ARIC Manuscript Proposal #2551

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife and late life vascular risk factors and white matter integrity assessed using diffusion tensor imaging: the ARIC-NCS study

b. Abbreviated Title (Length 26 characters): Vascular risk factors and DTI

2. Writing Group:

Writing group members: Rebecca Gottesman, Michael Griswold, Cliff Jack, Tom Mosley (senior), Melinda Power (first), 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:

Completion 4-6 months after approval and receipt of updated DTI data.

4. Rationale:

The presence of vascular risk factors, particularly hypertension, high cholesterol, and diabetes, appears to increase risk of subsequent cognitive decline and dementia, with the strongest evidence supporting a link between midlife risk factors and late life cognition.[1-3] As differences in white matter tract integrity are related to differences in cognitive performance,[4-7] effects of vascular risk factors on white matter tract integrity may partially mediate the adverse consequences of these vascular risk factors on cognition.

Diffusion tensor imaging (DTI) is an MRI imaging technique which measures the diffusion of water.[8] Commonly used DTI measures include fractional anistotrophy (FA), which measures directional constraint of water diffusion, and mean diffusivity (MD), which measures the average rate of diffusion in any direction. As white matter is generally anisotrophic (i.e. the direction of water diffusion is highly constrained), lower FA and higher MD are thought to reflect worse white matter tract integrity, at least in regions lacking white matter tract crossings. Supporting its importance in the maintenance of brain function, white matter integrity, assessed with DTI, appears to decline with age,[9-11] and also appears to both predict cognitive test performance and to mediate the association between age and cognitive test performance.[4-7] DTI complements other neuroimaging techniques because it appears to be sensitive to microscopic white matter integrity changes which may not be quantifiable using other MRI imaging techniques. Specifically, consideration of FA and MD provides additional information above and beyond that provided by white matter hyperintensity (WMH) volumes which, when observed in older adults, likely reflect ischemic damage to areas of white matter and small vessel disease.[12] For example, in a small study of health adults with both regional WMH volumes and DTI-based measures of white matter integrity, regional WMH volumes were predictive of regional FA and a measure of global diffusivity for only some regions, and when associated, accounted for only a small portion of the variance in the DTI measures.[9] DTI-based measures also appear to provide earlier evidence of white matter integrity damage than WMH or WM volumes,[13,14] and may predict subsequent white matter loss.[15]

Multiple studies suggest worse white matter integrity in those with hypertension.[9,13,16-23] For example, in a small study of healthy adults, age-related reductions in posterior white matter integrity were stronger with diagnosed hypertension as well as increasing duration of hypertension, and pulse pressure was associated with decreased FA and increased diffusivity.[9] Likewise, in cross-sectional analyses considering 579 young adults (mean age 39 years) from the Framingham Heart Study,[13] higher systolic blood pressure was associated with decreased FA and increased MD in several regions, particularly the anterior corpus callosum, inferior fronto-occipital fasciculi, and the fibers projecting from the thalamus to the superior frontal gyrus. Similarly, in a small sample of African Americans, hypertension was associated with reduced FA in the genu of the corpus callosum, an association which was strongest in those who were not taking antihypertensive medications. [20] These findings are consistent with the established association between blood pressure and WMH.[24-45]

In comparison, there are relatively few studies looking at the association between cholesterol and DTI-based measures of white matter integrity. We are aware of only three studies linking serum lipid levels to white matter integrity, all of which used voxel-wise comparisons of FA in relation to measured lipid levels. In a sample of 125 healthy middle aged to older adults, voxel-wise analyses suggested higher LDL, and to a lesser extent total cholesterol and lower HDL, was associated with worse white matter integrity in multiple regions.[46] In a separate cohort of 403 young Australian twins, voxel-wise analyses suggested that elevated HDL, and perhaps surprisingly, elevated total cholesterol levels in adolescence were associated with higher FA (indicating greater white matter integrity) in early adulthood.[47] Finally, voxel-wise analyses in 49 young adults (mean age 33 years), suggested that higher plasma LDL levels were correlated with lower FA in the right frontal corticospinal tract in some subgroups (men, but not women; overweight/obese but not normal weight).[48]

Similarly, relatively few studies have investigated the association between type II diabetes and white matter integrity. In a study of 37 middle-aged adults, diabetics exhibited lower FA in the cingulum bundle and the uncinate fasciculi compared to non-diabetics.[49] In a small study of 40 type II adult diabetics and 97 non-diabetic controls, diabetes and duration of

diabetes was associated with higher global mean diffusivity.[50] In additional voxel-wise analyses, FA was decreased in the bilateral frontal white matter in diabetics and duration of diabetes was associated with differences in FA in multiple brain regions.[50] Similarly, voxel-wise analyses also indicated differences in white matter FA between controls and adolescents with type II diabetes,[51] adult diabetics[52] and adult diabetics with gastrointestinal symptoms. [53]

