ARIC Manuscript Proposal # 3068

1.a. Full Title: Association of Retinal Microvascular Abnormalities and Cognitive Status: The Atherosclerosis Risk in Communities Neurocognitive Study

  b. Abbreviated Title (Length 26 characters):

2. Writing Group:
    (Alphabetical) Ali Abraham, Jennifer A. Deal, Moon Jeong Lee, Pradeep Ramulu, A. Richey Sharrett

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

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3. Timeline:
The manuscript will be completed in 12 months.

4. Rationale:

Alzheimer's disease (AD) and vascular dementia are the two most common types of dementia among Western countries, accounting for approximately 80% of all dementias.[1] With the rapidly aging population and growing burden of dementia, understanding the neuropathology of various etiologies and finding early markers of dementia have become increasingly important.[2] Vascular contributions are common and they are important to cognitive impairment, both due to Alzheimer's disease and vascular dementia.[3] The vascular defects most strongly associated with

cognitive impairment/dementia have been cited as microvascular infarcts as opposed to the larger more visible cerebrovascular lesions detectable on MRI.[4,5]

There are several compelling reasons to believe that cerebral microvascular findings may be reflected in the retinal microvasculature. Both the retina and optic nerve share a common embryological origin, extending from the diencephalon during development.[6] In addition to shared embryology, there are close anatomic similarities between the microvasculature of the brain and retina.[7] The blood-ocular barrier shares similar regulatory processes with the blood-brain barrier in terms of autoregulation, low flow and oxygen extraction.[8] Based on shared embryology and structure, the eye and brain microvasculatures may share common physiology and susceptibility to disease processes.[6,9–11] This suggests that retinal microvasculature may serve as a reference for general microvascular health in the brain. Thus, using retinal fundus photography to examine retinal microvasculature is a potentially highly useful, noninvasive method of studying cerebral microvasculature.

Previous ARIC studies have demonstrated an association between retinal microvascular markers and both prevalence and progression of brain microvascular disease. Retinopathy (OR 3.18; 95% CI 1.71-5.89) and its components: microaneurysms (OR 3.06; 95% CI 1.33-7.07), retinal hemorrhage (OR 3.02; 95% CI 1.27-7.20), arteriovenous (AV) nicking (OR 1.93; 95% CI 1.24-3.02) and focal arteriolar narrowing (OR 1.76; 95% CI 1.19-2.59) were associated with a higher prevalence of new brain microvascular disease.[12] Cheung et al. also found that retinopathy was associated with cerebral infarcts (OR 2.82; 95% CI 1.42-5.60) and lacunar infarcts (OR 3.19; 95% CI 1.56-6.50).[13] AV nicking was also associated with cerebral infarcts (OR 2.82; 95% CI 1.66-6.47), lacunar infarcts (OR 2.48; 95% CI 1.39-4.40) and white matter lesions (OR 2.12; 95% CI 1.18-3.81).[13]

In addition, previous studies have found associations between retinal microvascular abnormalities and cognitive function. Wong et al. demonstrated that retinopathy was associated with lower cognitive test scores.[14] Individuals with Delayed Word Recall test scores 2 SD or lower than the mean had a higher odds of retinopathy (OR 2.60; 95% CI 1.30-2.91), microaneurysms (OR 3.00; 95% CI 1.91-4.98), retinal hemorrhage (OR 3.39; 95% CI 1.99-5.78) and soft exudates (OR 3.07; 95% CI 1.53-6.17).[14] In the Cardiovascular Health Study, there was an association between retinopathy and worse cognitive function in older individuals showing that persons with retinopathy had lower Digit Symbol Substitution Test Scores (OR 2.10; 95% CI 1.04-4.24).[15] Lesage et al. also found that retinopathy was associated with an average decline of -1.64 words per decade on the Word Fluency test (95%CI -3.3-(-0.02)) compared to no decline in those without retinopathy.[16] They also found that rapid decline in the Digit Symbol Substitution Test was associated with retinopathy (OR 2.18; 95% CI 1.02-4.64) suggesting that microvascular contributions to cognitive impairment may be detectable on retinal imaging.[16]

Thus, several studies have already demonstrated the potential to use retinal microvasculature as a reference for brain microvasculature and the association of retinal microvasculature abnormalities with cognition. This study will add to the current literature as a higher prevalence of retinal vascular abnormalities is expected at visit 5 compared to retinal findings analyzed previously at ARIC visit 3. This may elucidate associations between retinal abnormalities and cognitive status that have not previously been evident due to lower rates of observed

microvascular retinal abnormalities. These associations may differ between the two etiologies of MCI/dementia assessed in the ARIC study. If differential associations exist, retinal markers may offer a way to classify patients with cognitive impairment as MCI/dementia due to vascular disease vs. AD-related, allowing clinicians to more accurately predict the course of the disease. These cross-sectional associations at visit 5 are clinically applicable to patients presenting with cognitive deficits. The cross-sectional measurement of retinal signs in these patients may help clarify the underlying etiology of cognitive impairment.

5. Main Hypothesis/Study Questions:

We hypothesize that microvascular retinal abnormalities at visit 5 (2011-2013) are cross-sectionally associated with MCI and dementia due to cerebrovascular disease. These associations may be weaker in individuals with MCI and dementia due to AD.

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:

This cross-sectional observational study will involve analysis of retinal data and cognitive status collected at ARIC visit 5.

Inclusion/Exclusion criteria:

We will examine the data for all ARIC participants who underwent retinal photography at visit 5 who also completed cognitive testing at visit 5.

