ARIC Manuscript Proposal # 1062r

PC Reviewed: _03/11/05	**Status: _A__**	**Priority: ___2_**
SC Reviewed: _03/14/05	**Status: __A__**	**Priority: _2___**

1.a. Full Title: Association of Birth Weight And Leg Length With Retinal Microvascular Signs and Age-related Maculopathy

b. Abbreviated Title (Length 26 characters): Birth Weight and Retinal Diseases

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

The intent of this analysis is to investigate the longitudinal association of the birth weight and retinal diseases at Visit 3. Initial analyses and writing will take place between April and June 2005, and final writing and manuscript submission between July 2005 and Nov 2005.

4. Rationale:

Birth Weight, Leg Length and CVD

The is a some evidence that abnormal fetal development, reflected by birth parameters such as low birth weight, is associated with an increased risk of cardiovascular disease in adulthood, including risk of hypertension (1-4), diabetes (5-8) and coronary heart disease and mortality (9,10). These associations have not been consistently found in all studies, and underlying mechanisms remain undefined (11). One hypothesis is that impaired fetal growth predisposes to atherosclerosis development later in life (12,13), although the association between low birth weight and atherosclerosis has also not been established (14).

Childhood developmental factors have also been linked with future cardiovascular risk. While adult height is a marker for exposures influencing growth throughout childhood, leg length has been suggested as a marker for factors acting in the pre-pubertal period, as up until puberty, height increases appear to be attributable to leg growth rather than trunk growth (15). Two studies have reported an association between leg length (but not trunk length) and coronary heart disease risk factors (16,17). Shorter leg length has also been linked with hypertension (18), higher body mass index (18) and insulin resistance (17). Thus, studying the associations of birth weight and leg length may provide insights into the relative effects of in-utero and early childhood factors on future cardiovascular risks (19)

Several mechanisms have been proposed to explain the link between abnormal birth and childhood factors and cardiovascular disease. One possible process is microvascular disease (20). In particular, alterations in the small blood vessels offer an attractive hypothesis for the association between low birth weight and risk of hypertension (21-23). However, one study in young adults found no evidence that reduced capillary density explains the association between low birth weight and higher blood pressure (24).

Associations of Birth Weight and Retinal Microvascular Disease

The retinal blood vessels are accessible to non-invasive visualization and their structure may reflect the health of the systemic microcirculation. There have been a number of studies that have investigated the association between birth weight and retinal vascular morphology in small samples of highly selected subjects. In one study, Chapman and colleagues analyzed retinal arteriolar bifurcation angles (narrower angles have been linked with increased circulatory energy and lower microvascular density) in 100 men aged 64-74 years (25). The group with low birth weight was found to have significantly narrower bifurcation angles than those with higher birth weights. This supports the theory that alterations in retinal microvascular architecture might reflect persistent vascular damage associated with fetal growth impairment. Other studies show that individuals who were born pre-term or were small for gestational age were more likely to have abnormal retinal vascular pattern (increased length of the retinal arterioles and reduced number of vascular branch points, indicating "rarefaction" of the retinal microcirculation) (26,27). There have been no studies that have investigated associations of leg length and retinal microvascular disease

In the ARIC study, we have previously shown that narrowed retinal arterioles and other retinal microvascular changes predicted incident coronary heart disease in women, and incident hypertension and diabetes in men and women. In the current analysis, we will examine the relationship of birth weight, leg length and retinal microvascular changes.

Associations of Birth Weight and Age-Related Maculopathy

Age-related maculopathy (ARM) is the leading cause of blindness in elderly people in the United States. The etiology of ARM is not well understood. Abnormal fetal growth and development has been suggested as a possible risk factor for ARM. Such a hypothesis is supported by the normal embryonic changes in the macula during life. The macula appears at approximately 11 to 13 weeks of gestation and by 13 weeks contains highly differentiated cone and retinal pigment epithelial cells (28). Because the pigment epithelium is a non-dividing system, and there is a net loss of cells with increasing age, insults that occur in utero may become apparent with increasing age, thus possibly increasing susceptibility to ARM development. Additionally, influences in fetal growth and low birth weight have been linked with risk of hypertension and atherosclerosis development in adulthood (see above), which are potential risk factors for ARM development as well (29-31).

However, we are aware of only one previous study that examined the association between birth weight and ARM, and this study's findings were unexpected (32). Hall and colleagues found that among 392 persons in the UK, after adjustment for age, gender, and other risk factors, subjects with *higher* birth weight were more likely to have ARM (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1–2.0 for each SD [1 lb, 5 oz] increase in birth weight). We are unaware of studies examining the association of leg length and ARM

The current study will provide a further opportunity to further explore the association between birth weight, leg length and early ARM development in middle-aged adults.

5. Main Hypothesis/Study Questions:

(1) Is low birth weight and shorter leg length associated with retinal microvascular abnormalities?
- Are the associations independent of blood pressure and other shared factors?
- Are the associations similar in individuals with and without hypertension and diabetes?

(2) Is low birth weight and shorter leg length associated with signs of age-related maculopathy
- Are the associations independent of cigarette smoking and other shared factors?
- Are the associations similar in whites and blacks?

Limitations of birth weight data and Analytical Approach

In the ARIC study, birth weight was assessed in two questions during interview. The first requested the continuous birth weight in pounds and ounces. If the participant did not know his exact birth weight, he was questioned if his birth weight was low, medium or high. As only about 40% of the participants related exact birth weight, these data, when reported, were converted to the metric system and categorized into three groups (<2.5 kg, 2.5-4kg and >4kg) which were combined with the qualitative birth weight categories obtained from other participants.

In the current study, we will use the quantitative data on the 40% of participants with this information as our primary approach. In separate analyses, we use the merged quantitative and qualitatitve data (low, medium or high birth weight) and determine if these latter analyses are the same as the primary analyses using only quantitative data.

We have used this approach successfully in the ARIC paper, "Low birthweight and markers of inflammation and endothelial activation in adults" (paper in preparation with Bruce Duncan et al)

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

(1) Retinal microvascular variables: Retinopathy, focal arteriolar narrowing, arterio-venous nicking, arteriolar and venular diameters, AV ratio

(2) ARM variables. Any ARM, early ARM, late ARM and specific ARM lesions (drusen, pigmentary changes)

(3) Self-reported birth weight, adult weight, adult height, leg length (standing height -sitting height).

(4) Covariates: age, sex, race, center, education, socio-economic status, prevalent CHD and MI, diabetes and hypertension status, blood pressure, cigarette smoking, alcohol consumption, body mass index, waist hip ratio, hemostatic function indicators (von Willebrand factor, factor VIII, fibrinogen, WBC), variables from ARIC visit 3, except for von Willebrand factor, factor VIII, and WBC, ARIC visit 1 only

(5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, born premature, twin births, with missing/ungradeable retinal photographs and missing birth weight data.

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 ICTDER01 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 ICTDER01 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 ICTDER01 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

_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. primiarly 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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