ARIC Manuscript Proposal #3156

PC Reviewed: 10/09/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: 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

b. Abbreviated Title (Length 26 characters): Visual Function in the Elderly

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:

Analysis and manuscript draft will be completed in 12 months.

4. Rationale:

Approximately 440 million people are visually impaired or blind worldwide, and over 80% are aged 50 years and above. Although the age-specific prevalence has decreased from 1990 to 2015,

the estimated number of people with impaired vision increased by 17% as a result of the ageing of the population.[1] Further visual impairment and associated age-related retinal pathology have significant consequences, impacting cognitive function, quality of life, and social engagement in the older populations. [2-4]

Racial differences in genetic makeup, access to care or environment may produce differing profiles in visual function or retinal pathology. Such differences may also affect the relationships between visual function and quality of life outcomes. Previous studies have reported racial differences in disease prevalence and the prevalence of visual impairment. The Baltimore Eye Survey revealed a significantly higher prevalence of open angle glaucoma in the African American population compared to the Caucasian population (4.7% vs. 1.3%, respectively) aged 40 years and older.[5] The Salisbury Eye Evaluation Glaucoma Study further showed race-specific differences in the prevalence of open angle glaucoma (23.2% in African-Americans vs. 9.4% in Caucasian participants 75 years and older).[6] Meanwhile, Caucasians are more susceptible to age-related macular degeneration for all disease stages.[7] Our own ARIC cohort data, along with analysis based on the NHANES and Multi-Ethnic Study of Atherosclerosis data, have shown that African Americans are at higher risk for diabetic retinopathy.[8-10] It has also been projected from pooled studies that African American populations are more likely to experience visual impairment and blindness by 2050.[11] However, functional outcomes other than visual acuity have been rarely assessed in these studies.

Retinal features can be assessed quantitatively by evaluating the pathological changes using retinal photos, and qualitatively by measuring the retinal tissue thickness using optic coherence tomography (OCT) scans. Both technology has been used routinely in ophthalmic care settings and selectively in population-based studies.[12, 13] Previous studies have shown that retinal structural measures assessed by OCT are associated with visual disabilities and quality of life in patients with predefined conditions.[14, 15] However, much is left unknown regarding the racial disparities in the associations between visual functions, qualitative and quantitative ocular pathology, qualify of life, and physical ability outcomes.

Differences between African Americans, largely from Jackson Mississippi, and Caucasians from the other ARIC communities, though they cannot be attributed to possible biological differences between the race groups, may nevertheless help describe expected differences between African Americans and Caucasians in the often very different communities they reside in. This study will also examine the associations of the ocular structural and visual findings with the social context in each race group.

Current population-based studies have mainly focused on individuals 40 years and older, with samples skewed towards the younger tail of that age distribution, with a poor representation of older adults. As the population ages, normative data for visual function in the oldest individuals are needed for public health planning, epidemiological, and clinical research purposes. The ARIC cohort provides the unique opportunity of examining this group of individuals with data on the other covariates including comprehensive medical history, socioeconomic considerations, lifestyle such as alcohol and smoke intake, etc. Here we aim to examine racial/community differences in visual functions (as judged by visual testing) and retinal pathology (as judged by photographs), and to explore their associations with quality of life in an older population sample from two communities: Jackson, MS, and Hagerstown, MD.

