ARIC Manuscript Proposal #4044

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: ___/___/___	**Status: _____**	**Priority: ____**

1.a. Full Title: Visual function and brain structure in older adults

b. Abbreviated Title (Length 26 characters): EyeDOC MRI/PET

2. Writing Group:

Writing group members: Ali Hamedani, Pradeep Ramulu, A. Richey Sharrett, Jennifer Deal, Xinxing Guo, Lubaina Arsiwala, YaNan Dong, Alex J. Spychalla, Clifford Jack, Aleks Mihailovic, Rebecca Gottesman, Bonnielin Swenor, Ali Abraham

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

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3. Timeline: Initial analysis in spring/summer 2022, first draft in September 2022.

4. Rationale:

Visual impairment has been associated with an increased risk of cognitive impairment and dementia in a number of studies including ARIC[1,2]. One hypothesized explanation for this is that reduced brain stimulation (whether of the occipital cortex due to reduced visual input or of other cortical regions due to secondary decreases in cognitively stimulating activities such as reading, social engagement, and exercise[3]) leads to accelerated neurodegeneration, resulting in atrophy and functional decline. However, the specific changes in brain structure associated with reduced visual function remain incompletely characterized. While studies have reported lower global and

regional gray matter volume in isolated disease populations such as age-related macular degeneration and glaucoma[4–7], these diseases may share underlying risk factors for neurodegenerative disease, confounding the relationship between visual function and brain volume, and population-based studies of reduced visual acuity (VA) (including that which may be reversible with refraction) and brain MRI are lacking. Contrast sensitivity (CS) has also emerged as a promising measure of visual function in the aging population, including prominent associations with Parkinson and Alzheimer disease, yet studies of CS and brain MRI are limited to young, healthy adults[8] and a single small study of cerebral amyloid deposition[9]. Finally, given known associations between retinal vascular disease and cerebral white matter disease and lacunar stroke[10–12], retinal OCT-angiography (OCT-A) has been proposed as a non-invasive surrogate marker of intracranial small vessel disease, but existing studies have used limited white matter hyperintensity quantification methods and have not explored other measures of white matter integrity[13,14]. In this study, we will examine the relationship of visual pathway structure (OCT, OCT-A) and visual function (visual acuity, contrast sensitivity) with MRI-based measures of gray and white matter change and brain amyloid PET deposition.

1 Shang X, Zhu Z, Wang W, Ha J, He M. The Association between Vision Impairment and Incidence of Dementia and Cognitive Impairment: A Systematic Review and Meta-analysis. *Ophthalmology* 2021;**128**:1135–49. https://doi.org/10.1016/j.ophtha.2020.12.029.

2 Arsiwala LT, Guo X, Ramulu PY, Sharrett AR, Mihailovic A, Swenor BK, *et al.* Associations of Visual Function With Cognitive Performance in Community-Based Older Adults: The Eye Determinants of Cognition Study. *J Gerontol A Biol Sci Med Sci* 2021:glab349. https://doi.org/10.1093/gerona/glab349.

3 Swenor BK, Lee MJ, Varadaraj V, Whitson HE, Ramulu PY. Aging With Vision Loss: A Framework for Assessing the Impact of Visual Impairment on Older Adults. *Gerontologist* 2020;**60**:989–95. https://doi.org/10.1093/geront/gnz117.

4 Boucard CC, Hernowo AT, Maguire RP, Jansonius NM, Roerdink JBTM, Hooymans JMM, *et al.* Changes in cortical grey matter density associated with long-standing retinal visual field defects. *Brain* 2009;**132**:1898–906. https://doi.org/10.1093/brain/awp119.

5 Hanson RLW, Gale RP, Gouws AD, Airody A, Scott MTW, Akthar F, *et al.* Following the Status of Visual Cortex Over Time in Patients With Macular Degeneration Reveals Atrophy of Visually Deprived Brain Regions. *Invest Ophthalmol Vis Sci* 2019;**60**:5045–51. https://doi.org/10.1167/iovs.18-25823.

6 Chen WW, Wang N, Cai S, Fang Z, Yu M, Wu Q, *et al.* Structural brain abnormalities in patients with primary open-angle glaucoma: a study with 3T MR imaging. *Invest Ophthalmol Vis Sci* 2013;**54**:545–54. https://doi.org/10.1167/iovs.12-9893.

7 Williams AL, Lackey J, Wizov SS, Chia TMT, Gatla S, Moster ML, *et al.* Evidence for widespread structural brain changes in glaucoma: a preliminary voxel-based MRI study. *Invest Ophthalmol Vis Sci* 2013;**54**:5880–7. https://doi.org/10.1167/iovs.13-11776.

