ARIC Manuscript Proposal # 1222

PC Reviewed: __2_/_13/07	**Status: _A____**	**Priority: __2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____-***

1.a. Full Title: The association of microvascular retinal abnormalities with cognitive decline and cognitive status after 10 years. (ARIC study)

b. Abbreviated Title (Length 26 characters): **10 y retina-cognitive assoc**

2. Writing Group:
(alphabetical listing) Diane Catellier Laura Coker, Ron Klein, David Knopman, Suzanne Lesage, Tom Mosley, A. Richey Sharrett, ,Moyses Szklo, Tien Y. Wong

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

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3. Timeline: Completed by February 2006, send to coauthors for final completion March 2006

4. Rationale:

Retinal vascular abnormalities have been demonstrated to be associated with cognitive impairment, incident clinical stroke and with various cerebral MRI imaging abnormalities including small or lacunar strokes, cerebral white matter lesions and cerebral atrophy. (Wong, 2002, Cooper, 2006, Wong 2003). In fact, retinal microvascular changes were associated with these findings independently of typical cerebrovascular risk factors such as hypertension and smoking, highlighting the importance of retinal microvascular changes as a potentially unique marker for the risk of cerebrovascular disease and related cognitive impairment. This study will expand upon the earlier finding of cognitive impairment and retinal microvascular changes by looking at cognitive status and cognitive decline 10 years after the determination of retinal microvascular changes. We hypothesize that retinal microvascular changes because they are

associated with small vessel cerebral vascular disease, will be associated with cognitive dysfunction particular to this disease process.

Wong et. al (Stroke 2002) demonstrated an association between retinal vascular abnormalities and current cognitive status, based on testing taken within three years of the retinal assessment. Again this association was notable for being independent of hypertension, diabetes and carotid IMT. In this study the strongest association between retinal microvascular changes and cognitive impairment was seen with the more marked retinal changes such as retinal hemorrhage and soft exudates. This finding is not unexpected given cognitive impairment would be at a minimum in a younger study population and that more subtle microvascular changes such as those affecting arteriolar narrowing would take time to show an association to a later consequence of the disease process such as cognitive impairment. Thus, one would expect not only to show a stronger association by analyzing cognitive status 10 year later, but it would also be of great interest to note if the more subtle retinal microvascular changes such as arteriolar or venule diameters could predict later cognitive impairment.

With the aging US population, cognitive decline and dementia have a great impact on healthcare. A significant portion of cognitive impairment in the elderly comes from vascular dementias. Recent reports have also started to recognize clinically relevant cognitive dysfunction related to cerebrovascular disease that is not characteristic of typical Alzheimer-type dementias. One of these clinically important entities is subcortical ischaemic vascular disease (SIVD) with and without dementia. SIVD is defined on the basis of clinical signs as well as brain imaging features including both lacunar infarcts, and subcortical as well as periventricular white matter disease. All of these entities are felt to be related to cerebral small vessel disease. (Erkinjunnitti 2000) Retinal microvascular changes have been demonstrated to be associated with both white matter disease and lacunar infarcts and thus represent a potentially useful marker of SIVD and its related cognitive impairment. SIVD as represented by white matter disease has been shown to be related to a particular pattern of cognitive impairment. (Boone 1992, Kramer, Prins 2005) Unlike Alzheimer's disease that often impacts verbal memory and learning early in the disease course, cerebral white matter disease results in deficits in attention, speed and executive function, features related to frontal lobe dysfunction. As part of the ancillary study "ARIC MRI and Neurocognitive Longitudinal Study" at contact year 16 (CY16) a complete battery of neurocognitive tests were completed. This more extensive testing allows for an analysis of cognitive impairment to be sectioned into cognitive domains. Cognitive domains are meant to better define cognitive function into neuroanatomical areas of the brain helping to differentiate between the many pathological insults that result in cognitive impairment. One example of these domains that will be utilized in this proposal is: 1. Memory 2. Psychomotor speed 3. Verbal Fluency 4. Executive function. Cognitive impairment preferentially affecting domains that have been demonstrated to be typical of SIVD would add specifically to the hypothesis relating retinal changes to cerebral small vessel disease.

