

## ARIC Manuscript Proposal #2169

PC Reviewed: 7/9/13  
SC Reviewed: \_\_\_\_\_

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Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Association of retinal microvascular abnormalities with 23-year cognitive decline: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** retinal, 23-yr cog change

### 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 3 months.

### 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.<sup>1-4</sup> 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.<sup>5</sup>

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,<sup>6</sup> including those too small to be visualized with brain imaging. Retinal vascular abnormalities are associated with increased cardiovascular risk, including incident stroke.<sup>7,8</sup>

Previous studies in ARIC have supported the hypothesis that retinal imaging is a marker for cerebrovascular changes within the brain, in both cross-sectional<sup>7,9,10</sup> and prospective<sup>11,12</sup> 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<sup>11</sup>. 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.<sup>12</sup>

Preliminary studies have also supported an association between retinal abnormalities and poorer cognitive function. In cross-sectional multivariate analyses that included adjustment for hypertension and diabetes, retinopathy was associated with poorer executive function and poorer verbal memory performance in middle-aged adults living in the community.<sup>13</sup> In 8,713 men and women from ARIC who were aged 51-70 years at the time of retinal photography, Wong and colleagues found an association between retinopathy and cognitive impairment (defined as a cognitive test score  $\leq 2$  standard deviations below the mean value) on the Digit Symbol Substitution Test (OR: 1.91, 95% CI: 1.04-3.49), the Word Fluency Test (OR: 2.03, 95% CI: 1.07-3.86), and the Delayed Word Recall Test (OR: 2.60, 95% CI: 1.70-3.99). Retinopathy has also been associated with poorer executive function in community-dwelling older adults in cross-sectional analysis.<sup>14</sup>

Among participants *with* hypertension, Liew et al reported a cross-sectional association between increased odds of Mini-Mental State Exam Score (MMSE)<sup>15</sup>  $\leq 23$  and two retinal measures: presence of retinopathy (OR: 1.7, 95% CI: 1.0-3.2) and venular widening (OR: 2.7, 95% CI: 1.2, 6.1); no association between retinal signs and cognitive impairment was observed for participants without hypertension.<sup>16</sup>

Few studies have assessed the longitudinal associations between retinal abnormalities and functional outcomes in older adults. Lesage et al. found that presence of retinal abnormalities was associated with faster rates of cognitive change on two tests related to executive function, the Digit Symbol Substitution Test<sup>17</sup> and the Word Fluency Task (WFT)<sup>18</sup> in ARIC, during 14 years of follow-up;<sup>19</sup> on the WFT, the difference in 10-year decline comparing participants with any retinopathy to participants with no retinopathy was -1.7 words (95% CI: -3.2, -0.02). Haan et al reported an association between presence of retinopathy in 511 women aged 65 years or older who were enrolled in the Women's Health Initiative, and lower Extended Mini-Mental State Exam scores (mean difference = 1.01 points,  $p=0.02$ ), but failed to document a difference in rates of cognitive decline over 10 years of follow-up by retinopathy status.<sup>20</sup> Burden of microvascular changes (as defined by presence of two or more of generalized arteriolar narrowing, generalized venular widening, retinopathy, arteriovenous nicking, and focal arteriolar narrowing) has also been associated with incident Activity of Daily Living (ADL) disability in community-dwelling older adults.<sup>21</sup>

Retinal photography may currently offer the only non-invasive means to visualize SVD, which may be a risk factor for cognitive decline. In this study, we propose to expand upon the previous study by Lesage to quantify the association between retinal abnormalities and cognitive decline over an additional 9 years of follow-up (23 total).

## 5. Main Hypothesis/Study Questions:

1. To test the hypothesis that microvascular retinal abnormalities are risk factors for cognitive decline over 23 years in adults who were middle-aged at baseline.

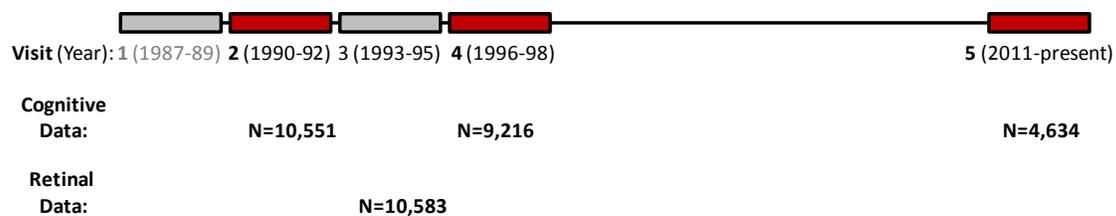
*We hypothesize that, compared to persons without microvascular retinal abnormalities, persons with microvascular retinal abnormalities measured at Visit 3 have a faster average rate of global and test-specific cognitive decline during follow-up.*

*Because neuronal processes important to executive function are thought to be localized to areas of the brain that may be most susceptible to microvascular disease, we hypothesize that associations between retinal abnormalities and cognitive decline are greater with tests related to executive function and attention (the Digit Symbol Substitution Test and Word Fluency Task) than to a test of memory (Delayed Word Recall).*

## 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 N=10,583 men and women who underwent retinal photography at Visit 3 (1993-95) and completed 3 neuropsychological tests at up to 3 visits during 23 years of follow-up (1990-present).

