ARIC Manuscript Proposal # 1629

1. a. Full Title:  Retinal Vascular Signs and Risk of Incident Diabetes in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Retinal vascular signs and incident diabetes

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

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3. **Timeline**: 6 months

4. **Rationale**:

Diabetes mellitus is a major health problem in young and middle-aged adults, affecting approximately 26 million people in the United States alone[1]. As the diabetes epidemic continues and the number of people with diabetes expected to rise to more than 400 million in the year 2030[1], developing a clearer understanding of the pathogenesis of diabetes is important as it may provide new strategies for screening, prevention, and treatment.

Microvascular disease has been hypothesized as a possible pathogenic factor in the development of diabetes. This hypothesis is based on studies demonstrating microvascular abnormalities (e.g. loss of vasodilatory reserve and impaired autoregulatory capacity) in individuals with newly diagnosed diabetes[2-4], as well as in people at high risk of developing diabetes, such as those with impaired glucose metabolism[5] and first-degree relatives of people with diabetes[6, 7]. However, these observations were based on small numbers of participants in highly specialized experimental settings that are not generalizable to the larger population.

The retina is a unique site where the human microvascular bed can be visualized non-invasively, offering the opportunity to explore the role of microvascular disease in diabetes development. Advances in image analysis techniques have also allowed microvascular characteristics (such as retinal vessel caliber and focal retinal lesions) to be reliably and objectively quantified.

Prospective data from recent population based studies have shown that changes in retinal vascular caliber may predict the risk of incident diabetes. The precise associations, however, have not been consistent. In two early reports, an association between smaller retinal arteriovenous ratios (AVR) and incident diabetes was found in the Atherosclerosis Risk in Communities (ARIC) Study [8] and the Beaver Dam Eye Study (BDES)[9]. This association was attributed to *narrowing of the retinal arterioles*. Subsequently, however, the Rotterdam Study demonstrated that the association between smaller AVR and incident diabetes was due to *wider venules* rather than narrower arterioles [10]. More recent prospective data from the Ausdiab Study[11] showed that *retinal arteriolar narrowing* was associated with a 5-year increased risk of incident diabetes whilst the Blue Mountain Eye Study (BMES) reported no significant association between retinal arteriolar or venular caliber with incident diabetes but demonstrated an association between *wider venular caliber with higher incidence of impaired fasting glucose (IFG)*[12]. Taken in totality, these findings suggest that retinal vascular caliber changes may be a marker of the pre-diabetes state and reflect the early microvascular changes that occur in the development of diabetes. The reason(s) for these equivocal findings, however, is still unclear and warrants further research.
Isolated retinopathy signs are also common fundus findings in the non-diabetic population and emerging studies have shown their presence may be associated with incident diabetes. The precise association of these signs with incident diabetes, however, is still unclear. The ARIC[13], BDES[14] and BMES[15, 16] reported no increased risk of diabetes development in nondiabetic individuals with retinopathy signs. However, there were notable exceptions. Firstly, in the ARIC study, **individuals with a family history of diabetes** had a two-fold higher risk of developing incident diabetes over three years [13]. Secondly, in the BDES, individuals with retinopathy signs who were **less than 65 years of age at the baseline examination** had an increased risk of developing diabetes over 15 years [14]. Thus, these findings suggest that retinopathy signs in individuals without diabetes may not necessarily be a marker of future diabetes risk, except perhaps in younger individuals and those with a family history of diabetes. These findings need further verification. Furthermore, another clinically relevant question is whether individuals who are already at higher risk of developing diabetes, e.g. those with IFG who have retinopathy signs are at increased risk of developing diabetes. Several cross-sectional studies have shown that retinopathy signs are associated with IFG [17, 18]. However, data on whether these signs relate prospectively to incident diabetes is unavailable.