Important aspects to neurocognitive impairment are two related symptoms depression and motor slowing. Cerebrovascular disease in particular ischemic white matter disease is associated with both of these entities.(Vataja 2004, Krishanan 2004) As part of the CY16 visit individuals underwent motor testing including finger tapping and walking as measured by a timed gait assessment along with a test for depressive symptoms the CES-D. In a secondary analysis we propose to look at the association of retinal microvascular changes with depression and motor impairment again as a proxy to small vessel cerebrovascular disease.

Race may modify the effect of the relationship of retinal microvascular changes with cognitive dysfunction. Dementia related to vascular disease has a greater incidence in blacks than in whites (Kuller 2005). This is consistent with evidence that blacks are at greater risk of intracranial vascular disease and resulting strokes compared to whites. Racial differences in stroke rates may have several underlying etiologic factors including underlying hypertension, socioeconomic factors, or ethnic differences in manifestations of cerebral vascular disease. (Bravata 2005, Howard 2006).

We propose to use the retinal variables measured at Visit 3 (see below for specific retinal variables to be included) as the primary independent variables. We will expand on the microvascular measurements used in previous ARIC reports to include retinal arteriolar and venular diameter measurements (rather than their

ratio only). This will be done based in part on results from the Rotterdam Study (Ikram 2006), which found a relationship of venular dilation to stroke. For participants in the "ARIC MRI and Neurocognitive Longitudinal Study", cognitive testing took place at four time points, Visit 2 (1990-1992), Visit 3 (1993-1995), Visit 4 (1996-1998) and the follow up MRI visit at CY16, (2004-2006). Baseline cognitive assessment will be taken from Visit 2 and will be named cognitive assessment 1(CA1), with subsequent testing to be labeled as follows, visit 3 will be the second cognitive assessment(CA2), visit 4 (CA3) and the follow-up CY16 visit will be the fourth cognitive assessment(CA4). Only limited testing as listed below was done at the first 3 cognitive assessments. The proposal will examine two main dependent variables, first is cognitive status based on the full battery of testing done at CA4 (10 year follow-up) and will look at both a total score as well as cognitive domains as presented above. Secondly cognitive change over the follow-up period will be analyzed using cognitive tests done repeatedly at visit 2 (CA1), visit 3(CA2), visit 4 (CA3) and CY16 (CA4).

References:

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Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, Couper DJ, Heiss G, Sorlie PD. Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction: The Atherosclerosis Risk in Communities Study. Stroke 2006;37:82-86

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Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, Mosley TH, Klein BE, Hubbard LD, Szklo M. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33:1487-1492

Wong TY, Mosley TH, Jr., Klein R, Klein BE, Sharrett AR, Couper DJ, Hubbard LD. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 2003;61:806-811.

5. Main Hypothesis/Study Questions:

Aim 1. Are retinal microvascular abnormalities associated with cognitive function assessed using a detailed battery of tests approximately 10 years after the retinal examination? Is the association of retinal microvascular changes and cognitive status at 10 years independent of BP and other cardiovascular risk factors?

Aim 2. Are baseline retinal microvascular abnormalities associated with a steeper cognitive change over a 10 year period? Are these associations independent of BP and other cardiovascular risk factors?

Aim 3. Are retinal microvascular abnormalities associated with specific patterns of cognitive dysfunction reflective of cerebral small vessel vascular disease? In particular, we will examine 4 cognitive domains (as noted below) Are these associations independent of BP and other cardiovascular 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).

Primary variables:

Primary Independent Variables:
Retinal Variables: (taken at Visit 3)

1. Evidence of *any* retinopathy- overall severity based on presence of microaneurysms, soft exudates, retinal hemorrhage, macular edema, intraretinal microvascular changes, venous beading, vitreous hemorrhage disc swelling, as well as the more frequent signs considered separately.
2. Retinal vessel measurements: arteriolar diameter (measured as central retinal arteriolar equivalent CRAE), venular diameter (CRVE)
3. Other arteriolar measures; focal narrowing, arterio/venous nicking

Primary dependent variable:
Cognitive Data: Taken from visit 2(CA1-cognitive assessment 1), visit 3 (CA2), visit 4 (CA3) and CY16 (CA4)

Aim 1. Relationship between retinal variables and single global measure of cognitive function at CA4. We will first compute the standardized scores (z scores) for each of the individual cognitive tests and then average the standardized scores into a single global measure of cognitive function. Relationship between retinal variables and individual test scores at CA4.

