

ARIC Manuscript Proposal # 3249

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Priority: _____

1.a. Full Title: Associations between OCT(A)-defined structural and vascular measures and cognition in a biracial older adult population

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

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __PYR_ [**please confirm with your initials electronically or in writing**]

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3. Timeline:

Analysis and draft will be completed in 18 months.

4. Rationale:

Previous work from ARIC has demonstrated that retinal findings can predict long term cognitive declines.¹ However, such retinal findings are not particularly helpful from a practical standpoint as they are dichotomous measures which only occur in a small percentage of individuals. Thus, while suggesting that the eye contains useful information which may reflect the brain and its function, they highlight the need for more precise, continuous retinal measures which might also predict impaired cognition, particularly at early, preclinical stages of impairment.

Over the last two decades, the ability to accurately measure the thickness of various retinal layers has been advanced by the introduction of Optical Coherence Tomography (OCT). A large body of work has demonstrated that persons with dementia demonstrate thinning of specific retinal structures as compared to cognitively normal older adults, specifically the peripapillary retinal nerve fiber layer (RNFL, consisting of the ganglion cell axons as they exit the retina to become the optic nerve), and the ganglion cell complex (GCC) in the macula.² Some articles have also demonstrated decreased thickness of these layers in persons with mild cognitive impairment as compared to controls.^{3,4} However, limited work has examined the OCT-cognition relationship with data which are longitudinal with regards to either OCT, cognition, or both. The importance of cognitive changes, as opposed to cross-sectional measures of cognition, is substantial given that baseline levels of cognitive ability are strongly affected by education and other potential confounding factors and also highly variable; thus persons with conditions producing cognitive decline are best recognized by a change in cognition from baseline, as opposed to a single cognitive assessment. To this end, **our study will serve as one of very few studies (and the largest) relating OCT measures (obtained cross-sectionally here) to cognitive change.**

A recent advance in OCT technology is the ability to obtain an angiogram of the retinal vasculature without the need for contrast dye, a technique known as OCT-Angiography (or OCTA for short). OCTA works by obtaining multiple closely-timed OCT scans and looking for decorrelation between consecutive images. Some of this decorrelation reflects areas of blood flow (red blood cells will not have the same location over time) and can be used to confirm the location of retinal blood vessels. Increasing sophistication in the scanning algorithms and analytic software help distinguish decorrelation due to blood flow from other causes of decorrelation (i.e. patient movement). The advent of OCTA has raised the possibility that OCTA measures, if associated with similar microvascular measures of the brain relevant to dementia, may also demonstrate associations with cognitive impairment, particularly cognitive impairment which is primarily vascular in origin. Indeed, one recent publication has demonstrated that the size of the foveal avascular zone, as judged by OCTA, is associated with several Alzheimer's Disease (AD) biomarkers.⁵ Thus, **we will examine the relationship between OCTA measures and overall cognitive decline as well.**

Finally, we explore whether OCT and OCTA measures will be able to distinguish the etiology of cognitive decline. Originally, we hypothesized that OCT measures would be associated with patterns of cognitive decline consistent with AD, while OCTA measures would be associated with patterns of cognitive decline consistent with cerebral small vessel disease. However, based on the recent study presented above,⁵ we will also specifically examine the association of OCTA measures with patterns of cognitive decline associated with AD.

1. Deal JA, Sharrett AR, Rawlings AM, Gottesman RF, Bandeen-Roche K, Albert M, Knopman D, Selvin E, Wasserman BA, Klein B, Klein R. Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study. *Neurology*. 2018 Mar 27;90 (13):e1158-e1166.
2. Lee MJ, Abraham AG, Swenor BK, Sharrett AR, Ramulu PY. Application of Optical Coherence Tomography in the Detection and Classification of Cognitive Decline. *J Curr Glaucoma Pract*. 2018 Jan-Apr;12(1):10-18.
3. He XF, Liu YT, Peng C, Zhang F, Zhuang S, Zhang JS. Optical coherence tomography assessed retinal nerve fiber layer thickness in patients with Alzheimer's disease: a metaanalysis. *Int J Ophthalmol* 2012 Jun;5(3):401-405.
4. Liu D, Zhang L, Li Z, Zhang X, Wu Y, Yang H, Min B, Zhang X, Ma D, Lu Y. Thinner changes of the retinal nerve fiber layer in patients with mild cognitive impairment and Alzheimer's disease. *BMC Neurol* 2015 Feb;15:14.
5. O'Bryhim BE, Apte RS, Kung N, Coble D, Va Stavem GP. Association of preclinical Alzheimer disease with optical coherence tomography angiography findings. *JAMA Ophthalmology*. Epub ahead of publication.