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2. Cimarolli, V.R. and D.S. Jopp, *Sensory impairments and their associations with functional disability in a sample of the oldest-old.* Qual Life Res, 2014. **23**(7): p. 1977-84.
3. Stevelink, S.A., E.M. Malcolm, and N.T. Fear, *Visual impairment, coping strategies and impact on daily life: a qualitative study among working-age UK ex-service personnel.* BMC Public Health, 2015. **15**: p. 1118.
4. Chen, S.P., J. Bhattacharya, and S. Pershing, *Association of Vision Loss With Cognition in Older Adults.* JAMA Ophthalmol, 2017. **135**(9): p. 963-970.
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6. Friedman, D.S., et al., *The prevalence of open-angle glaucoma among blacks and whites 73 years and older: the Salisbury Eye Evaluation Glaucoma Study.* Arch Ophthalmol, 2006. **124**(11): p. 1625-30.
7. Wong, W.L., et al., *Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis.* Lancet Glob Health, 2014. **2**(2): p. e106-16.
8. Klein, R., et al., *The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes : the atherosclerosis risk in communities study.* Ophthalmology, 2002. **109**(7): p. 1225-34.
9. Harris, M.I., et al., *Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study.* Diabetes Care, 1998. **21**(8): p. 1230-5.
10. Wong, T.Y., et al., *Diabetic retinopathy in a multi-ethnic cohort in the United States.* Am J Ophthalmol, 2006. **141**(3): p. 446-455.
11. Varma, R., et al., *Visual Impairment and Blindness in Adults in the United States: Demographic and Geographic Variations From 2015 to 2050.* JAMA Ophthalmol, 2016. **134**(7): p. 802-9.
12. Zhao L, Wang Y, Chen CX, et al. *Retinal nerve fiver layer thickness measured by Spectralis spectral domain optical coherence tomography: The Beijing Eye Study.* Acta Ophthalmol, 2014. **92**(1):e35-41.
13. Mutlu U, Colijin JM, Ikram MA, et al. *Association of retinal neurodegeneration on optical coherence tomography withi dementia: a population-based study*. JAMA Neurol, 2018. Epub ahead of print
14. Kalyani PS, Holland GN, FawziAA, et al. *Association between retinal nerve fiber layer thickness and abnormalities of vision in people with human immunodeficiency virus infection.* Am J Ophthalmol, 2012. **153**(4): 734-42.
15. Walter SD, Ishikawa H, Galetta KM, et al. *Ganglion cell loss in relation to visual disability in multiple sclerosis*. Ophthalmology, 2012. **119**(6):1250-7.

5. Main Hypothesis/Study Questions:

In the current study, we aim to address the following research questions in the two chosen communities, each with a population aged 75 years and older:

1. Determine the normative visual function data including distance and near visual acuity, contrast sensitivity, and reading speed;
2. Determine the prevalence of retinal pathological findings, i.e. preproliferative retinopathy, glaucomatous optic nerve neuropathy, age-related macular degeneration, etc.;
3. Evaluate the distributions of retina structural measures quantified by OCT scans;
4. Compare the differences between the populations from two distinct community and racial backgrounds, and to analyze the associations between visual function/retinal pathology and quality of life outcomes (i.e. depression, functional limitations).

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 6 or visit 7 (depending upon the closest proximity to the EyeDOC exam) and EyeDOC visits will be analyzed.

Inclusion/Exclusion criteria:

ARIC participants recruited in the EyeDOC ancillary study will be included. These include 500 participants with Mini-Mental Sate Examination (MMSE) scores no less than 22 from the Jackson study site and 500 participants with MMSE scores no less than 24 from the Hagerstown study site. Participants with extreme mobility limitations or incomplete vision assessment data will be excluded.

Primary outcome:

Visual assessment outcomes include:
- Distance and near visual acuity
- Contrast sensitivity
- Reading speed

Retinal pathology qualitative outcomes include the presence of the following pathology on retinal photographs:
- Preproliferative retinopathy
- Proliferative retinopathy
- Glaucomatous optic neuropathy
- Age-related macular degeneration

Retinal pathology quantitative outcomes include the following measures from OCT scans:
- Retinal nerve fiber layer thickness
- Ganglion cell layer / inner plexiform layer thickness

Quality of life outcomes including:
- Functional status assessed by physical ability questionnaires and depression scales

Other variables of interest:

Other variables collected during the ARIC visit 6/visit 7 follow-up will be included:
- Demographics and socioeconomics: age, gender, household income, education level
- Life style: smoking history
- Medical history: diabetes, hyperlipidemia, hypertension
- 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, where individuals with a MMSE score ≥ 22 are recruited from the Jackson site, and individuals with a MMSE score ≥ 24 are recruited from the Hagerstown site. Participants with mobility limitations impeding retinal imaging will be excluded from the retinal pathology analysis.

Visual functions

Descriptive statistics for visual functions including distance presenting logMAR visual acuity, near presenting logMAR visual acuity, and corrected logMAR visual acuity will be reported; contrast sensitivity will also be reported. Distributions will be described graphically. Inter-ocular correlations will be assessed with Pearson correlation analysis for logMAR visual acuity. LogMAR visual acuity and contrast sensitivity by racial group will be described continuously and categorically. 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. Reading speed is reported as the maximum reading speed obtained from the MNRead test.

