ARIC Manuscript Proposal # 1374

PC Reviewed: 06/10/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between Physical Activity and Retinal Microvascular Signs and Age-related Macular Degeneration

b. Abbreviated Title (Length 26 characters): Physical activity and retinal signs/ Age-related Macular Degeneration.

2. Writing Group:
Writing group members: Tikellis G, Klein R, Wong TY

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

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3. Timeline:

Manuscript proposal to Publication's Committee:	May 2008
Data analysis completed:	June 2008
Completed manuscript to Publication's Committee:	July 2008

4. Rationale:

Physical Activity and retinal vascular changes

Lack of physical activity has long been established as an independent risk factor for many disorders such as hypertension, diabetes, the metabolic syndrome, cardiovascular disease and mortality[1-3]. In the ARIC study, lower levels of physical activity have been associated with a higher risk of coronary heart disease, [4] ischemic stroke[5] and incident hypertension.[6] However, the specific underlying vascular changes associated with lack of physical activity are unclear.

The retinal vasculature provides an opportunity to determine systemic risk factors associated with microvascular disease. Studies have shown that narrower arterioles are associated with hypertension[7] and measures of atherosclerosis,[8] wider venules have been associated with diabetes,[9] the progression of diabetic retinopathy, [10]incident obesity,[11] systemic markers of inflammation[12] and hypertriglyceridemia.[13] Recent data from the ARIC study and the Blue Mountains Eye Study showed a significant association between obesity and retinal venular dilation, even in individuals without diabetes or hypertension.[11, 12] Furthermore, prospective data from the Blue Mountains Eye Study showed that persons with larger retinal venules at baseline were more likely to become obese at the five-year follow-up, thereby supporting a role for impaired microvascular function in the pathogenesis of weight gain.[11]

Obesity correlates with many common vascular risk markers of retinal vascular disease and retinopathy, including hyperglycemia, hypertension and dyslipidemia, and there is also some evidence that obesity might have a more direct role in the development of retinopathy. Elevated markers of endothelial activation and chronic low-grade inflammation have been reported in obese individuals, particularly in association with insulin resistance [14, 15] and have also been observed to correlate with retinal venular dilation.[15, 16] This suggests that inflammation is a possible mechanism underlying the associations between obesity and retinal vascular changes. Obesity is also linked with increased blood volume[17] and leptin levels, which might modulate vascular caliber through local mechanisms involving nitric oxide (NO) release.[18] These factors might interact to contribute to the larger venular diameter seen in obesity.

Whether physical activity is associated with presence of retinal microvascular signs is not known. In this proposal our objective is to investigate the association between levels of physical activity (from sport, leisure and work) and retinal microvascular signs to determine whether physical activity is associated with structural changes in the microvasculature.

Physical Activity and age-related macular degeneration (AMD)

Physical activity has also been linked to the incidence of age-related macular degeneration (AMD)[19, 20] and to a reduced rate of progression to geographic atrophy and exudative AMD.[20, 21] Although the number of studies is small, it is hypothesized that physical activity reduces systemic inflammation and endothelial dysfunction both believed to have a role in the pathogenesis of AMD.[22] In these studies, physical activity level was assessed from three questions and those physically active were compared to those physically inactive. The ARIC study provides an opportunity to examine physical activity in three areas: sport, leisure and work in a large cohort of middle-aged men and women using a semi-quantitative index. As a second objective to this proposal, we aim to examine the association between physical activity levels (sport, leisure and work) and the prevalence of early AMD.

5. Main Hypothesis/Study Questions:

1) Is higher levels of physical activity (as determined from sport, leisure and work activities) associated with reduced severity of retinal microvascular signs (i.e., lower prevalence of retinopathy, arterio-venous nicking, focal narrowing, wider retinal arteriolar caliber, narrower retinal venular caliber)?

2) Are higher levels of physical activity associated with lower prevalence of early AMD lesions (such as soft drusen and retinal pigment epithelium changes)?

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 methodological limitations or challenges if present).

A. Study sample: all ARIC cohort members, who participated in the eye examinations (at **Visit 3**) and had gradable fundus photographs for (i) retinal microvascular variables (arterio-venous nicking, focal arteriolar narrowing, retinopathy and retinal vessel caliber) and (ii) AMD (early AMD lesions such as soft drusen, retinal pigment epithelium changes, and early AMD) with physical activity measures determined at **Visit 3**.

B. Outcome variables: Retinal microvascular signs graded from retinal photographs taken at **Visit 3:** retinal arteriolar diameter, retinal venular diameter, arterio-venous nicking, focal arteriolar narrowing, retinopathy); early and late AMD.

C. Exposure variables: Physical activity (estimated from sport, leisure and sporting activities) as measured by the Baeke questionnaire at **Visit 3**.

D. Potential confounders: age, gender, race/ethnicity, hypertension, prevalent coronary heart disease, diabetes status, BMI, blood pressure, mean arterial blood pressure, cigarette smoking and pack-years of smoking, WBC (at baseline and Visit 3), fibrinogen (at baseline and Visit 3), serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, educational attainment as determined at **Visit 3**.

E. Plan of analysis:

i. We will examine cross-sectional associations of physical activity as measured during work, leisure and sport activities,) and retinal vascular changes and AMD, respectively, in the total sample.

ii. For these analyses, we will examine the relationships of work, sport and leisure physical activity indexes with (i) each of the specific retinal microvascular sign (e.g., retinal vessel caliber, retinopathy, arterio-venous nicking) and (ii) early AMD lesions, any AMD, early AMD and late AMD. We will firstly examine the characteristics of the cohort incorporating both the exposure and potential confounding factors listed in C and D in age and gender adjusted logistic regression models for categorical outcomes and general linear models for continuous outcomes.

iii. In multivariable logistic regression models we will categorize work, leisure and sport indexes to examine the association with retinal microvascular signs/AMD adjusting for age, gender, race, post secondary education, BMI, current drinker, current smoker, MABP, and occupation category (for work physical activity).

In addition, we will categorize both indexes according to the mean value so that those above the mean value will be classified as "more active" and those less than or equal to the mean value will be classified as "less active". For work-related physical activity index we will stratify the analysis by occupation.

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 __X__ 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"?

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)?

We are aware of no ARIC manuscripts or proposals related to physical activity and retinal microvascular signs.

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.

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