes.[19]

Thus, the purpose of this study is to quantify the association between late-life measures of WM microstructural integrity and cognitive change, incident MCI, and incident dementia in relatively large sample of persons with DTI data and prospective cognitive assessment, using data from the Atherosclerosis Risk in Communities Study (ARIC).

**5. Main Hypothesis/Study Questions**:

*Study Aim:*

Assess whether measures of white matter microstructural integrity at Visit 5 are associated with post-Visit 5 cognitive outcomes, including incident dementia, development of MCI and cognitive decline.

*Hypothesis:*

Worse overall white matter microstructural integrity at Visit 5 is associated with higher risk of incident dementia, development of MCI, and more cognitive decline. We will also determine whether regional white matter microstructural integrity is preferentially associated with decline in specific domains of cognitive function.

We additionally hypothesize that the relationship between white matter microstructural integrity and post-Visit 5 cognitive outcomes is independent of the severity of WMH, WM volumes, and/or hippocampal or AD signature region gray matter volumes at baseline.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

***Study design***

Longitudinal cohort study (Visit 5 to Visit 6)

***Exclusion criteria***

In all analyses, we will exclude participants with:

- No DTI data at Visit 5
- Prevalent stroke at Visit 5
- Neither black nor white

- Non-white from MN or MD sites
- Disallow use of genetic data or analyses for non-CVD research

In analyses of cognitive decline, we will restrict our analytical sample to those with complete Visit 5 cognitive data.

In analyses of incident MCI, we will restrict our sample to Visit 5 attendees deemed cognitively normal at Visit 5.

In analyses of incident dementia, we will restrict our sample to Visit 5 attendees without a diagnosis of dementia (Level 1, 2 or 3) at Visit 5.

***Cognitive Outcomes***

1) Cognitive decline: We will quantify cognitive change using global and domain-specific cognitive summary scores derived via latent variable methods as described previously.[55]
2) Incident MCI: We will consider persons who have incident MCI at Visit 6 if they were free of MCI or dementia at Visit 5 and the adjudicated diagnosis, based on Visit 6 cognitive assessment, is a diagnosis of MCI. We plan to censor persons with dementia at V6; however, depending on the number of MCI cases, we may consider a combined "incident MCI/dementia" outcome, which would also allow inclusion of those with cognitive impairment on surveillance that does not reach criteria for dementia.
3) Incident dementia: We will classify persons as having incident dementia between Visit 5 and Visit 6 if they were dementia-free at Visit 5 and were identified as having dementia according to (a) adjudicated diagnosis based on Visit 6 cognitive assessment, (b) dementia surveillance classification based on the AD8 and Six Item Screener administered as part of annual follow-up calls, or (c) based on a hospital discharge code/death code.

***Exposures***

We will consider white matter fractional anisotrophy (WM FA) and white matter mean diffusivity (WM MD) for seven regions of interest (ROIs): frontal, temporal, occipital, and parietal lobes, anterior and posterior corpus callosum, and an overall measure created by taking a weighted average of these six ROIs (capsular WM is not included), as derived previously[15]. Unless there is evidence of significant differences by regional ROI, we will focus on the overall measure.

***Covariates***

*(Note, the timing of assessment for hypertension and diabetes covariates was chosen based on prior work showing time-specific associations between vascular risk factors and WM FA or WM MD in ARIC[15] and known time-specific associations between vascular risk factors and cognition[56]. From this we conclude that midlife and late-life hypertension, and midlife diabetes may confound the association between DTI at Visit 5 and late-life cognitive outcomes.)*

We will adjust for age at Visit 5, gender, race-center, Visit 5 smoking status (current, former, never), body mass index (BMI) at Visit 5, apolipoprotein E ε4 genotype, hypertension at Visit 1 and Visit 5, diabetes status at Visit 1, prevalent coronary heart disease prior to Visit 5, and depressive symptoms at Visit 5. If missing data on covariates is substantial, we will consider imputing missing covariate data.

***Statistical Analysis***

*Primary Analyses:*

We will use logistic regression to quantify the association between WM FA and WM MD with incident MCI or dementia through Visit 6. We will use linear mixed effects models to quantify the association between WM FA and WM MD with cognitive decline between Visit 5 and Visit 6. All analyses will be

weighted using the sampling weights derived to correct for the stratified random sampling approach used to select ARIC participants into the MRI sub-sample. Given small sample size, we will consider dropping unimportant covariates (non-significant, effect size near null) from our analyses to improve power.

*Secondary analyses:*
In secondary analyses, we will further adjust all primary analyses for WMH volume, WM volume (WM at risk), hippocampal/AD signature region volume, and (to normalize these volume measures) total intracranial volume.

*Sensitivity Analysis:*

a) *Account for cohort attrition.* It is possible that selection bias due to cohort attrition impacts our study findings. Thus, we will implement inverse probability for attrition weighting to address this potential issue, extending models previously developed for this purpose.[15, 57, 58] We will also consider using MICE to impute cognitive test scores at V6 for those who participate in annual follow-up surveillance calls but do not complete cognitive testing at V6.
b) *Understand the impact of sampling.* We will also run analyses without sampling weights to understand the impact of the stratified sampling approach used to select persons into the MRI subsample.
c) *Use of multiple cognitive impairment ascertainment methods.* We will run analyses to investigate whether our findings for the association between white matter microstructural integrity and incident dementia are influenced by mode of dementia ascertainment between Visit 5 and Visit 6 (Visit 6, AFU calls, or hospitalization/death certificate codes). As people can transition from MCI to normal cognition or dementia, we will also consider analyses linking WM FA and WM MD to prevalent MCI at Visit 6 in all Visit 5 participants without dementia at Visit 5 (i.e. including persons categorized as either cognitively normal or having MCI at Visit 5).
d) *Effect modification.* If sample size allows, we will consider effect modification by APOE E4 status and race.
e) *Choice of models.* Visit 5 and Visit 6 are separated by only 4-5 years, and timing of incident dementia diagnoses will be largely dictated by timing of data collection. However, to use what timing data we have, we will also consider using Cox Proportional Hazards models or discrete time survival models for analyses of incident dementia.

***Limitations/Challenges***

The primary limitations of this study are the relatively short follow-up and potentially small numbers of cases for analyses of incident MCI and incident dementia. The short follow-up limits ability to detect long-term effects of white matter microstructural integrity on incident cognitive impairment. The small number of cases limits study power, and will likely preclude evaluation of effect modification. We are also limited to one MRI, and so cannot quantify the impact of change in WM microstructural integrity on our outcomes. In addition, we will focus on regional summaries of WM FA and WM MD, rather than measures based on tractography or analyses using voxel-wise comparisons. Similarly, we quantify WM FA and WM MD in total white matter, not normal appearing white matter. While this choice reflects the difficulties in segmentation, it differs from the most common approach. In this context, adjustment for WMH will also allow us to address issues related to differences in WM MD or WM FA due to differences in WMH burden, in addition to showing independent contributions of these two measures to cognition.[59] Bias is always a potential issue in epidemiologic studies. However, we will explore issues of residual

confounding, will address selection bias in our sensitivity analyses, and will anticipate measurement error will be non-differential and hence most likely conservative.

**7.a. Will the data be used for non-CVD analysis in this manuscript? _x__ Yes ____ No**

**b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _x__ Yes ____ No**
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?**
**__X__ Yes ____ No**

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes ____ No**

**9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

Previous studies proposed on brain MRI measurement and cognitive outcome include:
#2288, Associations of Brain Imaging with Cognitive Change over 20 years
#2266, Associations between brain vascular imaging features and regional volumetrics
#2586, Neural correlates of prior domain-specific cognitive decline: a voxel-based morphometry study

Other manuscript proposals dealing with DTI measures:
#2999 - Arterial stiffness, pressure pulsatility, and white matter integrity assessed by diffusion tensor imaging. The ARIC-NCS study

#3045 - Association of atrial fibrillation with white matter microstructural integrity using diffusion tensor imaging – The ARIC-NCS
#3035 - Physical activity in adulthood and subclinical brain MRI markers: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)
#2822 - Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET Study
#2729 - Neurocognitive correlates of mobility: ARIC-NCS

This paper also builds on published prior work by Dr. Power and many of the writing group members:
MP#2551 - Power, M. C., et al. (2017). "Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study." J Am Heart Assoc **6**(5).

We are also aware of a similar submitted MP by Aozhou Zhou on other MRI markers and our outcomes. We will coordinate with his efforts to allow parallel analyses.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No** ARIC-NCS

**11.b. If yes, is the proposal**

**_X__ A. primarily the result of an ancillary study (list number* _2008.06__)**

**___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

**13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication**. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

***Reference***


1. Alexander AL, Lee JE, Lazar M and Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics*. 2007;4:316-29.
2. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, Carmichael O, Wolf PA and DeCarli C. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol*. 2012;11:1039-47.
3. Salat DH, Tuch DS, Hevelone ND, Fischl B, Corkin S, Rosas HD and Dale AM. Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Ann N Y Acad Sci*. 2005;1064:37-49.
4. Ly M, Canu E, Xu G, Oh J, McLaren DG, Dowling NM, Alexander AL, Sager MA, Johnson SC and Bendlin BB. Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults. *Hum Brain Mapp*. 2014;35:2044-54.
5. Maillard P, Fletcher E, Lockhart SN, Roach AE, Reed B, Mungas D, DeCarli C and Carmichael OT. White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. *Stroke*. 2014;45:1721-6.

6. Maillard P, Carmichael O, Harvey D, Fletcher E, Reed B, Mungas D and DeCarli C. FLAIR and diffusion MRI signals are independent predictors of white matter hyperintensities. *AJNR Am J Neuroradiol*. 2013;34:54-61.
7. Maillard P, Fletcher E, Harvey D, Carmichael O, Reed B, Mungas D and DeCarli C. White matter hyperintensity penumbra. *Stroke*. 2011;42:1917-22.
8. Brickman AM, Zimmerman ME, Paul RH, Grieve SM, Tate DF, Cohen RA, Williams LM, Clark CR and Gordon E. Regional white matter and neuropsychological functioning across the adult lifespan. *Biol Psychiatry*. 2006;60:444-53.
9. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, Jack CR, Jr., Weiner M and DeCarli C. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol*. 2010;67:1370-8.
10. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA and DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461-8.
11. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D and DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology*. 2012;79:442-8.
12. Carmichael O, Mungas D, Beckett L, Harvey D, Tomaszewski Farias S, Reed B, Olichney J, Miller J and Decarli C. MRI predictors of cognitive change in a diverse and carefully characterized elderly population. *Neurobiol Aging*. 2012;33:83-95.
13. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, Hofman A and Breteler MM. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain*. 2005;128:2034-41.
14. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A and Breteler MM. Cerebral white matter lesions and the risk of dementia. *Arch Neurol*. 2004;61:1531-4.
15. Power MC, Tingle JV, Reid RI, Huang J, Sharrett AR, Coresh J, Griswold M, Kantarci K, Jack CR, Jr., Knopman D, Gottesman RF and Mosley TH. Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study. *J Am Heart Assoc*. 2017;6.
16. Teipel SJ, Meindl T, Wagner M, Stieltjes B, Reuter S, Hauenstein KH, Filippi M, Ernemann U, Reiser MF and Hampel H. Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. *J Alzheimers Dis*. 2010;22:507-22.
17. Nitkunan A, Barrick TR, Charlton RA, Clark CA and Markus HS. Multimodal MRI in cerebral small vessel disease: its relationship with cognition and sensitivity to change over time. *Stroke*. 2008;39:1999-2005.
18. Barrick TR, Charlton RA, Clark CA and Markus HS. White matter structural decline in normal ageing: a prospective longitudinal study using tract-based spatial statistics. *Neuroimage*. 2010;51:565-77.
19. Charlton RA, Schiavone F, Barrick TR, Morris RG and Markus HS. Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. *J Neurol Neurosurg Psychiatry*. 2010;81:13-9.
20. Bagepally BS, Halahalli HN, John JP, Kota L, Purushottam M, Mukherjee O, Sivakumar PT, Bharath S, Jain S and Varghese M. Apolipoprotein E4 and brain white matter integrity in Alzheimer's disease: tract-based spatial statistics study under 3-Tesla MRI. *Neurodegener Dis*. 2012;10:145-8.

