ARIC Manuscript Proposal #4116

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

1.a. Full Title: Obstructive sleep apnea and retinal microvasculature signs

b. Abbreviated Title (Length 26 characters): OSA and retinopathy

2. Writing Group: Nathan Hoeft, Kelsie Full, Kamakshi Lakshminarayan, Jennifer A. Deal, Srishti Shrestha, Pamela Lutsey

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **NH 2/27/22**

First author: **Nathan Hoeft**
Address: 2700 University Ave W, Apt. 344
St. Paul, MN 55114

Phone: (507) 829-8848 Fax: N/A
E-mail: hoeft101@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Dr. Pamela L. Lutsey
Address: 1300 South 2nd St, Suite 300
Minneapolis, MN 55126

Phone: (612) 624-5812 Fax: (612) 624-0315
E-mail: lutsey@umn.edu

3. Timeline: Data analysis to begin immediately, anticipated draft completion April/May 2022

4. Rationale:

Retinal microvascular abnormalities (such as microaneurysms, focal arteriolar narrowing, arteriovenous nicking, soft/hard exudates, etc.)[1,2] can arise within the retinal microvasculature through several pathophysiologic pathways. Retinal microvascular abnormalities are one of the most common complications of diabetes[3]. Both their presence and severity have been associated with hyperglycemia[4], though the results of three population-based studies have shown the prevalence of retinal microvascular abnormalities to be common in non-diabetics, as well[5]. A strong association between retinal microvascular abnormalities and hypertension also exists[2,6]. A

study within a non-diabetic population estimated the prevalence of retinal microvascular abnormalities in hypertensive individuals as 11% and normotensive individuals as 6%[7]. Chronic inflammation may also have a role in the development of retinal microvascular abnormalities[8]. The relationship with both age and sex is unclear[2].

Since the retinal microvasculature can be imaged non-invasively and shares similar anatomy to cerebral circulation[1,2], it presents a unique opportunity to study the role of microcirculation in relation to cerebrovascular disease. Prior research has suggested retinal microvascular abnormalities may be associated with increased risk of stroke[9,10], a tremendous cause of morbidity and mortality within the developed world. Given associations between retinal microvascular signs and CVD, as well as morbidity directly associated with retinal microvascular abnormalities, there is need for a deeper understanding of the possible risk factors for development of retinal microvascular abnormalities to help identify opportunities for intervention.

Obstructive sleep apnea (OSA), a relatively common and often undiagnosed condition, is characterized by an upper airway obstruction causing brief periods of partial or total cessation of airflow[11,12]. OSA is linked to many cardiovascular outcomes, including stroke[13,14]. Several pathways have been identified within this association including hypertension[13,14] and diabetes/prediabetes[13–15]. OSA can also lead to oxidative stress and chronic inflammation due to the repetitive nature of hypoxemia and reoxygenation[13,14]. Each of these pathways lead to an increased risk for cardiovascular disease (CVD).

Hypertension, diabetes, and inflammation are known to be common pathways in which OSA impacts macrovascular CVD. Prior research has suggested these pathways may also play a role in the development of retinal microvascular abnormalities; thus, it is plausible that OSA is also associated with retinal microvascular abnormalities. An association was identified within a diabetic population in at least one previous study[16]. We recently learned of a prior Sleep Heart Health Study (SHHS) paper that evaluated this broad question using ARIC and CHS data. However, the authors defined OSA according to respiratory disturbance index (RDI) quartiles, with quartile 4 having a lower bound of 11.7 and did not evaluate retinal diameters aside from as a ratio[17]. These prior findings were null. Our analysis is unique as we will use clinically meaningful OSA cutpoints (>/=30 events/hour for severe disease; 15 to 29.9 events/hour for moderate) and will evaluate central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)indices. The association between OSA and most outcomes is nonlinear, with elevated disease often only occurring with severe OSA.

