ARIC Manuscript Proposal #3516

PC Reviewed: 12/10/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of visual acuity and contrast sensitivity with retinal neuronal and retinal vascular characteristics

b. Abbreviated Title (Length 26 characters): Vision and retina vasculature

2. Writing Group:

Writing group members:

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

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3. Timeline:

First set of analysis December 2019. First draft December 2020.

4. Rationale:

Over 80% of visually impaired and blind people are 50 years and older worldwide.[1] In the US, 7.5% people over the age of 40 years suffer from vision impairment.[2] As the population ages, age-related eye diseases have become a public health problem, with the burden of vision impairment projected to increase significantly in the following decades. Retinal microstructural health undergoes age-related changes and may provide important biological information indicative of visual function. Understanding the associations between visual function and retinal microstructures in the general population provides fundamental knowledge about structural-functional relationships of the visual system, and is the first step in predicting eye disease development and progression, and their associations with functional changes in vision.

Optical coherence tomography (OCT) and OCT angiography (OCTA) are novel, non-invasive imaging techniques that provide microstructural details of the retina and choroid.[3] OCT imaging is the current standard of clinical care for diagnosis, treatment planning, and follow up evaluations in a variety of ocular disorders including glaucoma, macular degeneration, diabetic retinopathy, etc.[4,5] Compared to other imaging techniques, i.e. retinal photos, fluorescein angiography, OCT imaging provides rapid, non-invasive quantitative assessments of neuronal and microvascular retinal measures that are essential for disease early detection and progression monitoring.

Previously, studies have shown that retinal nerve fiber layer thickness and vessel density, the respective primary measures of retinal neuronal and vascular characteristics, are associated with visual function outcomes. Locally, thinner retinal nerve fiber layers are associated with lower visual acuity, restricted visual field, or lower contrast sensitivity in patients with different stages of glaucoma.[6,7] Similarly, there are significant associations of retinal layer thickness, macular vessel density, foveal avascular zone (FAZ) with visual acuity outcomes in patients with diabetic retinopathy or retinal vein occlusion.[8-10] Surgically, pre-operative retinal nerve fiber layer thickness is predictive of visual acuity outcomes after trabeculectomy[11] or endoscopic endonasal surgeries for suprasellar tumors.[12] Systemically, thinner retinal nerve fiber layer thickness or ganglion cell-inner plexiform complex have been associated with lower visual acuity in multiple sclerosis,[13] Alzheimer's disease,[14] Lewy body disease,[15] bipolar disorder,[16] and others.

Most of these investigations have been conducted in the clinical settings and with case-control study designs, focusing on specific eye diseases or systemic conditions. We aim to examine the associations of visual function with retinal microstructure parameters as measured by OCT and OCTA in an older population sample from two communities: Jackson, MS, and Washington County, MD.

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5. Main Hypothesis/Study Questions:

We aim to assess the following study questions using The Atherosclerosis Risk in Communities (ARIC) cohort ancillary study Eye Determinants of Cognition (EyeDOC) data:

1) Describe the normative distributions of retinal vascular and neuronal outcomes as measured by OCT and OCTA in 2 community-based older adult samples;

2) Evaluate the associations of visual function – presenting and corrected distance and near visual acuity, contrast sensitivity – with OCTA retinal vascular outcomes;

3) Evaluate the associations of visual function – distance and near visual acuity, contrast sensitivity – with OCT retinal neuronal outcomes.

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 is a cross-sectional, observational study; data from the ARIC visit 5, visit 6 or visit 7 (depending upon the closest proximity to the EyeDOC exam) and EyeDOC visits will be used in the analysis.

Inclusion/Exclusion criteria:

ARIC participants recruited in the EyeDOC ancillary study will be included. These include approximately 500 participants with Mini-Mental Sate Examination (MMSE) scores no less than 22 from the Jackson, MS study site and approximately 500 participants with MMSE scores no less than 24 from the Washington County, MD study site. Participants with extreme mobility limitations or incomplete vision assessment data will be excluded. Participants with clinically significant retinal pathology, determined by retinal photography and OCT imaging assessment, will be evaluated separately.