Given that retinopathy lesions and retinal vascular caliber may predict future development of diabetes, further research to clarify the associations of these lesions is warranted. In this current study, we will examine the following associations using long-term data from the 12 year follow-up examination of the ARIC study:

1. The association between retinal vascular caliber and retinopathy signs with incident diabetes in **all non-diabetic participants of the ARIC study**
2. The association between retinal vascular caliber and retinopathy signs with incident diabetes in **individuals with IFG**
3. The association between retinal vascular caliber and retinopathy signs with incident diabetes in individuals **stratified by age groups** (e.g. ≤45 years; 46-75 years, ≥ 76 years), **race/ethnicity, and risk factors for diabetes** such as family history of diabetes, fasting glucose, fasting insulin levels, BMI, waist-hip-ratio, blood pressure and level of physical activity.

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

1. Retinal arteriolar narrowing and/or venular widening may predict the risk of incident diabetes in nondiabetic individuals independent of blood pressure, smoking, measures of obesity, fasting glucose and other risk factors.
2. Isolated retinopathy signs may predict risk of incident diabetes in subgroups of people predisposed to developing diabetes such as those with pre-existing IFG.
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).

Data (variables to be used, sample inclusions/exclusions):

Sample: All non-diabetic ARIC participants (including those with IFG; defined below) who had retinal photographs taken at Exam 3 (1993-1995) to look at incident diabetes at the 12 year follow up (2005 – 2007).

Exposure variables:
(1) Demographic data at Exam 3: Age, gender, race/ethnicity, income, educational attainment, occupation
(2) Risk factors at Exam 3:
• Systolic and diastolic blood pressure, anti-hypertensive medications, fasting glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, use of lipid lowering agents, cigarette smoking status (current, past never), pack-years of cigarette smoking, alcohol use, waist hip ratio, body mass index, fasting insulin concentration, sports activity index, family history of diabetes.
(3) Retinal vascular signs at Exam 3: Retinal arteriolar and venular diameters, focal arteriolar narrowing, focal retinopathy signs (i.e. microaneurysms, retinal haemorrhages, cotton wool spots, hard exudates)

Outcome variables:
(4) Incident diabetes ascertained at 12 year telephone interview follow-up.
• Incident diabetes will be defined on the basis of self-reported diabetes diagnosis or diabetes medication use during the subsequent annual telephone calls for a maximum of 12 years follow-up (1993-1993 through to 2005-2007)[19]

Brief analysis plan and methods:
(1) Baseline retinal arteriolar and venular diameters will be measured from digitized retinal photographs taken at Exam 3 and summarized as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE).
(2) Digitized retinal photographs will be graded for retinopathy lesions using standardized protocols.
(3) CRAE and CRVE will be analyzed as ordinal categorical variables (divided into quartiles, with the 1st quartile indicating the smallest and the 4th quartile the largest diameter) and also as continuous variables (per SD change in arteriolar and venular diameters).
(4) Other retinal microvascular signs (i.e. microaneurysms, retinal haemorrhages, cotton wool spots, hard exudates, focal arteriolar narrowing, arteriovenous nicking, etc.) will be analyzed as binary traits (i.e. absent vs. present).
(5) Risk factors will be analyzed as present vs. absent for binary traits (e.g., hypertension) and categorized into quartiles or tertiles for continuous traits (e.g., quartiles of blood pressure) where appropriate.
(6) We will use logistic regression models to estimate odds ratios for incident diabetes with each increasing quartile of CRAE and CRVE.
(7) We will use logistic regression models to estimate odds ratio for incident diabetes with the presence of retinopathy lesions.
(8) In multivariable analysis, we will select variables for inclusion in regression models if candidate variables are significant at p<0.10 in the age-adjusted models or are considered potential confounders or risk factors be traditionally associated with incident diabetes (e.g. fasting glucose levels).

Summary/conclusion:
This study offers the potential to further improve our understanding of the role of retinal vascular caliber and retinopathy signs in predicting the risk of incident diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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?  ____ Yes  ____ No

(This file ICTDER03 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  ____ 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.csec.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)?

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/

12. 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.
References