5. Main Hypothesis/Study Questions: The current study will integrate the cognitive data obtained from visits 5, 6, and (eventually 7) to the OCT and OCTA data obtained from the Washington County and Jackson EyeDOC participants in order to evaluate the following Aims:

Aim 1: Evaluate associations of OCT-defined retinal neurodegenerative measures with: (1) incident Mild Cognitive Impairment (MCI), (2) overall cognitive decline, and (3) a pattern of cognitive decline consistent with Alzheimer's disease. The primary focus will be on declines in overall cognition or specific cognitive measures reflecting memory, assessed by Delayed Word Recall, Logical Memory I and II, and Incidental Learning tests. OCT-defined retinal neurodegenerative measures will include lower GCC and NFL thickness, both of which reflect ganglion cell loss. Initial analyses will examine the cross-sectional association between our specified OCT measures and cognition defined in Visit 6. Subsequently, we will examine the association of these OCT measures with cognitive change between visits 5 and 6 and, when visit 7 is available, between visits 6 and 7. *Hypothesis: In models adjusting for age and other covariates, OCT-defined retinal neurodegenerative measures will be associated with greater declines in overall cognition and cognitive tests of memory, as well as a higher likelihood of incident MCI.* Ocular covariates will include intraocular pressure and axial length, both of which can influence GCC and NFL thickness but have not been evaluated as covariates in prior work relating OCT parameters to cognitive outcomes.

Aim 2: Evaluate the associations of OCTA-defined retinal microvascular abnormalities with: (1) incident MCI, (2) overall cognitive decline, and (3) a pattern of cognitive decline consistent with cerebral small vessel disease. The primary focus will be on declines in overall cognition or specific cognitive measures reflecting executive function/processing speed, assessed by Trails A&B, Digit Symbol Substitution and Digit Span Backwards tests. OCTA-defined retinal microvasculature measures will include layer-specific measures of retinal blood vessel density and area of foveal non-perfusion (i.e.

size of the foveal avascular zone). Initial analyses will examine the cross-sectional association between our specified OCTA measures and cognition defined in Visit 6. Subsequently, we will examine the association of these OCT measures with cognitive change between visits 5 and 6 and, when visit 7 is available, between visits 6 and 7. *Hypothesis: In models adjusting for age and other covariates, OCTA-defined retinal microvascular measures will be associated with greater declines in overall cognition and cognitive tests of executive function/processing speed, as well as a higher likelihood of incident MCI.*

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

As specified above, we will analyze the relationship between cross sectional OCT and OCTA measures with: (1) cross-sectional measures of cognition derived from visit 6, and (2) longitudinal measures of cognitive change between visits 5-6 and 6-7.

Inclusion/Exclusion Criteria

ARIC participants recruited for the EyeDOC ancillary study will be included in this analysis. Participants will have been recruited into EyeDOC only if they had a Mini-Mental State Examination (MMSE) score of 22 or greater from Jackson study site, or 24 or greater from Washington County study site. Participants will be excluded if retinal photography demonstrated an ocular condition which might influence the OCT/OCTA measure of interest (i.e. glaucoma, retinal vein occlusion, choroidal neovascularization, or macular edema), or if imaging was deemed to be unsuitable for accurately obtained the desired measures.

Primary Outcomes (Dependent variable)

1. Incident MCI. Diagnosis of normal cognition, MCI or dementia at ARIC-NCS visits 6 and 7 will be determined, as at visit 5, by a panel of ARIC-NCS clinicians based on: 1) the cognitive battery, 2) comparison of test scores to population-appropriate race- and education based norms, 3) nurse-performed neurologic exams including the NIH Stroke Scale, the Unified Parkinson's Disease Rating Scale, and the Clinical Dementia Rate interview (CDR) with both subject and informant interviews, the Functional Assessment Questionnaire (FAQ) and medical history. Incident dementia cases will also be ascertained by ARIC's dementia surveillance.
2. Memory ability, evaluated as the mean value, in z-score units, of performance in the Delayed Word Recall, Logical Memory I and II, and Incidental Learning tests.
 - a. Evaluated at visit 6
 - b. Evaluated as a change score, in z-score units, between V5-V6 or V6-V7. Of note, the performance distribution will be calculated for Visit 5, and z-score units at subsequent visits will be assigned using the V5 performance distributions.
3. Ability in cognitive tests reflecting cerebral small vessel disease (i.e. tests of executive function and processing speed), evaluated as the mean value, in z-score units, of performance in the Trails A&B, Digit Symbol Substitution, and Digit Span Backwards tests.