The literature linking hypertension, cholesterol and diabetes to DTI-based measures of white matter integrity has a number of notable limitations. First, this body of literature is almost exclusively cross-sectional, linking current risk factor status to current white matter integrity. Prospective studies are needed to identify etiologically relevant exposure periods. Of particular interest is whether midlife or late life exposures are most relevant to poor late life white matter integrity, given evidence of stronger associations between midlife risk factors and late life cognition. Second, many also consider white matter integrity in participants who are too young to be diagnosed with dementia or exhibit symptoms of cognitive decline; therefore it is difficult to use these studies to support claims or hypotheses assuming that declines white matter integrity mediates the relation between these risk factors and dementia risk. Third, these studies are typically very small by epidemiologic standards - many enroll only 15 to 150 persons – which makes chance findings more likely and precludes adequate adjustment for many potential confounders. Participant samples are also often convenience samples; replication in community-based studies is warranted to ensure the selection process has not induced associations which are lacking in the general population. Finally, most studies have focused on just a few pre-selected ROIs of used a voxel-wise approach. Exploratory investigation of multiple ROIs of potential interest (as opposed to one or two ROIs chosen a priori) may yield more information on which areas (and potentially the order of areas) affected by these risk factor. An ROI approach may also have reduced chances of a type 1 error compared to studies using a voxel-wise approach, which can be employed for similar purposes. Studies using the ROI approach are also more reproducible and comparable, which may help build the case for an effect of vascular risk factors on white matter integrity.

As such, we propose to evaluate the relation between vascular risk factors (specifically hypertension, high cholesterol, and diabetes) in midlife and late life and DTI-based measures of white matter integrity, FA and MD, in a sample of ARIC-NCS participants who completed brain MRI in late life.

5. Main Hypothesis/Study Questions:

We hypothesize that presence of vascular risk factors, specifically hypertension, high cholesterol, and diabetes, in both midlife and late life will be associated with worse white matter integrity, operationalized as lower fractional anisotrophy (FA) and higher mean diffusivity (MD). We further hypothesize that these associations will be stronger in analyses considering midlife vascular risk factors than those considering late life vascular risk factors.

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:
Cross-temporal study of the association between Visit 1 vascular risk factors and Visit 5 DTI.
Cross-sectional study of the association between Visit 5 vascular risk factors and Visit 5 DTI.

Exclusions for inclusion in primary analyses:
No DTI data from ARIC-NCS. Prevalent stroke at Visit 5. Not black or white. Black from MD or MN. Not allowed to use DNA. Note: Sensitivity analyses and analyses comparing participants to non-participants will include additional participants.

Dependent variables:
Primary analyses will consider average fractional anisotrophy (FA) and mean diffusivity (MD) in white matter in regions of interest (ROIs) defined using the Lobar-22 atlas. Secondary analyses may also consider mean diffusivity (MD) in gray matter and white+gray matter in ROIs defined using the same atlas, or use of median, rather than average FA and MD. We may also consider summary measures of MD or FA over larger regions.

Independent variables:
Exposures at Visit 1 and Visit 5: Diabetes, fasting glucose and/or HBA1C, hypertension (yes/no), systolic blood pressure, diastolic blood pressure, total cholesterol, LDL, HDL, triglycerides.

Effect modifiers:
Race-center, age, gender, APOE4.

Statistical Analyses:

We will use separate weighted linear regression models to assess the relation between each of our vascular risk factors and each of our DTI outcomes; for primary analyses we will incorporate the ARIC-NCS MRI sampling weights. All models will be adjusted for age, gender, race/center, APOE4, education, BMI, smoking status. Models for diabetes and fasting glucose and/or HBA1C will be additionally adjusted for use of diabetic medications, hypertension and total cholesterol. Models for hypertension and blood pressure will be additionally adjusted for anti-hypertensive medication use, diabetes status and total cholesterol. Models for lipids will be additionally adjusted for statin or other lipid therapy, diabetes and hypertension. We will use multiple imputation to account for missing exposure and covariate data. We additionally propose several secondary analyses. First, we will stratify based on cognitive status (normal versus adjudicated MCI/dementia). Second, we will repeat all of the above analyses adjusting for white matter hyperintensity volumes to provide a sense of what DTI offers over and above WMH. Sensitivity analyses will omit use of sampling weights and add use of inverse probability weighting to account for attrition from Visit 1 to Visit 5. Additional analyses may also consider risk factor status at an intermediate time point (e.g. Visit 4) or use of median FA and MD as the outcome.

Limitations/Challenges:
We have only one measure of FA and MD, and so are limited to cross-sectional or cross-temporal analyses. In addition, we will focus on regional summaries of FA and MD, rather than measures based on tractography or analyses using voxel-wise comparisons. While we will adjust for a priori specified confounders and incorporate sampling weights, and in sensitivity analyses, inverse probability of attrition weights, the possibility of residual bias due to confounding or selection remains. Some misclassification of our exposure variable is expected; however it is expected to be independent of FA/MD and so any resulting bias is expected to be towards the null. We currently propose to use only Visit 1 and Visit 5 risk factor status; however, we may also consider an intermediate time point and we expect that this analysis will be followed by more in-depth considerations of these risk factors in relation to white matter integrity. Finally, while we will consider medication use as a confounder, we will not specifically address questions of the utility of treatment.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __ X__ 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? ____ 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)?

#2315 Association of diabetes with brain magnetic resonance imaging

#2351 Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI

#1894 Retinal microvascular abnormalities predict progression of white matter disease and incident lacunar infarcts: The ARIC MRI study

#1387 Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI Study

Knopman, D. S., et al. (2011). "Vascular risk factors and longitudinal changes on brain MRI: the ARIC study." Neurology **76**(22): 1879-1885.

Gottesman, R. F., et al. (2010). "Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study." Stroke 41(1): 3-8.

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

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number ARIC NCS 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.

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