ARIC Manuscript Proposal #2797

PC Reviewed: 7/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Retinal signs and incident dementia in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

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

2. Writing Group:
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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]**

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3. Timeline:
Manuscript will be completed in 6 months.

4. Rationale:
Cerebrovascular small vessel disease, evidenced through brain imaging as lacunes and white matter hyperintensities, is a potentially important contributor to cognitive decline and dementia in older adults.[1] Vascular disease that is apparent primarily at autopsy (e.g., microinfarcts less than 1 mm in size) may be more strongly related to late-life cognitive impairment than vascular lesions that are more readily detectible by standard brain imaging.[1-4] The overall effect of vascular disease in the pathogenesis of cognitive decline and dementia may therefore be greater than has been previously estimated.[2,5]

Retinal fundus photography offers a non-invasive means to visualize arteriolar and 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 a broad range of small vessel changes within the brain,[6] including those lesions too small to be visualized with brain imaging.

Previous studies in ARIC support the hypothesis that retinal imaging signs are markers for incident clinical stroke[7,8] as well as early and largely silent 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), respectively[11]. 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]

Cross-sectional studies also suggest an association between retinal signs and poorer cognitive function.[13,14] In a longitudinal analysis in ARIC, we found that a retinal vascular score (created using 4 retinal signs: retinopathy severity, arteriovenous nicking, focal arteriolar narrowing and generalized arteriolar narrowing) was associated with a faster rate of decline in global function over 20 years of follow-up (difference in 20-year cognitive change comparing high to low retinal score = -0.35 SD, 95% CI: -0.46, -0.24) (Deal, MP#2169, manuscript currently under journal review). Estimated differences in decline were greater in participants with diabetes, but qualitatively similar to differences in decline estimated for participants without diabetes.

Population-based epidemiologic studies regarding the relationship between retinal signs and dementia are few in number and mostly cross-sectional. In the Cardiovascular Health Study, retinopathy and focal arteriolar narrowing [multivariable-adjusted ORs and 95% CIs: 2.10 (1.04-4.24), N=760; and 3.02 (1.51- 6.02), N=784, respectively], but only in participants with hypertension; no associations between retinal signs and dementia were observed in participants without hypertension.[13] In a cross-sectional study of 3,906 participants (mean age 76 years) in the AGES-Reykjavik Study, retinopathy was associated with vascular dementia (multivariable-adjusted OR: 1.98, 95% CI: 1.10, 3.56) but not with AD dementia (OR: 1.20, 95% CI: 0.73, 1.98).[15] In the Rotterdam Study, retinopathy was cross-sectionally associated with prevalent dementia (both AD dementia and vascular dementia, age and sex-adjusted OR: 2.0, 95% CI: 1.3-3.1). However, in prospective analysis, no association was found between baseline retinopathy and risk of incident dementia (either subtype, age and sex-adjusted OR: 1.2, 95% CI: 0.9, 1.5; N=6,078) over a mean of 11 years of follow-up.[16] In this same cohort, retinal venular widening was associated with increased risk of dementia (age- and sex-adjusted HR: 1.09, 95% CI: 1.01, 1.18 N=5553); this association was driven largely by the relationship

with vascular dementia (HR: 1.31, 95% CI: 1.06-1.64), compared to a HR of 1.06 (95% CI: 0.97, 1.16) with AD dementia.[17]

This prospective study will add to the literature with its long follow up (up to 20 years), large sample size (over 12,000 participants), large proportion of African American participants, and retinal signs first assessed in midlife.

5. Main Hypothesis/Study Questions:
Microvascular retinal signs measured in 1993-95 are associated with incident all-cause dementia. We hypothesize that these associations:

1. Are similar in persons with and without diabetes and
2. Are stronger in persons with ≥1 *APOE* e4 allele

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 12,303 men and women who underwent retinal photography at Visit 3 (1993-95) and who have complete education and diabetes data and are dementia-free at the time of fundus photography. Due to small numbers, this analytic sample (N=12,303) also excludes participants who self-report Asian, American Indian or Alaskan Indian race (N=38), and participants who are non-white from Minneapolis or Washington County (N=42).

Outcome: The primary outcome will be incident all-cause dementia (without information about reviewer classification of dementia etiology). Dementia diagnosis will be defined per MS#2020 (Gottesman et al., diagnosis level 3).
In secondary analyses, we will quantify the relationship between retinal signs and dementia subtype: Alzheimer's dementia (N=195) and vascular dementia (N=79) (dementia diagnosis level 1).

Exposures: Retinal photographs were collected for the first time in ARIC at Visit 3 (1993-95) and again at Visit 5 (2011-13). For this analysis, we will use data collected at Visit 3. 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' characteristics, including hypertensive and diabetic status. [18] The four most frequently observed retinal signs will be included in the analysis: retinopathy, focal arteriolar narrowing, arteriovenous (AV) nicking, and generalized arteriolar narrowing.[18,19]

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 ≥50 □m in diameter that had a constricted area ≤ 2/3 the width of proximal and distal vessel segments.[18] For the current analysis, arterioloar narrowing will be considered present given a grade of "definite".[20]

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.[18] 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:[18]

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

$$where\ W_c = the\ caliber\ of\ the\ trunk\ vessel$$
$$W_a = the\ caliber\ of\ the\ smaller\ branch,\ and$$
$$W_b = the\ caliber\ of\ the\ larger\ branch$$

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.[19]

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

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:
Cox proportional hazards models will be used to estimate the association of definite retinal signs at visit 3 and subsequent dementia diagnosis during follow-up. The origin will be time since visit 3 and participants will exit the risk set at the time of dementia diagnosis (earliest date that dementia was detected), or at the time of censoring (in keeping with work in MS#2020c; administrative censoring date is Sept 1, 2013). The assumption of proportional hazards will be verified by assessing correlation between scaled Schoenfeld residuals and transformed survival times.

We will test for a possible statistical interaction of diabetes and/or *APOE* e4 status with retinal signs, with respect to estimating the hazard ratio of incident dementia, by stratification and inclusion of interaction terms in the model. Because of the strong

association between retinopathy and diabetes, diabetes-stratified analyses will be presented in the final paper.

We will employ a two-step model building process for adjustment. Model 1 will incorporate demographic covariates, including age, sex, and ARIC clinic site. Based on previous work in this cohort, we anticipate the need to flexibly model age (e.g., quadratic or cubic spline). Model 2 will include those covariates in Model 1, as well as additional risk factors for dementia, including smoking status, drinking status, BMI, prevalent coronary heart disease, prevalent stroke, and hypertension. Covariate values will be from Visit 3 (at the time of retinal photography).

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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? 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 __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"? 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.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)?

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* 2008.06)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

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.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.