8 Yang Y, Wang Y, Zhang C, Zhu J, Yu Y. Neuroanatomical substrates underlying contrast sensitivity. *Quant Imaging Med Surg* 2019;**9**:503–9. https://doi.org/10.21037/qims.2019.03.03.

9 Risacher SL, WuDunn D, Tallman EF, West JD, Gao S, Farlow MR, *et al.* Visual contrast sensitivity is associated with the presence of cerebral amyloid and tau deposition. *Brain Commun* 2020;**2**:fcaa019. https://doi.org/10.1093/braincomms/fcaa019.

10 Hanff TC, Sharrett AR, Mosley TH, Shibata D, Knopman DS, Klein R, *et al.* Retinal microvascular abnormalities predict progression of brain microvascular disease: an atherosclerosis risk in communities magnetic resonance imaging study. *Stroke* 2014;**45**:1012–7. https://doi.org/10.1161/STROKEAHA.113.004166.

11 Yatsuya H, Folsom AR, Wong TY, Klein R, Klein BEK, Sharrett AR, *et al.* Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. *Stroke* 2010;**41**:1349–55. https://doi.org/10.1161/STROKEAHA.110.580837.

12 Cheung N, Mosley T, Islam A, Kawasaki R, Sharrett AR, Klein R, *et al.* Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. *Brain* 2010;**133**:1987–93. https://doi.org/10.1093/brain/awq127.

13 Gao Y, Kwapong WR, Zhang Y, Yan Y, Jin X, Tao Y, *et al.* Retinal microvascular changes in white matter hyperintensities investigated by swept source optical coherence tomography angiography. *BMC Ophthalmol* 2022;**22**:77. https://doi.org/10.1186/s12886-021-02143-7.
14 Peng C, Kwapong WR, Xu S, Muse FM, Yan J, Qu M, *et al.* Structural and Microvascular Changes in the Macular Are Associated With Severity of White Matter Lesions. *Front Neurol* 2020;**11**:521. https://doi.org/10.3389/fneur.2020.00521.
15 Gottesman RF, Schneider ALC, Zhou Y, Chen X, Green E, Gupta N, *et al.* The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. *Neurology* 2016;**87**:473–80. https://doi.org/10.1212/WNL.0000000000002914.
16 Schneider ALC, Senjem ML, Wu A, Gross A, Knopman DS, Gunter JL, *et al.* Neural correlates of domain-specific cognitive decline: The ARIC-NCS Study. *Neurology* 2019;**92**:e1051–63. https://doi.org/10.1212/WNL.0000000000007042.

5. Main Hypothesis/Study Questions:

1. What neuroimaging profiles are most strongly associated with reduced VA and CS?
    a. We hypothesize that VA and CS will be associated with occipital gray matter volume, and that CS will additionally be associated with gray matter volume in regions outside the occipital lobe.
    b. We hypothesize that reduced visual function will be associated with greater amyloid PET burden, and we will explore whether this is different for CS and VA.
2. What neuroimaging profiles are most strongly associated with reduced retinal ganglion cell volume and vascular density?
    a. We hypothesize that retinal ganglion cell thickness will be associated with cerebral gray matter volume, and that retinal vascular density will be associated with cerebral white matter changes (specifically, white hyperintensity volume and microstructural integrity).

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 and sample: We will perform a cross-sectional analysis of vision and MRI/PET using data from the EyeDOC study. EyeDOC recruited 1073 participants with Mini-Mental State Examination (MMSE) scores no less than 22 (from the Jackson study site) or 24 (from the Washington County study site). We will include all EyeDOC subjects with available V5 MRI data; for the PET hypotheses, we will examine the subset of EyeDOC participants who also have florbetapir PET data from the ARIC-PET study (n=170).

Primary exposure: visual acuity and OCT

1. The EyeDOC study included standardized measurements of both high-contrast acuity and contrast sensitivity. High-contrast VA was measured with subjects' habitual correction using retroilluminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a distance of four meters. Contrast sensitivity was measured using Mars Contrast Sensitivity charts. Each eye was tested separately, and the number of correctly read letters was log-transformed and converted to presenting distance acuity logMAR and log CS as detailed in the EyeDOC study protocol. For presenting distance acuity, a higher

logMAR indicates worse vision, and for CS, a higher log value indicates better vision. We will use data from the worse seeing eye for analysis.

