

ARIC Manuscript Proposal # 2565

PC Reviewed: 10/8/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Retinal Microvascular Abnormalities and Subsequent MRI Cerebrovascular and Neurodegenerative Signs: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

b. Abbreviated Title (Length 26 characters): Retinal MRI

2. Writing Group:

(Alphabetical) Marilyn Albert, Karen Bandeen-Roche, Jennifer Deal, Rebecca Gottesman, Mike Griswold, Barbara Klein, Ron Klein, David Knopman, Tom Mosley, Melinda C. Power, A. Richey Sharrett

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

Name: **Jennifer Deal**
Address: 2024 E. Monument St, Suite 2-700
Baltimore, MD 21205
Phone: 410 955-1909
E-mail: jdeal1@jhu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: A. Richey Sharrett
Address: 615 N Wolfe St, Room W6009B
Baltimore, MD 21205

3. Timeline:

Manuscript will be completed in 6 months. Abstract for 2020 AHA-Epi conference.

4. Rationale:

Cerebrovascular small vessel disease (SVD), as evidenced through brain imaging as lacunes and white matter hyperintensities, is a pathological substrate for cognitive decline and dementia in older adults. The overall importance of SVD in the pathogenesis of cognitive decline is not known precisely, and may be under-recognized clinically.¹⁻⁴ Notably, presence of SVD that is apparent at autopsy, but is too small to be seen using standard brain imaging techniques, is strongly related to vascular cognitive impairment assessed within months prior to death.⁵

Retinal fundus photography offers a non-invasive means to visualize microvascular changes in the eye. Because blood vessels in the eye are anatomically and physiologically similar to those in the brain, retinal photography may also offer insight into small vessel changes within the

brain,⁶ including those too small to be visualized with brain imaging, and these may be responsible for losses in brain volumes. Retinal vascular abnormalities are associated with increased cardiovascular risk, including incident stroke.^{7,8}

Previous studies in ARIC have supported the hypothesis that retinal imaging is a marker for cerebrovascular changes within the brain, in both cross-sectional^{7,9,10} and prospective^{11,12} analyses. In 810 ARIC participants, retinopathy and retinal arteriovenous (AV) nicking were associated with ventricular enlargement over 10 years; odds ratios and 95% confidence intervals were 2.03 (1.02-4.42) and 2.19 (1.23-3.90), respectively¹¹. Both retinopathy and AV nicking were also independently associated with incident silent cerebral infarct (OR: 2.82, 95% CI: 1.42-5.60; and OR: 2.82, 95% CI: 1.66-4.76, respectively), and, more specifically, incident silent lacunar infarct (OR: 3.19, 95% CI: 1.56-6.50; and OR: 2.48, 95% CI: 1.39-4.40, respectively). Additionally, AV nicking was related to the development of incident white matter lesions (OR: 2.12, 95% CI: 1.18, 3.81) and white matter progression (OR: 2.2, 95% CI: 1.00-5.88) during a median follow-up time of 10.5 years.¹²

5. Main Hypothesis/Study Questions:

Microvascular retinal abnormalities measured in 1993-95 are associated with subsequent cerebrovascular and neurodegenerative signs measured on brain MRI 18 years later at NCS/Visit 5 (2011-13). We hypothesize that these associations:

1. Are similar in persons with and without diabetes and
2. Are stronger in persons with apoE4

To evaluate the clinical utility of retinal signs as a marker of brain MRI signs, we will also assess the cross-sectional association of retinal abnormalities collected at Visit 5 (2011-13) with brain MRI at the same visit (NCS/Visit 5, 2011-13). One possible limitation of this analysis is failure of the retinal photography at Visit 5, as lack of dilation of the pupil in older eyes is common without eye drops.

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: Prospective observational study of men and women who underwent retinal photography at Visit 3 (1993-95) and brain MRI at NCS/Visit 5 (2011-13). Additionally, we will quantify the association between retinal signs at Visit 3 (1993-95) and change in MRI signs from the Brain MRI Study (2004-06) to MRI at NCS/Visit 5 (2011-13).

Outcomes: The primary outcome measures will be brain volume and markers of cerebrovascular disease as measured on brain MRI at NCS/Visit 5 (2011-13):

- White matter hyperintensities (volume and volume by location)
- Cortical infarcts (number and number by size: <10mm, ≥10mm)
- Lacunar infarcts (number and number by location)
- Volume (total and region-specific: frontal lobe, parietal lobe, occipital lobe, temporal lobe, deep gray matter, hippocampus and Alzheimer's disease (AD) signature region)
- Microhemorrhages (number and number by location: deep, subcortical versus lobar, cortical)

- Poorer white matter integrity as measured by diffusion tensor imaging (DTI), specifically with lower fractional anisotropy (FA) and higher mean diffusivity (MD)

As methods to evaluate change/ progression from Brain MRI (2004-06) to NCS/Visit 5 (2011-13) using rank-ordering are established, we will also quantify the association of retinal signs and change in MRI signs.

Exposures: Retinal photographs were collected for the first time in ARIC at Visit 3 (1993-95) and again at Visit 5 (2011-13). Photographs were obtained in a single eye for each participant by trained technicians using nonmydriatic fundus cameras. All photographs were assessed at a central reading center by trained, certified graders who were masked to participants' hypertensive and diabetic status.¹³

Four primary retinal measures will be included in the analysis: retinopathy, focal arteriolar narrowing, arteriovenous (AV) nicking, and generalized arteriolar narrowing.^{13,14} A combined retinal microvascular score (developed in the analysis of cognitive change (ARIC MP#2169) will also be included.