Primary dependent variable:
Cognitive data: (taken at visit 5)
The primary outcome will be cognitive status. The 3 categories of cognitive status that will be assessed are: normal, MCI and dementia. The combined group of MCI and dementia will also be sub-classified in two mutually exclusive groups: MCI/dementia with a primary or secondary diagnosis of cerebrovascular disease and MCI/dementia with a primary diagnosis of AD, consistent with ongoing work in ARIC (MP2797).

The algorithm used for diagnosis incorporated scores from the MMSE, the sum of the six domain ratings in the CDR, z-scores from the current neuropsychological test battery and change scores from the serial 3-test ARIC cognitive assessments and the FAQ. The expert dementia classification committee then reviewed the cases to render syndromic and etiologic diagnoses.[17]

Primary independent variables:
Retinal variables: (taken at visit 5)
In ARIC NCS, two fundus photographs were taken of each eye using a digital camera. All photographs were graded by trained, certified graders at the Ocular Epidemiology Reading Center (OREC) at the University of Wisconsin-Madison. The retinal variables of interest include retinopathy, hemorrhages and microaneurysms, soft exudates, AV nicking, focal narrowing and CRAE.

1) Retinopathy was defined by the "definite" detection of at least one of the following lesions: retinal microaneurysms, soft exudates, hard exudates, retinal hemorrhages, macular edema, intraretinal microvascular abnormalities, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels, vitreous hemorrhage, disc swelling, or laser photocoagulation scars.

2) Hemorrhages and Microaneurysms was defined as absent, questionable, definite microaneurysms only, definite retinal hemorrhage only, HMA < ETDRS Std. Photo #2A, and HMA ≥ ETDRS Std. Photo #2A. All punctate, blot and linear hemorrhages, and all microaneurysms are included. Microaneurysms will be considered present if graded as definite or HMA < ETDRS Std. Photo #2A, and HMA ≥ ETDRS Std. Photo #2A. Hemorrhages will be considered present if graded as definite or HMA < ETDRS Std. Photo #2A, and HMA ≥ ETDRS Std. Photo #2A.[18]

3) Soft exudates were defined as absent, definite or questionable. Soft exudates are areas of ischemia in the retina that appear white, pale yellow-white or gray-white areas with feathery edges. Soft exudates will be considered present if graded as definite.

4) Arterio-Venous Nicking was defined as absent, questionable and definite in each quadrant (superior temporal, superior nasal, inferior temporal, and inferior nasal). Definite requires tapering or narrowing of the venous blood column on three or all four sides of the crossing. Venous blood columns that appear tapered on only two sides of the crossing (not due to normal vessel undulation) is graded as questionable while venous columns with only one nicked side is considered absent. AV nicking will be considered present if graded as "definite".[18]

5) Focal narrowing was defined as absent, questionable and definite in each quadrant (superior temporal, superior nasal, inferior temporal, inferior nasal). Definite requires vessels to be at least 40u in diameter, or about 1/3 of the diameter of a vein at the disc margin and the constricted area must have a caliber less than or equal to ½ of the caliber of proximal and distal vessel segments. Focal pinches must be at least 250u in length to be considered definite. For constrictions in vessels less than 40u in diameter and focal pinches less than 250u in length, constrictions were graded as questionable. Focal narrowing will be considered present if graded as "definite".[18]

6) Retinal arteriolar diameters were calculated via computer processing of digital photographs. The diameters of arterioles present in a specified zone around the optic disc were assessed. The central retinal artery equivalent (CRAE) was calculated using the following formula:[19]

Arterioles $W_c = (0.87W_a^2 + 1.10W_b^2 - 0.22W_aW_b - 10.76)^{0.5}$
W_c = caliber of trunk vessel
W_a = caliber of smaller branch
W_b = caliber of larger branch

Based on this calculation, generalized arteriolar and venular narrowing were considered present if in the lowest 25% of the CRAE distribution.[16]

<u>Additional independent variables</u>:
1) Demographic variables collected at ARIC visit 1: age, sex, education, occupational class, income, race, study site and apoE4
2) Potential vascular confounding variables: hypertension status (normotensive, prehypertensive, hypertensive)[20], systolic and diastolic blood pressure, smoking status, inflammatory markers (WBC count, serum fibrinogen), lipids (high density lipoprotein cholesterol and triglyceride), body mass index, alcohol use, diabetes status

<u>Summary of Data Analysis</u>:
ANOVA and Chi square tests will be used to examine univariate associations of covariates with cognitive status. Multinomial logistic regressions will be used to investigate the association of retinal abnormalities with cognitive status. We will perform two analyses: the first will regress the multinomial outcome normal, MCI or dementia on retinal variables of interest, adjusted for potential confounders. The second will regress the multinomial outcome of normal, MCI/dementia with CV diagnosis or MCI/dementia without CV diagnosis on retinal variables, adjusted for confounders. Retinal variables will both be considered individually and grouped together in the model. Our models will adjust for potential demographic confounders including age, sex, race, center, education, occupation, apoE4 and other demographic variables. Our analysis will also adjust for potential disease confounders including hypertension status, diabetes status, smoking status, lipids, and alcohol use. Stratification by diabetes status will also be considered in light of the substantial vascular impact of diabetes.

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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? ____ Yes   __X__ 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"? ____ 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)?**

   1. ARIC #738: Retinal microvascular abnormalities and cognition: The Atherosclerosis Risk in Communities Study
   2. ARIC #2169: Association of retinal microvascular abnormalities with 23-year cognitive decline: The Atherosclerosis Risk in Communities Study
   3. ARIC #1222: The association of microvascular retinal abnormalities with cognitive decline and cognitive status after 10 years (ARIC study)
   4. ARIC #2797: Retinal signs and incident dementia in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ Yes   __X__ 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)* _____ _____ _____)

*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, approved manuscripts using 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 __X__ Yes ____ No.