

**ARIC Manuscript Proposal # 1057r**

**PC Reviewed:** \_\_03/11/05

**Status:** A

**Priority:** 2

**SC Reviewed:** \_\_03/14/05

**Status:** A

**Priority:** 2

**1.a. Full Title:**

**b. Abbreviated Title (Length 26 characters):** Retinal Microvascular Abnormalities and Weight gain

**2. Writing Group:**

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### **3. Timeline:**

This analysis is part of overall objective to investigate the cardiovascular associations of retinal microvascular abnormalities, based on photographic grading during the ARIC visit 3. Specifically, our proposed study will investigate whether retinal microvascular disease at visit 3 is related to weight gain between visits 3 and 4. After approval, the initial analyses and writing is anticipated to begin March 2005 with final analysis and writing completed by July 2005.

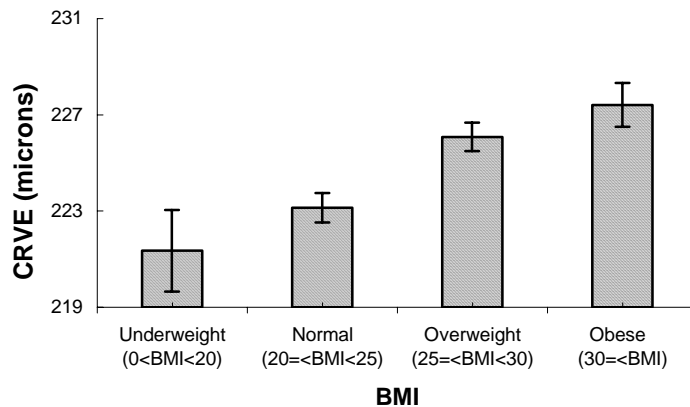
### **4. Rationale:**

The prevalence of obesity is increasing at an alarming rate worldwide (1). Obesity is the most obvious manifestation of the global problem of sedentary lifestyles and excessive energy intake (2). Associations have been observed between obesity and type 2 diabetes, metabolic syndrome, cardiovascular disease, some cancers and arthritis, each of which has major morbidity, mortality and socio-economic costs (3). Although our modern environment plays a clear role in the development of obesity, the growing pandemic inspires the need for a better understanding of the risk factors leading to weight gain and obesity.

In the ARIC study, microvascular processes such as retinal arteriolar narrowing, have been shown to be related to incident myocardial infarction, fatal coronary heart disease (CHD) in women (4), stroke (5), and with the development of major risk factors of CVD, including diabetes (6), hypertension (7), and markers of inflammation (8). There is also a small, but significant, body of evidence that suggests that microvascular changes may be linked to other related conditions such as obesity and overweight.

Much of the data linking retinal abnormalities to obesity and weight gain have arisen from studies in ARIC. Using cross-sectional data from this cohort, retinal abnormalities (lower A/V ratio) were first associated with greater body mass index (BMI), independent of mean arterial blood pressure, sex and race as early as 1999 (8). In 2004, using the same data, Wong et al. showed that large waist circumference was associated with AV nicking 1.28 (1.13, 1.44), focal narrowing 1.14 (1.00, 1.29), smaller CRAE 1.16 (1.05, 1.29) and larger CRVE 1.14 (1.03, 1.27) again after adjustment for conventional risk factors (9). Similar associations have also been cited elsewhere. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, retinal venular dilation was associated with increased duration of diabetes, elevated HBA1c and higher BMI (10) and in the Hoorn Study, BMI was an independent risk factor for retinopathy in people with diabetes and in those with pre-diabetes (11). However, of particular interest to this proposal is recent work from the Blue Mountain Eye study. Using prospective data, Wang and colleagues have demonstrated that retinal venule diameters are associated with a five year risk of obesity, independent of hypertension, diabetes, lipids and cigarette smoking (see Figure, unpublished data, submitted to Obesity Research). Together, the evidence from these studies suggests that microvascular processes may play a role in the development of obesity.