Therefore, we propose to explore the association between OSA and retinal microvascular abnormalities in the ARIC Sleep Heart Health Study sample. Since retinal microvascular abnormalities have been shown to be more prevalent in those with hypertension or diabetes, special attention will be paid to these conditions as well as if associations vary by age and sex.

5. Main Hypothesis/Study Questions: Obstructive sleep apnea is associated with retinal microvascular abnormalities and retinal diameters after controlling for potential confounders.

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).

<u>Study Design</u>

We will be analyzing the data cross-sectionally. However, sleep assessment took place around visit 4 (1996-1998) while retinal photography took place 3 years prior (1993-1995). We will explicitly document that this analysis is quasi-cross-sectional in the methods, and list this as a limitation.

Inclusion/Exclusion

Inclusion: Participation in SHHS with valid polysomnography data (only at MN and MD sites) and underwent retinal photography.

Variables

Exposure: Data derived from the Sleep Heart Health Study's (1996-1998) use of in-home polysomnography will be used to identify participants with obstructive sleep apnea (OSA). OSA severity will be defined using the Apnea Hypopnea Index (AHI), which sums the number of apneas and hypopneas experienced per hour of sleep.

Apnea-Hypopnea index (AHI) OSA severity categories:

<5.0 events/hour of sleep (normal)
5.0-14.9 events/hour of sleep (mild)
15.0-29.9 events/hour of sleep (moderate)
>/= 30.0 events/hour of sleep (severe).

Note: Events defined as either apnea (absence/near absence of airflow) or hypopnea (30% decrease in amplitude of airflow) for at least 10 seconds.[15]

Outcome:[1] Data from the ARIC visit 3 (1993-1995) will be used in which retinal photography was performed to identify participants with retinal microvascular abnormalities and diameters. A participant was categorized as having a retinal microvascular abnormality if any abnormality was detected (see below for complete list of abnormalities). For diameters, trained graders estimated the caliber of individual retinal arterioles and venules by a computer-assisted technique.

Binary variable: Retinal microvascular abnormalities (present/absent). Defined as present if any of the following lesions was detected by retinal photography: arteriovenous nicking, focal arteriolar narrowing, microaneurysms, blot/flame-shaped retinal hemorrhages, soft/hard exudates, or other less common lesions.

Continuous variables: Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) indices.

Potential confounders and/or effect modifiers: Age, sex, ARIC field center, education, physical activity, smoking status, BMI, hypertension, inflammation, diabetes, eGFR, CHD, LDL-C, HDL-C, and triglycerides.

Data Analysis

Though the ARIC study is a prospective cohort, the dates of polysomnography and retinal photography do not allow temporality to be assessed. Therefore, this study design will be treated as cross-sectional. Baseline characteristics of study participants will be described using means/proportions. These values will be stratified by levels of OSA severity. A series of progressively adjusted logistic regression models will be used to explore the relationship

between OSA severity and retinal microvascular abnormalities. Linear regression will be used to evaluate associations of OSA with CRAE and CRVE.

Model 1 will adjust for age and sex. Model 2 will additionally adjust for education, physical activity, smoking status, alcohol, and BMI. Model 3 will further adjust for prevalent hypertension, diabetes, and inflammation as well as eGFR, CHD, LDL-C, HDL-C, and triglycerides. Cross-product terms will be used to evaluate whether sex, hypertension, or diabetes modifies the association between OSA and retinal microvascular abnormalities. Stratified results will be presented, if appropriate.

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? ____ 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 current derived consent file ICTDER05 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/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)?

There are no ARIC paper proposals examining this relationship.

During the process of our literature review we identified the paper noted in the rationale (PMID: 15164900). It was published in 2004; the 1st author was Lori Boland and the last author Anne Newman. It includes no active ARIC authors. There was no ARIC proposal for this paper, however, we speculate it may have been approved through the SHHS processes.

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* 1995.12 SHHS)

___ 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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