

ARIC Manuscript Proposal # 914

PC Reviewed: 11/13/02

Status: A

Priority: 2

SC Reviewed: 11/15/02

Status: A

Priority: 2

1.a. Full Title: The relationship between components of height and intima-media thickness in middle-age: The ARIC Study.

b. Abbreviated Title (Length 26 characters): Leg and trunk length 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:

Associations between components of adult height and cardiovascular risk

An inverse relation between adult height and risk of coronary heart disease (CHD) has been reported in various studies (1;2). This relationship has been shown to be attenuated, but not removed, when adjusted for other adult cardiovascular risk factors (including smoking) (1). Increased height is associated with more favorable socioeconomic position, but this does not wholly explain the association between height and CHD. Adjusting for adult and childhood socioeconomic factors do not remove the association between height and cardiovascular disease risk (3;4).

There are several potential explanations for the apparent relationship between height and cardiovascular disease risk: height reflects fetal or intra-uterine growth; the relationship could be due to reverse causation as early stages of disease or bad health in adulthood lead to reductions in height and increased CVD risk; the apparent relationship could act through the association between height and adult socioeconomic status; there may be genes associated with both growth and cardiovascular disease risk; and finally, height reflects childhood growth, nutrition and

socioeconomic status, and thus the relationship is due to height acting as a marker for these influences.

Further understanding of the association between height and CHD may be gained from looking at the associations between components of height and CHD. Leg length is a useful biomarker of pre-pubertal environmental exposures that affect growth (5-7). Leg length in childhood was the component of childhood height most strongly related to socioeconomic status, diet and living conditions (8). Leg length was also the component of childhood height most strongly related to adult CHD in this cohort study (9). The relationships between height, leg and trunk length and adult CHD were altered very little by adjustment for childhood diet, socioeconomic exposures and adult deprivation score.

In two studies of adults, leg length has been found to be the component of height that is specifically associated with CVD risk factors, in particular insulin resistance, abnormal lipids and diabetes (10;11).

In one study, leg length in adulthood has been shown to be the component of adult height most strongly related to coronary heart disease (12). Again, adjusting for potential confounding factors including other adult risk factors attenuated, but did not remove, the inverse association between leg length and coronary heart disease.

We aim to examine the relationship between height and its components (trunk and leg length) and intima-media thickness (IMT) in the ARIC participants. Advantages over previous studies include a large sample size, a continuous measure of pre-symptomatic disease as a clinical outcome measure, information on childhood and adult socio-economic position and recalled birthweight (as well as other potential confounding factors).

Reference List

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- (2) Han TS, Hooper JP, Morrison CE, Lean ME. Skeletal proportions and metabolic disorders in adults. *Eur J Clin Nutr* 1997; 51(12):804-809.
- (3) McCarron P, Okasha M, McEwen J, Davey Smith G. Height in young adulthood and risk of death from cardiorespiratory disease: a prospective study of male former students of Glasgow University, Scotland. *Am J Epidemiol* 2002; 155(8):683-687.
- (4) Davey Smith G, Hart C, Upton M, Hole D, Gillis C, Watt G et al. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. *J Epidemiol Community Health* 2000; 54(2):97-103.

- (5) Gerver WJ, De Bruin R. Relationship between height, sitting height and subischial leg length in Dutch children: presentation of normal values. *Acta Paediatr* 1995; 84(5):532-535.
- (6) Gunnell D. Can adult anthropometry be used as a 'biomarker' for prenatal and childhood exposures? *Int J Epidemiol* 2002; 31(2):390-394.
- (7) Wadsworth ME, Hardy RJ, Paul AA, Marshall SF, Cole TJ. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. *Int J Epidemiol* 2002; 31(2):383-390.
- (8) Gunnell DJ, Davey Smith G, Frankel SJ, Kemp M, Peters TJ. Socio-economic and dietary influences on leg length and trunk length in childhood: a reanalysis of the Carnegie (Boyd Orr) survey of diet and health in prewar Britain (1937-39). *Paediatr Perinat Epidemiol* 1998; 12 Suppl 1:96-113.
- (9) Gunnell DJ, Davey Smith G, Frankel S, Nanchahal K, Braddon FE, Pemberton J et al. Childhood leg length and adult mortality: follow up of the Carnegie (Boyd Orr) Survey of Diet and Health in Pre-war Britain. *J Epidemiol Community Health* 1998; 52(3):142-152.
- (10) Gunnell D, Whitely E, Upton M, McConnachie A, Davey Smith G, Watt G. Height, leg length and lung function: their association with cardiovascular risk factors and prevalent coronary heart disease in the Midspan Family Study. *Journal of Epidemiology & Community Health* 2002; in press.
- (11) Lawlor DA, Ebrahim S, Davey Smith G. The association between components of adult height and Type II diabetes and insulin resistance: British Women's Heart and Health Study. *Diabetologia* 2002; 45(8):1097-1106.
- (12) Davey Smith G, Greenwood R, Gunnell D, Sweetnam P, Yarnell J, Elwood P. Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. *J Epidemiol Community Health* 2001; 55(12):867-872.