2. EyeDOC also included optical coherence tomography (OCT) and OCT-angiography imaging of the retina. After pharmacologic dilation, macular OCT images were collected and then processed at the image reading center using customized software. Macular ganglion cell complex (GCC, which reflects a combination of the ganglion cell and inner plexiform layers) thickness will be averaged across the superior, inferior, nasal, and temporal quadrants of the inner 3mm Early Treatment of Diabetic Retinopathy Study grid. Retinal vascular density is calculated from OCT-A images in three distinct layers of the retina from 6mm images: superficial vascular complex, intermediate capillary plexus, and deep capillary plexus. For all OCT and OCT-A analyses, the right and left eye will be averaged for analysis unless one eye is limited by image quality or availability, in which case a single eye will be used.

<u>Primary outcome: brain volume and amyloid PET</u>

We will explore two neuroimaging markers of neurodegeneration:

1. MRI - Brain volumes are measured using MRI data from V5 (2011-2013). The ARIC MRI Reading Center calculates gray matter (GM) volumes from MP-RAGE sequences, white matter hyperintensity (WMH) volumes from FLAIR images, and measures of white matter integrity [fractional inosotropy (FA) and mean diffusivity (MD)] from diffusion tensor images. GM volume will be calculated for the entire brain as well as for regions of interest (e.g. occipital, temporal lobes) and voxel-based analyses (see below). WMH volume is summed across the entire brain, and global FA and MD are calculated as weighted averages based on the number of voxels in each region according to standard ARIC protocols.
2. Amyloid PET – Florbetapir PET scans were performed as part of the ARIC-PET substudy within one year of V5 MRI. Standardized uptake value ratios (SUVR) were calculated at each of 34 regions of interest and spatially normalized and averaged to create a global cortical measure of β-amyloid (Aβ) as previously described[15].

<u>Secondary covariates for adjustment:</u> Other covariates will be selected primarily based on their potential association with the primary outcome and informed by previous neuroimaging studies in ARIC:

1. Age
2. Race/study center (Black/Jackson and White/Washington County)
3. Gender
4. Education (3 classes)
5. Smoking history
6. Alcohol history
7. Hypertension
8. Diabetes
9. Total serum cholesterol
10. History of stroke
11. *APOE* ε4 allele status
12. Total intracranial volume (for MRI analyses)

Statistical Analysis:

1. VA/CS and brain MRI – We will work with the ARIC MRI Reading Center to conduct voxel-based morphometry (VBM) analyses of GM as a function of logMAR-VA and logCS. For these analyses, visual function will be dichotomized as follows:
    a. logMAR-VA will be dichotomized at ≥0.3 vs. <0.3. A logMAR of 0.3 corresponds to a Snellen equivalent of 20/40, which is associated with meaningful differences in vision-related activity (e.g. restricted driving privileges in most U.S. states) and quality of life and has been used in previous vision/MRI studies (https://www.medrxiv.org/content/10.1101/2021.01.09.21249189v1.full). About 25% of the EyeDOC cohort has a presenting distance logMAR-VA of 0.3 or worse, ensuring reasonable statistical power for this analysis.
    b. logCS will be dichotomized at the median.

   For VBM analyses, GM images are spatially normalized and smoothed, and then used in the SPM12 general linear model framework to estimate models of associations between logMAR-VA and logCS groups and GM volume on a voxel-wise basis as previously performed in ARIC[16]. The results of these VBM analyses will be used to identify signature regions of interest associated with reduced VA and CS, respectively, which will then be formally compared in separate linear regression models adjusting for covariates. We will construct additional models for other prespecified regions of interest (e.g. occipital, temporal) and global GM volume as well.
2. VA/CS and amyloid PET – We will use logistic regression to assess the association between global cortical β-amyloid burden and logMAR-VA or logCS adjusting for the above covariates. For these analyses, amyloid SUVR will be dichotomized at the median due to its highly skewed distribution, and logMAR-VA and logCS will be analyzed as continuous exposure variables.
3. Macular GCC thickness and brain MRI – Similar to our approach with VA and CS, we will conduct VBM analyses of GM volume according to macular GCC thickness to derive a signature region of interest associated with ganglion cell thinning. For this analysis, GCC thickness will be divided into quartiles, and we will compare the bottom (thinnest) quartile to the top three quartiles. Associations between global and regional GM volume and macular GCC thickness will then be assessed using linear regression adjusting for confounders.
4. Macular retinal vessel density and brain MRI – We will use linear regression to determine the association between WMH volume, FA, and MD as a function of retinal vascular density adjusting for covariates. We will construct separate models for each white matter outcome variable and retinal vascular layer. Retinal vascular density will be analyzed as a continuous variable in these analyses.

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? _x_ Yes _ No

8.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"? _x_ 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/mantrack/maintain/search/dtSearch.html

_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)?