Aim 2. Relationship between retinal variables and cognitive change for the three cognitive tests administered at CA1, CA2, CA3 and CA4: Delayed word recall (DWR), Word fluency (FAS), Digit Symbol Substitution (DSS)

Aim 3. Relationship between retinal variables and 4 domains of cognitive function at CA4. The standardized scores are averaged into the domains as follows:

Memory: Delayed Word Recall, Logical Memory (I and II),
Psychomotor Speed: DSS, Trials Making Test (A)
Verbal Fluency: FAS and animal naming
Executive Function: Stroop (Interference Color-Word), and Trails Making Test (Trails Test B-Trails Test A)

Secondary dependent variables:

Depression:

Relationship between retinal variables and depression as indicated by scores on the CES-D test done at CA4.

Motor skill:

Relationship between retinal variables and motor skills. Finger tapping and timed gait measurements taken at CA4.

Inclusion: ARIC participants from Forsyth county and Jackson who underwent microvascular retinal photography at visit 3 and participated in the ARIC MRI Study. Participants will be required to have completed the cognitive testing at CA4 (CY16) and one of the prior testing cognitive assessments (CA1, CA2, CA3). Total number of participants with completed cognitive tests is 1134.

Exclusion: Participants whose race is not black and not white will be excluded. This permits adjustment for race-center using 3 categories: Jackson (black), Forsyth Co. (black), and Forsyth Co. (white).

Other variables of interest:

Visit 1- Education level, gender, race, exam center, systolic BP, diastolic blood pressure, fasting glucose.

Visit 2 (CA1)- Age, occupational status, apoE genotype, fasting blood sugar, history of diabetes, fasting glucose, smoking pack years, hypertension status, antihypertensive medications, systolic blood pressure and diastolic pressure, BMI, carotid IMT(right and left sides), alcohol consumption, total cholesterol, LDL-c, HDL-c, triglycerides, Lp(a),

Depression as assessed with vital exhaustion question at CA1, CA2 and CA3 and CES-D score at CA4

CNS medications (antidepressants, neuroleptics, antianxiolytics, benzodiazepines, antiepileptics) at each visit (CA1, CA2, CA3, CA4)

Statistical Analysis:

Sample size/power estimate:

Based on estimates from mean scores between those with and without retinopathy from V2 and V4 reported in Wong Stroke 2003. An estimated sample size of 950 (based on participants participating in CY16 testing with estimation of those without retinal photos) with alpha set at 0.05 and a mean difference in scores of 1.0 with a SD estimate of 1.20 gives an estimated power to detect a difference of 100%. The power estimate for detecting “cognitive impairment” is below based on an alpha set at 0.05 and the proportion with retinopathy in controls as .025.

OR	1.5	1.8	2.0	2.2
Power	.60	.89	.96	1.00

Assessment of Cognitive Tests:
Aim 1 and Aim 3: Linear regression models will be used to test whether retinal variables done at V3 are associated with cognitive variables at CA4 (Global score (aim 1) or domain scores (aim 3). Logistic regression models will be used to test whether retinal variables are associated with "cognitive impairment" as determined by individuals that fall in the lowest 10% of scores both for global scores and domain scores.

Aim 2: Mixed models will be used to test whether retinal variables at V3 are associated with the rate of cognitive decline on the 3 cognitive tests done at visits CA1, CA2, CA3 and CA4. This model assumes that an individual's initial level of cognitive performance(intercept) and rate of change(slope) over time follow those of the population with the exception of random effects that contribute to variability in the intercept and slope. This approach is advantageous because it accounts for the correlation between cognitive test scores at repeated assessments while also allowing a more precise estimate of the error of variability.

The basic model will consist of terms for the retinal variable of interest(centered at the mean if continuous),age(years centered at 65 years),sex, education, race, the time(years) since baseline, and the interaction of time with the retinal variable. The term for time refers to the annual rate of change in the cognitive test score in the reference group or at the mean value of the retinal variable (for categorical and continuous retinal variable, respectively), and the interaction term reflects the additional effect of a unit increase in the retinal variable on the annual rate of change.

