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| **PC Reviewed:  11/8/11** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a.  Full Title**:

Systematic review and individual participant meta-analysis of the association between retinal vessel caliber and hypertension and diabetes

  **b.  Abbreviated Title (Length 26 characters)**:

Meta-analysis of retinal vessel caliber and risk for hypertension and diabetes

**2.    Writing Group**:
        Writing group members:

Ding J, Ikram K, Klein R, Klein B, Cotch MF, Wang JJ, Mitchell P, Witteman J, Shaw JS, Yamashita H, Kato T, Kawasaki R, Sharrett AR, Wong TY, others from different cohorts; Meta-Eye Study group

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

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**3.     Timeline**:

1 year. Several prospective studies have reported on the association between retinal microvascular signs and risk for cardiovascular diseases, including hypertension and diabetes. In order to obtain not only more precise values for the magnitude of the association between retinal vascular calibers and these cardiovascular diseases, but also evaluate the additional predictive value of the measurements, we would like to perform a meta-analysis based on all published data. Previously, we have performed two such meta-analyses in which we focused on stroke[1] and coronary heart disease[2]. We are now extending this project and propose to perform the following two meta-analyses:
1.    Retinal vascular caliber and the risk for hypertension.
2.    Retinal vascular caliber and the risk for diabetes mellitus

We have conducted a systematic search of the literature and have identified the ARIC study as one of the studies which have extensive data on caliber measurements, incident outcomes (hypertension, diabetes) and data on additional confounders. The principal investigators of the Blue Mountains Eye Study, Beaver Dam Eye Study, AusDiab, the Multi-Ethnic Study of Atherosclerosis, Rotterdam study and Funagata study have agreed to provide their raw individual level data for this study. Initial analyses and writing will take place between August 2011 and November 2011, and final writing and manuscript submission between December 2011and July 2011.

**4.   Rationale**:
Over the last 10 years several large population-based studies have examined the role of the microcirculation in the development of cardiovascular diseases. This has been done by using a semi-automated system to quantitative assess the retinal vascular calibers. The focus has been on several cardiovascular diseases including stroke, heart diseases, hypertension and diabetes mellitus. With respect to hypertension, there has been a remarkable consistency across individual studies showing that retinal arteriolar narrowing increases hypertension risk. In contrast, the results on association of retinal vessel caliber with diabetes are inconsistent. Furthermore, uncertainties remain regarding the subgroups in which these effects are manifest most strongly and the additional value of retinal vascular calibre measurements above that of the traditional cardiovascular risk factors in the prediction of these diseases.

**Specific aims**
Two meta-analyses are proposed that will combine the individual participant data from ARIC and the other studies that have been identified from a systematic literature search. The primary objectives of the analyses are

- To explore potential differences in the association between retinal vessel caliber and incident hypertension and diabetes by age, sex and other risk factors, such as family history of diabetes and BMI.

- To determine whether the associations are independent of other traditional and non-traditional cardiovascular risk factors
- To determine the extent to which risk scores improve on addition of retinal vessel caliber to the predictive ability of current hypertension and diabetes risk prediction methods
- To explore the possible sources of heterogeneity between studies including study and participant level characteristics
- To explore associations of retinal vessel caliber with progression, regression, and control of hypertension

**Literature search**

The electronic databases Medline and Embase have been searched for studies that meet the following criteria (1) prospective cohort studies that have used retinal photography to record the presence of retinal microvascular signs and/or the diameters of retinal calibers at baseline, (2) have at least one year of follow-up available, (3) data available on hypertension and diabetes outcomes.

Table 1 lists the studies that have been identified from the literature search and that will be approached to contribute the individual participant data to be included in the meta-analyses.

Table 1: Studies that have recorded retinal signs and outcomes of hypertension and diabetes

| Study | Sample Size |
| --- | --- |
| Atherosclerosis Risk in Communities Study[3,4] | 12887 |
| Blue Mountains Eye Study[5-7] | 3654 |
| Beaver Dam Eye Study[8,9] | 4926 |
| Rotterdam Study[10,11] | 5540 |
| Multi-Ethnic Study of Atherosclerosis[12] | 6237 |
| AusDiab[13] | 2177 |
| Funagata study[14] | 1058 |

These studies listed are all community based cohort studies that have recorded retinal vascular caliber. A number of other studies that have been carried out amongst specific populations (eg people with diabetes) or amongst general population but which have not recorded retinal calibers have also been identified. However, the focus of the analyses will be on the investigation of the association between retinal arteriolar and venular calibers and risk for hypertension and diabetes in a general population.

The quality of studies that match the selection criteria will be assessed using the guidelines published in by Hayden et al.[15] These guidelines recommend assessing the following aspects of each study - study participation, study attrition, measurement of prognostic factor, outcome, confounding factors, and analysis – to determine the risk of

bias. The heterogeneity of results between studies of different quality will then be examined.

**5.    Main Hypothesis/Study Questions**:
1. What are the age and sex-specific associations between retinal arteriolar and venular calibres and incident hypertension and diabetes?
2. Are these associations are independent of other traditional and non-traditional cardiovascular risk factors?
3. Do the retinal arteriolar and venular calibers add to the predictive ability of current hypertension and diabetes risk prediction?
4. What study and participant level characteristics are associated with the differences in effect measures between studies?

**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).**

1. Study design: Meta analyses of individual participant data
2. Inclusion criteria: Participants attending third visit (1993-1995)
3. Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude those whose race is not black/white, with ungradable retinal photographs or missing retinal variable at visit 3, and with prevalent hypertension or diabetes at baseline or prior to visit 3 or missing blood pressure or glucose data.
4. Outcomes: Incident hypertension and diabetes within 12 years (2005-2007) of visit 3
5. Study factor: Retinal arteriolar and venular caliber. The raw vessel calibers are requested as well as the summary measures central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). This will allow the retinal calibers to be summarized using the Knudtson as well as the Parr-Hubbard formulas.
6. Covariates: age, sex, race, field center, family history of hypertension and diabetes, prevalent cardiovascular diseases, hypertension and diabetes status, blood pressure, fasting glucose level, HbA1c, lipids (total cholesterol, LDL-C, HDL-C, TG), hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index and waist to hip ratio, sports activity index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only) and use of anti-hypertensive and anti-diabetic medications. Where appropriate, adjustment will be made for covariates averaged over ARIC visit 1-3 (e.g., 6-year averaged blood pressure, 6- year averaged glucose, 6- year averaged BMI, etc). Additional measurements of these variables recorded before, during or after visit 3 are also requested to adjust for regression dilution.

7. Data analysis: Cox proportional hazards models will be used to estimate the association between the microvascular retinal signs and hypertension outcomes. The

estimated hazard ratios will be adjusted for the traditional and non-traditional risk factors. Hierarchical models will be used to explore heterogeneity and combine the individual patient data in the meta-analysis.[16,17] Adjustment for regression dilution will be carried out for studies that have repeat measurements available for the study factors and/or covariates.[18]

**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 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**
      **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](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)?** ARIC MS# 1110, "Risk Prediction of Coronary Heart Disease based on Retinal Vascular Caliber: The Atherosclerosis Risk in Communities Study"

**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.**

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