

ARIC Manuscript Proposal # 1432

PC Reviewed: 10/14/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Retinal Signs and Risk of Incident MRI Brain Abnormalities

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

2. Writing Group:

Writing group members: Cheung N, Islam FMA, Kawasaki R, Sharrett A, Klein R, Catellier D, Mosley T, Coker L, Knopman D, Shibata D, Wong TY

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NC

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3. Timeline:

Manuscript proposal to Publication's Committee:	Sep 2008
Data analysis completed:	Jan 2009
Completed manuscript to Publication's Committee:	Jun 2009

4. Rationale:

Stroke is a major cause of mortality and morbidity worldwide. Despite significant progress being made in understanding stroke etiology and pathogenesis, most advances have been confined to the relationship of strokes with large vessel disease (i.e. carotid or intracranial atherosclerosis). However, one fifth of symptomatic strokes (or a quarter of ischemic strokes) could be attributed to disease of the small arteries/arterioles in the cerebral circulation.¹ Research into cerebrovascular disease caused by small vessel disease has been limited by the paucity of non-invasive tools to objectively and reliably assess the cerebral microvasculature.

The retinal and cerebral vasculatures share similar embryological origin, anatomical features and physiological properties.²⁻⁴ Pathological changes in the retinal vasculature (e.g., hypertensive or diabetic retinopathy signs) may therefore reflect similar vascular disease processes occurring in the brain, predisposing people to future development of cerebrovascular disease. In support of this hypothesis, previous studies, including the ARIC study, have consistently shown associations of various retinal vascular changes with increased risk of clinical stroke and other cerebrovascular disorders, after adjusting for stroke-related risk factors.⁴⁻¹¹ In addition to retinal vascular disease, neurodegenerative disease of the retina, such as age-related macular degeneration (AMD), has also been associated with incident clinical stroke, independent of shared risk factors.^{12, 13}

However, despite increasing interest in silent cerebral infarcts and other cerebrovascular abnormalities (e.g., white matter lesions) detectable by MRI scans,^{14, 15} data on the relationships between retinal signs and MRI brain abnormalities remain limited. Cross-sectional data from the ARIC and other studies suggest that retinopathy signs and variations in retinal vascular caliber (e.g., wider retinal venules) are associated with MRI brain infarcts, white matter lesions and cerebral microbleeds (in diabetes).^{9, 16-20} To date, nevertheless, there is a lack of prospective data to verify whether these retinal vascular changes precede the development of MRI cerebrovascular abnormalities.

In this study, we propose to address this important question and examine the prospective associations of retinal signs with MRI brain abnormalities in the ARIC cohort.

5. Main Hypothesis/Study Questions:

Retinal vascular changes (e.g., retinopathy signs, retinal arteriolar narrowing) and AMD signs (e.g., drusen) are associated with incident cerebrovascular abnormalities (white matter lesions, infarcts) on MRI brain scans in people without previous history of clinical stroke or MRI brain abnormalities at baseline.

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 methodological limitations or challenges if present).

- A.** Study sample: all ARIC cohort members, who participated in the eye examinations (at **Visit 3**) and had gradable fundus photographs for (1) AMD signs and (2) retinal vascular variables, with MRI brain data collected at **Visit 3** and **the ARIC Brain MRI Study (2004-6)**. MRI brain data are available for 1031 participants both visits 3 and the ARIC Brain Study visit. After exclusion the individuals with prevalent MRI cerebral infarcts, white matter lesion > grade 3 at visit 3, final dataset will be about 900 individuals.
- B.** Exposure variables:
 - i. Retinal microvascular variables at **Visit 3**: retinal arteriolar diameter, retinal venular diameter, arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinopathy severity, microaneurysms, retinal hemorrhages, soft (cotton-wool spots) and hard exudates, and macular edema.
 - ii. AMD variables at **Visit 3**: any AMD, early AMD, late AMD and specific AMD lesions (drusen, RPE de-pigmentation, any pigmentary changes)
- C.** Outcome variables:

- i. MRI brain abnormalities at **Visit 3 and the ARIC Brain MRI Study (2004-6)**: Incident MRI cerebral infarct, lacunar infarct, white matter lesion (grades and progression) and cerebral atrophy (sulcal widening, ventricular enlargement)
- D. Potential confounders (in addition to age, gender, race/ethnicity and study centers):**
 - i. Cardiovascular risk factors at **Visit 1, 2 and 3**: BMI, hypertension, blood pressure at all prior visits, diabetes, cigarette smoking and pack-years of smoking, anti-hypertensive medications use, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, fasting glucose, creatinine (at Visit 1, 2, 4), HbA1c (at Visit 2).
 - ii. Educational attainment and income.
 - iii. Markers of inflammation (e.g., white cell count, fibrinogen) and endothelial dysfunction (e.g., Von Willebrand factor).
- E. Plan of analysis:**
 - i. We will examine associations of various retinal signs with incidence of MRI brain abnormalities in the total sample and in each race/ethnic group.
 - ii. We will examine interactions of various retinal signs and race/ethnicity and other potential effect modifiers (e.g., smoking) for incident MRI brain abnormalities.
 - iii. We will first examine each retinal variable in age- and gender-adjusted logistic models by outcome. Final models will then be built to adjust for other potential confounders. Appropriate interaction terms will be added into regression models to evaluate interactions.
 - iv. Study Power

In our study population, the retinal signs range from 3-15% (retinal hemorrhage=3%, microaneurysms=4%, retinopathy=7%, AV nicking=13% and focal narrowing=15%). Retinal vascular calibers are dichotomised at the 75th centile for sample size calculation, but will be analyzed as continuous variables (thus increasing power). For an incidence of at least 17% of the endpoint (incidence of small infarcts), we are able to have 80% power to detect a RR of 1.8 to 2.5 for various retinal vascular changes with prevalence of at least 4%.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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.csc.unc.edu/ARIC/search.php> Yes

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)?

Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA* 2002;288:67-74.

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;37:82-86.

We are aware of no ARIC manuscripts or proposals related to retinal signs and incident MRI brain abnormalities.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number*ARIC Brain MRI: 1999.01)

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.csc.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.

References

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