1.a. **Full Title:** Association of Optic Nerve Damage and Brain Microvascular Disease: An ARIC MRI Study

b. **Abbreviated Title (Length 26 characters):** Optic Nerve Damage and Brain Microvascular Disease

2. **Writing Group:**
   (Alphabetical) Ali Abraham, Jennifer A. Deal, Pradeep Ramulu, A. Richey Sharrett, Jithin Yohannan

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

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3. **Timeline:**
The manuscript will be completed in 12 months.

4. **Rationale:**

   Alzheimer’s disease and vascular dementia account for 80% of all dementias. 1 Over the next 20 years, as the world population ages, the number of people living with dementia is expected to double and the economic impact of dementia is expected to climb 85% from $604 billion in 2010 to $1.2 trillion by 2030. 2 Finding early markers of dementia is important to identify patients at risk as well. Vascular changes play a significant role in cognitive impairment
and dementia.\textsuperscript{3} In particular, white matter hyperintensity volume and lacunar infarcts identified on MRI are strongly associated with cognitive impairment and dementia.\textsuperscript{4}

There are several compelling reasons to believe that cerebral microvascular changes may be reflected in changes to the optic nerve head. The optic nerve head is comprised of axons from retinal ganglion cells whose fibers are essentially CNS axons.\textsuperscript{5} Therefore any microvascular changes affecting these axons in the optic nerve head may be an indicator of similar vascular changes within the CNS. However, glaucoma, the second leading cause of blindness worldwide, is the most common disease causing death of retinal ganglion cells, and is defined by damage to the optic nerve.\textsuperscript{6} Further, there is evidence that glaucomatous optic nerve changes may be caused, in part, by microvascular dysfunction. Recent work using optical coherence tomography (OCT) angiography of the optic nerve head has shown that attenuation of the microvascular structure of the optic nerve head is more likely to occur in patients with glaucoma.\textsuperscript{7} Additionally, prior work has demonstrated that open angle glaucoma (OAG) is associated with vascular insufficiency in the posterior cerebellar arteries measured using transcranial Doppler sonography.\textsuperscript{8}

Several large studies have looked at the association between glaucoma and a clinical diagnosis of dementia, though not necessarily dementia due to cerebrovascular changes. Helmer et al found that in a longitudinal cohort of patients, those with open angle glaucoma were more likely to be diagnosed with dementia over the 3-year follow-up period (OR 3.9, 95% CI 1.5-10.4).\textsuperscript{9} In a large retrospective population based cohort study, Cheng et al found that individuals with open angle glaucoma (OAG) were more likely to be diagnosed with dementia (HR: 1.21, 95% CI: 0.95-1.26).\textsuperscript{10} One large cohort study found a modest association between OAG and dementia specifically classified as the vascular type (RR: 1.10, 95% CI 1.05-1.16) but no association was noted between OAG and Alzheimer’s dementia.\textsuperscript{11}

Thus, although several large studies have looked at the association of optic nerve damage from glaucoma and clinical dementia (Alzheimer’s and vascular types), no studies assessed the association between optic nerve damage from glaucoma and microvascular changes on MRI -- which may be the earliest precursors to vascular dementia and vascular cognitive impairment.\textsuperscript{3} This proposed study will investigate the exam findings of large cup to disc ratio (a marker of glaucomatous optic damage) as well as other retinal signs associated with optic nerve damage (optic nerve hemorrhages\textsuperscript{12} and parapapillary atrophy\textsuperscript{13}) at ARIC visit 3 to small vessel disease changes on MRI taken at visit 3.

5. Main Hypothesis/Study Questions:

We hypothesize that optic nerve damage consistent with glaucoma (evidenced by an enlarged cup to disk ratio) observed at visit 3 will be associated with more frequent/pronounced microvascular changes noted on the MRI at visit 3.

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:
This study will involve cross-sectional analysis of retinal image and MRI data obtained at visit 3.

**Inclusion/Exclusion criteria:**

We will examine the data for all ARIC participants who underwent retinal photography at visit 3 who also completed MRI testing at visit 3.

**Primary dependent variable:**

White Matter Hyperintensities Score:

White matter hyperinsities seen on MRI reflect subclinical small vessel disease, specifically white matter damage due to hypoperfusion or thrombosis of arterioles\textsuperscript{14,15}. As described in previous work done on these same ARIC data\textsuperscript{16}, we will use a white matter hyperintensties score (range 0-9) as developed in the cardiovascular health study\textsuperscript{17} as the primary dependent variable.

**Primary independent variables:**

Retinal variables: (taken at visit 3)

In ARIC, two fundus photographs were taken of each eye using a digital camera. All photographs were graded by trained, certified graders at the Ocular Epidemiology Reading Center (OREC) at the University of Wisconsin-Madison. The retinal variables of interest include large cup to disk ratio, retinal hemorrhage within the disc margin and peripapillary atrophy, each of which reflects optic nerve damage.

1. **Enlarged Cup to Disc Ratio:** This is a sign of optic nerve damage. Cup to disc ratio is considered enlarged if >0.7. It is a categorical variable with three levels, yes, no and questionable.
2. **Retinal Hemorrhage within the disc margin:** An exam finding may that may be suggestive of optic nerve damage but not as sensitive or specific as enlarged cup to disc ratio. It is a categorical variable with three levels, yes, no and questionable.
3. **Peripapillary Atrophy:** An exam finding may that may be is associated with optic nerve damage but not as sensitive or specific as the two findings above. It is a categorical variable with three levels, yes, no and questionable.

Additional independent variables:

1) Demographic variables collected at ARIC visit 1: age, sex, education, occupational class, income, race, study site and apoE4
2) Potential vascular confounding variables: hypertension status (normotensive, pre-hypertensive, hypertensive), systolic and diastolic blood pressure, smoking status, inflammatory markers (WBC count, serum fibrinogen), lipids (total cholesterol and triglyceride), body mass index, alcohol use, diabetes status

**Summary of Data Analysis:**

ANOVA and Chi square tests will be used to examine univariate associations of covariates with White matter hyperintensities score and the independent variables. Adjusted and non-
adjusted linear regressions will be used to investigate the association of the independent variables and White matter hyperintensities. Our models will adjust for potential demographic confounders including age, sex, race, center, education, apoE4 and other demographic variables. Our analysis will also adjust for potential disease confounders including hypertension status, diabetes status, smoking status, lipids, and alcohol use. Stratification by diabetes status will also be considered in light of the substantial vascular impact of diabetes.

References:


7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __X__ 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   __X__ No

    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”? ____ 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

    __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):
a. Retinal Microvascular Abnormalities Predict Progression of Brain Microvascular Disease: An ARIC MRI Study

b. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study

c. Smoking and white matter hyperintensity progression

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

11.b. If yes, is the proposal

___ 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)* _________ _________ _________)

*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 shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.