21. Heise V, Filippini N, Ebmeier KP and Mackay CE. The APOE varepsilon4 allele modulates brain white matter integrity in healthy adults. *Mol Psychiatry*. 2011;16:908-16.
22. Honea RA, Vidoni E, Harsha A and Burns JM. Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. *J Alzheimers Dis*. 2009;18:553-64.
23. Kljajevic V, Meyer P, Holzmann C, Dyrba M, Kasper E, Bokde AL, Fellgiebel A, Meindl T, Hampel H and Teipel S. The epsilon4 genotype of apolipoprotein E and white matter integrity in Alzheimer's disease. *Alzheimers Dement*. 2014;10:401-4.
24. O'Dwyer L, Lamberton F, Matura S, Scheibe M, Miller J, Rujescu D, Prvulovic D and Hampel H. White matter differences between healthy young ApoE4 carriers and non-carriers identified with tractography and support vector machines. *PLoS One*. 2012;7:e36024.
25. Newlander SM, Chu A, Sinha US, Lu PH and Bartzokis G. Methodological improvements in voxel-based analysis of diffusion tensor images: applications to study the impact of apolipoprotein E on white matter integrity. *Journal of magnetic resonance imaging : JMRI*. 2014;39:387-97.
26. Smith CD, Chebrolu H, Andersen AH, Powell DA, Lovell MA, Xiong S and Gold BT. White matter diffusion alterations in normal women at risk of Alzheimer's disease. *Neurobiol Aging*. 2010;31:1122-31.
27. Patel KT, Stevens MC, Pearlson GD, Winkler AM, Hawkins KA, Skudlarski P and Bauer LO. Default mode network activity and white matter integrity in healthy middle-aged ApoE4 carriers. *Brain imaging and behavior*. 2013;7:60-7.
28. Brown JA, Terashima KH, Burggren AC, Ercoli LM, Miller KJ, Small GW and Bookheimer SY. Brain network local interconnectivity loss in aging APOE-4 allele carriers. *Proc Natl Acad Sci U S A*. 2011;108:20760-5.
29. Burgmans S, Gronenschild EH, Fandakova Y, Shing YL, van Boxtel MP, Vuurman EF, Uylings HB, Jolles J and Raz N. Age differences in speed of processing are partially mediated by differences in axonal integrity. *Neuroimage*. 2011;55:1287-97.
30. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK and Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et biophysica acta*. 2012;1822:386-400.
31. Madden DJ, Spaniol J, Costello MC, Bucur B, White LE, Cabeza R, Davis SW, Dennis NA, Provenzale JM and Huettel SA. Cerebral white matter integrity mediates adult age differences in cognitive performance. *J Cogn Neurosci*. 2009;21:289-302.
32. Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR and Provenzale JM. Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage*. 2004;21:1174-81.
33. Salami A, Eriksson J, Nilsson LG and Nyberg L. Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. *Biochimica et biophysica acta*. 2012;1822:408-15.
34. Charlton RA, Landau S, Schiavone F, Barrick TR, Clark CA, Markus HS and Morris RG. A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. *Neurobiol Aging*. 2008;29:1547-55.
35. O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC and Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*. 2001;57:632-8.

36. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, Niessen WJ, Van der Lugt A and Breteler MM. White matter microstructural integrity and cognitive function in a general elderly population. *Arch Gen Psychiatry*. 2009;66:545-53.
37. Sedaghat S, Cremers LGM, de Groot M, Hofman A, van der Lugt A, Niessen WJ, Franco OH, Dehghan A, Ikram MA and Vernooij MW. Lower microstructural integrity of brain white matter is related to higher mortality. *Neurology*. 2016;87:927-934.
38. Charlton RA, Barrick TR, McIntyre DJ, Shen Y, O'Sullivan M, Howe FA, Clark CA, Morris RG and Markus HS. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology*. 2006;66:217-22.
39. Schiavone F, Charlton RA, Barrick TR, Morris RG and Markus HS. Imaging age-related cognitive decline: A comparison of diffusion tensor and magnetization transfer MRI. *Journal of magnetic resonance imaging : JMRI*. 2009;29:23-30.
40. Sala M, de Roos A, Blauw GJ, Middelkoop HA, Jukema JW, Mooijaart SP, van Buchem MA, de Craen AJ and van der Grond J. Association between changes in brain microstructure and cognition in older subjects at increased risk for vascular disease. *BMC Neurol*. 2015;15:133.
41. Ukmar M, Makuc E, Onor ML, Garbin G, Trevisiol M and Cova MA. Evaluation of white matter damage in patients with Alzheimer's disease and in patients with mild cognitive impairment by using diffusion tensor imaging. *La Radiologia medica*. 2008;113:915-22.
42. Tuladhar AM, van Norden AG, de Laat KF, Zwiers MP, van Dijk EJ, Norris DG and de Leeuw FE. White matter integrity in small vessel disease is related to cognition. *NeuroImage Clinical*. 2015;7:518-24.
43. van Norden AG, de Laat KF, van Dijk EJ, van Uden IW, van Oudheusden LJ, Gons RA, Norris DG, Zwiers MP and de Leeuw FE. Diffusion tensor imaging and cognition in cerebral small vessel disease: the RUN DMC study. *Biochimica et biophysica acta*. 2012;1822:401-7.
44. Chua TC, Wen W, Slavin MJ and Sachdev PS. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. *Current opinion in neurology*. 2008;21:83-92.
45. Huang J and Auchus AP. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. *Ann N Y Acad Sci*. 2007;1097:259-64.
46. Huang J, Friedland RP and Auchus AP. Diffusion tensor imaging of normal-appearing white matter in mild cognitive impairment and early Alzheimer disease: preliminary evidence of axonal degeneration in the temporal lobe. *AJNR Am J Neuroradiol*. 2007;28:1943-8.
47. Naggara O, Oppenheim C, Rieu D, Raoux N, Rodrigo S, Dalla Barba G and Meder JF. Diffusion tensor imaging in early Alzheimer's disease. *Psychiatry Res*. 2006;146:243-9.
48. Medina D, DeToledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, Bennett DA, Leurgans S, Turner DA and Stebbins GT. White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiol Aging*. 2006;27:663-72.
49. Oishi K, Mielke MM, Albert M, Lyketsos CG and Mori S. DTI analyses and clinical applications in Alzheimer's disease. *J Alzheimers Dis*. 2011;26 Suppl 3:287-96.
50. Stebbins GT and Murphy CM. Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. *Behavioural neurology*. 2009;21:39-49.
51. Fellgiebel A, Wille P, Muller MJ, Winterer G, Scheurich A, Vucurevic G, Schmidt LG and Stoeter P. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. *Dement Geriatr Cogn Disord*. 2004;18:101-8.

52. van Uden IWM, van der Holst HM, Schaapsmeerders P, Tuladhar AM, van Norden AGW, de Laat KF, Norris DG, Claassen J, van Dijk EJ, Richard E, Kessels RPC and de Leeuw FE. Baseline white matter microstructural integrity is not related to cognitive decline after 5 years: The RUN DMC study. *BBA Clinical*. 2015;4:108-114.
53. van Uden IW, van der Holst HM, Tuladhar AM, van Norden AG, de Laat KF, Rutten-Jacobs LC, Norris DG, Claassen JA, van Dijk EJ, Kessels RP and de Leeuw FE. White Matter and Hippocampal Volume Predict the Risk of Dementia in Patients with Cerebral Small Vessel Disease: The RUN DMC Study. *J Alzheimers Dis*. 2016;49:863-73.
54. Jokinen H, Schmidt R, Ropele S, Fazekas F, Gouw AA, Barkhof F, Scheltens P, Madureira S, Verdelho A, Ferro JM, Wallin A, Poggesi A, Inzitari D, Pantoni L and Erkinjuntti T. Diffusion changes predict cognitive and functional outcome: the LADIS study. *Ann Neurol*. 2013;73:576-83.
55. Gross AL, Power MC, Albert MS, Deal JA, Gottesman RF, Griswold M, Wruck LM, Mosley TH, Jr., Coresh J, Sharrett AR and Bandeen-Roche K. Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiology*. 2015;26:878-87.
56. Qiu C, Winblad B and Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4:487-99.
57. Power MC, Deal JA, Sharrett AR, Jack CR, Jr., Knopman D, Mosley TH and Gottesman RF. Smoking and white matter hyperintensity progression: The ARIC-MRI Study. *Neurology*. 2015.
58. Power MC, Schneider AL, Wruck L, Griswold M, Coker LH, Alonso A, Jack CR, Jr., Knopman D, Mosley TH and Gottesman RF. Life-course blood pressure in relation to brain volumes. *Alzheimers Dement*. 2016;12:890-9.
59. Svard D, Nilsson M, Lampinen B, Latt J, Sundgren PC, Stomrud E, Minthon L, Hansson O and van Westen D. The effect of white matter hyperintensities on statistical analysis of diffusion tensor imaging in cognitively healthy elderly and prodromal Alzheimer's disease. *PLoS One*. 2017;12:e0185239.