Figure. Adjusted mean central retinal arteriolar equivalent (CRVE) by WHO defined categories of BMI in the Blue Mountains Eye Study population (adjusted for age, gender, smoking, fasting glucose level and mean arterial blood pressure).



The mechanism(s) by which this relationship is mediated is unknown. Other analyses from ARIC showing that inflammatory markers such as fibrinogen and white cell count predict weight gain (12) suggests that inflammatory pathways may be involved. However, the interaction between these factors is clearly complex and requires additional research to explore the possible pathways of association between retinal vascular signs, weight gain, obesity and inflammation.

In the proposed study, we will investigate the association of retinal microvascular disease to weight gain and incident obesity, and determine if these associations are independent of other risk markers for CVD. Findings will lead to a clearer understanding of the pathogenesis and mechanisms of weight gain/ obesity.

## 5. Main Hypothesis/Study Questions:

Are retinal microvascular abnormalities at ARIC visit 3 associated with weight gain/incident obesity between visit 3 and visit 4?

If so,

- Are the associations independent of DM, hypertension, fasting glucose and smoking?
- Are the associations different in people with and without DM and hypertension?
- Are the associations different in men and women?
- Are the associations different by cigarette smoking status?
- Are these associations restricted to particular weight groups?

### a) Outcome measurement

1) Weight gain measured as a continuous outcome by:

- i) Weight gain in kg from visit 3 to visit 4
- ii) Increase in BMI from visit 3 to visit 4
- iii) Change in waist circumference from visit 3 to visit 4
- iv) % increase in body mass (kg) from visit 3 to visit 4

2) Weight as a categorical outcome:

Large weight gain is defined as weight gain between visit 3 and visit 4 of greater or equal to those in the 90th percentile gain

3) Incidence of obesity

**b) Exposure measurement:**

Retinal microvascular signs measured using standard variables at visit 3.

**Other analysis issues:**

Subjects with large weight losses during the period will also be excluded. These will be defined as those with weight loss in the top 5 % of the group.

Analysis will consider adjustment for potential confounders such as DM, hypertension, cigarette smoking, lipids and inflammatory factors (e.g., factor VII and fibrinogen).

Reverse causality can be partly addressed by including weight increase ( kg) or % increase in weight between visit 1 and 3 as a confounder in the analysis

**6. Data (variables, time window, source, inclusions/exclusions):**

- (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent at visit 4.
- (2) Weight, BMI, waist to hip ratio, waist circumference at visit 1, 2, 3 and 4
- (3) Demographic variables: age, sex, race, center, education, occupation
- (4) Other CVD risk factors/potential confounders: Cardiovascular history status (prevalent CHD, MI, angina and stroke), hypertension status, diabetes status, diastolic and systolic blood pressure at visits 3, serum lipids (total, HDL and LDL cholesterol, triglycerides), fasting glucose levels, cigarette smoking (ever/never, current/former/never, pack-years), alcohol consumption, hypertensive medications, diabetic medications, body mass index, waist to hip ratio, depression score, study centre sports/leisure/work activity index (variables from ARIC visit 3 and 4 ). Factor VII and Fibrinogen from visit 2
- (5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who did not participate in visit 3 and 4 with no retinal photographs or upgradeable photographs or exclude persons with missing body mass index variables at visits 3 and 4 and those lost to follow-up after visit 3.

**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 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?** \_\_\_\_\_ 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 ICTDER02 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.csc.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)?**

To my knowledge, several investigators of ARIC who have interest in this work have been contacted and invited to be collaborators in this proposal.

**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.csc.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

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12. Duncan BB., Schmidt MI, Chambless LE, Folsom A, Carpenter M, Heiss G. Fibrinogen, other putative markers of inflammation, and weight gain in middle aged adults- The ARIC study. *Obesity Research*. 8:279-28, 2000.