# ARIC Manuscript Proposal #771

**1.a. Full Title:** Cognitive function and its relation to age-related maculopathy:  The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters):** Cognition and AMD

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

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**3. Timeline:**

The intent of this analysis is to investigate the relation of cognitive decline and age-related maculopathy (ARM). Specifically, this proposal will involve a cross-sectional analysis of ARM at Visit 3 to the average cognitive function scores of Visits 2 and 4, and the change in cognitive function from Visit 2 to 4. Estimated sample size for the study, n=8,000 (persons who participated in Visits 2, 3 and 4, with ARM and cognitive function tests)

After approval, the initial analyses and writing will take place between March to May 2001, final analysis between June 2001 and August 2001, and final writing and submission of manuscript between September 2001 and December 2001.

**4. Rationale:**

ARM is the leading irreversible cause of blindness in the elderly. Despite extensive research, much remains to be elucidated regarding its etiology. Cognitive decline, in association with Alzheimer's disease, reflects chronic degenerative changes in the brain with age.

ARM and cognitive dysfunction have been hypothesized to share common neurodegenerative pathways, based on similar pathological changes related to neuronal cell loss in both conditions.  Histopathologically, early ARM changes include deposition of drusens (lipid like waste products), pigment epithelial degeneration and atrophy. In the later stages, photoreceptor cell death occurs. In Alzheimer's disease, there is cerebral accumulation of amlyoid and other waste products, formation of senile plaques and neurofibrillary tangles, leading finally to neuronal malfunction and cell death. Furthermore, there is some evidence that both ARM and Alzheimer's disease may be linked with apolipoprotein E.

However, few data are available regarding the relation of cognitive decline and ARM. In the Rotterdam Study, a prospective population-based study, subjects aged 75 years or older with late ARM at baseline showed an increased 2-year risk of incident Alzheimer's disease (relative risk = 2.1, 95% confidence interval: 1.1, 4.3; adjusted for age and gender) that was attenuated after adjustment for smoking and atherosclerosis (relative risk = 1.5, 95% confidence interval: 0.6, 3.5). These findings suggest that the degenerative changes occurring in ARM and Alzheimer's disease may possibly have a common pathogenesis.

In ARIC, both ARM and cognitive function were evaluated in a standardized fashion, and have been previously described. During visit 3, ARM was graded from 45-degree retinal photographs of one randomly selected eye, based on the Wisconsin Age-related Maculopathy grading system. We have previously documented the prevalence of ARM in the ARIC population and showed that ARM was significantly more common in whites (5.6%) than blacks (3.7%), but related inconsistently to atherosclerosis and its risk factors.

Cognitive function was assessed on all participants at visits 2 and 4, and a sample at visit 3, using 3 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 test results were related, among other variables, to age, smoking, increased fibrinogen levels and greater carotid intima-media thickness (ARIC# 148).

The purpose of this present analysis is to evaluate the cross-sectional relation between ARM (at visit 3), to the average cognitive function scores of Visit 2 and 4 (sum of scores, divided by two) and the 6-year decline in scores (from visits 2 to 4) and ARM at visit 3. The information may provide clues to the etiology and pathogenesis of both conditions.

**5. Main Hypothesis/Study Questions:**
   (1) After controlling for age, race, sex, and education, persons with ARM will have lower cognitive test scores and a greater 6-year decline in cognitive test scores
   (2) The associations in (1) will be attenuated after adjusting for possible ARM risk factors (such as cigarette smoking)
   (3) The association between early ARM and cognitive test scores may differ between young versus old, and whites versus blacks (i.e. we will test for interaction for early ARM, but will not have sufficient power to evaluate interaction for late ARM)

**6. Data (variables, time window, source, inclusions/exclusions):**
   (1) Retinal variables: Early ARM, late ARM, any ARM, soft drusens, increased retinal pigments, RPE depigmentation, any pigmentary abnormality
   (2) Cognition variables: DWR, DSS, WT
   (3) Demographic variables: age at visit 3, sex, race, examination center, education, occupation, marital status.
   (4) Potential confounding variables: Hypertension status, diabetes status, hypertensive medications, diabetic medications, mean arterial BP, systolic and diastolic BP, serum lipids (total, HDL and LDL cholesterol, TG, lp(a), apo A1 and B), fasting glucose levels, hemostatic function indicators (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators, body mass index, sports/leisure/work index, aspirin use and carotid-intima-media thickness (all variables from ARIC visit 3, except for hypertension status, diabetes status, mean arterial BP, systolic and diastolic BP, from ARIC visit 1 to 3, and

for lp(a), apo A1 and B, von Willebrand factor, factor VIIIc, and cigarette pack-years, from ARIC visit 1 only)

(5) Exclusion criteria: From participants at ARIC visit 3, exclude persons who did not participate in visit 2, whose race is neither black nor white, with no retinal photographs or upgradeable photographs at visit 3, taking anti-psychotic medications at visit 2, 3 or 4, and a history of stroke at visit 2, or between visit 2 and December 31, 1997.

**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