**ARIC Manuscript Proposal #2009**

| | | |
|---|---|---|
| **PC Reviewed: 10/9/12** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Ideal Cardiovascular Health and Retinal Findings

**b. Abbreviated Title (Length 26 characters)**: CV Health-retinal findings

**2. Writing Group**:

Writing group members: Raymond Ogagarue, Pamela Lutsey, Ronald Klein, Barbara Klein, Aaron Folsom

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


**First author**: Raymond Ogagarue

Address: Division of Epidemiology and Community Health
University of Minnesota

Phone: 612-242-1796 Fax:

E-mail: ogaga001@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: Aaron Folsom

Address: Division of Epidemiology and Community Health
University of Minnesota

Phone: 612-626-8862 Fax: 612-624-0315

E-mail: folso001@umn.edu


**3. Timeline**: Finish by early summer, 2013.

**4. Rationale**:

The American Heart Association (AHA) recently set a goal to improve the cardiovascular health of all Americans by 20% in 2020, while also aiming to reduce deaths from cardiovascular diseases and stroke by 20%. (1) It also developed definitions for 'ideal' cardiovascular health, 'intermediate' cardiovascular health (having at least one intermediate metric and no poor metrics) and 'poor' cardiovascular health (at least one poor metric) based on seven cardiovascular risk factors and health behaviors. The factors comprising Ideal CV health would be the absence of smoking, BMI < 25, untreated BP <120/<80 mmHg, total cholesterol <200mg/dl, fasting glucose <100mg/dl, physical activity and healthy diet score. As shown by Folsom et al, Ideal CV Health is associated with lower incidence of cardiovascular diseases in ARIC (2), but no study has yet shown a relationship between ideal CV health and retinal findings, which is what this study will address.

Previous studies have established that CV risk factors are associated with retinal findings. For example, greater incidence of retinopathy has been associated with higher levels of blood pressure, serum glucose, plasma fibrinogen and plasma total cholesterol in a previous ARIC study. (3). Also, a lower mean arteriolar-venular A/V ratio has been associated with higher blood pressure, lower HDL cholesterol, higher plasma triglycerides, inflammatory markers (reduced albumin and higher fibrinogen levels), greater body mass index, smoking, and alcohol consumption in another ARIC study. (4) In the Beaver Dam Eye Study, 5 year follow up of participants showed that a narrower Central Retinal Arteriolar Equivalent (CRAE) was independently associated with higher blood pressure, smoking status, greater BMI and heavy drinking. (5)

Retinopathy is a marker of systemic microvascular disease, and has been shown to be an independent predictor of Congestive Heart Failure and CHD (6), while abnormalities in the retinal microvasculature (arteriolar diameters) are found to predict Ischemic Heart Disease and Stroke. (7) This study aims to determine the association between retinal findings in ARIC and the AHA definition of Ideal CV health.

**5. Main Hypothesis/Study Questions**:

Based on previous publications an association between abnormal retinal findings and cardiovascular risk factors is very likely, so it is not novel in itself. However, given AHA's emphasis on Ideal CV Health, we believe this paper will emphasize that the benefits of Ideal CV risks factors extend to the eye. It will be the first to determine the association between all (seven) cardiovascular risk factors (as per AHA's definition) and retinal findings.

**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 at visit 3

Exposure: Ideal, intermediate and poor cardiovascular health at ARIC visit 3

Outcome: Retinal findings at visit 3, as previously defined by ARIC. This will be in two categories; retinopathy and arteriolar diameters. Retinopathy signs are retinal microaneurysm, hemorrhage (blot or flame shaped), cotton wool spots (soft exudates) or hard exudates, intraretinal microvascular abnormalities or venous beading (3). Arteriolar diameters will be analyzed by CRAE and venular diameters as CRVE, as derived by the Wisconsin reading center (4,5,7)

Covariates for **adjustment**: age, sex, race

Analysis:

1. Exclude those with missing data which will include those with non-gradable retinal findings or missing Ideal CV Health factors. Also, participants with past or current stroke and CHD will be excluded.
2. Define prevalence of CVD health categories at ARIC visit 3, using the same definitions Folsom et al. used for baseline.
3. Compute the prevalence of retinopathy by Ideal Health categories and by the number of Ideal Health factors. Will use the logistic regression models for covariate adjustment and testing of interaction by age, race and sex. If no interaction, we will adjust for age, race and sex as potential confounders.
4. Calculate the mean arteriolar and venular diameters by Ideal Health categories and by the number of Ideal Health factors. Cut points for mean arteriolar and venular diameters will be given, when using logistic regression models for covariate adjustment and testing of interaction by age, race and sex. If no interaction, we will adjust for age, race and sex as potential confounders.

**7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __x__ 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? ____ 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/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)?**

There are currently no directly related manuscript proposals. Other studies have shown relationship between some CV risk factors and retinopathy or some CV risk factors and arteriolar diameters. This study will consider all seven (Ideal) CV risk factors and both retinal findings. Folsom et al has a relationship between ideal CV health and cardiovascular disease incidence.

**Folsom AR**, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence.

Wong TY, Klein R, Amirul Islam FM, Cotch MF, Couper DJ, Klein BE, Hubbard LD, Sharrett AR.Am J Ophthalmol. 2007 Jun;143(6):970-6. Epub 2007 Apr 2. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study

Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vasc Biol. 2000;20:1644–1650

Klein R, Myers CE, Knudtson MD, Lee KE, Gangnon R, Wong TY, Klein BE. Arch Ophthalmol. 2012 Aug 1;130(8):1019-27. Relationship of blood pressure and other factors to serial retinal arteriolar diameter measurements over time: the beaver dam eye study.

Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom AR, Klein R Retinopathy and risk of congestive heart failure. JAMA. 2005 Jan 5;293(1):63-9.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ 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 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.

## References.


1. Lloyd-Jones DM, Hong Y, Labarthe D, et al., on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586–613.

2. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators.J Am Coll Cardiol. 2011 Apr 19;57(16):1690-6. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence.

3.Wong TY, Klein R, Amirul Islam FM, Cotch MF, Couper DJ, Klein BE, Hubbard LD, Sharrett AR.Am J Ophthalmol. 2007 Jun;143(6):970-6. Epub 2007 Apr 2. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study.

4. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vasc Biol. 2000;20:1644–1650

5. Klein R, Myers CE, Knudtson MD, Lee KE, Gangnon R, Wong TY, Klein BE. Arch Ophthalmol. 2012 Aug 1;130(8):1019-27. Relationship of blood pressure and other factors to serial retinal arteriolar diameter measurements over time: the beaver dam eye study.

6. Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom AR, Klein R Retinopathy and risk of congestive heart failure. JAMA. 2005 Jan 5;293(1):63-9.

7. Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R, McNamara M, Thom SA, Klein R.Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke.Hypertension. 2006 May;47(5):975-81. Epub 2006 Apr 3.