1. Arsiwala LT, Guo X, Ramulu PY, Sharrett AR, Mihailovic A, Swenor BK, *et al.* Associations of Visual Function With Cognitive Performance in Community-Based Older Adults: The Eye Determinants of Cognition Study. *J Gerontol A Biol Sci Med Sci* 2021:glab349. https://doi.org/10.1093/gerona/glab349.
2. Abraham AG, Guo X, Arsiwala LT, et al. Cognitive decline in older adults: What can we learn from optical coherence tomography (OCT)-based retinal vascular imaging? *J Am Geriatr Soc*. 2021;69(9):2524-2535. doi:10.1111/jgs.17272
2. Casanova R, Hsu FC, Barnard RT, et al. Comparing data-driven and hypothesis-driven MRI-based predictors of cognitive impairment in individuals from the Atherosclerosis Risk in Communities (ARIC) study. *Alzheimers Dement*. Published online July 26, 2021. doi:10.1002/alz.12427
3. Deal JA, Sharrett AR, Albert M, et al. Retinal signs and risk of incident dementia in the Atherosclerosis Risk in Communities study. *Alzheimers Dement*. 2019;15(3):477-486. doi:10.1016/j.jalz.2018.10.002
4. Deal JA, Sharrett AR, Rawlings AM, et al. Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study. *Neurology*. 2018;90(13):e1158-e1166. doi:10.1212/WNL.0000000000005205
5. Hanff TC, Sharrett AR, Mosley TH, et al. Retinal microvascular abnormalities predict progression of brain microvascular disease: an atherosclerosis risk in communities magnetic resonance imaging study. *Stroke*. 2014;45(4):1012-1017. doi:10.1161/STROKEAHA.113.004166
6. Johnson EL, Krauss GL, Lee AK, et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. *Neurology*. 2019;92(9):e988-e995. doi:10.1212/WNL.0000000000007010
7. Kawasaki R, Cheung N, Mosley T, et al. Retinal microvascular signs and 10-year risk of cerebral atrophy: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2010;41(8):1826-1828. doi:10.1161/STROKEAHA.110.585042

8. Knopman DS, Griswold ME, Lirette ST, et al. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke*. 2015;46(2):433-440. doi:10.1161/STROKEAHA.114.007847
9. Lee MJ, Deal JA, Ramulu PY, Sharrett AR, Abraham AG. Prevalence of Retinal Signs and Association With Cognitive Status: The ARIC Neurocognitive Study. *J Am Geriatr Soc*. 2019;67(6):1197-1203. doi:10.1111/jgs.15795
10. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. *Neurology*. 2009;73(11):862-868. doi:10.1212/WNL.0b013e3181b78436
11. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. *Neurology*. 2009;73(11):862-868. doi:10.1212/WNL.0b013e3181b78436
12. Moazzami K, Shao IY, Chen LY, et al. Atrial Fibrillation, Brain Volumes, and Subclinical Cerebrovascular Disease (from the Atherosclerosis Risk in Communities Neurocognitive Study [ARIC-NCS]). *Am J Cardiol*. 2020;125(2):222-228. doi:10.1016/j.amjcard.2019.10.010
13. Mosley TH, Knopman DS, Catellier DJ, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology*. 2005;64(12):2056-2062. doi:10.1212/01.WNL.0000165985.97397.88
14. Schneider ALC, Selvin E, Sharrett AR, et al. Diabetes, Prediabetes, and Brain Volumes and Subclinical Cerebrovascular Disease on MRI: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Diabetes Care*. 2017;40(11):1514-1521. doi:10.2337/dc17-1185
15. Walker KA, Chawla S, Nogueras-Ortiz C, et al. Neuronal insulin signaling and brain structure in nondemented older adults: the Atherosclerosis Risk in Communities Study. *Neurobiol Aging*. 2021;97:65-72. doi:10.1016/j.neurobiolaging.2020.09.022
16. Wong TY, Mosley TH, Klein R, et al. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. *Neurology*. 2003;61(6):806-811. doi:10.1212/01.wnl.0000086372.05488.8d
17. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. *Stroke*. 2002;33(6):1487-1492. doi:10.1161/01.str.0000016789.56668.43
18. Walker KA, Silverstein N, Zhou Y, et al. Brain White Matter Structure and Amyloid Deposition in Black and White Older Adults: The ARIC-PET Study. *J Am Heart Assoc*. 2021;10(17):e022087. doi:10.1161/JAHA.121.022087
19. Gottesman RF, Schneider ALC, Zhou Y, et al. The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. *Neurology*. 2016;87(5):473-480. doi:10.1212/WNL.0000000000002914

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

_x_ A. primarily the result of an ancillary study (no. 2014.38)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.cscc.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.