Retinopathy will be defined as the 'definite' presence of at least one of the following lesions: retinal microaneurysms, soft exudates, hard exudates, retinal hemorrhages, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels, vitreous hemorrhage, disc swelling, or laser photocoagulation scars.

Focal arteriolar narrowing was defined as absent, definite or questionable based on the number and grading of arterioles estimated to be $\geq 50 \mu\text{m}$ in diameter that had a constricted area $\leq 2/3$ the width of proximal and distal vessel segments.¹³ For the current analysis, arteriolar narrowing will be considered present given a grade of "definite".¹⁵

AV nicking was defined as absent, definite or questionable based on the number and grading of at least one venous blood column(s) that was(were) tapered on both sides of its crossing underneath an arteriole.¹³ For the current analysis, AV nicking will be considered present given a grade of "definite".

Generalized arteriolar narrowing was evaluated using enhanced digital images and image processing software. Arteriolar diameters within a pre-specified zone surrounding the optic nerve were combined quantified as the central retinal arteriolar equivalent (CRAE) using the following formula in order to adjust for branching:¹³

$$\text{Arterioles } W_c = \sqrt{0.87 * W_a^2 + 1.01 * W_b^2 - 0.22 * W_a * W_b - 10.76}$$

where W_c = the caliber of the trunk vessel

W_a = the caliber of the smaller branch, and

W_b = the caliber of the larger branch

In keeping with previous analysis in this cohort, presence of generalized narrowing will be defined in this study as the lowest 25th percentile of CRAE.¹⁴

Additional independent variables:

Demographic information was collected at Visit 1, including age (years), sex, education, occupational class, income, race/ethnicity, study site and apoE4.

Disease and health behavior covariates were collected at each study visit, including self-reported cigarette smoking status and drinking status (never, former or current) and body mass index (BMI) (kg/m²). Hypertension will be considered present based on a diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥ 140 mmHg, or use of hypertensive medications. Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes.

Statistical analysis:

Multiple linear regression will be used to estimate the associations between retinal abnormalities and brain volumes and white matter integrity measures (FA and MD). Poisson regression or negative binomial (if overdispersion is present) will be used to estimate the association between retinal abnormalities and counts of MRI markers (microhemorrhages, etc). In keeping with MRI workgroup recommendations, analyses will be weighted to account for brain MRI sampling and refusals. Analyses will be adjusted for demographic, behavioral and disease covariates, as well as total intracranial volume. In sensitivity analysis, we will conduct inverse probability of attrition weighting (IPAW) to account for attrition prior to NCS/Visit 5.

References:

1. Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: White matter hyperintensity progression matters. *Neurology*. 2009;73(2):120-125.
2. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke*. 1998;29(2):388-398.
3. Kuller LH, Lopez OL, Jagust WJ, et al. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. *Neurology*. 2005;64(9):1548-1552.
4. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the Cardiovascular Health Cognition Study. *Neuroepidemiology*. 2003;22(1):13-22.
5. White L. Brain lesions at autopsy in older Japanese-american men as related to cognitive impairment and dementia in the final years of life: A summary report from the honolulu-asia aging study. *J Alzheimers Dis*. 2009;18(3):713-725.
6. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: A rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. 2005;206(4):319-348.
7. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA*. 2002;288(1):67-74.
8. Kuller LH, Longstreth WT, Jr, Arnold AM, et al. White matter hyperintensity on cranial magnetic resonance imaging: A predictor of stroke. *Stroke*. 2004;35(8):1821-1825.
9. Cooper LS, Wong TY, Klein R, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: The atherosclerosis risk in communities study. *Stroke*. 2006;37(1):82-86.
10. Wong TY, Mosley TH, Jr, Klein R, et al. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. *Neurology*. 2003;61(6):806-811.
11. Kawasaki R, Cheung N, Mosley T, et al. Retinal microvascular signs and 10-year risk of cerebral atrophy: The Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2010;41(8):1826-1828.
12. Cheung N, Mosley T, Islam A, et al. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: A prospective study. *Brain*. 2010;133(Pt 7):1987-1993.

13. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology*. 1999;106(12):2269-2280.
14. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: The ARIC 14-year follow-up study. *Neurology*. 2009;73(11):862-868.
15. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: The Atherosclerosis Risk in Communities Study. *Stroke*. 2002;33(6):1487-1492.

7.a. Will the data be used for non-CVD analysis in this manuscript?

☐ 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? N/A**

☐ 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?

☐ 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"? N/A**

☐ 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.cscce.unc.edu/ARIC/search.php>

☒ 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)?**

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

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

☒ **A. primarily the result of an ancillary study (list number* _____)**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _1999.01_____)**

1991.01 [MRI and Neurocognitive Longitudinal Study \(BrainMRI\)](#) (Mosley)

2008.06 Prediction of cognitive impairment from mid-life vascular risk factors and markers: The ARIC Neurocognitive Study (ARIC-NCS)

*ancillary studies are listed by number at <http://www.csc.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.csc.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.