To more fully adjust for potential confounding, we will include terms to control for other factors that may be related to cognitive function, including depression or "vital exhaustion"(using measures of vital exhaustion at CA1, hypertension (using measures of SBP and DBP at each visit and an average of these measure of CA1, CA2, CA3 and CA4, diagnosis of hypertension, and antihypertensive medications), diabetes(using measures of fasting glucose, diagnosis of diabetes), carotid IMT(right and left sides), alcohol consumption, total cholesterol, LDL-c, HDL-c, triglycerides, Lp(a), smoking status, CNS medications (antidepressants, neuroleptics, antianxiolytics, benzodiazepines, antiepileptics) and ApoE genotype. Any potential confounder that does not alter the retinal changes variable in the regression model will not be included in the final fully adjusted model.

For aim 1 and 3 we will adjust for baseline cognitive status using an average of the cognitive function scores at CA1, CA2 and CA3 for each of the three cognitive tests (DSS, DWR and FAS). If our analyses shows no or a weak association between the average cognitive status score at these visits and retinal changes, we will not adjust for baseline status in the final model.

We will refit the fully adjusted model after excluding individuals with the lowest 5% of scores on the cognitive tests (DWR, FAS, and DSS) from CA1 to account for the possibility that these represent individuals with preclinical dementia. We will also refit the fully adjusted model excluding those with a score less than 23 on the Mini Mental Status Exam done at CA4 as another measure of dementia.

We will refit the fully adjusted model after excluding individuals with depression using measures of vital exhaustion at CA1 and CES-D at CA4 to account for the effect of depression on cognitive testing.

We will refit the fully adjusted model excluding participants with a history of neurological disorder (ie. multiple sclerosis, Parkinson's disease, brain injury (traumatic), other neurodegenerative disease taken from hospital discharge codes or as coded in medical history interview at CA4.

We will refit the fully adjusted model after excluding individuals with prevalent or incident stroke; ARIC-diagnosed stroke prior to CA1 or between CA1 and CA4, respectively. If a strong reduction in the association between retinal changes and cognitive change is noted, suggesting that stroke is a potential

mechanism for the cognitive decline attributable to retinal vascular changes, then we will also consider effects of exclusions of specific stroke types(thrombotic v. embolic and TIA's)

Measurement error: In order to correct for the bias caused by measurement error in baseline level of cognitive function (in aims 1 and 3), the observed values of cognitive function will be replaced by Stein estimates of the true values, conditional on the values of variables in the model that are measured without error (Chambless and Davis, 2003). (see previous reference list)

Interactions: We will stratify the results based on, race, gender, ApoE genotype and presence or absence of hypertension, to look for interactions in the retinal-cognition associations. We will stratify by 2 broad age categories based on the median age at CA1 (age 59) to analyze if accounting for possible differences in length of time with retinopathy alters the retinal-cognitive relationship.

Retinal Variables: Analyses using CRAE as a predictor will consider the effect of including CRVE in the model, since CRAE associations have been clarified by this strategy and other similar models may also consider the effects of simultaneous inclusion of more than one correlated retinal variable.

Limitations: To asses the degree of selection bias, because of participants who did not return for the 2003-2005 follow- up, we will compare those who returned with those who did not return with respect to baseline characteristics as well as outcomes (mortality data etc.)

We realize the potential for residual bias especially in regards to the inadequacy of adjustments for education or socioeconomic status measurements in relation to cognitive testing. Bias attributable to imprecision in the retinal measurement is expected to be towards the null with nondifferential misclassification. The ARIC reliability data (Couper) will be used to estimate the effect of correction for this error on the association measures.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

The most relevant ARIC analyses, listed below, are already published. They relate to cerebral endpoints (cognitive function and MRI variables) collected within the core ARIC study, whereas the current proposal relates to cerebral endpoints collected as key variables in Mosley's grant - the "ARIC longitudinal MRI study". There are no proposals to date relating retinal variables to cerebral endpoints collected in the Mosley grant.

Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, Mosley TH, Klein BE, Hubbard LD, Szklo M. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33:1487-1492.

Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67-74.

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Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, Couper DJ, Heiss G, Sorlie PD. Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction: The Atherosclerosis Risk in Communities Study. Stroke 2006;37:82-86.

Wong TY, Mosley TH, Jr., Klein R, Klein BE, Sharrett AR, Couper DJ, Hubbard LD. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 2003;61:806-811.

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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

___ A. primarily the result of an ancillary study (list number* ___Tom, please provide the number_____)

___ B. primiarly 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/

12. 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.