Primary outcome:

- Visual function outcomes include:
  - Presenting and Autorefractor-corrected distance visual acuity and presenting near visual acuity
  - Contrast sensitivity

- Quantitative retinal neuronal outcomes include the following measures from OCT and OCTA scans:
  - Retinal nerve fiber layer thickness at the optic nerve head (ONH) region
  - Ganglion cell layer, total retinal thickness, inner plexiform layer thickness at the macular region

- Quantitative retinal vascular outcomes include the following measures from OCTA scans:
  - Vessel density of the superficial, intermediate, and deep retinal layers at the macular region
  - Vessel density of the retinal nerve fiber layer, superficial, and deep retinal layers at the ONH region
  - Foveal avascular zone (FAZ) at the macular region

Other variables of interest:

- Other variables collected during the ARIC visit 5/visit 6/visit 7 follow-up will be included:

- Demographics and socioeconomics: age, gender, household income, education level (3 categories)
- Lifestyle: smoking habits (ever/never), alcohol consumption
- Medical history: diabetes mellitus, hyperlipidemia, hypertension (each defined by ARIC as combinations of measured levels and treatment)
- Access to medical care (ARIC visit 5)

- Other variables collected during the EyeDOC study will be included:
  - Refraction
  - History of cataract surgery
  - Access to eye care

Summary of data analysis:

Study population

Study population will include all participants in the EyeDOC study with available data on both OCT and vision function variables of interest

Visual function

LogMAR visual acuity (presenting near and distance) and logCS contrast sensitivity will be described, as continuous and categorical variables. Visual impairment is defined in accordance with the World Health Organization's classifications, and as corrected visual acuity worse than 20/40 in the better-seeing eye. Contrast sensitivity impairment is defined as log CS≤1.48.

Quantitative OCT and OCTA retinal vascular and neuronal assessments

Structural and angiography OCT scans are obtained in one eye per individual in most cases in the EyeDOC study; in a random 10% subsample of the study population, OCT and OCTA scans are obtained in both eyes allowing for comparisons between eyes within an individual.

Proposed analysis

Graphical analysis of the distributions of the visual function measures and the OCT/OCTA neuronal and vascular metrics will be performed to look for outliers and ranges as well as distributional shape. We will examine OCT/OCTA metrics as a function of area on the retina to understand differences in quadrants or sections of the eye. Pearson and Spearman correlations as well as scatter plots will be constructed between vision function metrics and OCT/OCTA metrics to evaluate strength of relationships. These assessments will also be stratified by categories of above and below median age and by gender. Regression models will be constructed to understand the impact of other factors on the relationship, such as medical history elements, lifestyle, etc. We will estimate: (1) the associations of visual functions with OCT retinal neuronal measures; (2) the associations of visual functions with OCTA retinal vascular measures, controlling for additional demographic and behavioral factors to understand contributors to the association of OCT metrics with vision function metrics.

While primary analyses will be continuous, we will also examine accepted thresholds for visual function and compare OCT/OCTA metrics by category of vision function.

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

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.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)?

[#3229 Elizabeth Couser] Associations between of Visual Function and Cognition in an Older Adult Population

[#3156 Xinxing Guo] Visual Function, Retinal Pathology, OCT Measures, and Associations with Quality of Life in a Bi-community Population 75 Years and Older: The Eye Determinants of

Cognition Study
[#3249 Pradeep Ramulu] Associations between OCT(A)-defined structural and vascular measures and cognition in a biracial older adult population

[#3433 Jennifer Deal] Visual Function, Retinal Pathology, OCT Measures, and Associations with Quality of Life in a Bi-community Population 75 Years and Older: The Eye Determinants of Cognition Study

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 (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ___2014.38_____)

*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.