5. Main Hypothesis/Study Questions:

The main hypothesis is that height, leg and trunk length are inversely related to average IMT at the first ARIC visit.

Secondary hypotheses:

- a) The associations between components of height and IMT will be attenuated but not removed by including adult cardiovascular risk factors in the model
- b) The association between components of height and IMT will be attenuated but not removed by including adult and childhood socioeconomic status in the model
- c) Leg length will be the component of adult height most strongly associated with IMT.

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

Outcome variable: IMT at each of the 6 sites at visit 1. Adjustment will be made for the missing IMT data (i.e. as each person does not necessarily have a measurement for all 6 sites, and these are not missing at random).

Main exposure variables: Height, leg and trunk length, as measured at the first ARIC visit. Sitting height and standing height were both measured. We will take trunk length as being sitting height, and leg length as being (standing height-sitting height).

Confounding variables: *From the first visit except where stated:*

Adult CVD risk factors – drinker status, alcohol intake, current smoking status, cigarette years of smoking, diabetes present, triglycerides, total, LDL and HDL cholesterol (SI units), glucose (fasting), systolic and diastolic BP, hypertension and cholesterol medication, MI (according to ECG), prevalent CHD, stroke or TIA, family history of CHD, stroke, diabetes and high blood pressure.

Adult socio-demographic and anthropometric factors – waist-hip ratio, weight, educational attainment, retirement status*, income for the past 12 months*, most recent occupation*, age, sex, ethnic group, field center.

* Educational attainment will be used as a surrogate for socio-economic status in early adult life. We will also investigate the use of an indicator combining retirement status, and income and most recent occupation, as a surrogate for socio-economic status in adulthood. However, this may not be a good surrogate due to a high proportion of the study population having retired and a high proportion (20-30%) of women being homemakers.

Childhood risk factors – *from the fourth visit:* parental education at participant's birth, or education of the two adults caring for the child if these were not the parents (to be used as a surrogate for early childhood socioeconomic status). Birthweight (for the subset of participants who have recalled birthweight) and birthweight category (again, for the subset of participants with these data).

Time window: This will be an analysis of the ARIC cohort members at visit 1, with the addition of birthweight and parental SES history data obtained from the fourth visit.

Inclusions/exclusions: All subjects without IMT data (at the first visit) will be excluded. Those with ethnic origin other than Black or White will be excluded, as will black participants at the Minneapolis or Washington County Field Centers (as the vast majority of the participants at these field centers were white).

As triglycerides vary greatly with time since last meal, all analyses including this variable will be limited to those fasting at least 8 hrs before the blood was drawn.

Analysis plan

The relationship between exposures (height, leg and trunk length) and the outcome (IMT) will be examined univariately using standard statistical models (linear regression). The outcome will be categorized as in previous ARIC manuscripts, and the associations examined to test for non-linearity of the association.

These models will be repeated several times, adding more confounding variables each time. The first extended model will also include genetic/parental factors (including parental history of CHD), then these factors plus childhood risk factors, etc. in a hierarchy ending with adult risk factors. Each group of confounders will be added to the model simultaneously, and the association between IMT and height, leg and trunk length re-examined. We will particularly examine how the relationship between height, leg and trunk length and IMT changes when adult weight and adult social class are included in the model.

Analyses will be performed with and without the inclusion of triglycerides (see Inclusions/Exclusions, above) and with and without birthweight and childhood socioeconomic status (as these were queried at visit 4, and so information is not available for the entire cohort). Birthweight will be included both as a categorical variable and as a continuous variable, as fewer participants recalled an exact (continuous) birthweight than recalled a birthweight category. We will estimate the proportion of variation in adult IMT explained by height, leg and trunk length.

The analysis will be repeated, stratified by sex and race.

The analysis will then be repeated limited to those participants with complete data for the most complex model (including birthweight and childhood socioeconomic position, collected at the 4th visit only). This will allow us to ensure that the effect of selection bias (selecting those who survived to the 4th visit only) does not account for the differences between the various models. We will use this set of models to examine how the relationship between IMT and height, leg and trunk length changes when birthweight and childhood socioeconomic position are included in the model.

Missing data

We will perform a sensitivity analysis to examine the robustness of our conclusions to the missing IMT data, as these data may not be missing at random. This will be done by including all variable thought to be related to missingness of IMT (including arterial depth) in the analysis, and also by using IMT with the missing values imputed (based on age, sex, race, and adjusted for reader- and time-trends).

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/csc/ARIC/stdy/studymem.html>

Yes