**Figure 1.** Study design



**Outcome:** 23-year trajectories of global and test-specific cognitive function. Cognitive function was measured at up to 3 time points (Fig.1) using three standardized, neuropsychological tests: the **Delayed Word Recall Test (DWRT)**, the **Digit Symbol Substitution Test (DSST)**, and the **Word Fluency Test (WFT)**.

In the **DWRT**<sup>22</sup>, participants are asked to learn 10 common nouns by reading each noun and using it in a sentence. After an interval filled with a different neurocognitive test, participants are asked to recall the 10 nouns. The DWRT is scored as the total number of words correctly recalled and ranges from 0-10.

The **DSST**<sup>17</sup> is a test of speed and executive attention. Participants are provided with a key that uniquely associates a number with a nonsense symbol and then asked to translate a series of numbers to the corresponding symbol. The DSST is scored as the total number of symbols correctly completed within 90 seconds.

The **WFT**<sup>18</sup> is a test of verbal fluency consisting of 3 consecutive 1-minute word-naming trials. Participants are asked to list as many words as possible (excluding proper nouns) that begin with the letter “F”, “A” and “S” in each trial, respectively. WFT is scored as the total number of words generated during the 3 trials.

In order to facilitate comparisons of decline across tests, all tests will be standardized to z-scores in the primary analysis:  $z\text{-score} = (\text{observed test score} - \text{mean test score}) / \text{standard deviation of test score at baseline Visit 2}$ .

A **GLOBAL** cognitive score, as described by Gottesman et al (ARIC Manuscript Proposal 1982), will be created using the three neurocognitive tests.

**Exposure:** Retinal photographs were collected for the first time in ARIC at Visit 3 (1993-95) (Fig.1). 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.<sup>23</sup>

Four primary measures of retinal microvascular abnormalities will be included in the analysis: any retinopathy, focal arteriolar narrowing, arteriovenous (AV) nicking, and generalized arteriolar narrowing.<sup>19, 23</sup> Other, less frequent abnormalities (e.g., cotton wool spots) will also be explored.

A participant will be considered to have **any retinopathy** given the 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.<sup>23</sup> For the current analysis, arteriolar narrowing will be considered present given a grade of "definite" or "questionable".<sup>13</sup>

**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.<sup>23</sup> For the current analysis, AV nicking will be considered present given a grade of "definite" or "questionable".<sup>13</sup>

**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 and quantified as the central retinal arteriolar equivalent (CRAE) using the following formula in order to adjust for branching:<sup>23</sup>

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

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 25<sup>th</sup> percentile of CRAE.<sup>19</sup>

**Statistical analysis:** Generalized estimating equations using inverse probability of attrition weighting to account for informative dropout (Gottesman et al, ARIC Manuscript Proposal (MP) 1982) or a shared parameter model (as developed by Griswold et al, MP 2115) will be used to estimate the average difference in rates of cognitive change over time, comparing participants with and without retinal abnormalities as measured at Visit 3. Because of the strong confounding effect of age, and because of the inherent meaning of age as a time scale, age in years, rather than

time on study, will be modeled as the time scale; splines will be incorporated in the model to account for any non-linear associations of cognitive change with age. The Telephone Interview for Cognitive Status (TICS) in persons who failed to be examined at visit 5 will also be used to impute performance at visit 5 in supplementary analyses to examine the influence of attrition of the primary estimates of concern.

Analyses will adjust for possible demographic and disease confounders of the association of interest, including sex, race, ARIC clinic site, and smoking status. Because of the strong relationship between retinopathy and diabetes (retinopathy is a consequence of diabetes), the primary models will be stratified by diabetes status. This stratification will allow us to test if the association between retinal abnormalities and cognitive decline differs by diabetes status, but also to determine if there is an association in participants without diabetes. Because retinal abnormalities may also be a consequence of hypertension, additional models will adjust for hypertension to determine if retinal abnormalities may also be a marker of additional vascular susceptibility.

Retinal photograph data was first collected at Visit 3 (1993-95). Although use of Visit 2 cognitive data does not preserve temporality between the measurement of the exposure and outcome, the primary analysis will utilize cognitive data from all visits when cognitive data was routinely collected (2, 4 and 5), as it is unlikely that cognitive decline would be a cause of retinal abnormalities. Participants with data for all three neurocognitive exams at any of those three visits will be included in the analysis.

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**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.csc.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)?**

**MP1967.** Adjusting for Measurement Error in Baseline Measures of Cognitive Function: The ARIC Neurocognitive Study. Wruck L et al.

**MP1982.** Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS. Gottesman R. et al.

**MP2033.** Cognitive domains in elderly ARIC blacks and whites. Rawlings et al.

**MP2115.** Sensitivity Analyses with Shared-Parameter Models for studying Cognitive Change in the presence of potentially Informative Dropout – the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. Griswold et al.

**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** N/A

**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 \_\_\_\_\_)**

\*ancillary studies are listed by number at <http://www.cscce.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.cscce.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.