- a. Evaluated at visit 6
 - b. Evaluated as a change score, in z-score units, between V5-V6 or V6-V7. Of note, the performance distribution will be calculated for Visit 5, and z-score units at subsequent visits will be assigned using the V5 performance distributions.
4. Overall cognitive ability (10-factor score created by Gross et al.)
 - a. Evaluated at visit 6
 - b. Evaluated as a change score, in z-score units, between V5-V6 or V6-V7. Of note, the performance distribution will be calculated for Visit 5, and z-score units at subsequent visits will be assigned using the V5 performance distributions.

Other Variables of Interest

Demographic variables:

- a. Age
- b. Race
- c. Gender
- d. Education level (< high school, high school or equivalent, > high school)
- e. Diabetes status at Visit 6

Ocular variables

- a. Axial length
- b. Intraocular pressure in the imaged eye
- c. Coexisting disease in the imaged eye

Summary of Data Analysis

Study Population

ARIC participants recruited for the EyeDOC ancillary study will be included in this analysis if they demonstrate suitable imaging and are not excluded based on the presence of concurrent eye disease in the study eye.

Proposed Analysis

EyeDOC participants will be compared with invited non-participants with respect to education and demographic characteristics to understand generalizability of results. Additional comparisons will be made amongst EyeDOC participants with and without analyzable OCT or OCTA imaging to determine if exclusion of participants based on coexisting eye disease or the ability to obtain imaging generated a group dissimilar to the overall study population.

For the primary analyses, we will first examine whether the specified OCT or OCTA measures are associated with the specified V6 cognitive scores in cross-sectional analyses. Of note, many OCT and OCTA measures are available from the derived scans, and it is not clear which measure(s) are most likely to be associated with cognition. Thus, numerous measures will be evaluated. For OCT, these measures will reflect the thickness of various retinal layers derived from scans of varying locations (macula vs. optic nerve head). For OCT, these measures will

reflect vessel density in various retinal vascular plexi (i.e. superficial, intermediate or deep), varying locations (macula vs. optic nerve head), and different scan sizes (i.e. 3x3 or 6x6 mm macular scans).

Linear regression models will be used linking continuous outcome variables (cognition scores or change in cognition scores) with the OCT and OCTA measures, and model residuals will be evaluated to determine the appropriateness of these models. In cases with skewed residuals, robust regression estimates and/or bootstrapping methods will be considered. Logistic regression models will be employed in models evaluating incident MCI as an outcome. All models will be run with the age, race, gender and level of education. Additionally, models will be run within each individual racial group. Models evaluating the importance of OCTA measures will be run both with and without diabetes in the model. Both axial length and intraocular pressure will be included in models evaluating OCT measures, and will be evaluated as a potential covariate in models assessing OCTA measures.

Limitations

The paucity of prior research in this area makes it difficult to know which OCT/OCTA measures are most relevant to our outcomes of interest. Thus, we will need to explore many measures, subjecting our work to multiple comparison issues. Also, methods for clearly defining one measure as superior to another with regards to capturing variance in the outcome are poorly established. Given the large number of outcomes and exposure variables, p values will account for the multiple comparisons using either the Benjamini Hochberg false discovery rate or the Bonferroni correction method. Alternative approaches will include integrating multiple OCT measures through procedures such as principle components analysis to identify latent traits associated with the cognitive outcome of interest.

There is also a possibility that persons participating in the EyeDOC, receiving gradable images, or lacking concurrent eye disease, will not represent the full study population, introducing the potential for bias of uncertain directionality.

Initial work will only be able to look at past change in cognition, and not future change, which is of course of greater clinical significance. Finally, our OCT/OCTA measures are only obtained cross-sectionally, and it is not clear that deficiencies in these measures represent acquired defects as opposed to long-standing/developmental differences in the eye developed prenatally or during early life.

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

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)

The most related manuscript is below, and Dr. Sharrett will be heavily involved with the current project as well.

Deal JA, Sharrett AR, Rawlings AM, Gottesman RF, Bandeen-Roche K, Albert M, Knopman D, Selvin E, Wasserman BA, Klein B, Klein R. Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study. Neurology. 2018 Mar 27;90 (13):e1158-e1166.

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

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* EyeDOC)
 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.c.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.csc.c.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.