ARIC Manuscript Proposal # 835

PC Reviewed: 10/16/01	**Status: __D_**	**Priority: _____**
SC Reviewed: 10/17/01	**Status: __D_**	**Priority: _____**

1.a. Full Title: The relationship between birthweight and intima-media thickness in middle-age.

b. Abbreviated Title (Length 26 characters): Birthweight and IMT

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

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3. Timeline:
The manuscript is expected in 4-6 months.

4. Rationale:
Fetal programming of cardiovascular risk
The 'programming' of adult cardiovascular risk in fetal life was hypothesised by David Barker in the 1980's. One possible mechanism is that undernutrition of the fetus in the middle trimester raises the risk of adult disease by programming risk factors (1). Several studies show evidence of higher cardiovascular risk in adulthood with lower birthweight (2). Birthweight has been shown to be inversely associated with degree of carotid stenosis at age 49-51, although birthweight accounted for less than 2% of the variation in cardiovascular risk once adult risk factors were included in the model (3). Birthweight has also been shown to be inversely related to degree of carotid stenosis in people aged 70 (4). A Swedish study found that birthweight for gestational

age, rather than birthweight alone, was the important factor for cardiovascular risk (5), suggesting that it is fetal growth rather than birthweight per se which is important.

An extension of the “fetal origins” hypothesis is that childhood growth may modify the programming effect of birthweight (6). Other studies found the highest cardiovascular risk on low birthweight babies whose weight later caught up to normal levels, particularly for men (7;8).

Many studies have investigated the relationships between birthweight and blood pressure from childhood to adulthood. Birthweight was inversely related to systolic and diastolic blood pressure in children aged 3, although this only became significant after adjustment for current height, indicating that growth may be the more important factor (9). Similar associations were found in studies of 8-11 (10), 8 (11) and 9 year-olds (12), with the relationship between birthweight and blood pressure only emerging after adjustment for current body size. Path analysis in the latter study (12) separated the direct effect of birthweight from the indirect effect acting through variables such as current body size. After ages post-puberty a large number of studies have now shown birthweight to be inversely related to blood pressure.

There is evidence that part of the mechanism for this association might be maternal or fetal nutrition. Coronary heart disease was higher in those exposed prenatally to maternal malnutrition due to the Dutch famine in 1944-1945 than in those not exposed (13). It is also possible that common genetic factors may be related to both low birthweight and later cardiovascular disease risk. Thus infants with low birthweight have been shown to have mothers with higher risk of death from cardiovascular diseases (14), suggesting that high CVD risk and a propensity to low birthweight might be shared even when intrauterine nutrition amongst the group experiencing elevated CVD risk is not at issue. Other studies have also been taken as providing evidence of the common genetic factors hypothesis (15), but some studies in twins suggest that genetic factors or fixed maternal factors such as height or social class cannot wholly account for the birthweight – CVD risk association (11, 16).

Statistical Methods

The statistical methods used affect the conclusions which can be drawn from studies of birthweight, growth and later cardiovascular risk. One issue is whether current size should be included in any model of the effect of birthweight on cardiovascular risk factors (9). If the effect of current size is in the opposite direction to the effect of birthweight, particularly if there is no association with blood pressure unless current size is included, growth may be the important factor (17). The relative strength and directions of estimates adjusted and unadjusted for current size indicates the likely importance of both early size and later growth (17).

Standard statistical methods may be biased when confounders are also on the causal pathway (18). Here, current size may be one factor on the causal pathway between birthweight and current blood pressure. Recently developed statistical methods, including latent variable models, structural equation models and marginal structural models (19) may be more appropriate for examining these longitudinal relationships (20). Statistical methods which take into account the direction and possible causal pathway of such relationships may also help to separate the influences of hereditary factors and birthweight on later blood pressure.

We will use statistical methods including path analysis to examine the association between birthweight and IMT at the last ARIC visit. Models with and without current height, weight or BMI will be explored. Potential confounders or factors on the pathway including smoking, education level of participant and participant's parents, and cardiovascular risk factors other than IMT, will be investigated.

Reference List

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(18) Mark SD, Robins JM. Estimating the causal effect of smoking cessation in the presence of confounding factors using a rank preserving structural failure time model. Statistics in Medicine 1993; 12(17):1605-1628.
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5. Main Hypothesis/Study Questions:

The hypothesis is that weight at birth is inversely related to average IMT at the fourth ARIC visit.

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

For those participants who received ultrasound at the fourth visit, the data to be used are from the fourth visit, as that is when birthweight was queried. For those receiving ultrasound at the third visit, data to be used are from the third visit, except birthweight which is from the fourth visit. All subjects without IMT data will be excluded, as will all participants with missing birthweight data.

1) Exposure

Birthweight

Participant's belief about their birthweight (low, medium, high, unknown)

2) Outcome variables

Average IMT (at the third/fourth visit).

Ultrasound derived variables

Unadjusted ultrasound variables, from 1st scan only, from dataset UBMD3/4 (as appropriate).

Variable name	Description
id	
lbiaav45	Far wall thickness, left bifurcation
linaav45	Far wall thickness, left internal carotid
lopaav45	Far wall thickness, left common carotid
rbiaav45	Far wall thickness, right bifurcation
rinaav45	Far wall thickness, right internal carotid
ropaav45	Far wall thickness, right common carotid
qccnt	Number repeat scans

3) Covariates

From third/fourth visit, as appropriate.

Variable Name	Description
DRNKR41	Drinker status
PHXB17A	No. glasses wine per week (visit 4)

PHXB18A	No. bottles/cans beer per week (visit 4)
PHXB19A	No. shots hard liquor per week (visit 4)
WSTHPR41	Waist-hip ratio
SIT_HT01	Sitting height (visit 1)
ANTD42	Standing height (visit 4)
ANTD41	Weight (visit 4)
BMI41	BMI
DIABTS41	Diabetes present
LIPD2A	Triglycerides (mg/dl)
TCHSIU41	Total cholesterol in SI units
LDLSIU41	LDL cholesterol
HDLSIU41	HDL cholesterol
GL2SIU41	2 hour glucose
GLUSIU41	Fasting glucose
CIGT41	Smoking status
CURSMK41	Current cigarette smoker
CIGTYR41	Cigarette years of smoking
SBPD19	Systolic BP
SBPD20	Diastolic BP
V1DATE41	Visit Date
HYPTMD41	Hypertension medication
HYPTMD42	Hypertension medication
CHOLMD41	Cholesterol medication
CHOLMD42	Cholesterol medication
ECGMI41	MI according to adjudicated ECG
PRVCHD42	Prevalent CHD
STROKE41	Prevalent stroke
TIA41	Prevalent TIA

Also:
Fibrinogen (visit 3/4)
Leg length (visit 3/4)
Income for the past 12 months (visit 3/4)
Retirement status (visit 3/4)
Most recent occupation (visit 3/4)
Insulin (2 hour and fasting, visit 3/4)

Demographic data

Variable Name	Description
V1AGE41	Age
GENDER	Sex
RACEGRP	Ethnic group
ELEVEL41	Education level

Also:
Family history of CHD, stroke, diabetes, high blood pressure, cancer (and site), separately for mother and father.
Participant history of diabetes, high blood pressure, cancer (and site).

Parental education at participant's birth (mother and father separately), plus education of the two adults caring for each child.
Was the participant premature
Was the participant a twin

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 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? 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

Yes