1.a. Full Title: Prevalence and Risk Factors for Retinal Vein Occlusion: Pooling of Population-based Studies from the United States, Europe, Australia and Asia

b. Abbreviated Title (Length 26 characters): Meta-analysis Retinal Vein Occlusion

2. Writing Group:

Writing group members: Rogers S, McIntosh, Cheung N, Lim L, Wang JJ, Klein R, Klein B, Mitchell P, Wong TY and others from the International Eye Disease Consortium

I, SR the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NC

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3. Timeline:
Manuscript proposal to Publication's Committee: Jan 2009
Data analysis completed: Feb 2009
Completed manuscript to Publication's Committee: Feb 2009
4. **Rationale:**

Retinal vein occlusion (RVO) is the second most common retinal vascular disease and an important sight-threatening condition among middle-aged and older individuals. There had been no population-based data on the prevalence of RVO a decade ago. In early years, information regarding the frequency and risk factors of RVO was based on case series,\(^1\)\(^-\)\(^5\) case-control studies,\(^6\)\(^-\)\(^11\) and clinical trials.\(^12\)\(^-\)\(^14\) During the last decade, several population-based studies provided the prevalence of RVO in older persons, namely the Blue Mountains Eye Study (BMES),\(^15\) the Beaver Dam Eye Study (BDES)\(^16\) and the combined analysis of data of the Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS).\(^17\) The reported prevalence rates of RVO vary ranging from 0.3% to 1.6%.\(^15\)\(^-\)\(^17\) The reason for such variability is unclear but could be related to study methods used (e.g., number of photographic fields taken from each study participant) and different ethnic composites in these populations, with different frequency of risk factors (e.g., blacks have higher prevalence of hypertension). These previous studies lack the power to further evaluate the ethnic differences and risk factors associated with this condition as the numbers of persons identified with RVO and further stratified by different ethnicity, gender or age are frequently small, yielding unstable estimates. Furthermore, while previous studies have provided estimates of RVO prevalence, precise estimates of the prevalence of different RVO subtypes (e.g., central retinal vein occlusion [CRVO] or branch retinal vein occlusion [BRVO]) are less clear.

Recent research has demonstrated several treatment strategies that might potentially reverse some degree of vision that was lost due to RVO, using non-invasive (e.g., anticoagulants or antiplatelet agents, corticosteroids), minimally invasive (e.g., laser, intravitreal administration of anti-vascular endothelial growth factor and angiostatic agents) or invasive (e.g., surgical interventions) approaches. Policy planners require robust estimates of RVO prevalence and incidence to determine the likely impact of this condition and potential benefit from these treatment strategies and future therapies. Consequently there is a need for better understanding of the RVO prevalence and incidence among different age, gender and ethnic groups, as well as in those presumed to be at higher risk of RVO, such as persons with diabetes or hypertension.

We have already examined the prevalence and risk factors of RVO in the ARIC.\(^17\) In this proposed study, we will now collate and pool data from the ARIC with other major population-based studies in the United States, Australia and Asia, such as the Blue Mountains Eye Study (BMES), the Beaver Dam Eye Study (BDES), the Multi-Ethnic Study of Atherosclerosis (MESA), the Cardiovascular Health Study (CHS), the Los Angeles Latino Eye Study (LALES), the Funagata Eye Study, the Singapore Malay Eye Study and the Rotterdam Study. Pooling of these data will form a large dataset with the biggest number of RVO cases to date. This project will provide summary estimates of the prevalence and burden of RVO in the community according to age, gender and ethnic groups. This information will be important for increasing awareness of RVO in the community, and will be critical for driving new therapeutic strategies.

5. **Main Hypothesis/Study Questions:**
1. Prevalence rates of RVO and its subtypes (CRVO, BRVO) vary in different countries (United States, Australia, and Asia)

2. Risk factors for RVO vary in different ethnic groups (Caucasian whites, Hispanics, African Americans, Asians)

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).

Sample: ARIC participants who had retinal photographs at Exam 3.

Exposure variables:
(1) Demographic and socio-economic at Exam 3: Age, gender, race/ethnicity, income, educational attainment, occupation, marital status
(2) Cardiovascular risk factors at Exam 2:
   - Cardiovascular risk factors: cigarette smoking status, pack-years of cigarette smoking; alcohol use, systolic and diastolic blood pressure; hypertension stage; hypertension subtype; hypertension by JNC VI criteria, hip circumference, waist circumference, body mass index, anti-hypertensive medications, fasting glucose, diabetes self-report, diabetes mellitus by 1997 ADA fasting criteria, diabetes medications (type), total cholesterol, HDL-cholesterol, LDL cholesterol, triglycerides, glycosylated hemoglobin, use of lipid lowering agents, homocysteine
(3) Retinal vascular signs at Exam 3: Retinal arteriolar and venular diameters, focal arteriolar narrowing, and arteriovenous nicking, retinopathy

Outcome variable: Primary outcome variables at Exam 3: prevalent RVO (probable/definite)

Brief analysis plan and methods:
(1) We will pool the ARIC data with other population-based studies’ data and describe the overall prevalence and risk factors of RVO.
(2) RVO and its subtypes will be analyzed as a binary outcome variable (present vs. absent). Cardiovascular risk factors will be analyzed as present vs. absent for binary traits (e.g., hypertension) and categorized into quartiles for continuous traits (e.g., quartiles of blood pressure).
(3) We will use logistic regression models to estimate odds ratios for RVO for each risk factor, adjusting initially for age. Test for trend will be based on the Mantel-Haenszel method.
(4) 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.
(5) Modeling will be carried out in 2 stages; first considering only non-retinal variables and then adding retinal variables to see if they contributed further to the model.

7.a. Will the data be used for non-CVD analysis in this manuscript? No
b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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?  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____ 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  Yes

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?  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: