1.a. Full Title: An eye on kidney disease: the association of ocular pathology and retinal markers with chronic kidney disease.

b. Abbreviated Title (Length 26 characters): An eye on kidney disease

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. _____ [please confirm with your initials electronically or in writing]

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3. Timeline:
First set of analysis December 2019. First draft Dec2020

4. Rationale:
The risk and occurrence of kidney disease and ocular disease may be closely linked. The eye and the kidney share commonalities including structural, developmental, and genetic pathways. A growing number of studies have found associations of chronic kidney disease with eye diseases
such as age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract. These two disease entities have common vascular risk factors including diabetes, hypertension, smoking, and obesity, which likely contribute to association. However, retinal microvascular parameters have been shown to be predictive of chronic kidney disease, suggesting that common mechanisms and pathogenesis may be at play. Inflammation, oxidative stress, endothelial dysfunction, and microvascular dysfunction are postulated mechanisms leading to both eye disease and chronic kidney disease. Understanding the pathogenic mechanisms that link kidney and ocular disease could lead to the development of new treatment and screening strategies for both diseases.

Optical coherence tomography angiography (OCTA) is a novel non-invasive technique for imaging the neuronal and microvascular tissues of the retina and choroid. It has the potential to become an important tool for investigating neuronal and vascular diseases beyond the eye. Prior studies in ARIC have examined the relationships between measures of retinal health extracted from fundus images and measures of kidney dysfunction. In Wong et al (2004), lower arteriole-to-venule ratio was associated with a 6-year change in serum creatinine, although no significant association was found with incident renal dysfunction defined as death or hospitalization due to CKD. However, with newer measures from EyeDOC, including OCT assessment of retinal microvascular health and clinical assessment of vision function, evaluating relationships with a richer set of eye and vision parameters will add substantially to prior work. In addition, longer follow-up on participants will provide better classification of renal function decline.

Quantification of retinal microvascular changes using noninvasive imaging methods like OCT may allow the development of a biomarker for CKD that can predict patients at risk of progression to advanced CKD. Unlike for patients with diabetes and hypertension, there are no clinical guidelines for routine eye screening in CKD patients, as links have not been strongly established. Results from this study could provide evidence to support the screening of CKD patients for some associated ocular diseases.

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 Study population:
We will use both historical data on makers of kidney disease as well as current kidney disease status (from the ARIC visit 6 or visit 7, proximate to the EyeDOC exam). Eye and vision data will come from the EyeDOC visit. Inclusion/Exclusion criteria: ARIC participants recruited in the EyeDOC ancillary study will be included. These include ~500 participants with Mini-Mental State Examination (MMSE) scores no less than 22 from the Jackson study site and ~500 participants with MMSE scores no less than 24 from the Washington County study site. Study population will include all participants in the EyeDOC study with data on either retinal parameters or visual function and at least one kidney outcome of interest.

Primary ocular variables: Visual assessment outcomes include: Distance and near visual acuity and contrast sensitivity. Retinal pathology outcomes include the presence of the following pathology on retinal photographs: Retinopathy, glaucomatous optic neuropathy, age-related macular degeneration. Retinal neuronal and vascular parameters include: vessel density and retinal nerve fiber layer thickness. Retinal pathology is assessed using retinal photographs obtained in one eye per individual in most cases in the EyeDOC study. 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 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.

Other clinically relevant features associated with eye disease are also captured and include: intraocular pressure.

Primary kidney variables: serum creatinine, proteinuria, albuminuria, cystatin C, eGFR by CKDpi equation, prevalent CKD.

Other covariates of interest: Other variables collected during the ARIC follow-up will be included: demographics and socioeconomics: age, gender, household income, education level; behavioral factors: smoking history; comorbidities: diabetes, dyslipidemia, hypertension.

Proposed analysis: First we will look at the prevalence of risk factors for kidney disease (age, smoking, diabetes, hypertension, obesity and hyperlipidemia) comparing those with ocular pathology (retinopathy, glaucomatous optic neuropathy, age-related macular degeneration) to those without ocular pathology using chi-squared and exact tests. We will also compare mean vascular density and mean retinal nerve fiber layer thickness between strata of each kidney disease risk factor using t-tests and transformation of continuous variables as appropriate or rank sum tests. This will provide insight into relationships between kidney and ocular variables stemming from shared systemic pathologies and processes.

For aim 1, we will look at univariate Pearson and Spearman correlations between kidney disease continuous factors (serum creatinine, proteinuria, albuminuria, cystatin C, eGFR by CKDpi equation) and retinal parameters (vessel density and retinal nerve fiber layer thickness). For ocular pathology (Retinopathy, glaucomatous optic neuropathy, age-related macular...
degeneration), we will compare distributions of kidney disease continuous factors across strata of pathological features using analysis of variance. Adjusted regression models with appropriate link functions, adjusted for common comorbid causes, demographics and behaviors, will be used to evaluate the extent to which common risk factors explain associations between kidney disease indicators and eye pathology. We will also use contingency tables to evaluate overlap between prevalent CKD and ocular pathologies.

For longitudinal kidney disease related data, we will use two approaches. First we will use simple classification of kidney function change over time (<20%, 20-50% >50%) from baseline to V6. Second, individual trajectories will be classified using Nagin’s group based trajectory modeling approach\(^{10}\). Using these classifications we will employ similar strategies as above for cross sectional data.

For aim 2, we will look at spearman correlations between kidney disease continuous factors (serum creatinine, proteinuria, albuminuria, cystatin C, eGFR by CKDepi equation) and vision function (near and distance visual acuity and contrast sensitivity). Analyses will be similar to that for aim 2. Distance and near presenting visual acuity will be measured in logMAR units. Contrast sensitivity will be assessed using logCS units. As thresholds for defining impaired vision vary, we will look at continuous measures of vision function. However, secondary analyses will use 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.

For longitudinal kidney disease related data, we will use two approaches. First we will use simple classification of kidney function change over time (<20%, 20-50% >50%) from baseline to V6. Second, individual trajectories will be classified using Nagin’s group based trajectory modeling approach\(^{10}\). Using these classifications we will employ similar strategies as above for cross sectional data.

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)?

Retinal microvascular abnormalities and its relation to renal dysfunction: the ARIC study (MS769)  Wong, T.
Hemoglobin A1c (HbA1c) Cut-points and Risk of Kidney Disease and Prevalent Retinopathy (MS1539)  Selvin, E.
Systematic review and individual participant meta-analysis of the association between retinal vessel caliber and Chronic Kidn   (Proposal #2604) Charumathi Sabanayagam

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 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.csec.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.