

ARIC Manuscript Proposal #738

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1.a. Full Title: Retinal microvascular abnormalities and cognition: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Retinal changes and Cognition

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

This analysis is part of the overall objective of evaluating the role of microvascular pathology in cerebrovascular diseases, using retinal abnormalities as markers of microvascular disease. This proposal will be an extension on the retinal analysis from ARIC #334 (Retinal abnormalities and MRI-detected stroke) and ARIC #553 (Retinal abnormalities and Incident Clinical Stroke). Specifically, this manuscript will determine the association between retinal microvascular abnormalities and cognition.

This will involve 1) the cross-sectional evaluation of retinal abnormalities and cognition at the ARIC third examination (estimated n = 1,700) and 2) a prospective evaluation of 3-year cognitive change between the ARIC *third* and fourth examinations, based on presence versus absence of retinal lesions from the ARIC third examination (estimated n=1,450) and 3) a prospective evaluation of 6-year cognitive change between the ARIC *second* and fourth examinations based on retinal lesions evaluated at the ARIC third examination (estimated n = 9,400). A new dataset will be created to include retinal abnormalities at ARIC visit 3, cognition variables at visit 2, 3, and visit 4, among others.

After approval, the initial analyses and writing will take place between Sept 2000 and Jan 2001, with final analysis and submission of manuscript between Feb 2001 and May 2001.

4. Rationale:

Cognitive impairment in association with Alzheimer's disease or dementia is a leading cause of morbidity in the elderly. The etiology of cognitive decline is not known, but is likely to be complex, related to both genetic and environmental factors. A microvascular etiology has been suggested, but reliable data are not available. Studies have shown inconsistent associations

between cognition decline and hypertension, diabetes, physical activity, smoking, alcohol intake, aspirin, and a variety of hematological markers (e.g. fibrinogen, hematocrit). In ARIC, cognitive function was assessed in visits 2,3, and 4, by essentially three neuropsychological tests: the Delayed Word Recall Test (DWR), the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (DSS), and the Controlled Oral Word Association or Word Fluency Test (WT). A previous analysis in ARIC indicated that poorer cognition tests results were related, among other variables, to age, smoking, increased fibrinogen levels and greater carotid intima-media thickness, supporting a vascular etiology in cognitive decline (ARIC# 148).

Retinal changes, such as generalized and focal arteriolar narrowing, arteriovenous nicking (AV nicking), and various forms of retinopathy, reflect microvascular damage from aging and sustained elevated blood pressure. Since the retinal and cerebral microcirculation shares similar anatomical, physiological and even pathological characteristics, it has been hypothesized that these retinal changes may be markers for similar cerebral microvascular pathology. In ARIC, retinal abnormalities were quantified based on standardized photographic grading techniques, and on computer-assisted measurements of retinal arteriole calibers (to define generalized arteriolar narrowing). In ARIC #334 and #553, we showed that retinal microvascular abnormalities were associated with both subclinical small strokes detected on MRI (OR ranging from 2 to 3), and incident clinical strokes (RR ranging from 1.5 to 3), independent of blood pressure and other stroke risk factors. This supports evidence of a microvascular role in the pathogenesis of stroke.

The purpose of this present proposal is to evaluate the relation between retinal microvascular abnormalities and cognition in the ARIC population.

5. Main Hypothesis/Study Questions:

- (1) After controlling for age, sex, race, center, education, occupation, marital status, and other variables, retinal microvascular abnormalities are cross-sectionally associated with poorer cognition tests results (based on ARIC visit 3 data, n=1,700).
- (2) After controlling for similar variables, the presence of retinal microvascular abnormalities is associated with a greater risk of 3-year decline in cognition test results between ARIC visit 3 and visit 4 (using retinal variables in ARIC visit 3, and change in cognition between visit 3 and visit 4, n=1,450).
- (3) After controlling for similar variables, the presence of retinal microvascular abnormalities is associated with a greater risk of 6-year decline in cognition test results between ARIC visit 2 and visit 4 (using retinal variables in ARIC visit 3, and change in cognition between visit 2 and visit 4, n=9,400).
- (4) The association of retinal abnormalities and cognition is stronger for younger versus older persons, for persons with hypertension compared to those without, and for persons with diabetes compared to those without.

6. Data (variables, time window, source, inclusions/exclusions):

- (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates. Generalized arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent. (ARIC visit 3)
- (2) Cognition variables: DWR, DSS, WT (ARIC visit 2, 3, and 4)
- (3) Demographic variables: age (ARIC visit 2, 3, and 4), sex, race, and center

