ARIC Manuscript Proposal #4124

PC Reviewed: 9/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between retinal microstructure and vascularization and brain amyloid deposition in late life

b. Abbreviated Title (Length 26 characters):

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

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3. Timeline:

4. Rationale:

The pathology of β-amyloid (Aβ) is a key feature in the pathogenesis of Alzheimer's disease (AD) and can accumulate abnormally up to 20 years before the onset of clinical symptoms[1]. One way to detect Aβ abnormalities is using Florbetapir PET imaging[2]. However, due to its high cost, technical complexity, and invasiveness, PET imaging is not widely used in the general aging population. More easily obtainable, non-invasive measures are needed which would help to identify individuals at risk for AD and allow for a better understanding the AD pathogenesis.

Previous studies showed that midlife vascular risk factors and neurovascular dysfunction are important contributors to the onset and progression of AD pathology in the brain [3-5]. These findings are in line with the 2-hit vascular hypothesis of AD stating that vascular damage, as the initial insult, leads to oligemia and BBB dysfunction causing amyloid accumulation and neuronal injury in the brain [6, 7]. Unfortunately, to identify individuals at risk and to intervene at the early stages of disease, directly imaging the brain's small vessels and neuronal layers in vivo would be necessary which has been very challenging.

An alternative to imaging microvascular and neuronal changes in preclinical AD is to focus on the retinal manifestations of the neurodegenerative disease [8]. The retina, embryologically derived from the cranial part of the neural tube, shows high structural and physiological similarities with the brain [9]. As is the case in the neocortex, the retina has a neurovascular unit with a complex multi-cellular structure involving neurons, endothelial cells, glia, smooth muscle cells, and pericytes [10]. Recent technological advances such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) allow assessment of the retinal microstructure and the retinal vascularization of the retinal capillaries at a near-histological resolution. Using OCT and OCT-A may also allow us to analyze non-invasively the cascades of neurovascular injury and Aβ accumulation in the brain and to identify markers reflecting the disease's preclinical stage [11].

Previous studies employing various OCT and OCT-A measures so far however have shown inconsistent associations with Aβ and preclinical AD both in the cross-sectional and longitudinal study designs [11-18]. For instance, whereas an increase in foveal avascular zone (FAZ) was associated with preclinical AD in one study [14], no such evidence was found in another study [19].

The mixed findings may be explained by several factors mostly due to a lack of standardization across studies. First, methodological issues such as imbalanced study designs, low sample sizes resulting in insufficient statistical power, varying preclinical AD inclusion criteria, different OCT and OCT-A machines and different image software computations may have affected the results [11, 20]. Second, the stage of disease progression may be an important factor when testing the sensitivity of OCT measures in preclinical AD. Evidence suggests that the macular area may be first affected in the mild AD stage while peripapillary retinal nerve fiber layer thickness becomes more apparent as neurodegeneration progresses [17, 21]. Not fully describing the profile of preclinical AD population may lead to wrong conclusions regarding the sensitivity of OCT and OCT-A measures. Third, when it comes to the statistical analysis, covariates such as age and sex may also have not always been fully accounted for in the studies. As FAZ changes with normal ageing and as significant differences in the marker were particularly often found in studies with an older AD population, it remains to be seen whether the differences in FAZ reported in some studies are truly AD related or merely an age effect [20]. Fourth, there is often a lack of in detail reporting regarding the ophthalmological examinations making it difficult to compare studies [20].

This study proposes testing the cross-sectional association between OCT/ OCT-A markers and amyloid accumulation in late life. Methodological and statistical limitations outlined in the previous section will be addressed in this study and as much detail as possible will be provided. This will be the first large sample size cohort study focusing on preclinical and prodromal AD which includes both OCT and OCT-A parameters. The study's goals are to get a better understanding of the retinal vascularization and retinal microstructure implicated in preclinical and prodromal AD and to identify retinal markers that are associated with amyloid accumulation.

5. Main Hypothesis/Study Questions:

Main hypothesis: OCT and OCT-A measures, obtained around visit 6 and 7, are associated with elevated global cortical brain amyloid by PET at visit 5 when accounting for traditional vascular risk factors.

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).

Design: cross-sectional

Participant inclusion: All ARIC-PET participants without dementia who also participated in the EyeDOC study (the year 2017-2019) will be eligible for inclusion. 113 participants were enrolled and assessed in both ancillary studies. 1 ARIC-PET participant was recruited who ultimately was given a research diagnosis of dementia. This participant will be excluded from the analysis.

Outcome: Florbetapir PET global cortical SUVR. SUVR will be continuous and dichotomized at the study median of 1.2 as is standard in ARIC-PET analyses.

Exposures: OCT and OCT-A images were collected around ARIC visit 6 and visit 7. The OCT measures peripapillary retinal nerve fiber layer thickness (pRNFL), macular thickness and ganglion cell-inner plexiform layer (GC-IPL) as well as the OCT-A measures retinal vascular density (VD) and foveal avascular zone (FAZ) area will be included.

Other variables: Demographic variables such as age and vascular risk factors such as smoking status, drinking status, BMI, prevalent coronary heart disease, prevalent stroke, diabetes, and hypertension will be used as covariates from visit 5. The time-invariant variables educational status, race, sex, and APOE4 gene status will also be included as covariates.

Data analysis: Logistic and linear regression models will test the association between each OCT or OCT-A and global SUVR. The statistical assumptions underlying the regression models will be tested. In case the statistical assumptions are violated for the linear regression model, a robust linear regression model with bootstrapping or permutation will be employed.

We will use a four-step model building process for adjustment. In model 1 only the covariates age, educational status, race, APOE-4 status and sex will be included. In model 2 the OCT and OCT-A measures will be added in separate models, and it will be tested whether model 2 results in a better model fit than model 1 using the likelihood ratio test (LRT). In model 3, risk factors such as smoking status, drinking status, BMI, prevalent coronary heart disease, prevalent stroke, diabetes, and hypertension will be entered as additional covariates to model 2. To test whether a model containing OCT or OCT-A measures and traditional vascular risk factors (model 3) significantly better captures the data than a model with traditional vascular risk factors only (model 4), a likelihood ratio test (LRT) will be employed. The areas under the curve (AUCs) showing the accuracy of the models' classifications will be computed and compared. Multicollinearity will be checked using the variance inflation factor (VIF < 10).

In a Lasso logistic regression model, which includes all OCT and OCT-A measures showing a significant association in model 2, the retinal measures' major versus minor contributions to the amyloid accumulation in the brain will be determined. The accuracy of the resulting model's association will be assessed by computing the area under the receiver operating curve.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/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)?

MP # 2822. Gottesman et al., Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET study

MP #3433 Guo et al. 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

MP #3249 Ramulu et al. Associations between OCT(A)-defined structural and vascular measures and cognition in biracial older adult population

MP #3229 Couser et al. Associations between visual Function and cognition in Older Adult population

MP #4044 Hamedani et al. Visual function and brain structure in older adults

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

___ 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 https://sites.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.

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