Retinal pathology qualitative assessments

Retinal photographs are obtained in one eye per individual in most cases in the EyeDOC study; however, in a random 10% subsample of the study population, retinal photos are obtained in both eyes. Retinal pathology is determined based on the retinal photos in the selected eye if one eye is imaged, and in the right eye if both eyes are imaged and met grading criteria. Active proliferative retinopathy, preproliferative retinopathy, age-related macular degeneration, glaucomatous optic neuropathy, and other retinal pathology will be graded. Prevalent cases are identified and reported as the proportions in the two community samples, respectively.

Retinal pathology quantitative assessments

Structural 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 scans are obtained in both eyes. OCT scans are obtained in the same eye(s) retinal photos are captured. Structural measures including retinal nerve fiber layer thickness and ganglion cell layer / inner plexiform layer thickness were assessed.

Quality of life

Functional status is assessed in the ARIC study through the physical ability questionnaire in which items are grouped into functional limitations, activities of daily living, and instrumental activities of daily living. Based on the distribution of responses, functional limitations will be

categorized as none (no difficulty on any item), mild (some difficulty on any item), and severe (much difficulty or unable to do any item). Activities of daily living and instrumental activities of daily living will be dichotomized as no impairment or impairment (some or much difficulty or unable to do on any item). Depression is assessed through the depression scale.

Proposed analysis

Demographics, socioeconomics, and medical history will be compared between the two communities/racial groups. Measured visual acuity and contrast sensitivity, as well as the age and gender adjusted visual acuity and contrast sensitivity will be compared between the two community samples. Prevalence of retinal pathology by the two racial/community groups will be presented.

Logistic regression models will be used to estimate: (1) The associations of visual functions with community/racial group, socioeconomics, medical history, retinal pathology, and OCT structural measures. Visual function will be evaluated as dichotomous dependent variables of visual impairment (yes/no), and contrast sensitivity impairment (yes/no). Age in years, gender, race, household income, education level, smoking status, alcohol intake, medical history of diabetes, hypertension, refractive error, and presence of retinal pathology will be included as independent variables. Furthermore, the associations of these covariates with the visual findings will be examined in each race group separately. (2) The associations of functional limitations (activities of daily living, instrumental activities of daily living) with visual function (best-corrected visual acuity, contrast sensitivity, maximum reading speed, etc), adjusted for demographics, socioeconomics, medical history. We will also examine whether racial/community group has a modifying effect on relationships. Odds ratios with corresponding 95% confidence intervals will be reported. Univariate regression analysis will be conducted, followed by multivariate regression analysis.

Limitations and possible solutions

This is primarily a descriptive study to understand the distribution and prevalence of vision function deficits and pathology signs in two racially and geographically distinct community samples. The fact that the racial groups are selected from separate sites is an obvious limitation to inferences which can be drawn. Associations with physical function variables will be from cross-sectional analyses and thus temporality is not established; however, there is no evidence to suggest that physical function limitations affect vision. History of cataract surgery is an important covariate for visual function outcomes in this population; although EyeDOC has only self-reported cataract history (compared to ophthalmologists on site for slit-lamp examinations, which would be the gold standard), cataract surgery is generally felt to be reliably remembered though the specific eye involved may not. Other data collected through questionnaires may introduce recall bias however, such as access to ophthalmic care. For prevalence of retinal pathology, generalizability may be limited as those with more severe eye disease may potentially not participate in a research study. The other consideration is retinal images and OCT scans may not be obtainable in eyes with more severe ocular conditions, or the image quality may not be sufficient for determination of pathological findings or structural measures. As noted above, the comparison is not limited to racial differences, but also important contextual differences that will need to be emphasized to avoid overweighting the racial component of any disparities. To the

extent possible, we will evaluate covariates representing potential differences in health care history and health-related behaviors if sufficient variability exists within each site.

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"? N/A ____ 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/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)?

Manuscript proposals search has revealed that although Retinal pathology outcomes have been reported using the ARIC cohort data, only specific conditions (i.e. age-related retinopathy, diabetic retinopathy, etc.) have been studied, without assessment of visual outcomes.

#2186 Associations between dietary intake of lutein and zeaxanthin and diabetic retinopathy in a biracial cohort

#2473 Association between Dietary Xanthophyll Intake and Prevalent Early Age-Related Macular Degeneration

#3133 Diet Patterns and the Incidence and Progression of Age-Related Macular Degeneration: the Atherosclerosis Risk In Communities (ARIC) 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* _2014.38 __)

___ 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.cscc.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.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.